SYNTHESIS OF SOME

STARCH CARBAMATES AND RELATED COMPOUNDS.

A THESIS

submitted by

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a candidate for

the degree of

PHILOSOPHIAE DOCTOR.

University of Birmingham. October 1972.

SYNOPSIS.

This thesis describes two approaches to the preparation, from starch and model compounds, of carbamates derived from pesticidal amines and, in particular, alkylamino-1,3,5-triazines.

The first approach involved the preparation and reaction of a carbonate of starch containing 2,3-carbonates of the glucopyranoside residues. In model studies with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1), treatment with primary and secondary aliphatic amines gave mixtures of the methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-carbamates in high yield. However, the reaction of the 2,3-carbonate (1) with aniline required severe conditions and gave the 2- and 3-(N-phenylcarbamates) only in low yield, and carbamates could not be isolated from the reactions of a number of other aromatic amines with compound 1. It was therefore concluded that the carbonate method was not applicable to alkylamino-1,3,5-triazines. A carbonate of starch reacted satisfactorily with cyclohexylamine to give an N-cyclohexylcarbamoylstarch.

The second approach involved the preparations and reactions of carbamoyl chlorides. The reactions of N-methyl-N-phenylcarbamoyl chloride with a number of model alcohols, such as cis-2-phenyl-1,3-dioxan-5-ol, gave the expected N-methyl-N-phenylcarbamates under

mild conditions, and N-methyl-N-phenylcarbamoyl derivatives of starch and cellulose were also made. N-(2-Chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride (4) was prepared in good yield by the action of carbonyl chloride on 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine. The reaction of the carbamoyl chloride 4 with cis-2-phenyl-1,3-dioxan-5-ol gave 2-chloro-4-diethylamino-6-[N-ethyl-N-(cis-2-phenyl-1,3-dioxan-5-yl)-oxycarbonyl]amino-1,3,5-triazine. An N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoylstarch was made by the action of the compound 4 on starch in the presence of pyridine.

The sodium salt of cis-2-phenyl-1,3-dioxan-5-ol reacted with 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine to give 2-diethylamino-4-ethylamino-6-(cis-2-phenyl-1,3-dioxan-5-yl)oxy-1,3,5-triazine, and an analogous reaction occurred with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. When starch and cellulose were treated with 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine, only a very low incorporation of the triazine into the polysaccharide was observed.

The results of some preliminary biological tests are reported, and the significance of the compounds reported in this thesis is discussed briefly in relation to their known or potential biological activity.

ACKNOWLEDGMENTS.

The author wishes to express his thanks to Professor M.Stacey for the opportunity to pursue research. Dr. N.Baggett, Dr. M.H.B.Hayes and Dr. J.M.Webber are thanked for their collaboration in the supervision of this work and the guidance of Dr. J.M.Webber in the writing of this thesis is greatly appreciated.

Thanks are also due to many friends and colleagues for continual help, advice and discussion.

Acknowledgment is made to the staff of the National Vegetable Research Station, Wellesbourne, Warwick, and of Fisons Limited for carrying out biological tests.

Special thanks go to my mother for typing this work.

Ranks Hovis McDougall are thanked for the provision of a research grant.

C O N T E N T S

INTRODUCTION.

The work reported in this thesis is part of a study of some chemical reactions which could form a basis for increasing the utilization of starch and related products in industry.

Starch is used principally as a food[1], but it appears that it has fulfilled other functions since about 3000 B.C.[2]. Today starch has numerous applications in industry, such as in textile sizing and paper coating[3,4,5,6]. Applications are also found for chemically modified starches[4,7,8,9], and for dextrins and D-glucose produced by the acidic or enzymic hydrolysis of starch[4,10]. Statistics collected from England and Wales in 1963 and 1968 show that the annual production of starch and products derived from starch increased substantially over the intervening years, but the price of unprocessed starch fell by about twenty-five per cent over the same period[11].

Thus, starch is a plentiful and cheap material, and developments in the food industry (e.g. Ranks Hovis McDougall Ltd.) suggest that production is likely to increase. It seems that for baking purposes it is often necessary to enrich wheat flour with gluten (mainly protein) which is extracted from other batches of flour[12,13]. As a result of the extraction process a large quantity of starch is obtained as a by-product. Greater use of European wheat would necessitate wider application of the enrichment process because of the lower gluten content of flour from this source[13,14].

The possibility that the production of starch will increase has stimulated a search for new outlets, and it seemed that usage in agriculture might provide an outlet of suitable scale. Large amounts of chemicals are consumed in agriculture[15], but a survey of the structures of the compounds involved and those of the industrial starting materials reveals that little carbohydrate is consumed in the industry.

Carbohydrates and particularly polysaccharides are found widely in soils[16], and it is believed that they are responsible for the aggregation of soil particles[17]. Thus, it is possible that polysaccharides could be used as soil conditioners, and there are examples of the use of starch[18], starch derivatives[19] and industrial waste containing polysaccharides[20] for this purpose.

Other potential applications are in coatings for seeds and granules of chemicals, and in the supports used in the granulation of agricultural chemicals.

Coated seeds are used increasingly in agriculture and a variety of materials (e.g. clays, polystyrene and charcoal) are placed in the coatings[21]. Encasement of seeds in a film of polystyrene and india rubber causes their germination to be delayed[22]. The practice of coating seeds with chemicals to give them protection against infection is now widespread, but it is difficult to give each seed the same dose of protecting compounds, and much of the coatings may fall off the seeds before they are planted[23].

Thus, there is growing interest in the incorporation of seed protectives in adhesive coatings[24]. Novel methods of applying fertilizers such as in capsules of an organic polymer or in mixtures with inactive supports have also been described[25]. Other agricultural chemicals may be applied similarly[26,27], and, in general, the application of agricultural chemicals in granules is becoming more important[28].

Thus, a considerable outlet for starch and starch derivatives would become available if uses could be found for them in the formulation of agricultural chemicals. There are a number of examples, especially in pharmacy, of the use of various combinations of biologically active compounds with materials of high molecular weight to give some control of the rate of release of the active compounds into the site of absorption or reaction. At the time that this work was commenced, very little had been published about the preparation of such products for use in agriculture.

USE OF POLYMERS WITH BIOLOGICALLY ACTIVE COMPOUNDS.

There has been great interest for many years in the use of polymers as supports for biologically active materials. Various methods of binding the active compounds to the polymers confer multifarious properties on the products.

Wide use is now made of enzymes bound to supports which are insoluble in the aqueous media in which the enzymes act[29]. The protein can be trapped

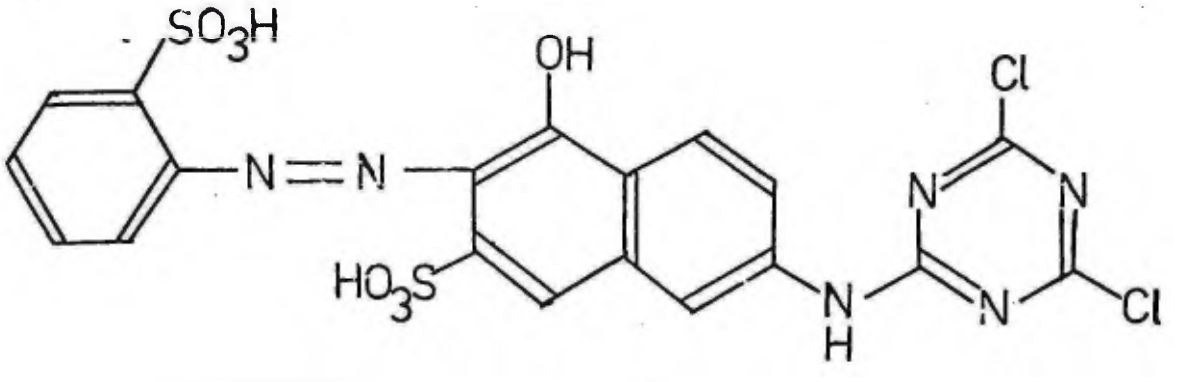


Fig.I. An example of a 'reactive' dye.

in a hydrophilic gel, bound ionically to an ion-exchange resin, or covalently linked to natural or synthetic polymers in such a way that the enzymic activity is not significantly diminished. Antigens bound to polymers are used in the separation and purification of antibodies[29,30,31]. A relevant example of the preparation of such a material is the conversion of the carboxyl groups of a cation-exchange resin to acid chlorides followed by their reaction with a solution of an antigen[32]. The presence of a covalent bond is advantageous here, as in the case of enzyme substrates linked to polymers for use in affinity chromatography[29], but there seems to be no evidence to suggest that covalent bonds between enzymes and polymers are especially important. Cellulose and cellulose derivatives are suitable as the insoluble supports for enzymes[29,33,34,35,36], enzyme substrates[37] and antigens[30,31], and a derivative of dialdehyde starch has been used successfully as an enzyme support[38].

Dyes and fluorescent whiteners are frequently bound to fibres by covalent bonds[39,40]. The usual method of accomplishing this is to react the nucleophilic groups of a fibre with a chromophoric molecule which is susceptible to nucleophilic displacement (a 'reactive' dye). Thus, for example, cellulose, in a basic medium, will displace a chlorine atom from the molecule shown in Fig.I to give an ether linkage between the dye and the polymer[39,41]. One reason for the success of these dyes is their 'fastness' caused by the stability of such linkages[42]. By the use of similar methods, it

is possible to prepare cellulose fibres which are resistant to fungal and bacterial attack[29,42,43]. Thus, for example, a chloro-1,3,5-triazine derivative (cyanurate) of cellulose has been reacted with pentachlorophenol to give a product which is very resistant to attack by fungi[44]. The mode of action of protecting groups which are covalently bound to the polymer is not clear since it is known that, in a series of compounds, anti-fungal activity diminishes with decreasing aqueous solubility. Allan claims that the chemical binding of biologically active compounds to cellulose and lignin prevents dermatological reaction[44].

Many methods are known for controlling the rate of release of drugs from the preparations which are administered to humans and animals. In general, the dispersion of a drug in a carrier such as urea or a material of high molecular weight, such as starch, increases its rate of absorption from the digestive tract[45]. However, dispersions of drugs in fatty alcohols or waxes[46], or compounds of drugs with polymers[47,48,49] have been found to make the physiologically active compounds available for absorption into the active sites over long periods. Use of such preparations eliminates the necessity for repeated administration and often leads to more efficient use of the active compound[47].

Polysaccharides are widely used as the supports in preparations giving slow release of drugs[47]. For example, Kratzl, Kaufmann et al. have demonstrated

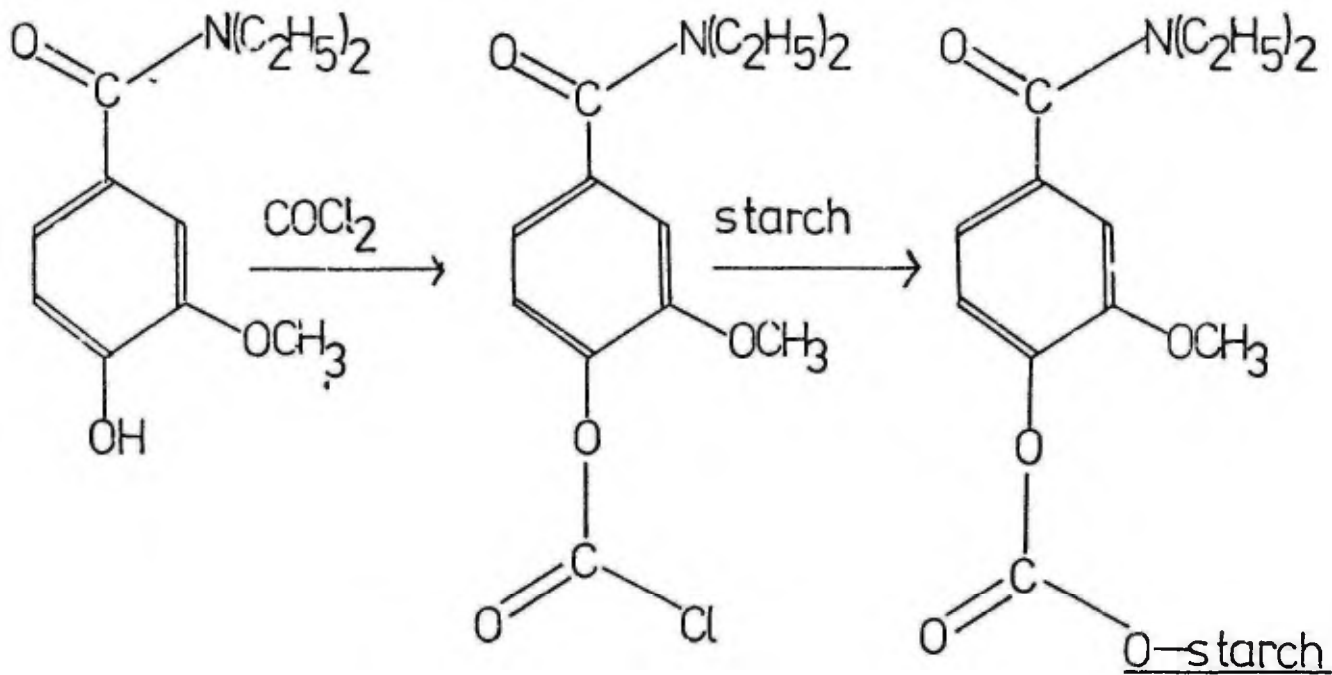


Fig.II. Preparation of a starch carbonate which releases a drug over a prolonged period[50].

methods of preparation and administration of a starch ester of acetylsalicylic acid[48,49]. When animals received intra-muscular injections of the ester in an isopropylideneglycerol, slow release of acetylsalicylic acid was observed by monitoring the concentrations in the blood and urine[49]. A similar effect was observed with 4-hydroxy-3-methoxybenzoic acid N,N-diethylamide linked to a starch carbonate as shown in Fig.II[50]. Polymers containing covalently bonded moieties of known physiological activity may have activity themselves, or the active compounds may be released by slow hydrolysis of the bonds to the polymeric support[47].

Recently, a number of patents have been filed which describe preparations in which pesticides (chemicals used in agriculture, such as herbicides, fungicides and insecticides; see page 7 and ref.57) are supported on or incorporated in polymers[26,27,51]. Some of these preparations release the pesticidal compounds over a long period. Some of Allan's work in this field[27] has been reported in greater detail. Allan and his co-workers have described the conversion of various herbicidal carboxylic acids to their acid chlorides and subsequently to their cellulose and lignin esters[52,53,54]. These esters have been tested under field conditions by a biological assay method based on the germination of lettuce seed[54,55]. For a particular dose of 2,4-dichlorophenoxyacetic acid, the cellulose and lignin esters maintained herbicidal

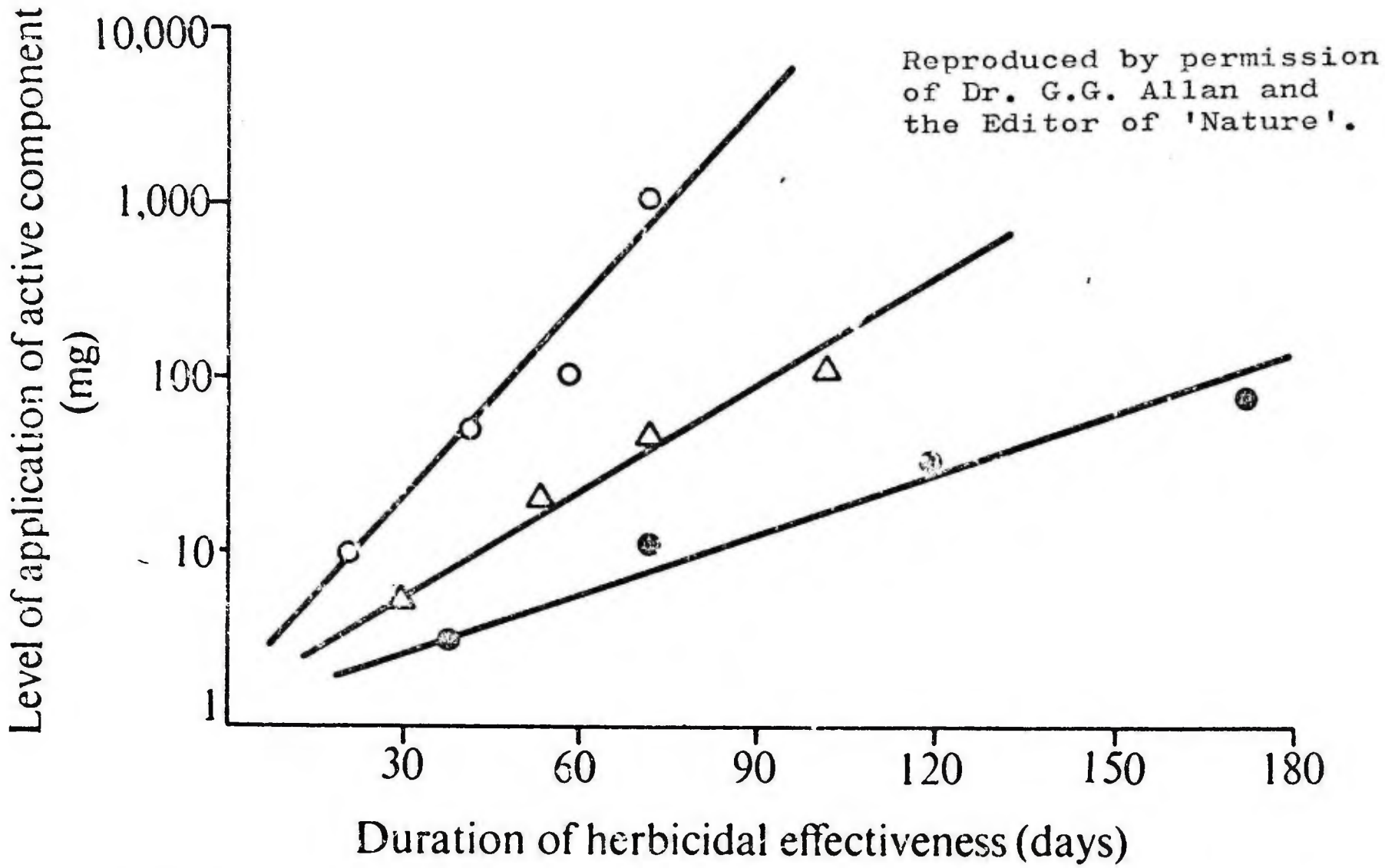
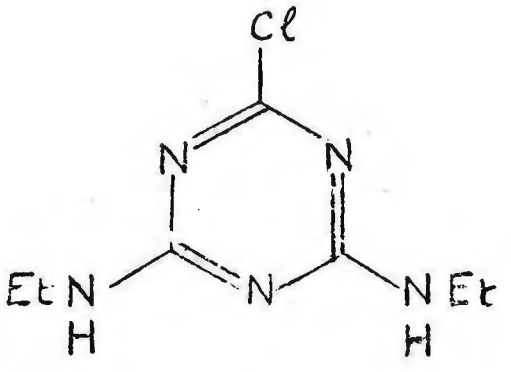
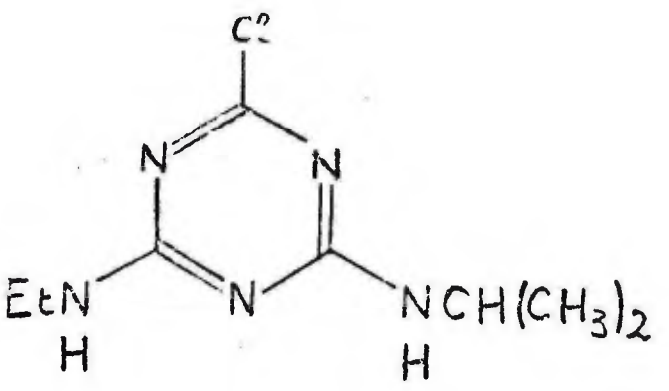


Fig. III. Relationship of duration of herbicidal effectiveness to level of application for 2,4-dichlorophenoxyacetic acid (2,4-D) chemically combined with water insoluble polymers. ○, 2,4-D alone; △, 19.7% 2,4-D/Douglas fir bark chemical combination; ●, 39% 2,4-D/kraft lignin chemical combination.



simazine



atrazine

Fig. IV. Examples of triazine herbicides.

activity for a longer period than the herbicidal acid alone. This is demonstrated in Fig.III[54]. It is apparent that this mode of application could lead to more efficient use of certain pesticides.

COMPOUNDS USED IN AGRICULTURE.

The number and quantities of chemicals produced for pest control in agriculture have increased greatly since 1948[15], probably because of the manifold benefits of their use[56]. Melnikov has defined some categories into which these compounds may be placed according to their biological activity (e.g. fungicides, insecticides, herbicides etc.)[57], but the structures of the compounds listed in each category are very diverse[57,58].

The amino group is found in numerous pesticides[58], and amino-1,3,5-triazines find use as fungicides[58,59], insecticides[58,60] and herbicides[58,61]. Diamino-1,3,5,triazines have been used as herbicides for nearly twenty years, and probably the most widely used of the triazine herbicides are 2-chloro-4,6-bis-(ethylamino)-1,3,5-triazine (simazine, Fig.IV) and 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine (atrazine, Fig.IV)[61]. It has been reported that a number of diamino-1,3,5-triazines cause growth and germination stimulation in plants[62].

Although Allan includes some pesticidal amino-1,3,5-triazines in his claim[27], there are no reports that these compounds have been linked to polymers.

In addition to the possibility that the use of triazines linked covalently to polysaccharides would cause slow release of the active compounds in the soil, it is possible that volatilization and leaching of the active compounds would be reduced. Substantial losses of triazine herbicides can occur by volatilization[63] and leaching[64] in certain soil and atmospheric conditions.

GENERAL OBJECTIVES.

It was decided that an investigation of some methods by which amines and particularly the triazine herbicides might be bonded covalently to starch would be relevant to the possibility of using starch as a carrier for agricultural chemicals. At the time that this work was commenced, Allan's articles about preparations giving prolonged release of herbicides[52,53,54] had not been published.

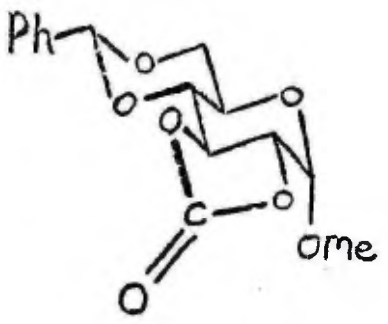
Simple alcohols and monosaccharides were chosen as model compounds for this study. The products of the model reactions contain groups such as carbamates or 1,3,5-triazines which are frequently found in biologically active compounds. Thus, it was thought that these compounds might themselves be active and have potentiality as pesticides. Such activity would also be important because degradation of the polysaccharide derivatives in the soil might give the same or similar compounds.

DISCUSSION.

At the outset, two approaches to the task of linking an amine to starch by covalent bonds were apparent. These were the modification of the amine followed by reaction with starch or the modification of starch followed by reaction with the amine. Also, it seemed possible that the steps of each procedure might be carried out simultaneously or without isolation of the intermediates.

MODIFICATION OF STARCH.

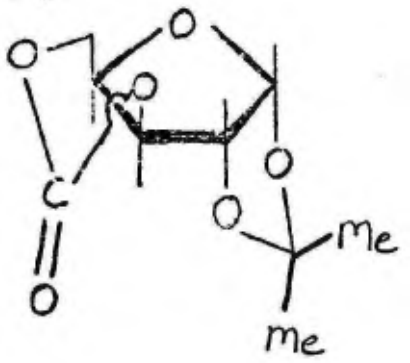
The recent reports of the preparation of dextrin and dextran carbonates containing cyclic trans-carbonate groups[65] and of a cyclic 2,3-carbonate of 6-O-triphenylmethylamylose[66] suggested that the preparation of a carbonate of starch containing 2,3-carbonate groups was a possibility. Furthermore it seemed likely that the properties of such groups would be analogous to those of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (see Fig.V) which has been shown[67,68] to react with some amines to give a mixture of the corresponding glucoside 2- and 3-carbamates (see Fig.VI). Also, compound 1 reacts with alcohols and thiols in the presence of triethylamine to give, respectively, mixtures of the 2- and 3-carbonates and thiolcarbonates of the glucoside (see Fig.VI)[67,68]. Thus, it was thought that a carbonate of starch might prove to be a suitable intermediate in the linking of a variety of pesticidal compounds to starch and an investigation of the preparation



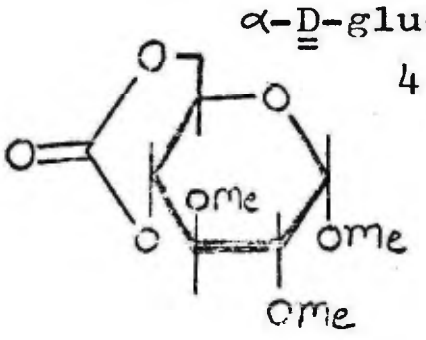
methyl 4,6-O-benzylidene-
α-D-glucopyranoside
2,3-carbonate (1)

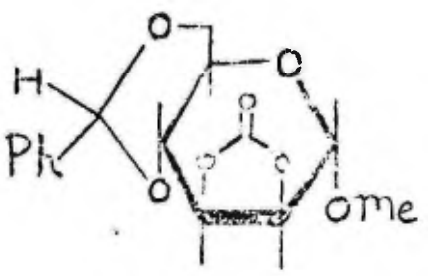
ethylene
carbonate

1,2-O-isopropylidene-
α-D-xylofuranose
3,5-carbonate.

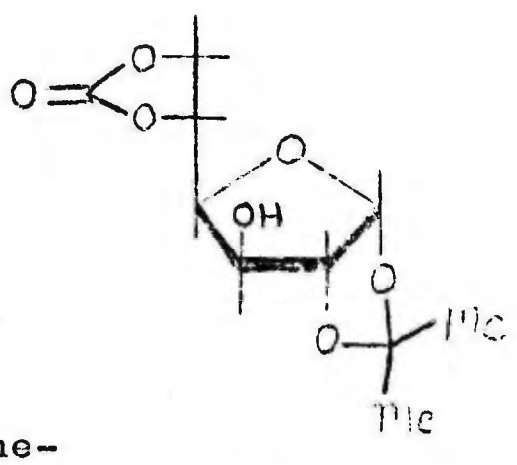


methyl 2,3-di-O-methyl-
α-D-glucopyranoside
4,6-carbonate.



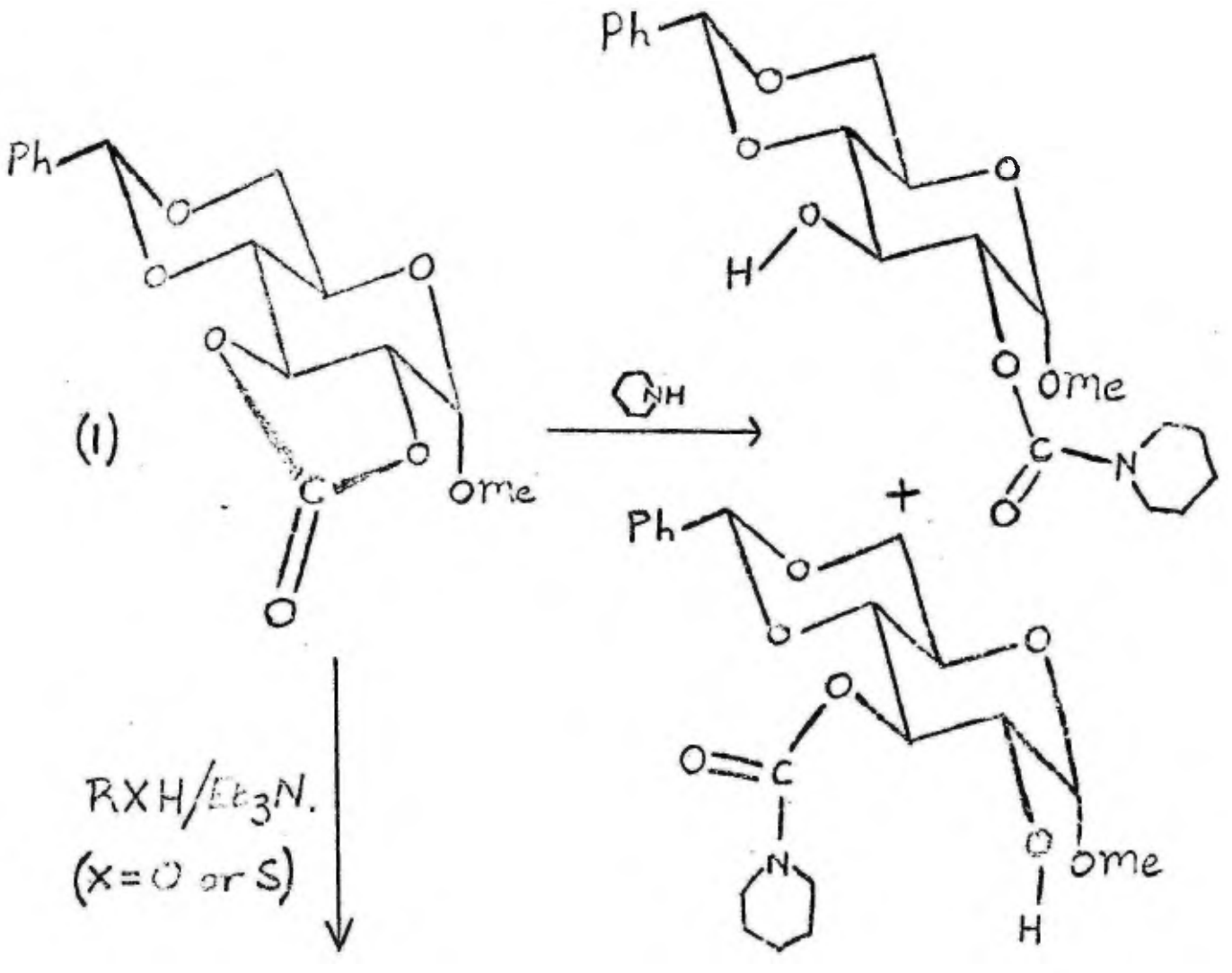


methyl 4,6-O-benzylidene-
α-D-mannopyranoside
2,3-carbonate.



1,2-O-isopropylidene-
α-D-glucofuranose
5,6-carbonate.

Fig.V. Some examples of cyclic carbonates.



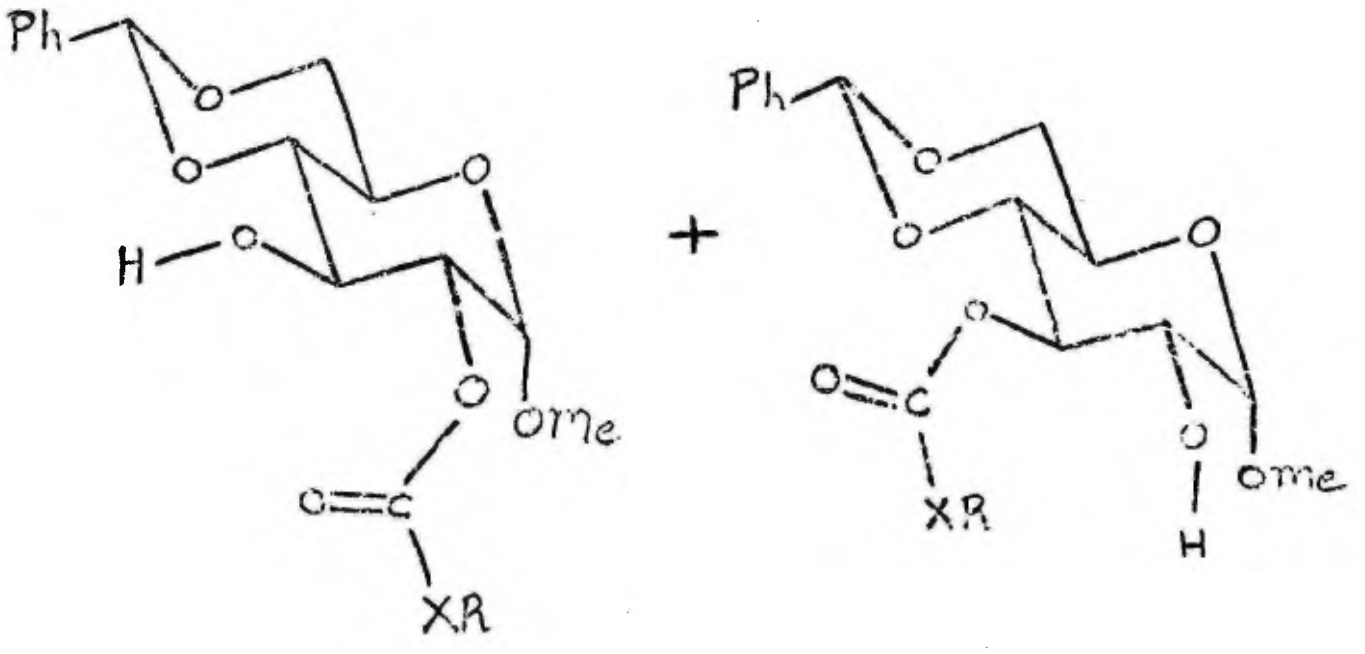


Fig. VI. Examples of the reactions of compound 1.

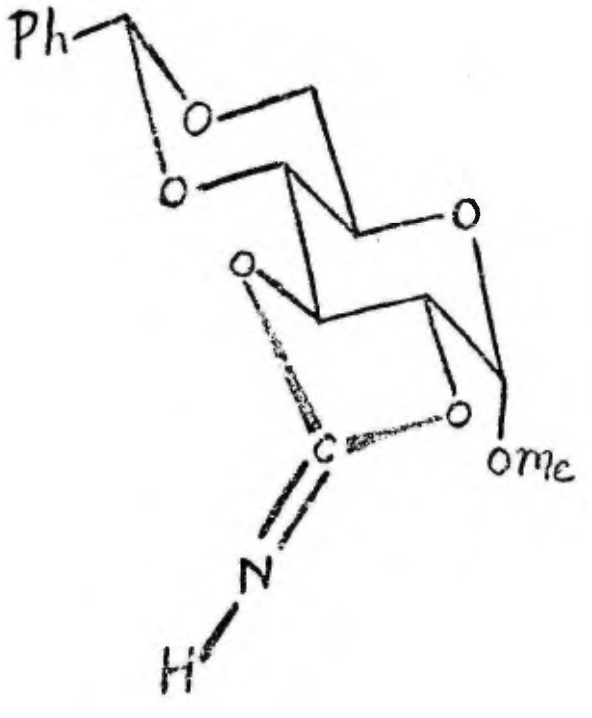


Fig.VII. Methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-imidocarbonate.

and properties of such a material seemed worth-while.

In this context it is worth noting that it has been claimed[69] that the method of coupling of enzymes to cellulosic materials in which the polysaccharide is first treated with cyanogen bromide involves the intermediacy of cyclic imidocarbonates analogous to the trans-fused cyclic carbonates reported by Doane et al. Recently the reaction of cyanogen bromide with methyl 4,6-O-benzylidene-α-D-glucopyranoside has been shown to give the 2,3-carbonate (1) in small amount together with what was thought to be methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-imidocarbonate (see Fig.VII)[70].

Chemistry of cyclic carbonates.

A thorough review of the chemistry of carbonates of carbohydrates was published in 1960[71], but most of the work dealing with the preparation and properties of trans-fused cyclic carbonates of carbohydrates has been published since that review.

The first cyclic carbonate, ethylene carbonate (Fig.V), was prepared by Nemirowsky in 1883 by the action of carbonyl chloride on ethylene glycol[72]. Haworth and co-workers prepared numerous cyclic carbonates of carbohydrates[71], but the structures of many of their products were assigned only provisionally. Cyclic carbonates have been used as acid-stable and alkali-labile blocking groups in the synthesis of carbohydrate derivatives[73], and in characterization, especially of

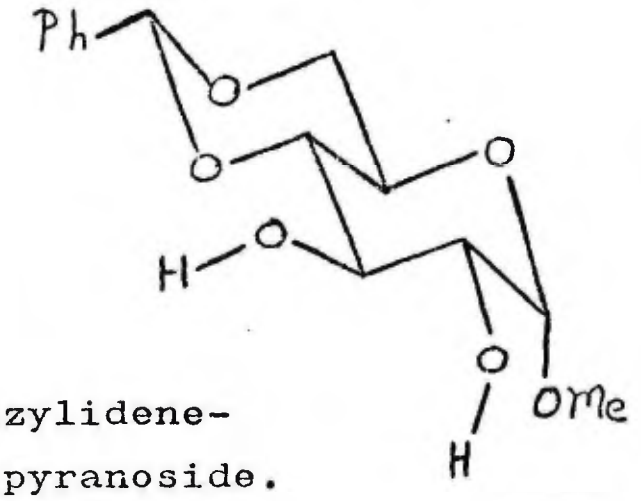
steroids[74] and flavans[75]. The preparation of a cyclic carbonate from vicinal trans-hydroxyl groups of a flavan by Bokadia et al.[76] disproved an earlier claim[77] that the formation of a cyclic carbonate from a pair of vicinal hydroxyl groups was diagnostic of a cis relationship. The subsequent syntheses of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (Fig.V) from the corresponding 2,3-thionocarbonate[66] and of methyl 4,6-O-benzylidene-β-D-galactopyranoside 2,3-carbonate from the correspondong 3-benzylthiolcarbonate[78] stimulated interest in this type of carbohydrate carbonate. Facile syntheses of the glucoside 2,3-carbonate (1) have been devised by its originators by the reaction of ethyl chloroformate[79] or carbonyl chloride[68] with methyl 4,6-O-benzylidene-α-D-glucopyranoside in the presence of triethylamine. An early report of the formation of a six-membered carbonate ring cis-fused to a xylopyranose system[80] (see Fig.V) has now been followed by the synthesis of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-carbonate[81] (Fig.V).

In general, carbonates may be hydrolysed by aqueous base[82]. Other nucleophilic reagents can cleave cyclic carbonates[80,68], but the susceptibility to attack probably reflects the strains and stereochemical interactions within the carbonate molecules. Thus, certain general conclusions may be drawn about the reactivity of carbonates from a knowledge of their chemical structures. It is well known, for instance,

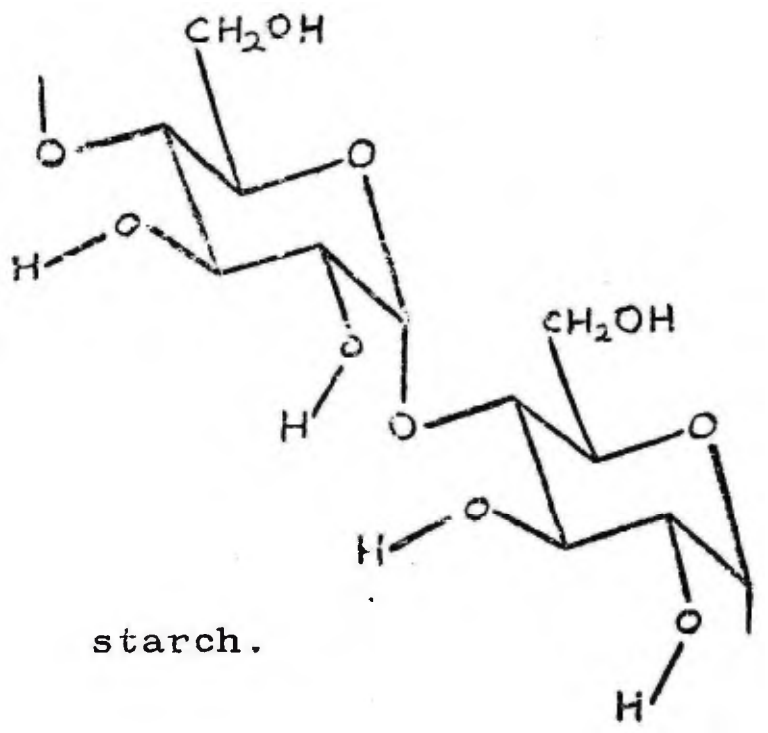
that simple six-membered carbonate rings are less stable than similar five-membered compounds in which the exocyclic double bond causes less strain[83]. In a comparative study[68] of the reactions of methanol with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1), methyl 4,6-O-benzylidene-α-D-mannopyranoside 2,3-carbonate (Fig.V) and 1,2-O-isopropylidene-α-D-glucofuranose 5,6-carbonate (Fig.V) in the presence of triethylamine, the rate of ring opening of the mannopyranoside 2,3-carbonate was found to be about half of that of the glucopyranoside 2,3-carbonate. This was related to the greater strain present in the trans-fused carbonate. The glucofuranose 5,6-carbonate did not react under the conditions used.

Doane et al.[68] demonstrated the reactivity of the trans-fused, five-membered carbonate by treating the glucopyranoside carbonate (1) with methanol, benzyl alcohol, α-toluenethiol and glycine in the presence of triethylamine. The reactions are typified in the scheme of Fig.VI. The carbonate (1) also reacted with ammonia and piperidine at room temperature without catalysis by triethylamine to give, in each case, a mixture of the glucoside 2- and 3-carbamates (Fig.VI) in the ratio of approximately 3:1[68].

At the commencement of this work the cyclic carbonates of dextrin and dextran had been reacted with starch[84,65], but no study had been made of the reactions of amines with polysaccharide carbonates. Methyl

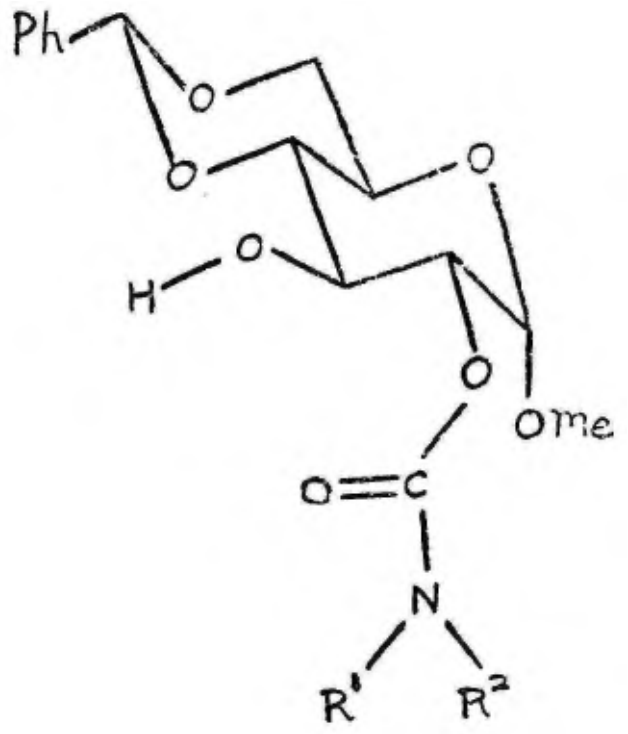


methyl
4,6-O-benzylidene-
α-D-glucopyranoside.

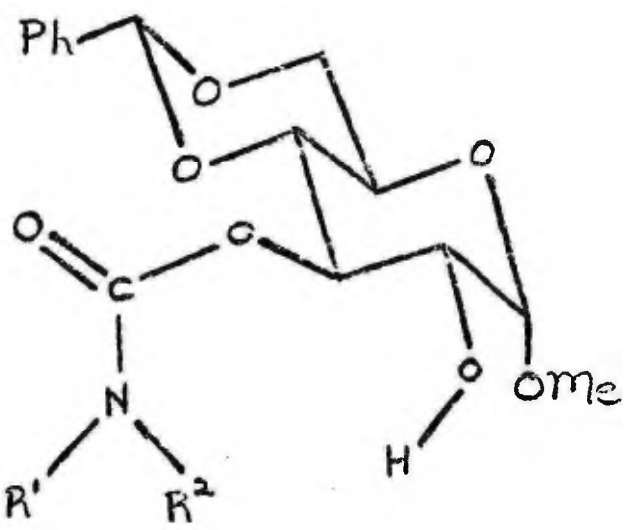


starch.

Fig. VIII. Analogy of structure of methyl 4,6-O-benzylidene-α-D-glucopyranoside with that of starch.



A (2-carbamate).



B (3-carbamate).

1; R^1 = H, R^2 = cyclohexyl.
2; R^1 = H, R^2 = ethyl
3; R^1 = R^2 = ethyl.
4; R^1 = H, R^2 = benzyl.
5; R^1 = R^2 = benzyl.
6; R^1 = H, R^2 = phenyl.

Fig.IX. Key to methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-carbamates.

4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) was considered to be a satisfactory model for a 2,3-carbonate of starch because of the similar relationships between the 2- and 3—hydroxyl groups (see Fig. VIII). Therefore, it was anticipated that a suitably prepared starch carbonate would be susceptible to attack by those reagents which cause ring opening of compound 1. Since amines showing biological activity are not confined to the triazine series, and since it was not known if all amines would show the same reactivity as ammonia and piperidine, a thorough investigation of the reactions of a variety of amines with the 2,3-carbonate (1) was instigated.

Reactions of amines with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1).

The glucoside 2,3-carbonate (1) was prepared in good yield (ca. 83%) by the method of Doane et al.[68] using the action of carbonyl chloride on methyl 4,6-O-benzylidene-α-D-glucopyranoside in the presence of triethylamine.

Aliphatic amines.—— The reactions of compound 1 with the primary amines cyclohexylamine, ethylamine and benzylamine (Experiments 1a-1c) proceeded readily at room temperature to give mixtures of the respective 2- and 3—carbamates (see Fig IX) in good yield (86-96%), and column chromatography of each mixture gave the isomers in the ratio of approximately 2:1.

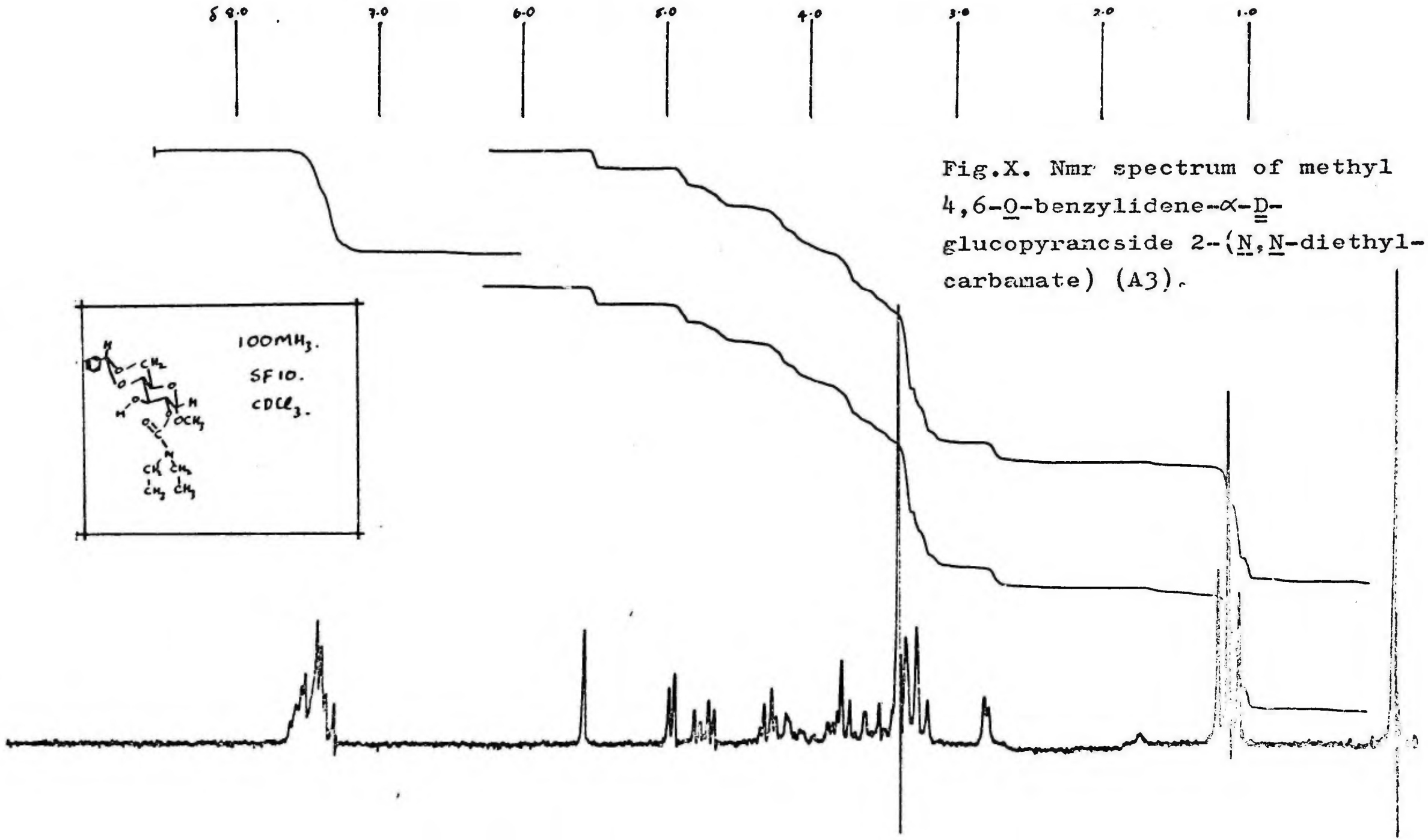


Fig.X. Nmr spectrum of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2-(N,N-diethylcarbamate) (A3).

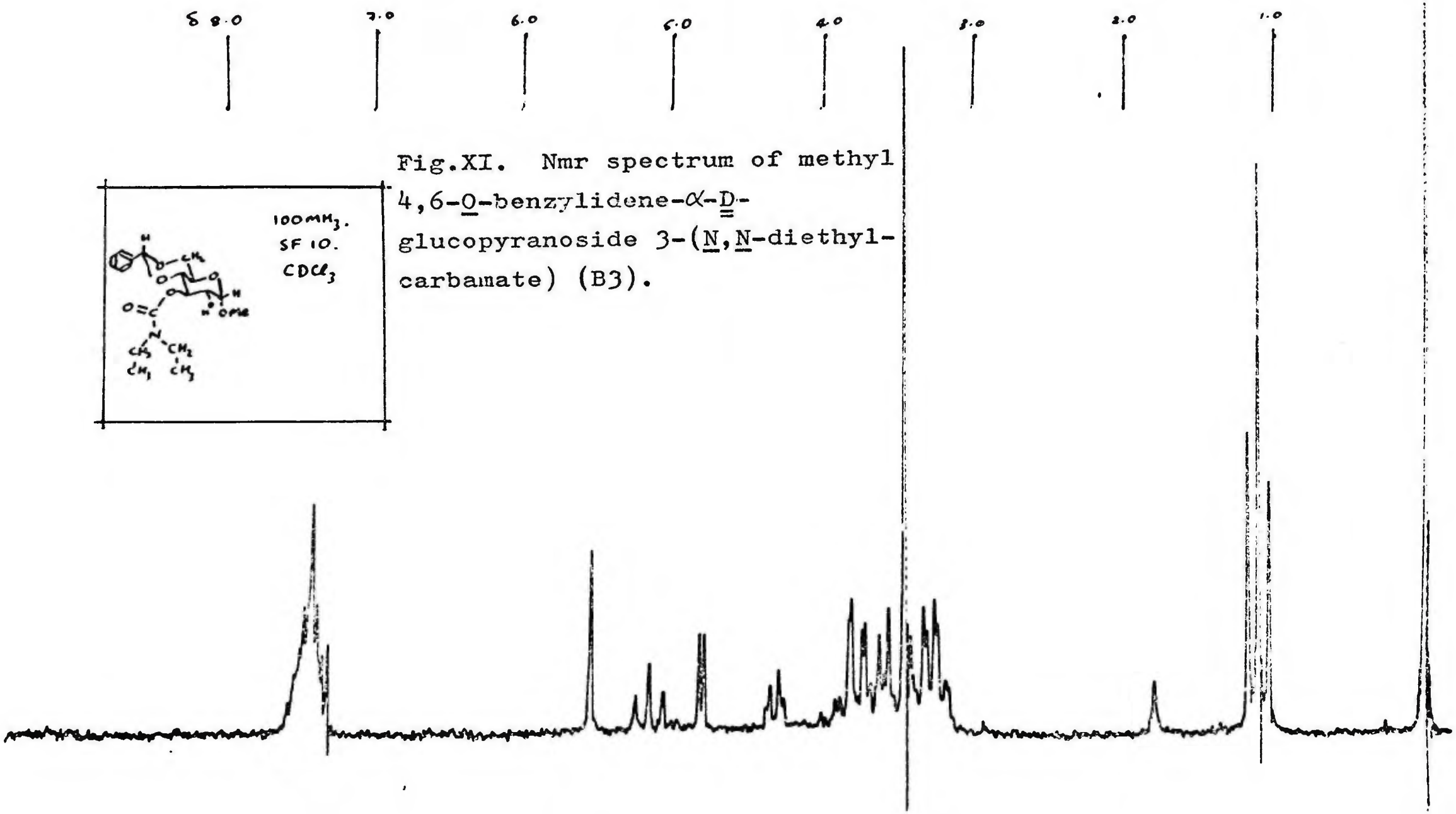


Fig.XI. Nmr spectrum of methyl 4,6-O-benzylidene-α-D-glucopyranoside 3-(N,N-diethylcarbamate) (B3).

The assignment of structures to the products of these reactions was based on the evidence afforded by their nuclear magnetic resonance (nmr) spectra. In the constrained methyl 4,6-O-benzylidene-α-D-glucopyranoside system the proton bonded to carbon one (H-1) and that bonded to carbon two (H-2) are in a cis equatorial-axial relationship, and H-2 and H-4 are each related to H-3 in a trans diaxial manner. Thus, the coupling constant $J_{1,2}$ is likely to be markedly smaller than $J_{2,3}$ or $J_{3,4}$ and therefore an electron-withdrawing (de-shielding) substituent at C-2 reveals a low-field signal clearly distinguishable from that revealed by an electron-withdrawing substituent at C-3. For example, compound A3 (Experiment 2a) in deuterio-chloroform shows a one-proton quartet at δ 4.75 (see Fig.X) and is identified as methyl 4,6-O-benzylidene-α-D-glucopyranoside 2-(N,N-diethylcarbamate), and compound B3 (Experiment 2c) shows a one-proton triplet at δ 5.16 (see Fig.X1) and is identified as the 3-(N,N-diethylcarbamate). All 2- and 3—substituted glucopyranoside derivatives isolated in this work have been identified similarly. Doane *et al*. had previously used this method to identify 2- and 3—substituted glucopyranosides[68].

The examples discussed on page 13 demonstrate clearly the ability of primary amines to react with the 2,3-carbonate (1) and the reaction of benzylamine is of interest since this amine shows insecticidal properties[57]. Since dibenzylamine is also an insecticide[57] its behaviour with the 2,3-carbonate (1) was examined. This reaction

(Experiment 1d) was less facile than that of benzylamine but on warming gave a 77% yield of the N,N-dibenzyl-carbamates (A5 and B5). The reaction with diethylamine was also examined, but some difficulty was encountered because of the presence of primary amine.

The initial attempt (Experiment 2a) to synthesize the methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-(N,N-diethylcarbamates) (A3 and B3) under the conditions of Experiment 1 gave a mixture of the 2-(N,N-diethylcarbamate) (A3) and the 2- and 3-(N-ethyl-carbamates) (A2 and B2). The apparently high yield of the 2-(N-ethylcarbamate) (component R) and the low recovery of a pure sample suggested that component R was contaminated with the 3-(N,N-diethylcarbamate) (B3), although this was not detected. At this stage it was not clear whether the monoethylcarbamates (A2 and B2) had been formed from ethylamine present as an impurity in the diethylamine, or by a dealkylation reaction. Further diethylamine of the batch used in Experiment 2a was not available, and therefore an attempt was made to purify a sample of another batch of diethylamine by re-crystallization of its hydrochloride and careful distillation of the recovered amine (Experiment 2b). Reaction of this material with the 2,3-carbonate again gave a mixture of mono- and dialkylcarbamates (containing at least three components). Gas chromatography of solutions of the amine remaining from the preparation and crystallization of the hydrochloride showed that

the commercial diethylamine contained at least 3.3% of ethylamine. Another sample of commercial diethylamine contained only approximately 0.05% of ethylamine but the reaction of this with the 2,3-carbonate (1) (Experiment 2c) again gave a mixture containing at least three components. A chromatographic separation gave methyl 4,6-O-benzylidene-α-D-glucopyranoside 2-(N,N-diethylcarbamate) (identical with compound A3 from Experiment 2a) in 64% yield and the corresponding 3-(N,N-diethylcarbamate) (B3) in 20% yield. A slow moving component corresponded to the 3-(N-ethylcarbamate) (B2). From the results described above it was concluded that the monoethylcarbamates formed in the diethylamine reactions resulted from reaction of ethylamine contaminant with the 2,3-carbonate. The yields of these products relative to the proportion of ethylamine in the diethylamine suggests that the rate of reaction of ethylamine is considerably faster than that of diethylamine. By analogy, the isolation of a small amount of a mixture of the 2- and 3-N-benzylcarbamates from the reaction of dibenzylamine (Experiment 1d) was ascribed to the presence of benzylamine contaminant.

Despite the complications arising from monoalkylamine impurities, the examples discussed above confirm the earlier work[68] in which piperidine reacted satisfactorily with the 2,3-carbonate (1). It seemed probable that steric factors cause the secondary amines to be less reactive than the primary amines, and to examine this possibility attempts were made to react

dicyclohexylamine with the 2,3-carbonate (1). Even at reflux temperature in the presence of triethylamine compound 1 remained intact (Experiment 5a). It is concluded that this lack of reactivity of dicyclohexylamine can be ascribed to steric hindrance of approach.

Aromatic amines.—— Special importance was attached to the reactions of aromatic amines with compound 1 because of the aromatic character of the amino-1,3,5-triazine herbicides. N-Methylaniline was chosen as a model compound because it was thought that the steric and electronic factors would be similar to those of a monoalkylamino-1,3,5-triazine. However, since there were no reports of the reactions of aromatic amines with trans-fused cyclic carbonates the reaction of aniline with the 2,3-carbonate (1) was studied first.

Aniline failed to react with compound 1 under the conditions of Experiment 1 and, under more severe conditions, complicated mixtures were obtained. Therefore, to assist identification, the desired products, the methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-(N-phenylcarbamates) (A6 and B6), were synthesized by the action of phenyl isocyanate on an excess of methyl 4,6-O-benzylidene-α-D-glucopyranoside (Experiment 3b). This reaction also gave an appreciable yield of the known 2,3-bis(N-phenylcarbamate) which was also synthesized in 29% yield by using an excess of the isocyanate (Experiment 3c). The low value of the optical rotation ($[\alpha]_D+29^\circ$) of this compound (in comparison with the literature value $[\alpha]_D+40^\circ$)

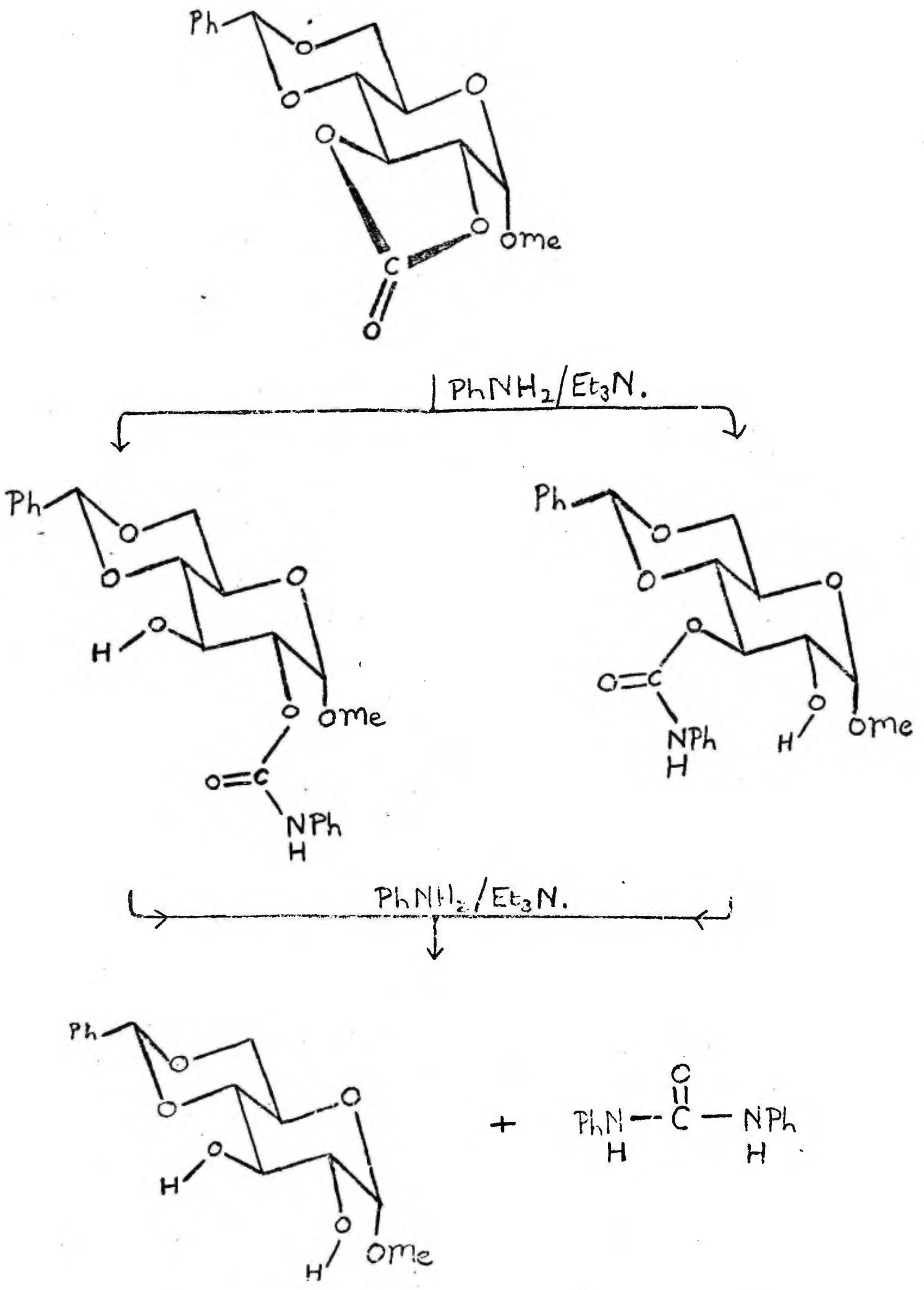
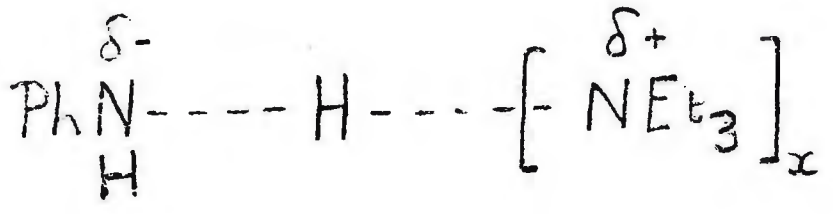


Fig. XII. Reaction of aniline with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (Experiment 3a).

remains unexplained. The biological testing of the biscarbamate is discussed on page 63(also see Appendix). Compound 1 reacted with a mixture of refluxing dry aniline and dry triethylamine to give a mixture of compounds (Experiment 3a). The first two fractions from a chromatographic separation of the products contained mixtures of 1,3-diphenylurea and the 2-(N-phenylcarbamate) (A6), each of which was isolated pure but only in low yield. The 3-(N-phenylcarbamate) (B6) was isolated in 22% yield (w.r.t. compound 1) from a subsequent fraction and the slow moving (tlc) component in the final fraction corresponded to methyl 4,6-O-benzylidene-α-D-glucopyranoside. The presence of 1,3-diphenylurea indicates that the reactivity of aniline with the 2,3-carbonate (1) is comparable with its reactivity towards the 2- and 3-(N-phenylcarbamates) to give methyl 4,6-O-benzylidene-α-D-glucopyranoside and the urea (see Fig.XII).

The conditions under which aniline reacted with compound 1 are similar to those reported by Doane et al[68] for the reaction of benzyl alcohol with compound 1. In a study of the mechanism of this reaction, it was found[85] that the rate was dependent upon the concentration of triethylamine. Moreover for a series of para-substituted benzyl alcohols, the rates correlated with the shift of the hydroxyl-stretching frequency observed on formation of alcohol/amine complexes in xylene solution, and the reaction was first order in compound 1 and in each amine/alcohol complex. The conclusion was drawn that

Reacting species in the benzyl alcohol/Et_3N/compound 1 system.



Proposed reacting species in the aniline/Et_3N/compound 1 system.

Fig. XIII.

the alcohol/triethylamine complexes (see Fig.XIII) were the reacting species. By analogy, it was thought that the reacting species in the aniline/triethylamine/compound 1 system (Experiment 3a) could be a complex between aniline and triethylamine as shown in Fig.XIII. Although infra-red data for complexes between triethylamine and a number of primary and secondary amines, including aniline and N-methylaniline, have been described[86,87], the spectra are more complicated than those of the alcohol/amine complexes. Therefore, it seemed unlikely that any quantitative work similar to that of Stout *et al.* would be possible. However, by analogy with the results of Stout, it was expected that, in the presence of triethylamine, N-methylaniline would be more reactive than aniline, because the shift of the N-H stretching frequency is larger ($157cm^{-1}$)[87] than for aniline ($63cm^{-1}$)[86].

Problems with water.—— In an attempt to react N-methylaniline with the 2,3-carbonate (Experiment 4a) two products were isolated by chromatography. These contained no nitrogen and showed ir bands at $1730-1750cm^{-1}$ indicative[88] of the presence of acyclic carbonate structures. The fast moving component (C) was assigned the structure bis(methyl 4,6-O-benzylidene-α-D-glucopyranoside) 2,2′-carbonate (see Fig.XIV) on the basis of its elemental analysis and nmr spectrum. The spectrum showed a low-field quartet at δ 4.62 which was assigned to H-2 and H-2′. The other product did not analyse for a similar bis-carbonate even after repeated

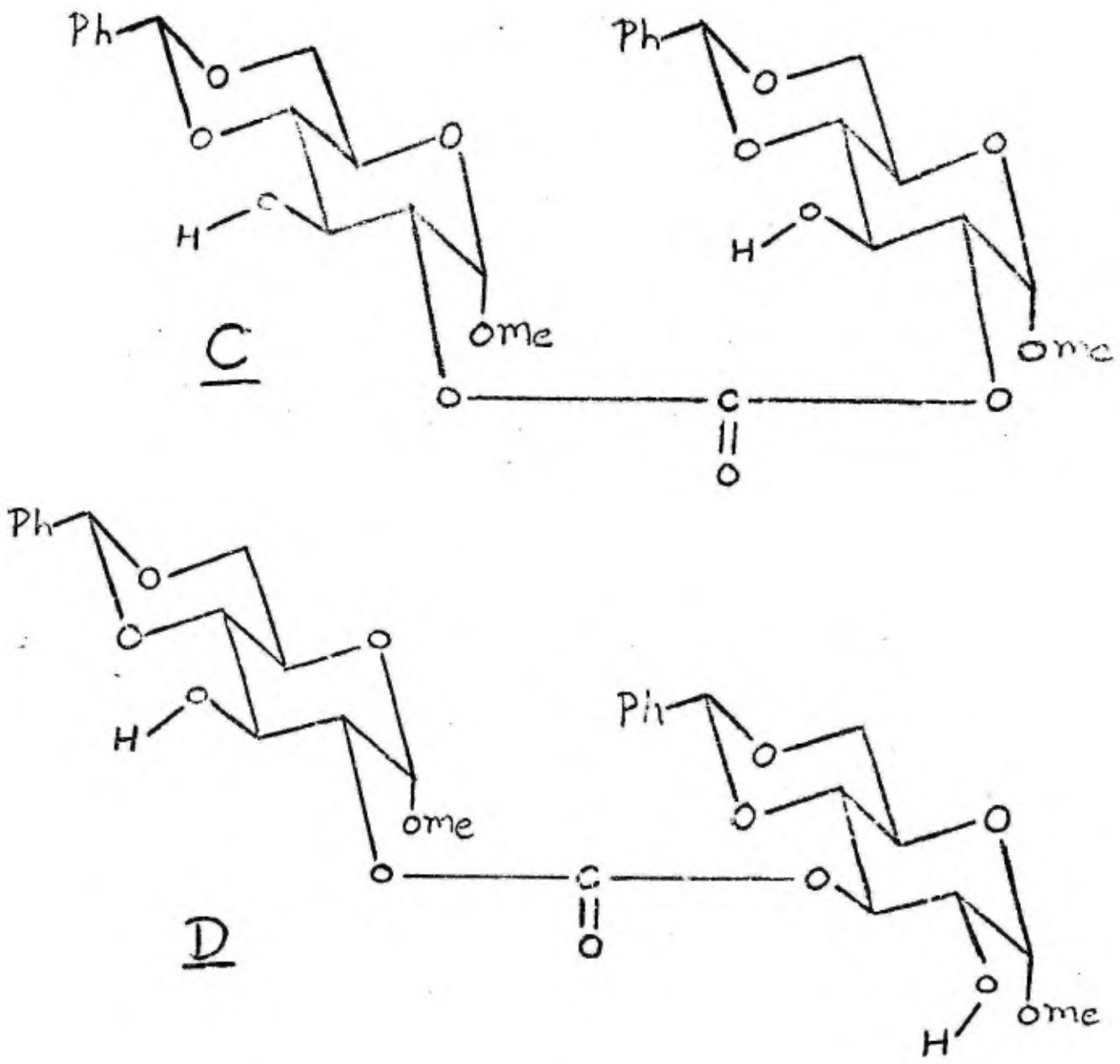


Fig. XIV. Proposed structures for the acyclic carbonates C and D (Experiments 4a and 4b).

precipitation from ethyl acetate:hexane, but its spectral properties were identical with those of bis(methyl 4,6-O-benzylidene-α-D-glucopyranoside) 2,3′-carbonate (D, see Fig.XIV) isolated in Experiment 4b and discussed below.

In order to rationalize the formation of the acyclic carbonates C and D when the 2,3-carbonate (1) was treated with N-methylaniline, compound 1 was treated with methyl 4,6-O-benzylidene-α-D-glucopyranoside in the presence of triethylamine in a sealed tube at 70° (Experiment 4b). This reaction gave two major products the spectral properties of which were indistinguishable from those of the acyclic carbonates C and D (Experiment 4a). Although a satisfactory elemental analysis of this sample of C was not obtained, the analysis of product D corresponded to that of bis(methyl 4,6-O-benzylidene-α-D-glucopyranoside) 2,3′-carbonate and the structure (Fig.XIV) was assigned from its nmr spectrum. A low-field quartet at δ 4.54 was ascribed to H-2 and a low field triplet at δ 5.12 was ascribed to H-3′.

Thus it was apparent that the bis(carbohydrate) carbonates formed in the attempt to react N-methylaniline with the 2,3-carbonate (1) (Experiment 4a) could have been formed by the reaction of compound 1 with methyl 4,6-O-benzylidene-α-D-glucopyranoside and it seemed likely that this was brought about because of initial hydrolysis of some of the 2,3-carbonate by water in the presence of triethylamine. When Experiment 4a was

repeated using similar conditions but scrupulously dried materials (Experiment 5b) the product contained (tlc) compound 1 and other materials, in small proportions, which could have been acyclic carbonates. Thus, it was concluded that further attempts to react N-methylaniline with the 2,3-carbonate in the presence of an organic base would not be of value because of the need to increase the severity of the reaction conditions. The poor reactivity of N-methylaniline compared with that of aniline does not correlate with the ir data discussed on page 19 and may be ascribed to steric factors. In addition to the problem, already encountered, of side products formed by reaction of water, it is possible that under strongly basic conditions starch and starch derivatives would degrade (see, for example, p's 31, 58 and 61). Also, if ring opening to give the desired carbamates could be achieved, they, like the N-phenylcarbamates (Experiment 3a), might be susceptible to attack by further reagent to give the corresponding urea (cf. Fig.XII).

4-Aminopyridine.—— Attempts to react 4-aminopyridine (Experiment 5c) and 2-diethylamino-4-ethylamino-1,3,5-triazine (Geigy G 10420) with the 2,3-carbonate in the presence of triethylamine were unsuccessful. No explanation can be forwarded at present for the apparent lack of reactivity of 4-aminopyridine. In many instances the nucleophilic strength of a reagent can be correlated with basicity[89].

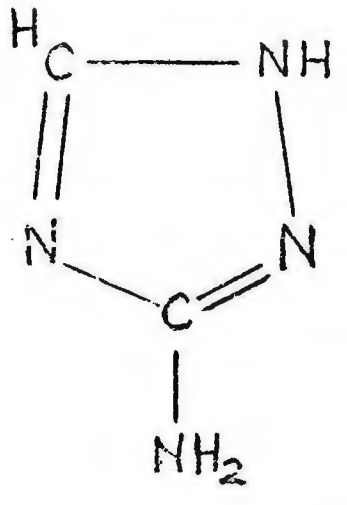


Fig. XV. 3-amino-1,2,4-triazole.

Since, in water at 25°, the pKa's of benzylamine, 4-aminopyridine, pyridine and aniline are 9.3, 9.1, 5.3 and 4.6, respectively[90], there must be some other factors acting in this instance.

3-Amino-1,2,4-triazole.—— Since 3-amino-1,2,4-triazole (Fig.XV) is very important commercially as a herbicide[58], its behaviour with the 2,3-carbonate (1) was studied. No reaction was observed under mild conditions but in refluxing N,N-dimethylformamide (DMF) (Experiment 6) a complicated mixture was obtained. Control experiments showed that the products were not formed in the absence of the triazole or of the 2,3-carbonate. A chromatographic separation gave compound 1, the bis(carbohydrate) carbonates (C and D) and, as the major product, methyl 4,6-O-benzylidene-α-D-glucopyranoside. This suggests that the initially formed carbamates are susceptible to attack by further amine. Since no carbamates were isolated and some 2,3-carbonate (1) remained, it appears that the reactions of the amine with the carbamates are faster than attack of the amine at the carbonate.

In order to investigate the fate of the triazole the aqueous washings from the work up were processed to yield two chloroform soluble components. The minor component was not identified but gave an elemental analysis in which the carbon (18%) and nitrogen (16%) results were lower than could be explained

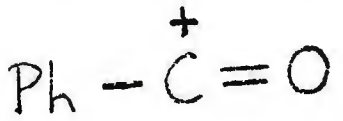
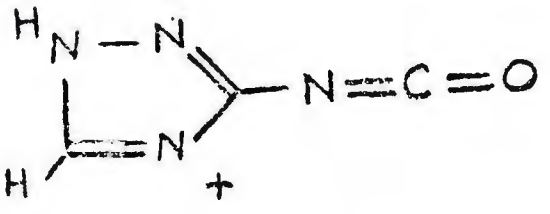
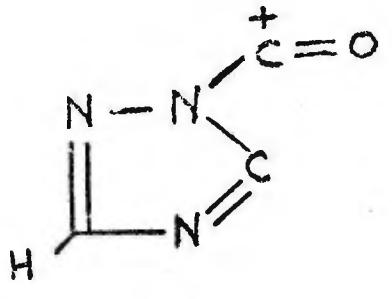
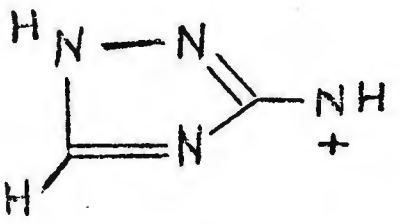
m/e	Proposed structure.
105	
110	
95	
83	
28	CO +

Fig.XVI. Proposed structures for ions observed in the mass spectrum of product Z (Experiment 6).

by the presence of triazole and carbohydrate residues only. The minor component (Z) was also not identified but it gave an elemental analysis which indicated the presence of triazole and carbohydrate residues. The mass spectrum of Z was very complicated and has not been fully interpreted. However, triazole structures could be assigned to some of the important fragments (see Fig.XVI). Since the recovery of material containing triazole residues was low the remainder was probably contained in the aqueous layer. This was not investigated further because materials derived from hydrolysis of the 2,3-carbonate (1) were the main products.

Use of lithium salts.—— A convenient method of increasing the nucleophilicity of amines is to convert them into alkali metal salts. Thus another approach to the preparation of carbamates from methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate involved the reaction of the lithium salt of aniline with compound 1. This was performed in ether solution at room temperature (Experiment 7a), and a complicated mixture of products was obtained from which a small yield (ca. 4%) of methyl 4,6-O-benzylidene-α-D-glucopyranoside 3-(N-phenyl-carbamate) (B6) was isolated by chromatography. Thus this procedure is not suitable as a means of preparation of monosaccharide carbamates and it seems unlikely that it would be suitable for use with starch.

Nevertheless, since the desired N-methyl-N-phenylcarbamates of methyl 4,6-O-benzylidene-α-D-

glucopyranoside had not been obtained, the procedure of Experiment 7a was repeated using N-methylaniline (Experiment 7b). The product mixture was very complicated and did not encourage further investigation.

The reasons for the large number of products from these reactions (Experiments 7a and 7b) could stem from the high reactivity of anilides. Carbanions are known to cleave acetals[91] and it has been demonstrated that cleavage of cyclic acetals in carbohydrate derivatives gives rise to unsaturated compounds[92]. It seems that similar reactions could account for some of the products. Another possible mode of degradation involves attack of the anilide at an initially formed carbamate.

Thus, the studies of the reactions of the model compound, methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate, with amines were concluded. No facile method of reacting an aromatic amine had been achieved, but it was clear that simple primary and secondary aliphatic amines react except where inhibited by the bulk of the alkyl groups. No conditions were found in which N-methylaniline or amino-1,3,5-triazines react with the 2,3-carbonate (1) to give the corresponding glucoside 2- and 3-carbamates.

Preparation of methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) and methyl α-D-glucopyranoside 2,3-carbonate.—— In order to prepare methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) for biological testing (see p.63 and Appendix), methyl 4,6-O-benzylidene-α-

D-glucopyranoside 2,3-bis(N-phenylcarbamate) (Experiment 3c) was submitted to hydrogenolysis (Experiment 8b). Although the glassy product (100%) was homogeneous (tlc), crystallization proved difficult and the compound melted over 5°. However, satisfactory analytical data were obtained.

It was also of interest to investigate the hydrogenolysis of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1). Carbonates are known to be hydrolysed by acid[93] and it seemed likely that just as the 2,3-carbonate was more susceptible to basic hydrolysis than less strained carbonates[68], it would be more susceptible to acid hydrolysis. Also, it seemed possible that the carbonate would migrate to the 3,4 or 4,6 positions once the benzylidene group had been removed in acid. Thus hydrogenolysis seemed the most suitable means of removing the benzylidene group from compound 1.

Treatment of an ethanolic solution of compound 1 with hydrogen in the presence of a palladium catalyst gave a mixture of products on some occasions, but use of distilled ethanol and a fresh batch of catalyst (Experiment 8a) gave a homogeneous syrup (99%). The analytical data were consistent with those expected for methyl α-D-glucopyranoside 2,3-carbonate (F). In the nmr spectrum (pyridine-d_5) of the product the signals centred at δ 5.36, 5.19 and 4.61 were reminiscent of the spectrum of compound 1, and have been assigned to

H-1, H-3 and H-2 respectively of a 2,3-carbonate. However, the signal attributed to H-4 also appeared at low field (δ 4.65) and this cannot be explained readily at present except by supposing that the proton is de-shielded by a specific solvent effect. It is concluded that hydrogenolysis of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate gives methyl α-D-glucopyranoside 2,3-carbonate but chemical confirmation is required.

Starch carbonate.

Although the model studies had indicated that it is unlikely that alkylamino-1,3,5-triazines would react with a glucopyranoside 2,3-carbonate under mild conditions, the facile reactions of primary and secondary aliphatic amines (Experiments 1 and 2) prompted an investigation of the preparation and properties of a carbonate of starch. It seemed that the reactions of alkylamines with such a carbonate might give useful starch derivatives since some such amines possess biological activity and new pesticides containing a reactive amine group could appear at any time.

A number of methods for the preparation of carbonates of starch have been reported[94,95], but little has been stated about the structure of the products. Doane et al. used ethyl chloroformate in the presence of triethylamine in the preparation of derivatives of 6-O-triphenylmethyl-amylose[79] and of dextrin and dextran[65] containing some trans-fused carbonate groups, and Jarowenko and Wurzburg[95] have prepared carbonates of

starch by similar methods. However, the latter workers did not use dry materials and did not give any information about the structure of their products. Thus a search for conditions for the preparation of a carbonate of starch containing a significant proportion of trans-fused cyclic carbonate groups was commenced.

Preparation of a starch carbonate.—— The reaction of starch with carbonyl chloride in the presence of triethylamine gave a product showing ir absorption bands in the region 1600-1700cm^{-1} probably indicative of the presence of acyclic carbonates. No bands indicative of 2,3-carbonate groups were obtained and this is in accord with the finding of Cho Tun[96] that the reaction of carbonyl chloride did not give a trans-fused cyclic carbonate of cellulose.

Thus various attempts were made to react ethyl chloroformate with starch under conditions similar to those used by Doane et al.[65] in the preparation of dextrin carbonate. The starch (R.H.M.) was pretreated in water and ethanol[97] to remove fats and proteins and the dried product contained no nitrogen (Experiment 9a). The starch was then treated with triethylamine in methyl sulphoxide:1,4-dioxan followed by reaction with ethyl chloroformate at room temperature. The products obtained were intractable gums except when a short reaction time (ca. 5min) was used. A granular product was isolated when the conditions were carefully

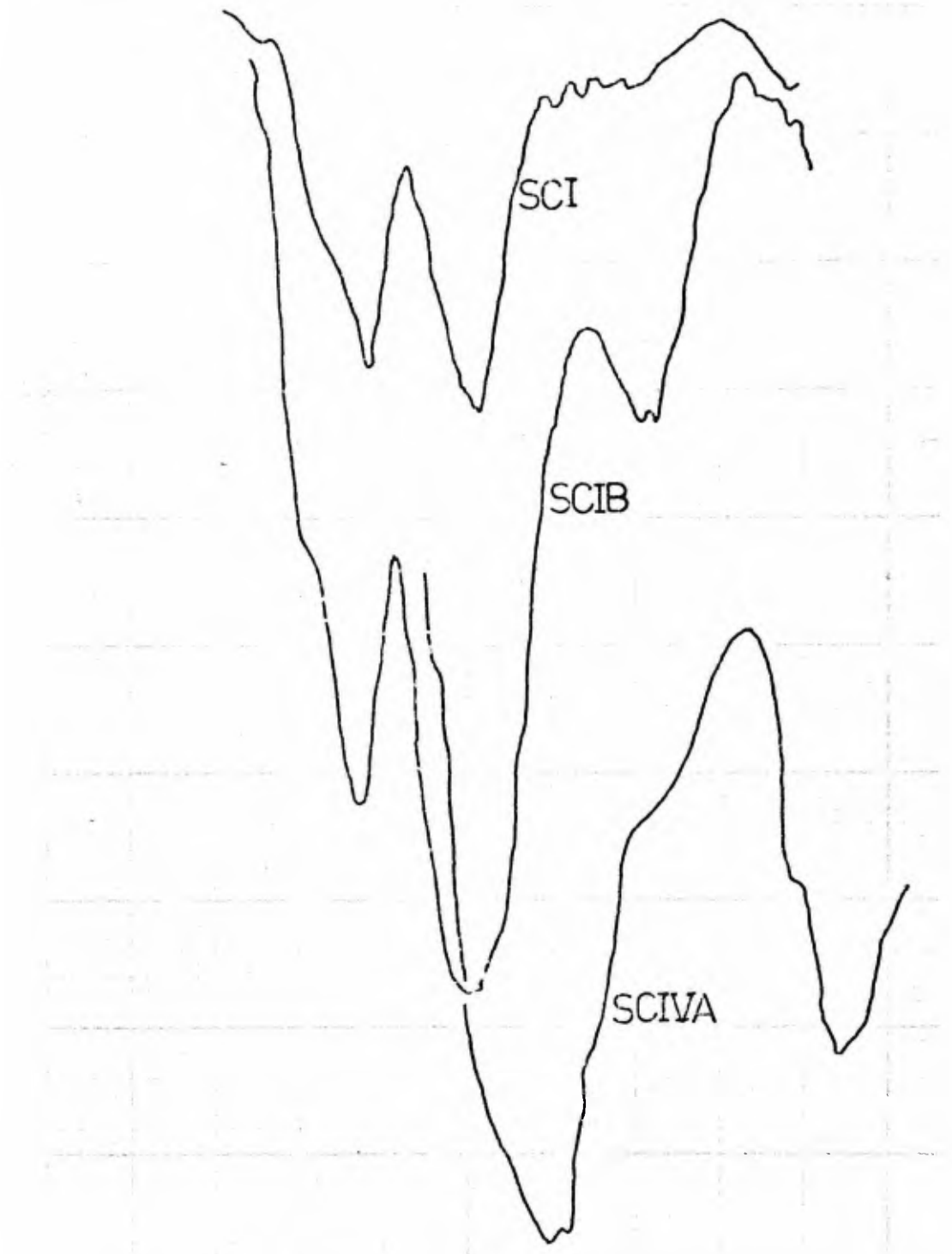


Fig. XVII. Infra-red spectra of starch derivatives SCI, SCIB and SCIVA measured from Nujol suspensions.

controlled (Experiment 9b). When performed on a larger scale some cooling was required immediately after the addition of the chloroformate. The starch carbonate SCI (Experiment 9b) had a nitrogen content of 3.6% which must have been derived from the triethylamine used as a catalyst and acid acceptor. An extraction of the starch carbonate with ether reduced the nitrogen content to 1.3% (product SCIA). The low solubility of triethylamine hydrochloride in ether and the low pH of an aqueous solution of the extracted material suggested that one of the contaminants of product SCI was triethylamine. The nitrogen remaining in the polymer could have been present as adsorbed triethylamine or triethylamine hydrochloride, and the ir spectrum showed bands characteristic of a hydrochloride[98]. After the carbonate SCI had been submitted to dialysis and freeze-drying a product (SCIB) was isolated which contained no nitrogen. The ir spectra (Experiment 9c) of the starch carbonates (SCI, SCIA and SCIB) showed bands characteristic of carbonate groups[99] (see Fig XVII). The band at ca. 1810cm^{-1} was assigned to 2,3-carbonates of glucopyranosyl residues by reference to the spectrum of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (1810cm^{-1}) (cf. ref.79) and the band at ca. 1750cm^{-1} was assigned to acyclic carbonates[99]. The ratio of the intensities of the cyclic to acyclic carbonate absorptions was approximately 9:10. Comparison with the carbonate of 6-O-triphenylmethylstarch[79] (ratio 3:2) shows that the hydroxyl group at C-6 plays an important

part in acyclic carbonate formation but that the groups at C-2 and C-3 are also involved. The reduction in the ratio of the intensities of the cyclic (1810cm^{-1}) to acyclic carbonate (1750cm^{-1}) bands after dialysis (8:10 in SCIB, see Fig.XVII) indicates that some aqueous hydrolysis (in the presence of triethylamine) has occurred. This also confirms the assignment of the ir bands because the cyclic carbonate groups would be expected to undergo faster hydrolysis than the acyclic carbonates (see page 12).

In order to obtain a measure of the degree of substitution (DS) of carbonate groups in the starch carbonate SCI, hydrolyses were conducted with barium hydroxide followed by titration of excess base with mineral acid (Experiments 11a and 11b). Haworth[82] first noted the susceptibility of carbohydrate carbonate to aqueous barium hydroxide and Doane et al.[65] have used this reaction as a quantitative method for the determination of the DS of acyclic carbonate. The results show that the starch carbonate (SCI) had a DS of carbonate of at least 0.5 (see Table I) based on the assumption that all the acyclic carbonate was present as bis(carbohydrate) carbonates. In support of this assumption, it was noted that the ir spectrum showed no absorptions for ethyl groups which would be indicative of the presence of ethoxycarbonyl groups. The presence of triethylamine in the starch carbonate (SCI) which was hydrolysed by this procedure would give

rise to a low value for the DS. The validity of this method was demonstrated by the titration of model substances (see Table I) and later by Disney[100] in the hydrolysis of a dextran carbonate. However, Yeo[101] found that a similar procedure was not applicable to a cellulose carbonate.

If it is assumed that the extinction coefficients of cyclic and acyclic carbonates are equal[102] then the ir spectrum of the starch carbonate SCI indicates that the ratio of cyclic to acyclic carbonate is 9:10. Therefore, the DS of cyclic carbonate is approximately 0.25.

Reactions of starch carbonate SCI with amines.—— Since satisfactory conditions had not been found for the reaction of aromatic amines with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) and Yeo's results[101] suggested that 1,3-diamino-benzene did not react with a cellulose carbonate the studies of the reactions of starch carbonate were confined to aliphatic amines.

The reactions of piperidine and cyclohexylamine with starch carbonate (SCI) in methyl sulphoxide at room temperature (Experiments 10a and 10b) resulted in only low incorporation of amine. The products showed no absorption band at 1810cm^{-1} (cyclic carbonate), but there were new bands at ca. 1680cm^{-1} attributable to carbamates. However the nitrogen contents of these products were lower than for the starch carbonate SCI

and this may be attributable to the removal of adsorbed triethylamine and triethylamine hydrochloride by the reagent or in the work-up.

In an experiment in which cyclohexylamine was mixed with starch carbonate SCI at room temperature without methyl sulphoxide, a product was isolated which showed some residual absorption at 1810cm^{-1}. Thus starch carbonate SCI was treated with refluxing cyclohexylamine for 5min (Experiment 10c) and starch derivatives were precipitated by ethanol and ether in three crops (SCIVA, SCIVB and SCIVC). Although the recovery of materials was satisfactory the difficulty in precipitating all of the product with ethanol suggests that there may have been partial degradation of the polymer. It seems unlikely that the amine would affect the glycosidic linkages since starch is known to be quite resistant to hydrazinolysis[103]. However, it is possible that acyclic carbonates are susceptible to attack in refluxing cyclohexylamine and this would reduce the degree of cross-linking in the product compared with the starch carbonate SCI. Thus, if degradation of the polymer chain had occurred in the preparation of the carbonate, reaction of the carbonate would have given a product of low molecular weight. It has not been established if such degradation occurred during the preparation or reaction of the starch carbonate.

The starch carbamates SCIVA and SCIVB had

nitrogen contents of 3% and product SCIVC had a nitrogen content of 5.9%. Since these values could have been caused by adsorbed amine, product SCIVA was subjected to a procedure which was designed to free it from any adsorbed amine and to hydrolyse carbonate groups selectively in the presence of carbamates. In this way it was hoped to obtain a product in which carbamate groups could be detected by nitrogen and ir analyses. The material used to establish the necessary procedure was starch carbonate SCI (having a nitrogen content of 3.6%). Treatment of starch carbonate SCI with 10m$\underline{\underline{M}}$ sodium hydroxide (Experiment 11c) was shown to result in almost complete hydrolysis of the carbonate groups (see Table I) and after dialysis and freeze-drying a product (SCIC) was isolated which contained no nitrogen and which showed only a small absorption in the ir spectrum attributable to carbonate groups. The use of sodium hydroxide was preferred to barium hydroxide because it proved difficult to isolate a starch derivative uncontaminated with barium carbonate from an experiment using barium hydroxide. Application of the sodium hydroxide treatment to product SCIVA (Experiment 11d) gave a starch carbamate (SCIVD) having a nitrogen content of 1.7% The ir spectrum of SCIVD showed absorptions (eg. 1530, 1650-1770 and 2860cm^{-1}) which are indicative of the presence of N-alkylcarbamate, and the nitrogen content indicates a degree of substitution of 0.2 for N-cyclohexylcarbamate. This

is in accordance with the estimated DS of cyclic carbonate (see p. 30) in the starch carbonate SCI used for this experiment.

Thus it is concluded that it is possible to make carbonates of starch containing reactive carbonate groups, probably as 2,3-carbonates. These groups react with alkylamines to give starch carbamates which also contain acyclic carbonate groups, probably as bis(carbohydrate) carbonates.

It is clear from this work that, in general, primary and secondary alkylamines react readily with glucopyranoside 2,3-carbonates to give carbamates. However, similar reactions with aromatic amines are difficult to achieve and it is concluded that the method is not applicable to the linking of alkylamino-1,3,5-triazines to starch. It is possible, however, that the starch carbonate (SCI) described here will find use in other fields. Recently Barker *et al.* have reported the preparation of a cellulose carbonate[104] and its reaction with β-D-glucosidase to give an enzymically active, insoluble derivative of the enzyme[36]. Starch carbonate may be suitable for use as a support for enzymes and the reactivity of the carbonate groups might be put to many other uses.

MODIFICATION OF AMINES.

Since it had been concluded that further attempts to react secondary N-alkyl-N-arylamines with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) would not be worth-while, another approach to the task of linking amines covalently to starch was sought. Any approach, such as that described above, which involves making a reactive derivative of starch requires two reactions at the polymer. Such reactions are often inefficient and the products of side-reactions are included in the resulting material of high molecular weight. Taking starch carbonate (Experiment 9) as an example, most of the carbonate was present as relatively unreactive acyclic carbonates and even if the reaction of the polysaccharide 2,3-carbonate with an amine was as efficient as the model reactions (Experiment 1) the yield of carbonate per mole of ethyl chloroformate used would be very poor. Thus a procedure involving the modification of an amine for reaction with starch was preferred.

In choosing a suitable amine derivative it was necessary to consider the nature of the products of reaction of the derivative with starch. This seemed to be important because the rate of hydrolysis of the linkage between the amine and the polysaccharide relative to the rates of the other degradative reactions would

probably determine the rate of release of the pesticidal amine into the soil. Studies have shown that, in the soil, the hydrolysis of N-alkyl- and N-arylcarbamates to the corresponding amines is a significant step in the degradation pathways[105]. Thus, it was decided to pursue the synthesis of secondary N-alkyl-N-arylcarbamates by a different route.

The methods of making derivatives of amines which can react with alcohols to give carbamates are the conversion of (a) primary amines into isocyanates and (b) primary and secondary amines into carbamoyl derivatives such as carbamoyl chlorides[106]. Isocyanates derived from amino-1,3,5-triazines are known and their reactions with alcohols and phenols have been studied[107]. Since the main concern in this work was the linking of alkylamino-1,3,5-triazines to starch the synthesis of a carbamoyl chloride from such a triazine was the method of choice for investigation.

Chemistry of carbamoyl chlorides.

The usual route to carbamoyl chlorides is by the reaction of carbonyl chloride with amines. Such reactions (see Fig.XVIII) are frequently carried out at room temperature[106].

The reactions of carbamoyl chlorides with amines[108,109], phenols[108,110] and thiols[108,111] are well known, and there are some reports of their reactions with alcohols. The reactions of N,N-diphenyl-

-carbamoyl chloride with furfuryl alcohol has been used to obtain a carbamate derivative[112] and Price has reported the reaction of N-methyl-N-phenyl-carbamoyl chloride with a number of alcohols, including glycerol, to give carbamates[113]. However, this latter work was concerned with the kinetics of the reaction and no carbamates were isolated. The report that ethylene glycol and glycerol reacted with the carbamoyl chloride too rapidly for measurement seems improbable in the light of the work reported here.

It is known that carbamoyl chlorides are quite stable to alcohols since ethanol is frequently used as a solvent for recrystallization[106,114]. Hiskey et al.[111] have used ethanol as a solvent in the reactions of thiols with N,N-diphenylcarbamoyl chloride in the presence of sodium, and Rivettand Wilshire[108] have made N,N-diphenylcarbamoyl derivatives of thiols, amines, imidazoles, amino acids and peptides in 50% aqueous ethanol in the presence of sodium hydrogen carbonate. In a study of the stability of N,N-diphenyl-carbamoyl chloride in the 50% aqueous ethanol medium, the latter workers recovered ethyl N,N-diphenylcarbamate in only 15% yield.

Thus, it was clear that, although carbamoyl chlorides react with alcohols to give the corresponding carbamates, a thorough investigation of the reaction was required in order to obtain acceptable yields and conditions suitable for use with a polysaccharide.

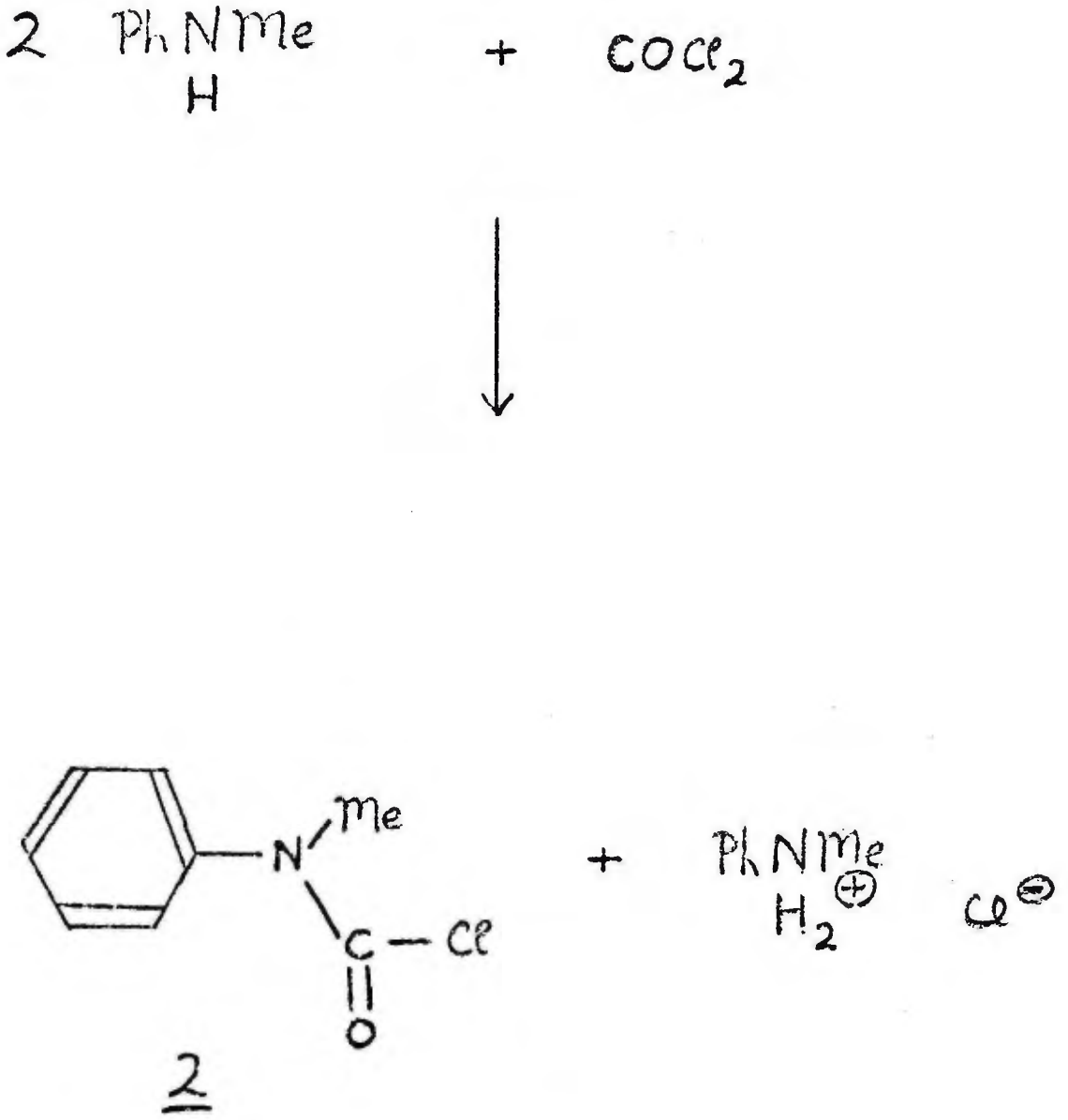


Fig. XVIII. Preparation of N-methyl-N-phenyl-carbamoyl chloride (2).

No reports are known of the preparation of disubstituted carbamates of carbohydrates from carbamoyl chlorides, but N-methyl-N-phenylcarbamates of xylan derivatives have been made by methylation of the N-phenylcarbamates[115]. Thus, it was decided that a study of the reactions of a known carbamoyl chloride with a series of alcohols should be undertaken initially.

Reactions of N-methyl-N-phenylcarbamoyl chloride (2).

Since N-methylaniline had already been chosen as a model for the reactions of alkylamino-1,3,5-triazines, N-methyl-N-phenylcarbamoyl chloride (2) (see Fig.XVIII) was chosen as a model carbamoyl chloride. Compound 2 was synthesized in approximately 70% yield by the action of carbonyl chloride on N-methylaniline in ethyl acetate solution at room temperature[114].

Reactions in pyridine.—— Because of the lack of reliable information about the reactivity of alcohols towards carbamoyl chlorides a simple alcohol was chosen for the initial study. Benzyl alcohol was taken, because of its similarity to the fungicidal[57] pentachlorobenzyl alcohol and pyridine was used as catalyst. Pyridine, which has been reported to form a complex with N,N-diphenylcarbamoyl chloride[110], has been used as a catalyst in the reaction of amines with carbamoyl chlorides[109]. When N-methyl-N-phenyl-carbamoyl chloride (2) was treated with benzyl alcohol in refluxing pyridine (Experiment 12), benzyl N-methyl-

N-phenylcarbamate was isolated in 38% yield after a long purification procedure to remove side-products. Although similar treatment of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan (1,2-O-isopropylideneglycerol) gave unresolved, complicated mixtures the method was applied to starch.

When starch was treated with compound 2 in the presence of pyridine (Experiment 16), the starch derivative (MPI), isolated by dialysis and freeze-drying, was yellow in colour and gave an elemental analysis which corresponded to an N-methyl-N-phenylcarbamoylstarch with a degree of substitution (DS) of approximately 1.5*. The ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O) which were indicative of the presence of N-methyl-N-phenylcarbamates (cf. the products of Experiments 13 and 15). An extraction of product MPI with chloroform gave a soluble fraction which showed signals in the nmr spectrum which were characteristic of N-phenyl and N-methyl groups. However, the nitrogen content of the insoluble fraction (82%) was greater than could be explained by the presence of an N-methyl-N-phenylcarbamate of starch only. This product was

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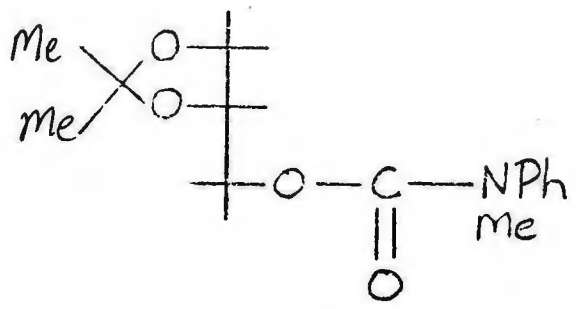
* Since the percentage of nitrogen in N-methyl-N-phenylcarbamates of starch and cellulose seemed to be a satisfactory guide to the DS of carbamate a graph (Fig.XXIX) was drawn which relates the nitrogen content to the degree of substitution. This was applicable to most of the products from Experiments 16,17 and 18.

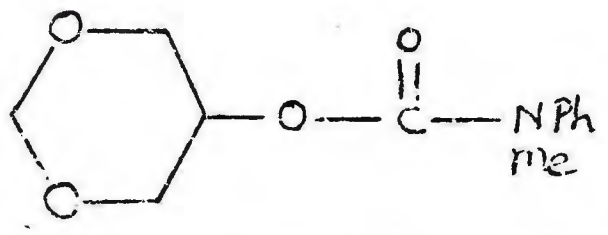
not examined further because a more satisfactory method for the preparation of an N-methyl-N-phenyl-carbamoylstarch had been developed.

Reaction with alkoxides.—— Alkali metal salts of glycerol derivatives[116], monosaccharide derivatives[117,118] and polysaccharides[119,120] are well known. Such materials have greater reactivity than the parent alcohols and have been used in the synthesis of ethers from alkyl halides[116,118,119] and of esters from acid halides[117]. It was therefore decided to investigate the reactions of the sodium salts of some model alcohols with N-methyl-N-phenyl-carbamoyl chloride (2). The alcohols chosen (Experiments 13a - 13e) were cyclic acetals derived from glycerol and monosaccharides because it was supposed that their reactivities would be similar to those of polysaccharides. Also, the pesticidal properties of the products of such reactions would be of interest especially in view of the recent report by Nikles[121] of the insecticidal properties of some cyclic acetals.

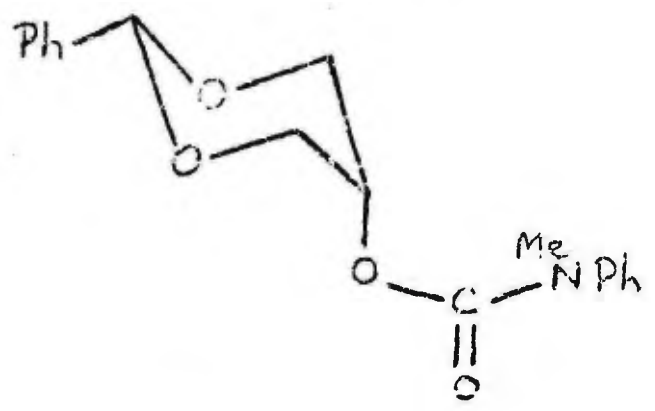
Since it proved difficult to achieve complete conversion of the alcohols into their sodium salts, it was found necessary to add the carbamoyl chloride (2) in the presence of the alkali metal reagent. Thus, sodium hydride was used in preference to sodium metal to avoid complications which might be caused by the reaction of elemental sodium with the



2,2-dimethyl-4-(N-methyl-N-phenylcarbamoyl)-oxymethyl-1,3-dioxolan.



5-(N-methyl-N-phenylcarbamoyl)oxy-1,3-dioxan.



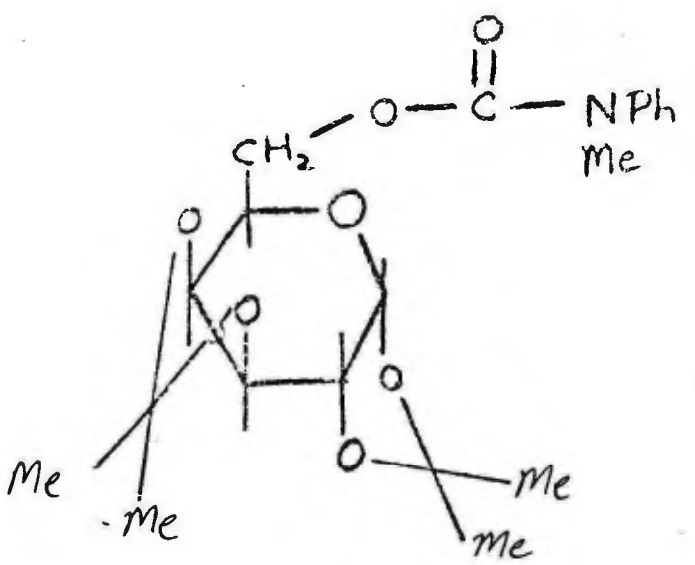
cis-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan.

Fig.XIX.

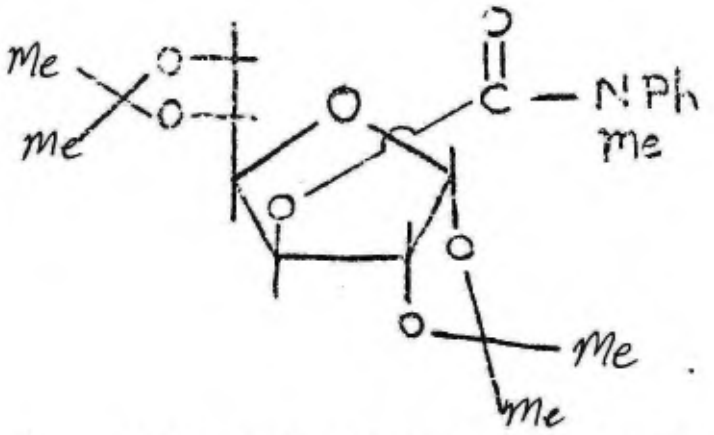
carbamoyl chloride to give the corresponding symmetrical urea[122].

Under mild conditions, reaction of compound 2 in ether with a mixture of sodium hydride and 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan (1,2-O-isopropylidene◇glycerol) gave syrupy 2,2-dimethyl-4-(N-methyl-N-phenylcarbamoyl)-oxymethyl-1,3-dioxolan (Fig.XIX) in 53% yield (Experiment 13a). In similar conditions 1,3-dioxan-5-ol (1,3-O-methyleneglycerol) gave syrupy 5-(N-methyl-N-phenylcarbamoyl)oxy-1,3-dioxan (Fig.XIX) in 59% yield (Experiment 13b). Thus the sodium salts of primary and secondary hydroxyl groups in glycerol react satisfactorily with compound 2. In a search for a crystalline derivative cis-2-phenyl-1,3-dioxan-5-ol (1,3-O-benzylidene◇glycerol) was treated in a similar manner (Experiment 13c) to give crystalline cis-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan (Fig XIX) in 90% yield. A small crop (0.8%) of trans-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan was also isolated from the product mixture by fractional crystallization. No trans-2-phenyl-1,3-dioxan-5-ol could be detected in the starting material by nmr spectroscopy. However, it is considered that traces of the trans-alcohol must have been present, since formation of the trans-carbamate by a cis-trans rearrangement would not be expected under the reaction conditions.

Following the successful reactions with the



1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-(N-methyl-N-phenylcarbamate).



1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-(N-methyl-N-phenylcarbamate).

Fig. XX.

glycerol derivatives, 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose was chosen as a model compound for examination of the reactivity of primary alcohols in carbohydrates. Although a longer reaction time (12h reflux in ether) was used for this diacetal (Experiment 13d) than for the preparation of the glycerol carbamates, some of the diacetal remained unchanged. However, the crystalline 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-(N-methyl-N-phenylcarbamate) (Fig.XX) was isolated in 60% yield. In similar conditions, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose gave crystalline 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-(N-methyl-N-phenylcarbamate) (Fig.XX) in 30% yield (Experiment 13e).

Thus, it was concluded that sodium salts of carbohydrates react readily with N-methyl-N-phenylcarbamoyl chloride and a method was sought by which such a reaction might be accomplished with an unblocked polysaccharide. An examination of model carbohydrates containing two or more unprotected hydroxyl groups was not undertaken because of the problems associated with partial reaction and fractionation of the products.

Reactions of 'alkali cellulose' and 'alkali starch'.

Sodium salts of cellulose are widely used to prepare substituted celluloses[120] and the most convenient method of preparing such salts is by the use of sodium hydroxide to produce an 'alkali cellulose'[122,123a].

Since carbamoyl chlorides are known to be hydrolysed rapidly in basic conditions[124], an experiment was set up to investigate the possibility of reacting a carbohydrate with N-methyl-N-phenylcarbamoyl chloride (2) in the presence of excess sodium hydroxide. Because of its crystallinity cis-5-(N-methyl-N-phenylcarbamoyl)-oxy-2-phenyl-1,3-dioxan (Experiment 13c) is readily purified and therefore cis-2-phenyl-1,3-dioxan-5-ol was used as the model alcohol in this study (Experiment 14). A mixture of compound 2 and the alcohol was treated with a 50% aqueous solution of sodium hydroxide at its boiling point for 15min. Column chromatography of the product mixture gave the desired carbamate in 19% yield and the other fractions contained N-methylaniline, 1,3-dimethyl-1,3-diphenylurea and the starting alcohol.

Thus, an investigation of the reaction of N-methyl-N-phenylcarbamoyl chloride (2) with polysaccharides in the presence of sodium hydroxide was justified. Since cellulose is less readily hydrolysed by aqueous base than is starch (compare ref's 123b and 125a) and a commercial 'alkali cellulose' was available, the initial carbamoylation reactions were carried out on this. There are many examples of reactions of cellulose carried out in the presence of organic solvents[123] and it has been reported that the use of a solvent in the methylation procedure[123c] enables the fibrous structure to be retained in the product. Thus fibrous alkali cellulose was treated with

a solution of compound 2 in a refluxing mixture of benzene and 1,4-dioxan (Experiment 17a). 1,4-Dioxan was used specifically to reduce the water content of the alkali cellulose because this had been reported to improve the reactivity in benzylation reactions[126]. However, the product of the reaction appeared to be unmodified cellulose.

Benzylations of cellulose may also be accomplished with an excess of benzyl chloride and no additional solvent[127]. Thus, the fibrous alkali cellulose (ca. 2.0mol of NaOH per glucose residue) was next mixed thoroughly with N-methyl-N-phenylcarbamoyl chloride (3.2mol per glucose residue) and the mixture was heated at 100° for 0.5h (Experiment 17b). The product (MPII) had a nitrogen content corresponding to a DS of N-methyl-N-phenylcarbamate of 0.6 (see Fig.XXIX), and the ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O) indicative of the presence of N-methyl-N-phenylcarbamates. The nitrogen content was not diminished by an extraction with hot ethanol, but was slightly diminished after extraction with DMF, dialysis and freeze-drying. Since some of the carbamoyl chloride (2) was recovered from the reaction the experiment was repeated using less of compound 2 (0.6mol per glucose residue). The product had a nitrogen content (1.4%) corresponding to a DS of 0.2 (see Fig.XXIX) and no compound 2 remained after the reaction. A nitrogen-free product was obtained when

the carbamoyl chloride was omitted from the treatment of the alkali cellulose (Experiment 17c).

In order to ascertain that similar results could be obtained with an alkali cellulose prepared in the laboratory a 'microgranular' cellulose was treated with sodium hydroxide solution to give a product similar to the commercial material in composition (Experiment 17d). The product could be used immediately or stored for up to a few weeks at -25°. When this alkali cellulose was treated (Experiment 17e) with N-methyl-N-phenylcarbamoyl chloride (2) under conditions similar to those used previously, the product (MPIII) had a nitrogen content corresponding to a DS of 0.2 (see Fig.XXIX). Cellulose carbamates prepared by this method did not absorb water readily and appeared to be strongly hydrophobic when placed on a surface of water.

Extraction of the 'microgranular' cellulose carbamate (MPIII) with chloroform caused the removal of a small amount (ca. 5%) of material, but did not affect its analytical properties significantly. The extracted material (MPIIIB) was isolated as a transparent film the nitrogen content of which corresponded to a cellulose N-methyl-N-phenylcarbamate of DS 1.6 (see Fig.XXIX), and its nmr spectrum showed signals characteristic of N-methyl-N-phenylcarbamates.

The success of the experiments with cellulose (Experiments 17) prompted an investigation of a similar reaction of N-methyl-N-phenylcarbamoyl chloride (2) with

starch (Experiment 18). 'Alkali starches' have been used in the preparation of starch esters[48]. Thus a pasty 'alkali starch' was made by mixing an aqueous solution of sodium hydroxide with starch such that the ratios of carbohydrate to sodium hydroxide and water were approximately equal to those in alkali cellulose. Treatment of this with compound 2 at 100° for 0.5h gave an N-methyl-N-phenylcarbamoylstarch (MPIV) of DS 1.7 (by nitrogen analysis, see Fig.XXIX). The ir spectrum was characteristic of an N-methyl-N-phenylcarbamate.

The possibility of using nmr spectroscopy to obtain more information about the starch carbamate MP IV was considered. Casu and co-workers[128] have obtained spectra for solutions of amyloses in methyl sulphoxide, but neither the pretreated starch (Experiment 9a) nor the product MPIV was sufficiently soluble in any solvent to obtain a spectrum. The solubility of starch derivatives in organic solvents is enhanced by esterification and well-resolved nmr spectra of deuteriochloroform solutions of benzoyl- and acetylamyloses have been obtained, especially at 220MHz[129]. An nmr examination of an acetylated N-methyl-N-phenylcarbamoylstarch was therefore considered. However, although experiments with a model compound (Experiment 15) indicated that N-methyl-N-phenylcarbamoyl groups were unaffected by the acetylation conditions, a well-resolved spectrum of a starch acetate (DS 3.0, prepared by the method of Wolff[130]) could not be obtained

at 60 and 100MHz and this approach was abandoned.

In the model experiment, crystalline glycerol 2-(N-methyl-N-phenylcarbamate) was obtained in >62% yield by hydrogenolysis of cis-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan (Experiment 15a). This compound was treated with acetic anhydride and pyridine under conditions similar to those used in the acetylation of starch[130] and syrupy 1,3-di-O-acetylglycerol 2-(N-methyl-N-phenylcarbamate) was obtained analytically and spectroscopically pure in 97% yield without distillation (Experiment 15b).

An attempt to procure information about the starch carbamate MPIV by methanolysis was also unsuccessful. It had been hoped that this would yield N-methyl-N-phenylcarbamoyl derivatives of methyl glucopyranosides which could then be characterized. However, when MPIV was subjected to prolonged treatment with refluxing methanol containing a high concentration of acid (Experiment 19)[125b], most (60%) of the starch derivative remained undissolved and apparently unchanged even after the addition of DMF. Acetylation of the material recovered from the methanolic solution yielded a mixture of products apparently consisting (tlc analysis) of oligosaccharide derivatives and smaller fragments including methyl α-D-glucopyranoside 2,3,4,6-tetra-acetate. Entlicher and BeMiller[131] have shown that under similar conditions no methanolysis of amylose triesters occurs until extensive deacylation

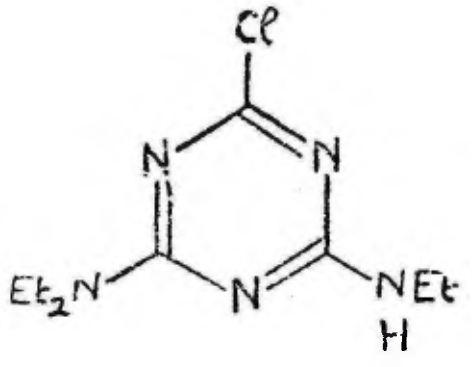


Fig. XXI. Trietazine (3).

has taken place and there are other examples of the resistance of starch esters to hydrolysis[132]. The stability of the N-methyl-N-phenylcarbamoylstarch of DS 1.7 probably reflects a similar effect of N-methyl-N-phenylcarbamates. That the polysaccharide was not fully hydrolysed after prolonged exposure to methanol and acid indicates that N-methyl-N-phenylcarbamates of carbohydrates are very resistant to acidic hydrolysis.

Although the attempts to obtain definitive evidence about the structure of product MPIV had been unsuccessful no evidence has been obtained to contradict the view that it was an N-methyl-N-phenylcarbamate of starch.

Preparation of carbamoyl chlorides from alkylamino-1,3,5-triazines.

The success in making carbamates of the model compounds and of starch from N-methyl-N-phenyl-carbamoyl chloride in the presence of pyridine or sodium hydroxide suggested that the method might be applicable to a pesticidal secondary amine suitable for conversion to a carbamoyl chloride. The interest in 2,4-diamino-6-chloro-1,3,5-triazines has been described already (see p.7). Thus, a member of this group of compounds was chosen which contained a single secondary amine to avoid complications in the preparation and reactions of the carbamoyl chloride. 2-Chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (trietazine, 3) (see Fig.XXI)

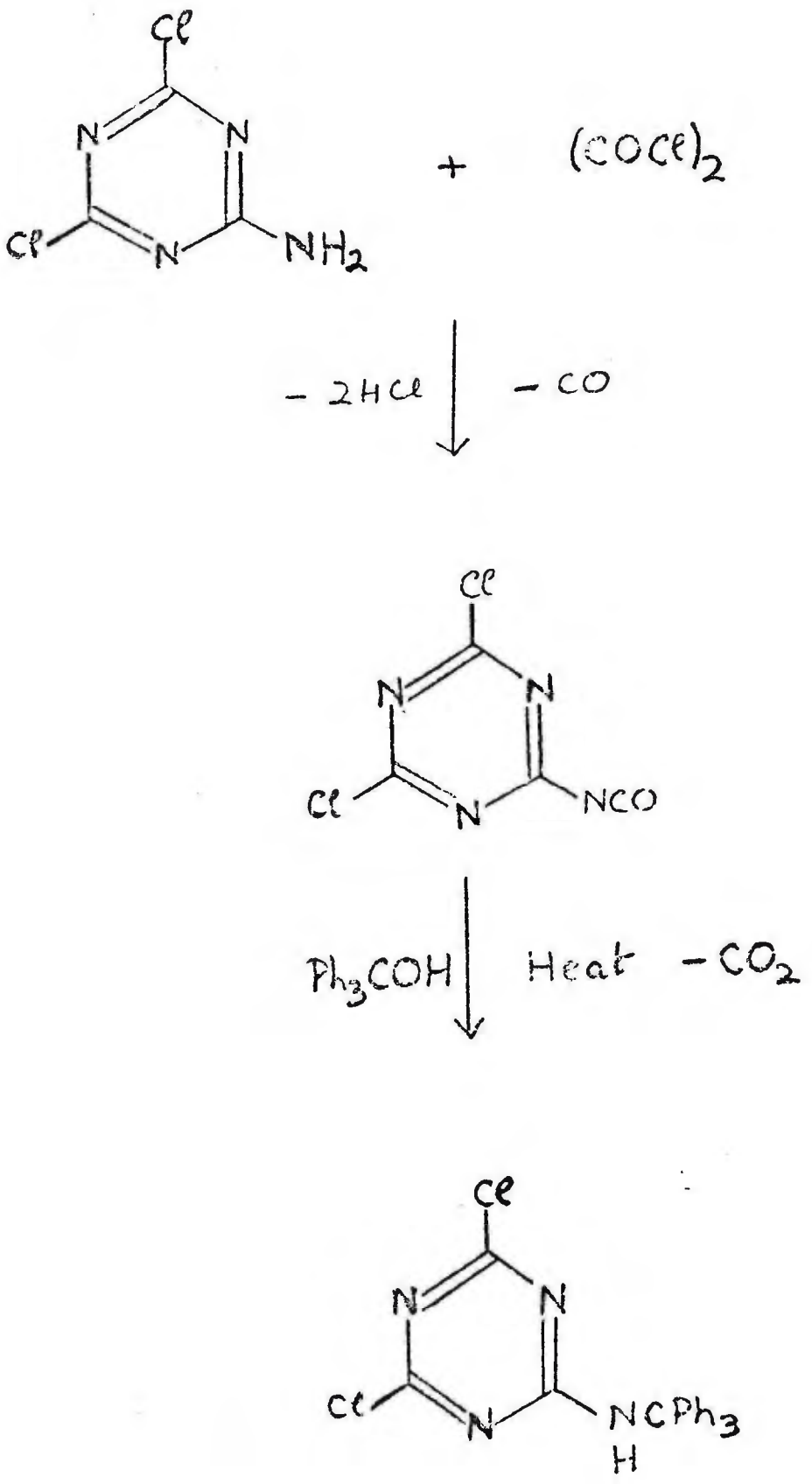


Fig. XXII. Preparation and reaction of an isocyanatotriazine.

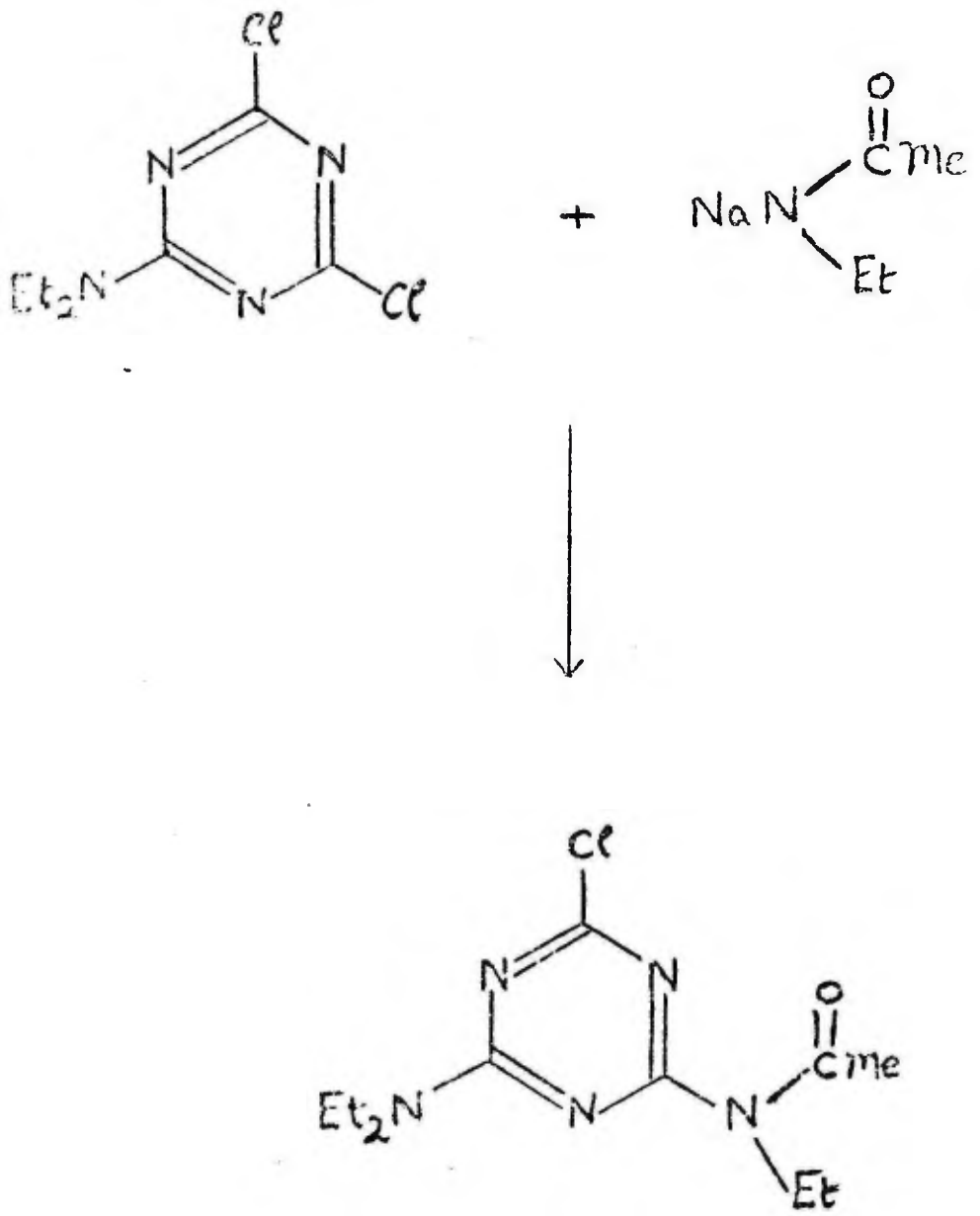


Fig.XXIII. Synthesis of 2-N-acetylethylamino-4-chloro-6-diethylamino-1,3,5-triazine.

was taken because it is a commercially available herbicide.

In contemplating the reaction of trietazine(3) with carbonyl chloride, it was noted that primary aminotriazines have been acylated readily with acid anhydrides[133]. For instance, some primary aminotriazines have been reacted with oxalyl chloride to give isocyanates[107] (see Fig. XXII). However, only one report has been found of the acylation of alkylamino-1,3,5-triazines and this involves the reaction with carbonyl chloride to give carbamoyl chlorides[134]. It appears that these products have not been examined further. Moreover, the usual route to acylamino-1,3,5-triazines appears to be by reaction of the sodium salt of a carbamate[135] or amide[136] with a chlorotriazine. For example, the herbicidal 2-N-acetylethylamino-4-chloro-6-diethylamino-1,3,5-triazine was prepared by use of the sodium salt of N-ethylacetamide[136], as shown in Fig. XXIII. However, this method is not applicable to the preparation of carbamoyl chlorides. It was noted that the reaction of triphenylmethanol with an isocyanatotriazine did not result in the isolation of a carbamate but was accompanied by decarboxylation to give an N-triphenylmethyl derivative[107](see Fig.XXII). However, analogous decarboxylations during reactions of carbohydrates and carbamoyl chlorides were not anticipated. From the above discussion it seemed that some problems might be encountered in the preparation and reaction of a

carbamoyl chloride derived from an alkylamino-1,3,5-triazine.

As was anticipated, difficulties were encountered in the acylation of 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3) with carbonyl chloride. Thus trietazine (3) was recovered unchanged from attempts to react it with carbonyl chloride at room temperature in ethyl acetate or in ethyl acetate in the presence of triethylamine.

Preparation of N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride.—— Therefore a solution of trietazine (3) in refluxing toluene was treated with carbonyl chloride gas in the apparatus shown in Fig.XXX by a method similar to that of Schwarze[134] (Experiment 20a). It was found that more efficient use was made of the carbonyl chloride by refluxing it by means of a condenser cooled with dry ice/acetone placed above the water-cooled condenser. After six hours the reaction had gone to completion and N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride (4, see Fig.XXIV) was isolated by distillation in 95% yield. The distinctive feature of the nmr spectrum was a two-proton methylene quartet at relatively low field (δ 4.09) which was assigned to the methylene protons of the N-ethylcarbamoyl group. The ir spectrum showed bands at 1580cm^{-1} (νC=N) and 1750cm^{-1} (νC=O) which were indicative of the presence of a triazine and a carbonyl group. The carbamoyl chloride 4 was unstable but could be stored for some months if suitable precautions were

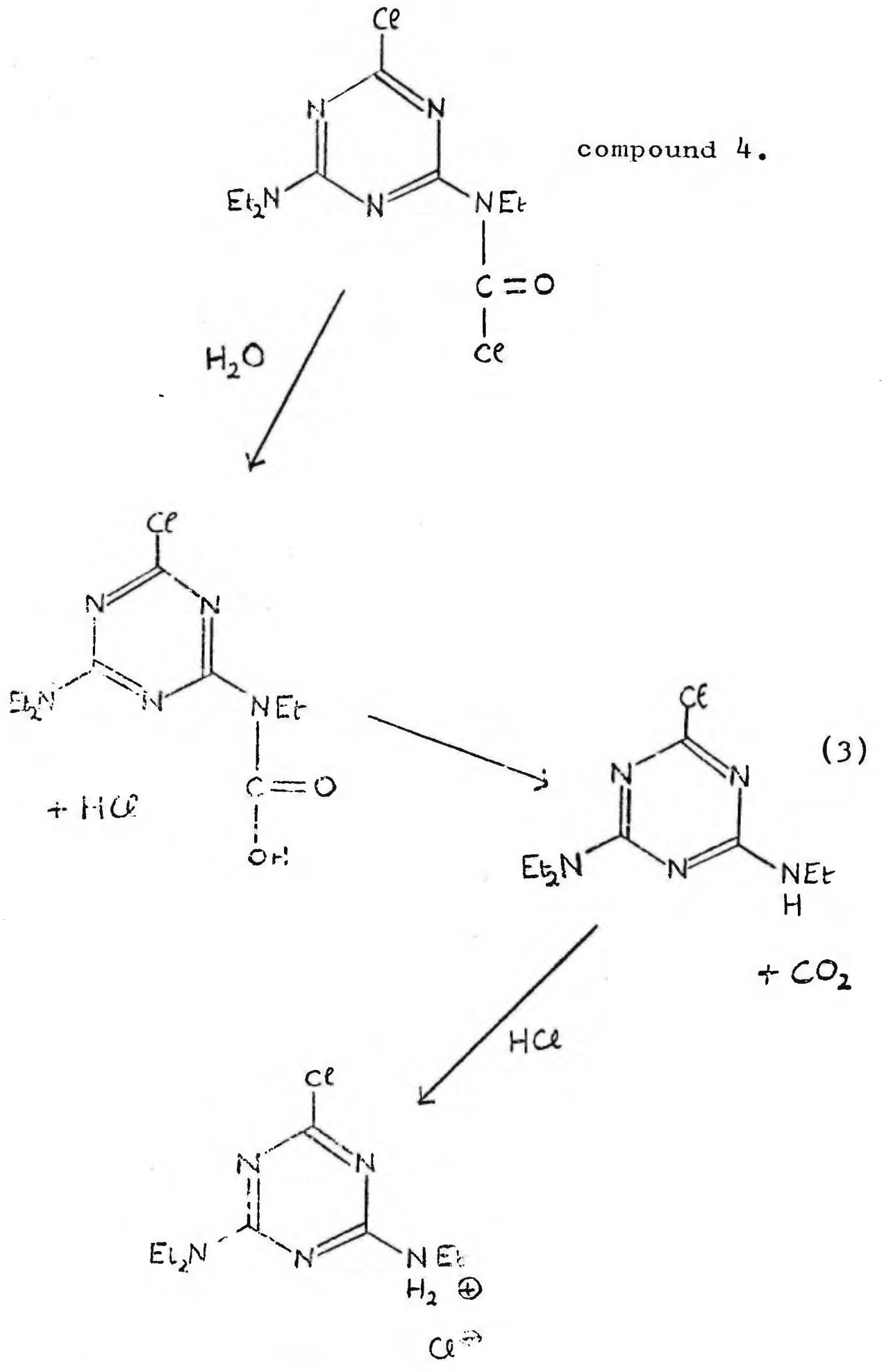


Fig.XXIV. Hydrolysis of compound 4 in hexane solution.

taken. When compound 4 was stored in a sealed flask, which was opened only to remove samples, a solid appeared after a short while. The ir spectrum of this material showed that it was not the carbamoyl chloride (4). The best method of storage was found to be in solution in dry hexane in a flask sealed with a serum cap through which samples could be removed with a calibrated syringe. After some months a small crop of crystals was collected from the solution. Although this material has not been rigorously identified its spectral (nmr and ir) properties were indistinguishable from those of a sample of 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine hydrochloride. An authentic sample of this hydrochloride was prepared by treatment of a solution of trietazine (3) in ether with dry hydrogen chloride gas (Experiment 20c), and the product gave analytical data consistent with the assignment of the structure of a mono-hydrochloride (see Fig.XXIV). It is concluded that this is also the structure of the product formed on storage of the carbamoyl chloride 4 and that it results from hydrolysis followed by decarboxylation and reaction of the resulting amine with hydrogen chloride (see Fig.XXIV).

In a preparation of the carbamoyl chloride 4 on a larger scale (Experiment 20b) a faster flow rate of carbonyl chloride gas and a longer time were employed, but the reaction did not go to completion and distillation gave a 60% yield of compound 4. A higher boiling fraction

was crystallized from hexane to give a compound which was identified by its spectral properties as 1,3-di(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-1,3-diethylurea. However, even after many recrystallizations a satisfactory nitrogen analysis was not obtained. It is thought that the urea resulted from reaction of unchanged trietazine (3) with the carbamoyl chloride during the distillation.

Reaction of carbonyl chloride with 2-chloro-4,6-bis(ethylamino)-1,3,5-triazine (simazine).—— There was considerable interest in simazine (see Fig.IV) because of its wide use as a herbicide. In his patent, Schwarze[134] reported that simazine gave a mono-carbamoyl chloride on reaction with carbonyl chloride. This seemed improbable and it should be noted that no analytical data were provided for this product. In the light of the finding that during the distillation of the carbamoyl chloride 4 unchanged trietazine (3) reacts with compound 4 to give a urea (Experiment 20b) it was thought that similar problems might occur with simazine. The situation would be even more complicated with a mono-substituted carbamoyl chloride derived from simazine. A solution of simazine in refluxing toluene was therefore treated with carbonyl chloride (Experiment 21). A small quantity of material was distilled from the syrupy product and the remainder solidified and could not be distilled. The distillate gave an elemental analysis corresponding with that expected for N-(2-chloro-

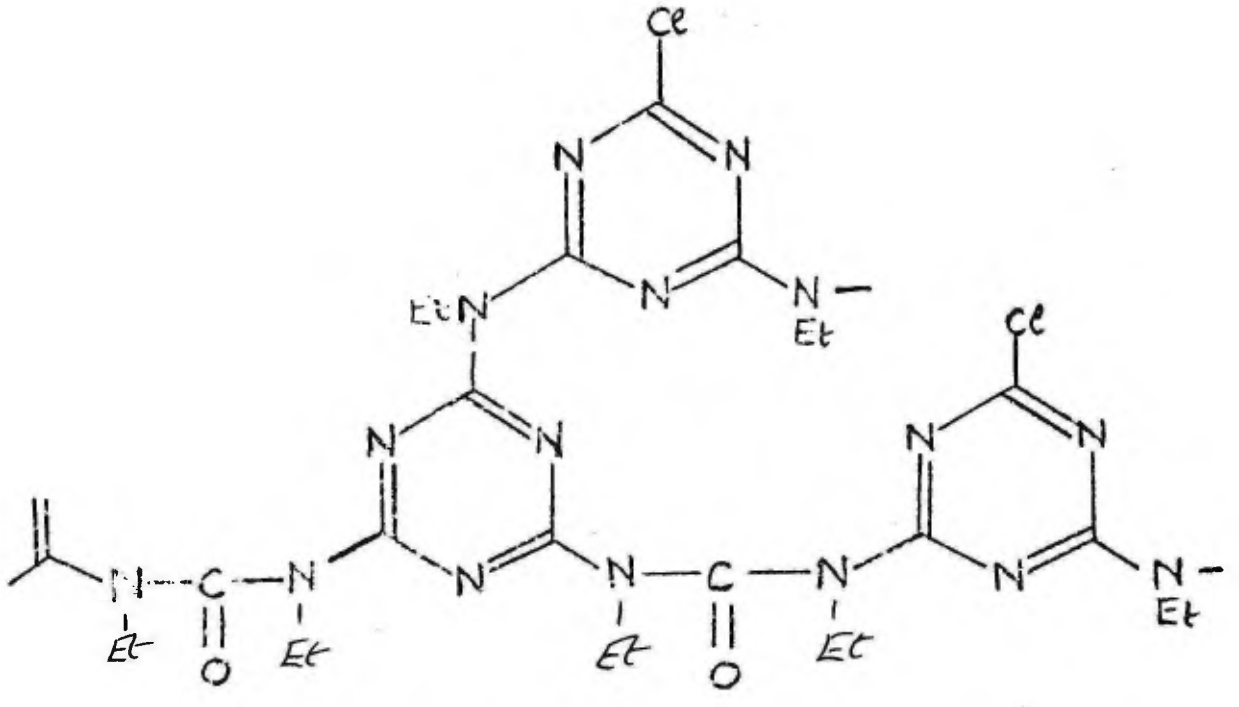


Fig.XXV. Possible structural features of product PS (Experiment 21).

-4-ethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride but the nmr spectrum showed the presence of a small amount of impurity. The physical nature and spectral properties of the undistilled material (PS) and the fractionated materials (PSI and PSII) suggested that they were of high molecular weight. Thus it was thought that poly-urea formation had occurred in an analogous manner to the urea formation observed with the carbamoyl chloride 4 (Experiment 20b) and discussed above (p.51). This confirms that a mono-carbamoyl chloride is formed by reaction of carbonyl chloride with trietazine (3) in refluxing toluene. The ir spectrum of the undistilled polymer showed bands at 1500-1650cm^{-1} (νC=N) and 1770cm^{-1} (νC=O) indicating the presence of triazine and carbonyl groups such as would be present in a poly-urea (see Fig.XXV). However, the chlorine content (12.3%) of product PSI was considerably lower than would be expected (15.6%) for such a product and, therefore, it was supposed that some displacement of ring chlorine atoms had occurred, perhaps to give a cross-linked polymer (see Fig.XXV).

Reaction of compound 4 with cis-2-phenyl-1,3-dioxan-5-ol.—— In order to find conditions in which the carbamoyl chloride 4 would react satisfactorily with starch, its reaction with cis-2-phenyl-1,3-dioxan-5-ol was studied. For use as a reference, the expected product, 2-chloro-4-diethylamino-6-[N-ethyl-N-(cis-2-phenyl-1,3-dioxan-5-yl)oxycarbonyl]amino-

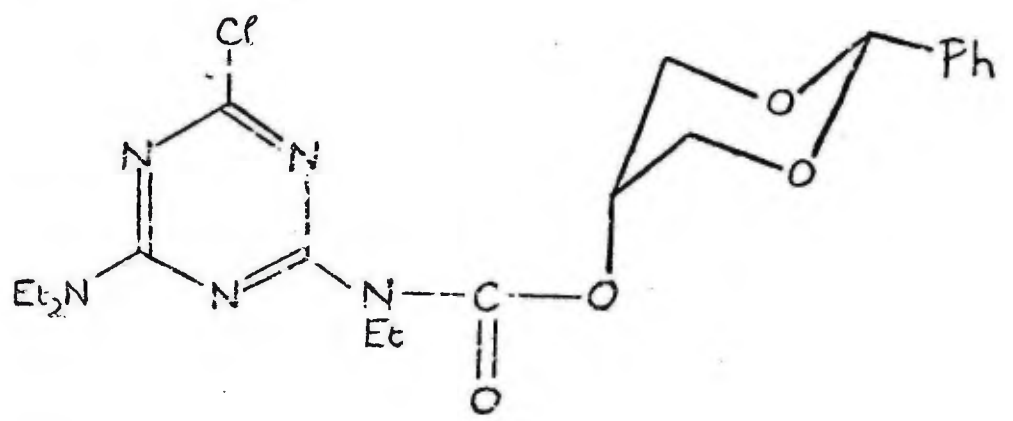


Fig.XXVI. Compound TRI.

1,3,5-triazine (TRI, see Fig.XXVI) was prepared under mild conditions using sodium hydride (Experiment 22a). The product TRI was isolated in 28% yield.

In a system which was designed to be a model for the reaction of an 'alkali starch' (Experiment 22b) sodium hydroxide was used as the base in the treatment of cis-2-phenyl-1,3-dioxan-5-ol. No desired product (TRI) or starting carbamoyl chloride (4) were observed in the product mixture and therefore it was concluded that the use of 'alkali starch' was not feasible with the carbamoyl chloride 4.

Since it seemed probable that hydrolysis of the carbamoyl chloride (4) was a factor contributing to the failure of cis-2-phenyl-1,3-dioxan-5-ol to react, the use of a milder base and anhydrous conditions in which hydrolytic reactions would be minimized were examined. In this reaction, treatment of compound 4 with cis-2-phenyl-1,3-dioxan-5-ol in the presence of anhydrous sodium carbonate (Experiment 22c) gave a good yield ($>$43% w.r.t. the alcohol) of compound TRI. The other isolated product (10% w.r.t. compound 4) was 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3). Although suitable for the reaction of the model alcohol, a procedure involving the use of solid sodium carbonate did not seem suitable for use with starch.

Since none of the conditions tried so far seemed suitable for use with starch, the use of pyridine was investigated (Experiment 22d). A syrupy product

was obtained from the reaction between compound 4 and cis-2-phenyl-1,3-dioxan-5-ol in the presence of pyridine at room temperature. Decolourization of the product followed by crystallization yielded the carbamate TRI in 13% yield.

Reaction with starch.—— Although the yield from these pyridine-catalysed reaction was poor and there appeared to be a number of side reactions, attempts were made to react the carbamoyl chloride (4) with starch under similar conditions (Experiment 23). Initially starch was recovered, apparently unchanged (Experiment 23b), but in the presence of DMF (Experiment 23c) a product was obtained which exhibited a small carbonyl absorption. Although the starch used in these experiments had already been pretreated (as in Experiment 9a) and this material swelled considerably in pyridine, it was decided that a further pretreatment might lead to greater reactivity. The method chosen involved treatment with hot pyridine by a method similar to that of Lohmar et al.[137]. After the resulting gelatinous suspension had been treated with the carbamoyl chloride 4 for three hours at room temperature (Experiment 23a) a product (TRPI) was isolated which showed absorptions in the ir spectrum at 1500-1650cm^{-1} (νC=N) and 1730cm^{-1} (ν C=O) which indicated the presence of triazine and carbamate groups.

Since it was important to establish that covalent bonds existed between the 1,3,5-triazine groups

and the starch, the product was extracted continuously with chloroform. Only a trace of unidentified material was taken into the chloroform, and the insoluble residue appeared to be unchanged product. However, the insoluble material had a nitrogen content of 7.8% and a chlorine content of 7.0% whereas the desired N-triazinylcarbamate should have nitrogen and chlorine contents in the ratio of approximately 2:1. Prolonged dialysis of the chloroform-insoluble product, followed by freeze-drying, resulted in the recovery of most (91%) of the material. This had an almost unchanged ir spectrum, and nitrogen and chlorine contents of 6.8% and 2.2% respectively. The diminution in the chlorine content of the dialysed product seemed indicative of the loss of hydrogen chloride from an amine hydrochloride but this has not been established. The ratio of the nitrogen to chlorine in the dialysed product was greater than the required 2:1 and it seemed that this may have been caused by the presence of adsorbed pyridine or by the presence of triazine products in which the ring chlorine atom had been displaced. However, it should be noted that the presence of products derived from displacement of the triazinyl chlorine atom by starch seems unlikely in the light of later work.
In this work (Experiment 25b), when cis-2-phenyl-1,3-dioxan-5-ol (1,3-O-benzylideneglycerol) was treated with trietazine (3) and pyridine at room temperature, the major components in the product mixture were the starting

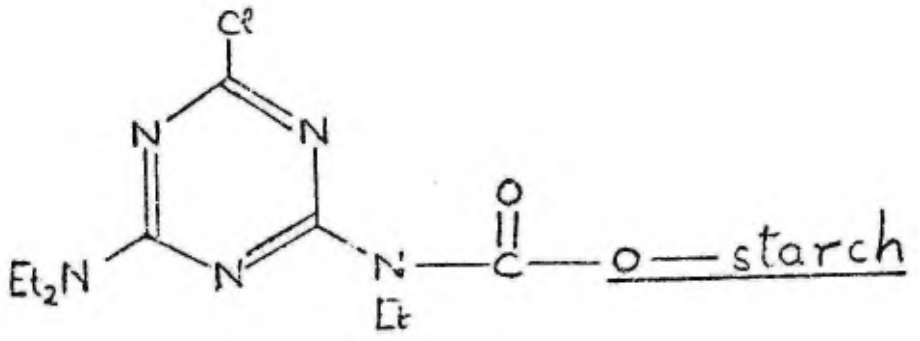


Fig.XXVII. Proposed structure for product TRPI.

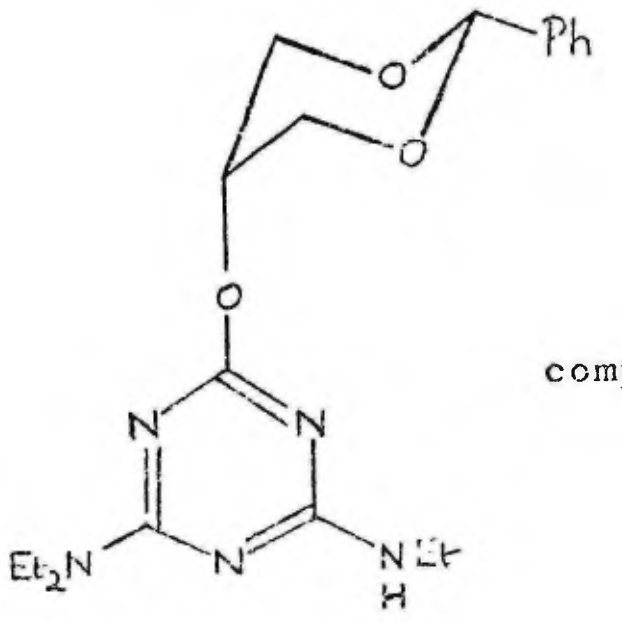
materials. None of the product of displacement of the chlorine atom of the triazine molecule by 1,3-O-benzylideneglycerol (see Experiment 24b) was observed.

In an attempt to obtain some more information about the origin of the discrepancy in the elemental analysis of TRPI, starch was treated with trietazine (3) in pyridine (Experiment 27b) under conditions similar to those of the carbamoylation (Experiment 23a). After prolonged dialysis followed by freeze-drying a product (TPV) was isolated from which some trietazine (3) was extracted with chloroform. The insoluble material (TPVA) contained 1.4% of nitrogen but did not show any distinctive bands in its ir spectrum. Thus the nature of the incorporated nitrogen compounds (in TRPI and TPVA) has not been determined. However, the reaction of cis-2-phenyl-1,3-dioxan-5-ol with compound 4 in pyridine gave the expected carbamate derived from trietazine, the ir spectrum of the starch derivative of compound 4 (TRPI) showed a significant carbonyl absorption (1730cm^{-1}) and product TRPI contained chlorine which could not be removed by extraction with chloroform or by dialysis against water. Thus it is concluded that the starch derivative TRPI contained N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamate groups (see Fig.XXVII).

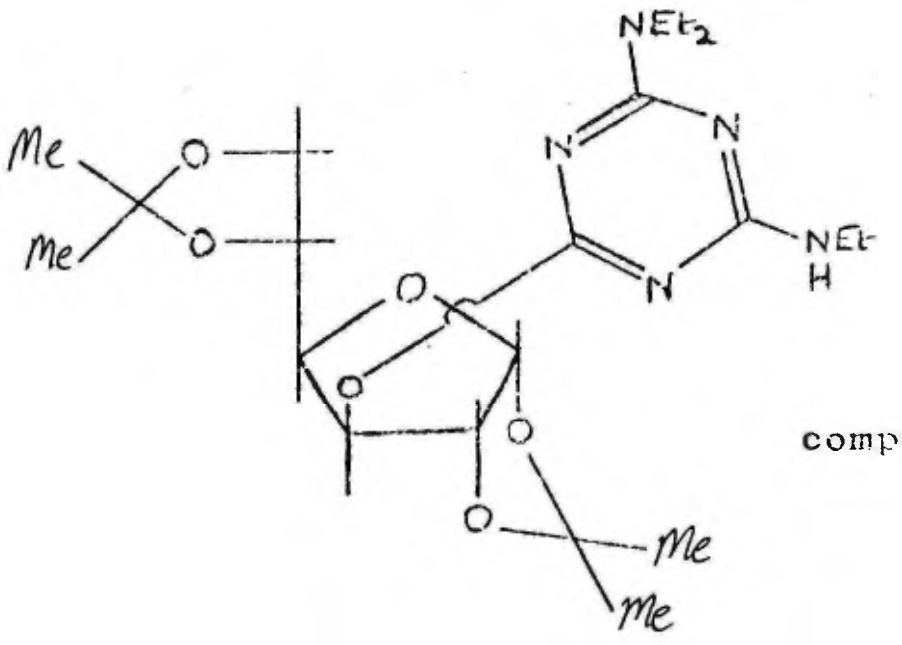
NUCLEOPHILIC DISPLACEMENTS AT 2-CHLORO-4-DIETHYLAMINO-6-ETHYLAMINO-1,3,5-TRIAZINE.

Because the main aim of this work was to make a derivative of starch from which a herbicide of known activity might be released into the soil, it was important that the triazine residue should remain intact in the prepartion of N-triazinylcarbamates (eg. TRPI). Although the reaction between the triazinylcarbamoyl chloride 4 and starch was eventually accomplished in pyridine, reaction conditions involving aqueous alkali had been investigated (see p.53 and Experiment 22b) at one stage. It seemed likely that some displacement of the ring chlorine atom would occur in the presence of alkoxide[138,139]. Thus an investigation of the conditions under which the sodium salts of a glycerol derivative, a monosaccharide derivative, and starch and cellulose react with a chlorodiaminotriazine was commenced. It was hoped to differentiate clearly between the reactivity of the ring chlorine atom and the carbamoyl chloride towards alcohols in the various reaction conditions.

Since some alkyloxydiaminotriazines, particularly the methoxy compounds, are herbicidal the glycerol and monosaccharide derivatives described in this section are of interest because of their potential biological activity. It has already been pointed out (p.8) that interest in the biological activity of materials made in this work cannot be confined



compound TRIII.



compound TRIV.

Fig.XXVIII.

to preparations from which compounds of known biological activities might be released. Thus two of the products described in this section have been tested for their biological activity (see p.64 and Appendix) and it is intended that others should be tested in the future.

Reactions of trietazine (3) with cis-2-phenyl-1,3-dioxan-5-ol and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.—— The reactions of simple alkoxides with chlorotriazines are well known[139]. It has now been found that, in a similar way, the sodium salt derived from cis-2-phenyl-1,3-dioxan-5-ol reacts with 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3) in refluxing toluene (Experiment 24b) to give crystalline 2-diethylamino-4-ethylamino-6-(cis-2-phenyl-1,3-dioxan-5-yl)oxy-1,3,5-triazine (TRIII, see Fig.XXVIII) in 55% yield. Similarly the sodium salt of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose reacted with trietazine (3) to give 1,2:5,6-di-O-isopropylidene-3-O-(2-diethylamino-4-ethylamino-1,3,5-triazin-6-yl)-α-D-glucofuranose (TRIV, see Fig.XXVIII) as a glass in 31% yield (Experiment 24c).

Reactions of trietazine with starch and cellulose.—— Treatment of alkali cellulose with trietazine at 100° for 0.5h (Experiment 26a) gave a 76% recovery of a polysaccharide material (TRPII), which did not contain nitrogen and seemed to be unmodified cellulose, and a mixture of unidentified compounds and trietazine (3). In a similar reaction

with starch (Experiment 26b), a polysaccharide was obtained which contained 0.9% nitrogen. The ir spectrum did not show any bands characteristic of 1,3,5-triazine residues and, if present, the DS would be very low. In order to discover if the 2-chloro group of trietazine could be displaced by alkoxide in the presence of sodium hydroxide, methanol and sodium hydroxide were reacted with trietazine (3) (Experiment 24a). The known 2-diethylamino-4-ethylamino-6-methoxy-1,3,5-triazine (TRII) was obtained in 74% yield. Thus the reason for the lack of reaction between alkali cellulose or alkali starch and trietazine is not apparent.

In view of this lack of reactivity it is important to note that chlorotriazine groups are used in 'reactive dyes' such as the compound shown in Fig.I[39,41]. In the presence of base such as aqueous sodium carbonate or sodium hydroxide (eg. 5M) such compounds react with cellulose to give ether linkages (esters of cyanuric acid)[140]. The monochloro-1,3,5-triazine dyes require a higher temperature or a much longer reaction time than the dichloro-1,3,5-triazine dyes[39]. The mechanisms of these dyeing reactions have received considerable attention and perhaps the most important discovery has been that the reacting molecule is first adsorbed onto the surface of the cellulose[141]. Then, under suitable conditions, the hydroxyl groups of the cellulose can readily

displace the chlorine atoms from the dye-stuff, without significant competition from hydrolytic reactions. Most molecules used for dyeing contain highly polar groups, such as sulphonates, which probably cause the adsorption of the dye at the cellulose surface[141]. For example, in a procedure used in the dyeing of polysaccharides with dichlorotriazines, sodium chloride is added to the solution of the dye and the polysaccharide and later sodium carbonate is added[142]. Therefore the reason for the lack of reactivity of 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine observed in the present work may be that it is not adsorbed onto the surface of cellulose or starch from the reaction media.

It has been reported[141] that the reactivity of chlorotriazines with cellulose is improved in the presence of tertiary nitrogen compounds such as pyridine. However, an attempt to react trietazine (3) with methanol and pyridine in refluxing 1,4-dioxan (Experiment 25a) gave only a trace of methoxytriazine that had been obtained previously by the use of methanol and sodium hydroxide (Experiment 24a) and an 82% recovery of trietazine (3). In spite of this result, cellulose was treated with trietazine (3) in the presence of refluxing pyridine (Experiment 27a) but this did not lead to successful incorporation of the triazine. Thus, the ir spectrum of the green product (TPIVA) showed no bands indicative of the presence of a 1,3,5-triazine, and TPIVA had only a

low content of nitrogen. The analytical data for this product were irreproducible and this may indicate inhomogeneity. However, it is clear that the nitrogen content of this material was very low and this indicates that, at best, only a low degree of incorporation of triazine groups had been achieved. Treatment of starch with a solution of trietazine (3) in refluxing pyridine gave a black intractable product (see Experiment 27b).

Thus, no triazinylstarch or -cellulose derived from the herbicidal 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine was obtained in this work. The finding that trietazine is quite strongly adsorbed onto starch and cellulose was not unexpected since there are other reports of the adsorption of amines onto carbohydrates[143]. The slight herbicidal activity shown by the cellulose derivative TRPII (see p.64 and Appendix) may be caused by a trace of adsorbed trietazine (despite the apparent absence of nitrogen) or may be caused by a product of the modification of cellulose. Thus the possibility of the presence of side-products or starting materials which have been incorporated into or adsorbed onto a polymeric product which is to be tested for biological activity should always be considered.

BIOLOGICAL ACTIVITY.

Some of the chemical groups, such as carbamates, 1,3,5-triazines and cyclic acetals occurring in the compounds made in this work are also found as the main structural units or as side groups in numerous pesticidal molecules. Carbamate groups are found in herbicides[58,144], insecticides[58,144], and fungicides[144], triazines in herbicides[58,61,145], insecticides[58,60] and fungicides[58,59], and cyclic acetals in insecticides[121]. However, it cannot be predicted that a new compound will have a particular activity on the basis of its chemical structure unless closely related compounds have been 'screened'[146]. A small difference in chemical structure may account for a large difference in biological activity. Thus the compounds, such as the glycerol and monosaccharide derivatives, which are described in this work have potentiality for useful biological activity. Some of the compounds have been submitted to 'screens' and the results are tabulated in the Appendix. Although none of the compounds shows outstanding activity a number of points seem worthy of discussion.

The first set of results (Tables II, III and IV) was supplied by the National Vegetable Research Station. A simple herbicidal 'screen' was set up for three glucoside N-phenylcarbamates and 1,3-diphenylurea. Simple O-alkyl-N-phenylcarbamates are used as herbicides[58,147],

but as far as is known no carbohydrate carbamates have been examined for their herbicidal activity. Methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (Experiment 3c), methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (Experiment 8b) and methyl 4,6-O-benzylidene-α-D-glucopyranoside 2-(N-phenylcarbamate) (Experiment 3b) were all readily available from this work. All three compounds (3, 1 and 4 respectively in the Tables) showed some activity in the root and shoot tests (Table II) but little or no effect in the soil (Table III) or post-emergence (Table IV) tests. The compound which showed the most activity in the root and shoot tests was methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-bis(N-phenylcarbamate). A significant feature seems to be that this compound has much greater activity against wheat and buckwheat than does the unblocked carbamate, methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate). Thus it seems that if the carbohydrate carbamates contain one or more hydroxyl group the herbicidal activity which is typical of carbamates is masked.

1,3-Diphenylurea (2 in the Tables) was included in the tests because although the carbamates had been rigorously purified, 1,3-diphenylurea was the most likely contaminant. It had been reported that 1,3-diphenylurea was a plant-growth stimulator[148] and thus it seemed important to test for this.

However, the urea exhibited very little activity. This confirms the recent finding that the activity reported for 1,3-diphenylurea was caused by impurities in the samples used in the tests[147].

The second set of results (Tables V to IX) was supplied by Fisons Limited. Only slight herbicidal activity was shown by the compounds tested in this section. cis-5-(N-Methyl-N-phenylcarbamoyl)-oxy-2-phenyl-1,3-dioxan (14150) showed the broadest spectrum of activity (Table V). It is, perhaps, surprising that the triazine derivative (14231) showed such low activity. The compounds also showed no significant insecticidal activity (Table VII). 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(N-methyl-N-phenylcarbamate) (14229) showed slight bacteristatic activity (Table VIII). In the in vivo tests (Table IX) compound 14150 gave slight control of bean rust at 500ppm, and compound 14229 and the N-methyl-N-phenylcarbamoylcellulose (compound 14230) gave slight control of late blight.

The low activity of all the compounds tested should not discourage further investigation of the biological activity of carbohydrate derivatives which might be of use in agriculture since, at this time, so few compounds have been tested that it is not possible to make any assessment of the range of activity of compounds in these series. From the point of view of biological activity, it is probable that the

most important material made in this work was the N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoylstarch (TRPI) because it is possible that the herbicidal compound trietazine (3) would be released from this preparation in a soil environment. No biological tests have been carried out yet on this material, but it is hoped that tests on this and similar materials will be possible in the future.

CONCLUSIONS.

The work reported in this thesis demonstrates clearly that a carbonate of starch may be made which will react with primary and secondary aliphatic amines to give carbamates. Although the use of this method for the preparation of a carbamate of starch derived from a pesticidal amine of this type has not been demonstrated, such amines are known. From the studies of model compounds it was concluded that the carbonate method was not applicable to the preparation of carbamates derived from aromatic amines and the herbicidal amino-1,3,5-triazines. However, the starch carbonate may find use in the preparation of starch carbonates and thiolcarbonates derived from pesticidal alcohols and thiols and there is a possibility that it could be used for insolubilizing enzymes.

The other approach to the preparation of carbamates of starch is by use of isocyanates or carbamoyl chlorides. The reactions of isocyanates with

starch are already well known[149] and products of high DS have been obtained. The reactions of carbamoyl chlorides which are reported here seem to be of equal usefulness. Although the general applicability of the method to pesticidal amines has not been determined, the use of carbamoyl chlorides in the preparation of carbamates of starch derived from pesticidal amines seems to be of wider applicability than the use of a starch carbonate. The carbamoyl chloride method is especially important in the preparation of starch carbamates derived from secondary aromatic amines.

The possibility that biologically active compounds would be released from starch carbamates placed in the soil has not yet been investigated and the biological activity of carbamate and 1,3,5-triazine derivatives of glycerol and monosaccharides requires further attention.

EXPERIMENTAL.

SECTION I

Techniques.

Melting points are uncorrected. Thin-layer chromatography (tlc) was carried out on glass plates coated with Silica gel G (Merck 7731) which were allowed to equilibrate in the atmosphere for at least 24h before use. The solvent mixtures most frequently used for irrigation were (X) ethyl acetate:hexane (1:1), and (Y) benzene:ether (9:1). Detection of materials was effected (a) by adsorption of iodine from the vapour phase, or (b) by heating the plate after treatment with a spray of vanillin in ethanol and concentrated sulphuric acid, or (c) by a combination of both techniques, that is removal of adsorbed iodine in a stream of warm air followed by the spray method.

Column chromatography was effected using Silica gel G (0.05-0.2mm, Merck 7734) as adsorbent. Tlc on Silica gel G (Merck 7731) was used to determine the most effective solvent or solvent mixture for elution. A solution of the mixture to be chromatographed was slurried with a little silica gel (about 2% of the adsorbent used in the column) and the solvent was removed slowly on the rotary evaporator. The powdery material so obtained was placed at the top of the column, and then elution was started.

In general, solvent evaporation was carried out using a rotary evaporator with the flask immersed in a water bath below 40^{o}. Water was removed from organic

solutions with powdered dry magnesium sulphate, except where otherwise stated.

Infra-red (ir) spectra were usually measured using a Pye-Unicam SP 200G instrument. Solids were prepared as Nujol mulls. Some salient features of the spectra are recorded here with assignments of the bands (sometimes tentative). The symbols ν and δ signify assignments as stretching or bending modes respectively.

Nuclear magnetic resonance (nmr) spectra were measured with a Perkin-Elmer R14 (100MHz) spectrometer except where it is stated otherwise. Chemical shifts were recorded on the δ scale with reference to the absorption of tetramethylsilane used as the internal standard.

Optical rotations were measured with the aid of a Perkin-Elmer model 141 polarimeter, and mass spectra were determined with an AEI MS9 instrument.

Preparation of Materials.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) was prepared by the action of phosgene on methyl 4,6-O-benzylidene-α-D-glucopyranoside in the presence of triethylamine, as reported by Doane et al.[68]. The compound was obtained in ca. 83% yield and a specimen which had been recrystallized from ether:hexane had mp 115-117° (lit.[66] 115-117°), mixed mp with an authentic sample* 115-117°, and $[\alpha]_D^{23}$ +68.8° (c 1.1, $CHCl_3$)

* Kindly supplied by the U.S. Department of Agriculture, Northern Utilization Research and Development Division, Peoria, Ill.

(lit.[66] $[\alpha]_D^{23}$+69° in $CHCl_3$).

N,N-Dimethylformamide (DMF) was refluxed over calcium hydride, distilled, and stored over calcium hydride.

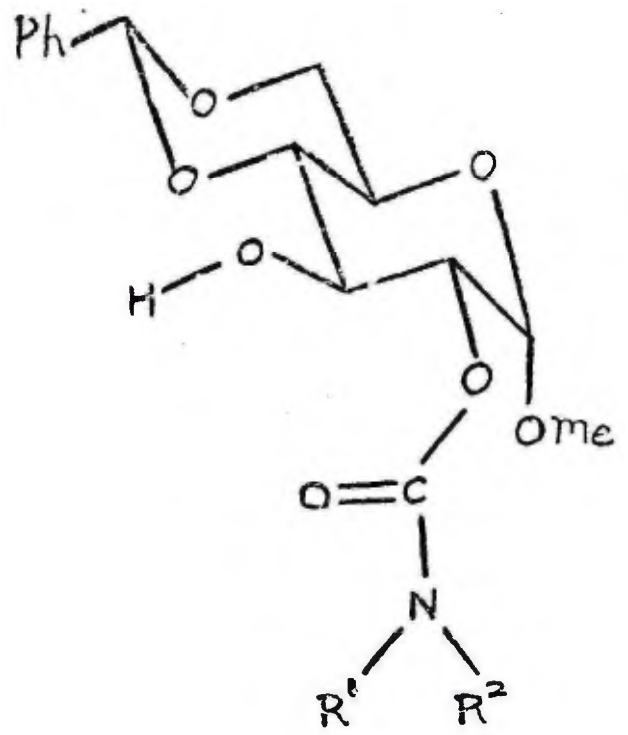
Methyl sulphoxide (Me_2SO) was refluxed gently over calcium hydride for at least 16h, and then distilled directly in dry apparatus onto molecular sieve (Type 3A) over which the dry solvent was stored.

Laboratory grade triethylamine was shaken with sodium hydroxide pellets, and allowed to stand over these for at least 24h. It was then decanted, distilled carefully from about 2% of phenyl isocyanate[150] and redistilled in dry apparatus. The fraction having bp 88-90°/760mmHg was collected and stored under nitrogen in a refrigerator.

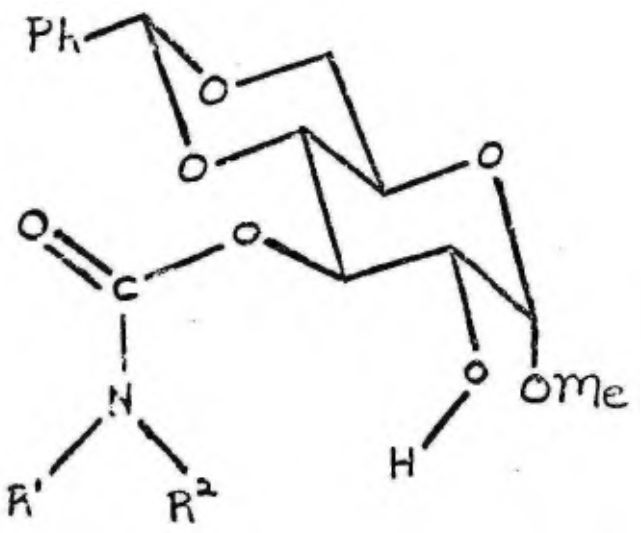
Pyridine was repeatedly distilled from phosphorus pentoxide and stored over sodium hydroxide pellets or molecular sieve (Type 3A).

Test for Purity of Triethylamine and Pyridine.

A portion of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (50mg) was dissolved in the solvent in dry apparatus. The solution was refluxed for 4h, cooled, diluted with ether (150cm^3), washed with ice-cold M aqueous hydrochloric acid (3x150cm^3) and brine (1x100cm^3), and dried. The purity of the solvent was judged to be satisfactory when tlc (X) showed compound 1 only in the recovered material.



A (2-carbamate).



B (3-carbamate).

1; R^1 = H, R^2 = cyclohexyl.
2; R^1 = H, R^2 = ethyl
3; R^1 = R^2 = ethyl.
4; R^1 = H, R^2 = benzyl.
5; R^1 = R^2 = benzyl.
6; R^1 = H, R^2 = phenyl.

Fig.IX. Key to methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-carbamates.

SECTION II

Reactions of amines with methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1).

Experiment 1a. Reaction of cyclohexylamine with Compound 1.

Compound 1 (100mg) was dissolved in freshly distilled cyclohexylamine ($5cm^3$), and the solution was left at room temperature overnight. The white solid remaining on evaporation of excess cyclohexylamine was taken up in ether ($100cm^3$), and the ethereal solution was washed briefly with ice-cold M aqueous hydrochloric acid ($3x100cm^3$) and water ($2x100cm^3$), dried and evaporated. Examination of the product by tlc (X) showed the presence of two compounds only (Rf's 0.4 and 0.6), but an attempted fractional crystallization using ethyl acetate:hexane was unsuccessful.

The entire yield was then applied to a column (270x12mm) of silica gel (20g) in the usual way. The compounds were eluted ($30cm^3$ fractions) with ethyl acetate:hexane (1:1), and a complete separation was achieved.

The faster moving component (A1; 76mg, 57.5%) was crystallized from ethyl acetate:hexane to give white, fluffy crystals, mp 183-184°, $[\alpha]_D^{18}$ +99° (c 0.4, $CHCl_3$) (Found: C, 62.3; H, 6.7; N, 3.5. $C_{21}H_{29}NO_7$ requires C, 61.9; H,7.2; N, 3.4%).

Nmr data ($CDCl_3$): δ 7.3-7.6 (5-proton multiplet, phenyl), 5.55 (1-proton singlet, benzylidene-H), 4.98 (1-proton doublet, $J_{1,2}$=3.6Hz, H-1), 4.70 (1-proton

apparent quartet, $J_{1,2}$=3.6, $J_{2,3}$=10.0Hz, H-2), 3.40 (3-proton singlet, methoxyl).

The ir spectrum showed absorption bands at 1550 (δ N-H), 1690 (ν C=O) and 3310cm^{-1} (ν N-H).

The slower moving compound (B1; 38mg, 29%) was crystallized from ethyl acetate:hexane to give white, fluffy crystals, mp 216-217°, $[\alpha]_D^{21}$+51° (c0.2, $CHCl_3$) (Found: C, 61.5; H, 6.8; N, 3.6. $C_{21}H_{29}NO_7$ requires C, 61.9; H, 7.2; N, 3.4%).

Nmr data ($CDCl_3$): δ 7.3-7.6 (5-proton multiplet, phenyl), 5.50 (1-proton singlet, benzylidene-H), 5.16 (1-proton apparent triplet, $J_{2,3}$=$J_{3,4}$=9.3Hz, H-3), 4.82 (1-proton doublet, $J_{1,2}$=3.6Hz, H-1), 3.46 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1550 (δ N-H), 1690 (ν C=O) and 3310cm^{-1} (ν N-H).

Experiment 1b. Reaction of ethylamine with compound 1.

A solution of compound 1 (1.0g) in ethylamine (20cm^3) was maintained at 0° for 2h with the aid of an ice bath and then the amine was allowed to evaporate in a fume cupboard overnight. The resulting white solid, which showed two components (Rf's 0.32 and 0.24) when examined by tlc (X), was fractionated on a column (760x20mm) of silica gel (100g), and the compounds were eluted (100cm^3 fractions) with ethyl acetate:hexane mixtures of increasing polarity (commencing with a 1:1 mixture). An excellent separation was achieved.

The faster moving component (A2; 0.68g, 61.5%)

was crystallized from chloroform:hexane to give needles, mp 173-173.5°, $[\alpha]_D^{19}$+85.4° (c0.9, $CHCl_3$) (Found: C, 57.7; H, 6.7; N, 3.8. $C_{17}H_{23}NO_7$ requires C, 57.8; H, 6.6; N, 4.0%).

Nmr data ($CDCl_3$): δ 7.35-7.65 (5-proton multiplet, phenyl), 5.58 (1-proton singlet, benzylidene-H), 5.00 (1-proton doublet, $J_{1,2}$=4.0Hz, H-1), 4.72 (1-proton apparent quartet, $J_{1,2}$=4.0, $J_{2,3}$=9.4Hz, H-2), 3.40 (3-proton singlet, methoxyl), 1.10 (3-proton triplet, J=7.2Hz, H_3C-CH_2-).

The ir spectrum showed bands at 1540 (δ N-H), 1680 (ν C=O) and 3340cm^{-1} (ν N-H).

The slower moving component (B2; 0.27g, 24.5%) was crystallized from ether:ethyl acetate:hexane to give fine white crystals, mp 212-213°, $[\alpha]_D^{23}$+56.8° (c0.7, $CHCl_3$) (Found: C, 57.8; H,6.7; N, 4.1. $C_{17}H_{23}NO_7$ requires C, 57.8; H. 6.6; N, 4.0%).

Nmr data ($CDCl_3$): δ 7.3-7.6 (5-proton multiplet, phenyl), 5.51 (1-proton singlet, benzylidene-H), 5.18 (1-proton apparent triplet, $J_{2,3}=J_{3,4}$=9.3Hz, H-3), 4.79 (1-proton doublet, $J_{1,2}$=4.3Hz, H-1), 3.48 (3-proton singlet, methoxyl), 1.10 (3-proton triplet, J=7.1Hz, H_3C-CH_2-).

The ir spectrum showed bands at 1550 (δ N-H), 1690 (ν C=O) and 3310cm^{-1} (ν N-H).

Experiment 1c. Reaction of benzylamine with compound 1.

A solution of compound 1 (0.30g) in benzylamine (5cm^3) was warmed briefly and then left at room temperature

for 1h. The solution was diluted with ether ($150cm^3$), washed briefly with ice-cold M aqueous hydrochloric acid ($4x100cm^3$) and water ($2x100cm^3$), dried and evaporated. The resulting material, which showed two components (Rf's 0.55 and 0.28) when examined by tlc (X), was applied to a column (760x20mm) of silica gel (100g) in the usual way, and elution ($100cm^3$ fractions) with ethyl acetate:hexane (1:1) achieved complete separation of the components.

The faster moving component (A4; 0.26g, 63%) was crystallized from ethyl acetate:hexane to yield a powdery solid, mp 177-177.5°, $[\alpha]_D^{20}$+81° (c 1.0, $CHCl_3$) (Found: C, 63.7; H, 6.2; N,3.2. $C_{22}H_{25}NO_7$ requires C, 63.6; H,6.1; N, 3.4%).

Nmr data ($CDCl_3$): δ 7.6-7.2 (10-proton multiplet, phenyl groups), 5.50 (1-proton singlet, benzylidene-H), 4.98 (1-proton doublet, $J_{1,2}$=3.9Hz, H-1), 4.72 (1-proton apparent quartet, $J_{1,2}$=3.9, $J_{2,3}$=10.3Hz, H-2), 3.36 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1540 (δ N-H), 1690 (ν C=O) and 3340cm^{-1} (ν N-H).

The slower moving component (B4; 0.13g, 33%) was crystallized from ethyl acetate:hexane to give fine crystals, mp 221.5-223°, $[\alpha]_D^{18}$+27° (c 1.1, $CHCl_3$) (Found: C, 63.3; H, 6.0; N, 3.4 . $C_{22}H_{25}NO_7$ requires C, 63.6; H, 6.1; N, 3.4%).

Nmr data ($CDCl_3$): δ 7.6-7.2 (10-proton multiplet, phenyl groups), 5.50 (1-proton singlet, benzylidene-H), 5.25 (1-proton apparent triplet,

$J_{2,3}=J_{3,4}=9.4$Hz, H-3), 4.82 (1-proton doublet, $J_{1,2}=4.0$Hz, H-1), 3.45 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1550 (δ N-H), 1690 (ν C=O) and 3310cm^{-1} (ν N-H).

Experiment 1d. Reaction of dibenzylamine with compound 1.

A solution of compound 1 (1.00g) in distilled (97°/0.2mmHg) dibenzylamine (2.0cm^3) was refluxed for 0.5h in dry apparatus. After cooling, a solution of the mixture in ether (200cm^3) was shaken with M aqueous hydrochloric acid (100cm^3), and dibenzylamine hydrochloride was filtered off and washed with a little ether. The combined ethereal solution was dried (Na_2CO_3) and evaporated to yield a syrup which showed the presence of two major components (Rf's 0.55 and 0.32) on examination by tlc (ethyl acetate:hexane, 1:2). A white solid (521mg) was obtained by trituration with ether:hexane, and crystals (115mg), mp 144-145°, were obtained by recrystallization from ether:hexane. The remaining mixture was separated on a column (400x33mm) of silica gel (150g) by eluting (70cm^3 fractions) with ethyl acetate:hexane mixtures of increasing polarity. The majority of the mixture was obtained in two fractions.

A chloroform solution of the syrupy first fraction was extracted with M aqueous hydrochloric acid (40cm^3), dried and evaporated to give a clear syrup (A5; 708mg, 43%) which, after prolonged evacuation and refrigeration, turned to an amorphous solid, mp 52-55°, $[\alpha]_D^{17}+74.4°$ (c 1.0, $CHCl_3$) (Found: C, 68.9: H, 6.0; N,2.7. $C_{29}H_{31}NO_7$ requires C, 68.9; H, 6.2; N, 2.8%).

Nmr data ($CDCl_3$): δ 7.80-7.15 (15-proton multiplet, phenyl groups), 5.45 (1-proton singlet, benzylidene-H), 5.04 (1-proton doublet, $J_{1,2}$=4.3Hz, H-1), 4.79 (1-proton apparent quartet, $J_{1,2}$=4.3, $J_{2,3}$=9.5Hz, H-2) 3.41 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1700 (νC=O) and 3450cm^{-1} (νO-H).

The second fraction, a faintly yellow solid (B5; 438mg), had an Rf value (tlc, ethyl acetate:hexane, 1:2) identical with that of the crystals collected before chromatography (total yield of B5=553mg, 34%). Two crystallizations from ethyl acetate:hexane yielded a sample, mp 146-147°, $[\alpha]_D^{17}$+38.0° (c0.9, $CHCl_3$) (Found: C, 68.8; H, 6.2; N, 2.8. $C_{29}H_{31}NO_7$ requires C, 68.9; H, 6.2; N, 2.8%).

Nmr data ($CDCl_3$): δ 7.60-7.10 (15-proton multiplet, phenyl groups), 5.47 (1-proton singlet, benzylidene-H), 5.39 (1-proton apparent triplet, $J_{2,3}$=$J_{3,4}$=9.2Hz, H-3), 4.84 (1-proton doublet, $J_{1,2}$=3.9Hz, H-1), 3.49 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1690 (ν C=O), and 3240 and 3480cm^{-1} (ν O-H).

Examination of a further fraction (30mg) by tlc (ethyl acetate:hexane, 1:2) showed the presence of two components only (Rf's 0.31 and 0.16) which corresponded exactly with compounds A4 and B4.

Experiment 2a. Treatment of compound 1 with diethylamine.

A solution of compound 1 (1.0g) in distilled diethylamine ($20cm^3$) was left at room temperature overnight and then evaporated. Tlc (X, vanillin development) of the residue showed two components (R and S, Rf's 0.37 and 0.25). The material was applied to a column (830x20mm) of silica gel (110g) in the usual way, and the compounds were eluted ($100cm^3$ fractions) with ethyl acetate:hexane (1:1).

The first compound to be eluted, P, was visible with vanillin development only when heavily spotted on tlc plates, but was clearly visible with iodine development (Rf 0.66). An excellent separation of the three components was achieved.

Compound P (A3) was a glass (0.55g, 44%), mp 44-45°, $[\alpha]_D^{20}$+85.5° (c1.2, $CHCl_3$) (Found: C, 59.5; H, 7.3; N, 4.0. $C_{19}H_{27}NO_7$ requires C, 59.8; H, 7.1; N, 3.7%).

Nmr data ($CDCl_3$): δ 7.65-7.35 (5-proton multiplet, phenyl), 5.60 (1-proton singlet, benzylidene -H), 5.00 (1-proton doublet, $J_{1,2}$=4.0Hz, H-1), 4.75 (1-proton apparent quartet, $J_{1,2}$=4.0, $J_{2,3}$=9.7Hz, H-2), 3.41 (3-proton singlet, methoxyl), 1.14 (6-proton triplet, J=7.1Hz, H_3C-CH_2-) (see Fig.X).

The ir spectrum showed a band at $1700cm^{-1}$ (ν C=O, broad).

Crystallization of component R (A2; 0.58g, 50%?) from chloroform:hexane gave a product (0.45g) having mp 168°. The nmr and ir spectra of this material were indistinguishable from those of compound A2 in Experiment 1b.

Further crystallizations from chloroform:hexane gave fine needles (27mg), mp 173-173.5°, mixed mp (with compound A2 from Experiment 1b) 173°, $[\alpha]_D^{23}$+89° (c0.3, $CHCl_3$) (compound A2, Experiment 1b, had $[\alpha]_D^{23}$+85.4°).

The nmr and ir spectra of component S (B2; 0.12g, 10%) were indistinguishable from those of compound B2 in Experiment 1b. Crystallization from ether:hexane gave a fluffy white material (25mg), mp 212-213°, mixed mp (with compound B2 from Experiment 1b) 211-212°, $[\alpha]_D^{20}$+50° (c0.8, $CHCl_3$) (compound B2, Experiment 1b, had $[\alpha]_D^{23}$+56.8°) (Found: C, 58.1; H, 6.1; N, 3.6. $C_{17}H_{23}NO_7$ requires C, 57.8; H, 6.6; N, 4.0%).

The total yield of the mono(N-ethylcarbamates) A2 and B2 was ca. 0.70g which required the presence of 89mg (0.63%) of ethylamine in the solution of compound 1 in diethylamine.

Experiment 2b. Attempted purification of diethylamine and reaction with compound 1.

A sample of commercial (B.D.H.) diethylamine (220cm^3) was distilled, and the fraction having bp 54-56°/760mmHg was dissolved in ether (1000cm^3). Hydrogen chloride gas was passed slowly into the solution, which was swirled occasionally, until the rate of formation of hydrochloride appeared to be quite low, and then the white solid was collected by filtration.

The entire yield (ca. 240g) of hydrochloride

was crystallized in three batches, twice from ethanol:ether, and once from chloroform:hexane. The product (31.3g), mp 227-228° (translucent plates), was dissolved in water (250cm^3), and the solution was layered beneath pure xylene (350cm^3) and made strongly alkaline by the addition of a solution of sodium hydroxide (20g) in water (100cm^3). Vigorous shaking and salting out (addition of NaCl) completed the extraction of the amine, and the organic layer was dried and then passed through a column of activated alumina into a dry distillation apparatus having an adiabatic column (300mm). A fraction (10cm^3) boiling at 55°/760mmHg was collected directly onto a sample of compound 1 (0.50g) which was dissolved by warming. The solution was maintained at room temperature for 2h, and excess amine was then removed under vacuum.

Examination of the residue by tlc (X) showed the presence of at least three components [Rf's 0.62 (A3), 0.40 (A2+B3?) and 0.22 (B2)].

The mother liquors from the recrystallizations of the amine hydrochloride were combined and evaporated. The residue was dissolved in water, the amines were released into ether by addition of sodium hydroxide, and the ethereal solution (solution T) was dried.

Solution T was analysed by gas chromatography using a Phasepak[151] (polystyrene matrix) column (900x4mm) at 80°, with nitrogen carrier gas and flame-ionization detection. By reference to standard solutions, it was

shown that solution T contained ethylamine and diethylamine in the ratio of ca. $4.3:10^2$. The ethereal solution remaining from the preparation of the amine hydrochlorides contained ethylamine and diethylamine in the ratio of ca. $7:10^4$. It was calculated that solution T (containing a total of ca. 123.6g of amines) contained ca. 5.1g of ethylamine. This is equivalent to a minimum of 3.3% of ethylamine in the crude amine mixture.

Experiment 2c. Reaction of a sample of diethylamine containing only 0.05% of ethylamine with compound 1.

Gas chromatography (Phasepak, as in Experiment 2b) of a fresh batch of commercial diethylamine showed it to contain ca. 0.05% of ethylamine.

A solution of compound 1 (0.50g) in a sample ($10cm^3$) of this amine was left at room temperature overnight, and then diluted with ether ($150cm^3$). The ethereal solution was washed briefly with ice-cold M aqueous hydrochloric acid ($3x100cm^3$), dried and evaporated. Tlc (X) showed the presence of at least three components (Rf's 0.64, 0.42 and 0.25).

The material was applied to a column (600x20mm) of silica gel (80g) in the usual way and the compounds were eluted ($50cm^3$ fractions) with ethyl acetate:hexane (1:1), giving the following fractions:-

I; 0.396g, Rf 0.64.

II; 0.017g, Rf's 0.64 and 0.42.

III; 0.123g, Rf 0.42.

IV; 0.014g, Rf's 0.42 and 0.25.

V; 0.025g, Rf 0.25.

Fraction I (A3; 64%) was a glass, mp 44-45°, mixed mp (with A3 from Experiment 2a) 44-45°, $[\alpha]_D^{19}$+87.9° (c1.0, $CHCl_3$). The nmr and ir spectra were identical with those of compound A3 in Experiment 2a.

Fraction III (B3; 20%) was crystallized from ether:hexane and chloroform:hexane to yield a white powdery material, mp 100-102°, $[\alpha]_D^{19}$+26° (c0.2, $CHCl_3$) (Found: C, 60.1; H, 7.1; N, 3.6. $C_{19}H_{27}NO_7$ requires C, 59.8; H, 7.1; N, 3.7%).

Nmr data ($CDCl_3$): δ 7.60-7.35 (5-proton multiplet, phenyl), 5.58 (1-proton singlet, benzylidene-H), 5.16 (1-proton apparent triplet, $J_{2,3}=J_{3,4}$=9.1Hz, H-3), 4.82 (1-proton doublet, $J_{1,2}$=3,7Hz, H-1), 3.47 (3-proton singlet, methoxyl), 1.11 (6-proton triplet, J=6.9Hz, H_3C-CH_2-) (see Fig.XI).

The ir spectrum showed bands at 1680 (ν C=O) and 3420cm^{-1} (ν N-H).

The compound in fraction V had an Rf value (tlc, X) identical with that of compound B2 (Experiment 1b), and was not examined further.

Experiment 3a. Reaction of aniline with compound 1.

Laboratory grade aniline was stored over sodium hydroxide pellets, decanted, and distilled with care from a little zinc dust[152].

Compound 1 (1.0g) was dissolved in a mixture of dry aniline ($25cm^3$, prepared as described above) and dry triethylamine ($25cm^3$). The solution was maintained at reflux temperature for 2h, cooled, and then diluted with ether ($300cm^3$). The ethereal solution was washed with ice-cold M aqueous hydrochloric acid ($6x300cm^3$) and brine ($300cm^3$). A little ethyl acetate was added to solubilize some material which had precipitated and the resulting solution was dried and concentrated.

The residue (1.3g) showed four components on examination by tlc (X) [Rf's 0.70 (faint), 0.64 (green in vanillin), 0.33 (green in vanillin), and 0.20 (faint)], and was applied to a column (840x20mm) of silica gel (110g) in the usual way. The components were eluted ($100cm^3$ fractions) with ethyl acetate:hexane mixtures of increasing polarity, commencing with a 1:1 mixture. The initial fractions were contaminated with an oily material (supposedly aniline) which was separated by precipitation of the carbohydrate with hexane. An excellent separation was achieved as follows:-

I; 0.147g, Rf's 0.64 (green in vanillin) and 0.70 (faint).

II; 0.528g (40.5%), Rf 0.64 (green in vanillin).

III; Trace, Rf 0.42.

IV; 0.335g (25.8%), Rf 0.33 (green in vanillin).

V; 0.074g, Rf's 0.33 (green in vanillin) and 0.20 (faint).

Repeated recrystallizations of combined fractions I and II from ethanol:water gave a product (Q; 210mg) consistently melting at ca. 195°. The nmr spectrum ($(CD_3)_2CO$) of this product was indistinguishable from that of compound A6 (Experiment 3b). The ir spectrum was indistinguishable from that of compound A6 (Experiment 3b) except for the presence of a minute absorption at 1650cm^{-1} (corresponding to the ν C=O absorption of 1,3-diphenylurea).

Careful fractional crystallization of a portion of Q (140mg) from ethyl acetate gave small crops of 1,3-diphenylurea (12+3mg), mp 242-243°, mixed mp with an authentic specimen 242-243°. The compound was also identified by its nmr and ir spectra. The next crop (55mg), mp 197-199°, on further recrystallization, gave the 2-(N-phenylcarbamate) (A6; 6mg), mp 200-201°, mixed mp (with authentic compound A6, Experiment 3b) 199-200°.

Fraction IV was crystallized from ethanol: water to yield the 3-(N-phenylcarbamate) (B6) as fine white crystals (291 mg, 22%), mp 246-247° (lit.[153] 245-247°), mixed mp (with B6, Experiment 3b) 245-246°; $[\alpha]_D^{23}$+56.5° (c1.0, pyridine) (lit.[153] $[\alpha]_D^{27}$+50°, c0.4 in pyridine). The nmr spectrum ($(CD_3)_2SO$) and ir spectrum

were indistinguishable from those of compound B6 (Experiment 3b).

Experiment 3b. Preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2- and 3-(N-phenyl-carbamates), using phenyl isocyanate.

Dry (vacuum-oven overnight, ca. 40°) methyl 4,6-O-benzylidene-α-D-glucopyranoside (2.0g) was placed in a dry flask (fitted with a mechanical stirrer, dropping funnel, and a Dean and Stark trap with condenser) and dissolved in dry pyridine ($30cm^3$) and dry (Na wire) benzene ($40cm^3$). After the solution had been brought to reflux temperature (oil bath), phenyl isocyanate (0.5g) in dry benzene ($50cm^3$) was added over 5.5h. Much of the pyridine was then azeotroped off with benzene with the aid of the Dean and Stark trap, and, after cooling, the solution was poured into light petroleum (100-120°) ($500cm^3$). The solid (1.49g) which had settled after storage for 2h in the refrigerator was filtered off and washed with light petroleum ($100cm^3$). Examination by tlc (X) showed four components [Rf's 0.69, 0.64, 0.33 (all green in vanillin), and 0.14 (starting material)].

The material was applied to a column (480x35mm) of silica gel (170g) in benzene:ether, and elution ($30cm^3$ fractions) with benzene:ether mixtures of increasing polarity (commencing with 8:1) gave a separation as follows:-

I; 0.500g, Rf's 0.69 and 0.64.

II; 0.150g, Rf 0.64.

III; 0.100g. Rf 0.33.

Fraction II was recrystallized from ether:hexane and ethanol:water to yield the 2-(N-phenylcarbamate) (A6) as fine white crystals (40mg), mp 200-201.5°, $[\alpha]_D^{19}$+71.5° (c0.7, pyridine) (Found: C, 62.5; H, 5.7; N, 3.4. $C_{21}H_{23}NO_7$ requires C, 62.5; H, 5.7; N, 3.4%).

Nmr data ($(CD_3)_2CO$): δ 7.7-7.2 (10-proton multiplet, phenyl groups), 5.63 (1-proton singlet, benzylidene-H), 4.97 (1-proton doublet, $J_{1,2}$=3.8Hz, H-1), 4.76 (1-proton apparent quartet, $J_{1,2}$=3.8, $J_{2,3}$=9.7Hz, H-2), 3.40 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1600 (C=C multiple bond stretching) 1700 (νC=O) and 3290cm^{-1} (ν N-H).

Fraction III was crystallized consecutively from ether:hexane and ethanol:water to yield the 3-(N-phenylcarbamate)(B6) as fine white crystals (32mg), mp 246-248° (lit.[153] 245-247°), $[\alpha]_D^{22}$+54° (c0.7, pyridine) (lit.[153] $[\alpha]_D^{17}$+50°, c0.4 in pyridine) (Found: C, 62.9; H, 5.7; N, 3.4. $C_{21}H_{23}NO_7$ calc: C, 62.5; H, 5.7; N, 3.4%).

Nmr data ($(CD_3)_2CO$): δ 7.7-6.9 (10-proton multiplet, phenyl groups), 5.57 (1-proton singlet, benzylidene-H), 5.27 (1-proton apparent triplet, $J_{2,3}=J_{3,4}$=9.2Hz, H-3), 4.81 (1-proton doublet, $J_{1,2}$=3.7Hz, H-1), 3.46 (3-proton singlet, methoxyl). Nmr data ($(CD_3)_2SO$): 7.7-7.0 (10-proton multiplet, phenyl groups), 5.65 (1-proton singlet, benzylidene-H) 5.25 (1-proton apparent triplet, $J_{2,3}=J_{3,4}$=8.6Hz. H-3), 4.82 (1-proton

doublet, $J_{1,2}$=3.7Hz, H-1), 3.43 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1600 (C=C multiple bond stretching), 1710 (νC=O) and 3360cm^{-1} (νN-H and O-H).

The component in fraction I having Rf 0.69 was indistinguishable (tlc) from methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-bis-(N-phenylcarbamate) (Experiment 3c).

Experiment 3c. Preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (E)

Dried methyl 4,6-O-benzylidene-α-D-glucopyranoside (2.0g) was placed in the dry apparatus described in Experiment 3b, and dissolved in a mixture of dry pyridine (50cm^3) and dry benzene (50cm^3). The solution was brought to reflux for 10min and cooled a little, and phenylisocyanate (5.0g) was then added carefully. The solution boiled spontaneously, and heat was reapplied to give a gentle reflux for 6.5h. The mixture was then refluxed more strongly as dry benzene (100cm^3) was added and pyridine:benzene mixtures were removed from the Dean and Stark trap. After cooling, the reaction mixture was poured into light petroleum (100-120°) (300cm^3). Three crops of crystals were collected, as follows:-

I; 2.11g, Rf ca. 0.7 (elongated spot, yellow in vanillin).

II; 3.41g, Rf 0.69 (green in vanillin); superimposed on a large yellow spot.

III; 1.50g, Tlc as for II.

Crops II and III were washed briefly with ethyl acetate at room temperature, and tlc examination of the filtered washings (W) showed only a distinct spot at Rf 0.69 (green in vanillin).

The remaining crystalline material was taken with crop I and recrystallized from hot ethyl acetate to yield 1,3-diphenylurea (total yield=2.45g), mp 245-246° mixed mp 242-243°. (Found: C, 74.0; H, 5.8; N, 13.5. $C_{13}H_{12}N_2O$ calc: C, 73.6; H, 5.7; N, 13.2%).

The nmr and ir spectra were identical with those of authentic samples. Nmr data ($(CD_3)_2SO$): δ 8.71 (2-proton singlet, N-H), 7.66-6.92 (10-proton multiplet, phenyl groups).

The filtrate (W) was evaporated to give a white solid (3.6g). Crystallization from ethanol:light petroleum (80-100°) yielded the bis(N-phenylcarbamate) (E) as fine white crystals (1.08g, 29%), mp 219-220° (lit.[154] 216-217°), $[\alpha]_D^{20}$+29.1° (c1.4, $CHCl_3$) (lit.[154] $[\alpha]_D^{25}$+40°, c1.0 in $CHCl_3$) (Found: C, 64.7; H, 5.2; N, 5.2. $C_{28}H_{28}N_2O_8$ calc: C, 64.6; H, 5.4; N, 5.4%).

Nmr data ($(CD_3)_2CO$): δ 7.70-6.95 (15-proton multiplet, phenyl groups), 5.69 (1-proton singlet, benzylidene-H), 5.54 (1-proton apparent triplet, $J_{2,3}=J_{3,4}$=10Hz, H-3), 5.11 (1-proton doublet, $J_{1,2}$=3.6Hz, H-1), 4.91 (1-proton apparent quartet, $J_{1,2}$=3.6,

$J_{2,3}$=10Hz,H-2), 3.47 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1600 (2 sharp peaks, C=C multiple bond stretching), 1700 (νC=O) and 3320cm^{-1} (νN-H).

Further crops were collected (total 1.46g) with melting points depressed by the presence of small amounts of 1,3-diphenylurea (detected by the presence in the ir spectrum of a small peak at 1650cm^{-1}).

Experiment 4a. An attempt to react N-methylaniline with compound 1.

A mixture of compound 1 (1.0g), dry triethylamine (15cm^3) and distilled N-methylaniline (15cm^3) in a sealed tube was placed in an oven at 70° for 15h. After cooling, the mixture was diluted into an ethereal solution which was washed with M aqueous hydrochloric acid (6x200cm^3) and brine (200cm^3), dried and evaporated.

Examination of the residue by tlc (X) showed the presence of at least four components [Rf's 0.95 (blue in vanillin), 0.65, 0.54 and 0.29]. The material was applied to a column (840x20mm) of silica gel (110g) and elution (100cm^3 fractions) was effected with ethyl acetate:hexane (1:1) to give the following fractions:-

I; 0.337g of an oil, Rf's 0.95 (blue in vanillin) and 0.65.

II; 0.772g of an oil, Rf's 0.95 (blue in vanillin), 0.65 (faint) and 0.54.

III; 1.048g of an oil, Rf's 0.95 (blue in vanillin), 0.65 (faint) and 0.29.

Fraction I failed to give a solid on trituration and was not identified.

Fraction II solidified on trituration with light petroleum (80-100°) and was re-precipitated from ethyl acetate:hexane to yield the acyclic carbonate C (cf. Experiment 4b) as a white solid (110mg), which turned glassy at 142°, mp 210° (Found: C, 59.3; H, 6.1; N, 0. $C_{29}H_{34}O_{13}$ requires C, 59.0; H, 5.8%). Examination by tlc (X) showed one intense spot (Rf 0.54) with some tailing.

Nmr data ($(CD_3)_2CO$): δ 7.70-7.35 (10-proton multiplet, phenyl groups), 5.65 (2-proton singlet, benzylidene-H's). 5.00 (2-proton doublet, $J_{1,2}$=4.0Hz, H-1's), 4.62 (2-proton apparent quartet, $J_{1,2}$=4.0, $J_{2,3}$=9.7Hz, H-2's), 3.40 (6-proton singlet, methoxyls).

The ir spectrum showed bands at 1750 (νC=O) and at ca. 3450cm^{-1} (νO-H).

Fraction III solidified on trituration with light petroleum (80-100°) and was precipitated from ethyl acetate:hexane to yield a powdery white solid (D, 250mg), mp 180-181° (Found: C, 57.7; H, 5.9; N, 0. $C_{29}H_{34}O_{13}$ requires C, 59.0; H, 5.8%). Further crystallization did not give a product with improved analytical properties, but the nmr spectrum ($(CD_3)_2CO$) and ir spectrum were identical with those of the acyclic carbonate D obtained in Experiment 4b. Examination

of the product by tlc (X) showed one spot (Rf 0.29).

Experiment 4b. Reaction of methyl 4,6-O-benzylidene-α-D-glucopyranoside with compound 1.

Compound 1 (500mg) and methyl 4,6-O-benzylidene-α-D-glucopyranoside (500mg) were dissolved in triethylamine ($30cm^3$) and the solution was heated in a sealed tube at 70^o for 18h. An ethereal solution ($150cm^3$) of the cooled reaction mixture was extracted with ice-cold M aqueous hydrochloric acid ($5x100cm^3$), washed with brine ($100cm^3$) and dried. Examination by tlc (X) showed spots (Rf's 0.54 and 0.29) corresponding exactly to those of the two products isolated in Experiment 4a.

Chromatography on a column (760x20mm) of silica gel (100g) using ethyl acetate:hexane (1:1) as eluant ($100cm^3$ fractions) yielded two major fractions as follows:-

I; 0.121g of a white solid, Rf's 0.76 (faint), 0.54 and 0.29 (faint).

II; 0.329g of a white solid, Rf 0.29.

Fraction I was crystallized from chloroform:hexane to give a white amorphous material (C; 73mg), mp ca. 220^o (Found: C, 56.3; H, 5.7, $C_{29}H_{34}O_{13}$ requires C, 59.0; H, 5.8%). It proved impossible to improve the melting point and elemental analysis of this material by further crystallization, but its nmr spectrum ($(CD_3)_2CO$) and ir spectrum were

identical with those of the acyclic carbonate C obtained in Experiment 4a.

Fraction II was crystallized from chloroform:hexane to yield the acyclic carbonate D as a white amorphous solid (199mg), mp 218-227° (decomposition?), $[\alpha]_D^{20}$+101° (c1.0, $CHCl_3$) (Found: C, 58.6; H, 5.7. $C_{29}H_{34}O_{13}$ requires C, 59.0; H, 5.8%).

Nmr data ($(CD_3)_2CO$): δ 7.65-7.28 (10-proton multiplet, phenyl groups), 5.64 (2-proton singlet, benzylidene-H's), 5.12 (1-proton triplet, $J_{2,3}=J_{3,4}=$ 9.7Hz, one H-3), 4.98 (1-proton doublet, $J_{1,2}=3.7$Hz, one H-1), 4.83 (1-proton doublet, $J_{1,2}=4.0$Hz, one H-1), 4.54 (1-proton quartet, $J_{1,2}=4.0$, $J_{2,3}=10.0$Hz, one H-2), 3.37 and 3.46 (both 3-proton singlets, methoxyls).

The ir spectrum showed bands at 1730 (νC=O) and 3460cm^{-1} (νO-H).

Experiment 5. Treatment of compound 1 with various amines.

a. Dicyclohexylamine. — Dicyclohexylamine was distilled (72°/0.25mmHg) and stored over sodium hydroxide pellets. A solution of compound 1 (50mg) in a mixture of dicyclohexylamine (1.0cm^3), dry triethylamine (1.0cm^3) and DMF (1.0cm^3) was stored at room temperature for 20h and then heated at 85° for 0.5h. Tlc (X) examination of the material obtained by removal of the solvent from aliquots taken from the reaction mixture at the 20h stage and after heating showed the presence of compound 1 and a small proportion of material of very low mobility.

The ir spectrum of the residue showed, *inter alia*, a band at 1810cm^{-1} (cyclic carbonate).

b. *N*-Methylaniline. —— Commercial *N*-methylaniline was distilled to remove most of the colour, stored over sodium hydroxide pellets for 24h, and then distilled (72-73°/6-7mmHg) twice with care from zinc dust and once without zinc. A final distillation (189°/749mmHg) (lit.[90] 192-193°/760mmHg) then gave a colourless liquid which was stored in the dark, under nitrogen in a refrigerator. Gas-liquid chromatography on Carbowax (Pye-Argon chromatograph) and nmr spectroscopy showed the presence of only a minor impurity corresponding to *N*,*N*-dimethylaniline.

Compound 1 (25mg), dry triethylamine (2.5cm^3) and purified *N*-methylaniline (2.5cm^3) were heated in a dry Carius tube at 70° for 20h. Most of the amine was then evaporated at 40° under vacuum, and an ethereal solution (50cm^3) of the resulting yellow liquid was extracted with cold M aqueous hydrochloric acid (2x50cm^3) and dried. Examination by tlc (X) showed the presence of compound 1 (Rf 0.71), three other components (Rf's 0.60, 0.53 and 0.28) in relatively small proportions, and some material of zero mobility. The spots at Rf's 0.53 and 0.28 corresponded very closely to those of compounds C and D (Experiment 4).

c. 4-Aminopyridine. —— A mixture of dry triethylamine (15cm^3) and dry pyridine (15cm^3) was distilled (under vacuum in a rigorously dried apparatus)

from molecular sieve (Type 3A) directly onto 4-aminopyridine (1.0g, mp 156-159°; lit.[155] mp 158-159°) and compound 1 (30mg) contained in a Carius tube cooled in liquid air. The apparatus was then sealed from the pump and the materials in the Carius tube were allowed to warm to room temperature in order to de-gas the solution. The mixture was then frozen again in liquid air, and the tube was sealed and placed in an oven at 70° for 19h.

After cooling, the mixture was dissolved in ether ($100cm^3$) and the ethereal solution was washed with ice-cold M aqueous hydrochloric acid ($2x100cm^3$), water ($100cm^3$) and brine ($100cm^3$), and dried. The solvent was evaporated to yield a white solid and tlc (X) showed that this consisted mostly of compound 1, with minor, slower-moving components (Rf's 0.53 and 0.29 with tailing).

The combined aqueous washings were saturated with sodium chloride and extracted with ether, and the ethereal solution was dried and evaporated. Tlc (X) showed that the residue consisted mostly of compound 1.

Experiment 6. Reaction of compound 1 with 3-amino-1,2,4-triazole.

A solution of compound 1 (1.00g) and 3-amino-1,2,4-triazole* (0.55g, ca. 2mol.) in dry

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* 3-amino-1,2,4-triazole (Murphy Chemical Co., Wheathampstead) was kindly supplied by Dr. G.G. Briggs (Rothamsted Experimental Station).

DMF ($50cm^3$) was refluxed gently for 1.5h. After cooling, the mixture was partitioned between chloroform ($100cm^3$) and water ($100cm^3$). The aqueous layer was extracted with a further portion ($100cm^3$) of chloroform and the chloroform solutions were combined, washed with water ($100cm^3$) and dried. Examination by tlc (X, vanillin development) showed the presence of compound 1 (Rf 0.71) and components having Rf's 0.59 (faint), 0.48 (faint), 0.31 and 0.16.

The chloroform was evaporated and some DMF was removed under vacuum. The oily product (2.14g) was eluted ($50cm^3$ fractions) through a column (340x22mm) of silica gel (150g) with ethyl acetate:hexane mixtures of increasing polarity (commencing with a 1:2 mixture). A rather poor separation was achieved and the products were collected in the following portions:-

I; 118mg, Rf's 0.71 and 0.65.

II; 46 mg, Rf's 0.59 and 0.48.

III; 20 mg, Rf's 0.59 (faint), 0.48, 0.31 (faint) and 0.16 (faint).

IV; 133mg, Rf's 0.31 and 0.16 (faint).

V; 509mg, Rf's 0.31 (faint) and 0.16.

Crystallization of fraction I from ether:hexane gave compound 1 (31mg), mp 114-117°, mixed mp 113-115° (lit.[66] mp 115-117°).

The nmr spectrum ($(CD_3)_2CO$) of fraction II was indistinguishable from that of the acyclic carbonate C (Experiments 4a and 4b), and the nmr spectrum ($(CD_3)_2CO$)

of fraction IV was almost identical with that of the acyclic carbonate D (Experiments 4a and 4b). Fraction IV yielded a solid product, mp 220-225°, from ether:hexane.

The nmr spectrum ($CDCl_3$) of fraction V was indistinguishable from that of an authentic specimen of methyl 4,6-O-benzylidene-α-D-glucopyranoside. Crystals (103mg), mp 160-162° (lit.[156] mp 163-164°), were obtained from ether:hexane and the identity of the compound was confirmed by comparison of its ir spectrum with that of an authentic sample.

The aqueous layer (and washings) of the reaction mixture was extracted continuously with chloroform for 60h, and the chloroform solution was dried and evaporated to give an oil from which a small amount of solid (23mg) was obtained by precipitation with hexane. This material showed a transition at 230° and charred a little at ca. 335° (Found: C, 17.9; H, 2.4; N, 16.4%). The hexane was then evaporated from the solution and some residual DMF was removed under vacuum to give a white solid Z (178mg) (Found: C, 38.9; H, 4.7; N, 38.9%).

The mass spectrum of Z showed a top mass peak of m/e 279 (unidentified) and, inter alia, peaks at m/e 110, 105, 95, 83 and 28 (see Fig. XVI).

Experiment 7a. Reaction of compound 1 with lithium anilide.

An apparatus was assembled which was similar to that used by Westwood[157]. It consisted of two

reaction chambers one above the other, separated by a tap with facilities for keeping both chambers flushed with dry nitrogen gas throughout the experiment. The lower chamber was charged with a solution of compound 1 (500 mg) in dry ether ($100cm^3$) which was cooled to the temperature of a dry-ice/acetone bath. The upper chamber was charged with a solution of pure, dry aniline (1.0g, prepared as in Experiment 3a) in dry ether ($40cm^3$). A 0.76$\underline{M}$ ethereal solution of butyl-lithium[152] ($2.5cm^3$, $\underline{ca}$. 1.2mol w.r.t. compound 1) was diluted with dry ether ($50\ cm^3$) and added slowly, with stirring, to the contents of the upper chamber. The resulting, slightly cloudy solution was stirred for 0.5h at room temperature and then run into the cooled lower chamber during 0.5h. The final mixture was stirred for 1h at the dry-ice/acetone temperature before being allowed to warm to room temperature. The ethereal solution was washed with ice-cold $\underline{M}$ aqueous hydrochloric acid ($3x100cm^3$), dried and evaporated to yield an oil (0.35g). Tlc (X) showed the presence of at least four components [Rf's 0.58, 0.45, 0.34 (green on vanillin development), and 0.10].

Chromatography on a column (610x20mm) of silica gel (80g), using ethyl acetate:hexane (1:1) ($50cm^3$ fractions), yielded only one homogeneous [Rf 0.34 (green in vanillin)] component. This material (56mg) was recrystallized from ethanol:water to yield a white product (28mg), mp 226-231°, the nmr and ir spectra of

which were identical with those of the 3-(N-phenylcarbamate) B6 (Experiments 3a and 3b). Further crystallizations from ethanol:water yielded white crystals (9mg), mp 245° (compound B6, Experiment 3b, had mp 246-248°).

Experiment 7b. Reaction of compound 1 with lithium N-methylanilide.

The apparatus and method employed were identical with those of Emperiment 7a. Lithium N-methylanilide was prepared from butyl-lithium (1.2 mol w.r.t. compound 1) and pure, dry N-methylaniline (prepared as in Experiment 5b).

The ethereal solution (170cm^3) containing the products (derived from 500mg of compound 1) was washed with M aqueous hydrochloric acid (3x150cm^3), dried and evaporated. The oily residue (310mg) showed at least six components on tlc (X; Rf's 0.75, 0.66, 0.60, 0.52, 0.38, and 0.16). Although chromatography on a column of silica gel yielded a number of homogeneous fractions, there was insufficient material for full identification.

Experiment 8a. Hydrogenolysis of compound 1.

A solution of compound 1 (200mg) in distilled ethanol (50cm^3) was shaken with palladium catalyst (5% on charcoal) (200mg) under hydrogen for 4h. The solution was filtered through paper and then through

a pad of Celite and evaporated to give a colourless syrup (141mg, 99%) which showed a single spot on tlc (Rf 0.10, X; 0.46, ethyl acetate). The compound (F) had $[\alpha]_D^{18}$+106° (c0.9, C_2H_5OH) (Found: C, 43.5; H, 5.6. $C_8H_{12}O_7$ requires C, 43.6; H, 5.5%).

Nmr data (pyridine-$\underline{d}_5$): δ 5.36 (1-proton doublet, $J_{1,2}$=2.9Hz, H-1), 5.19 (1-proton multiplet, $J_{2,3}$= 12.0, $J_{3,4}$= 9.2Hz, H-3), 4.65 (1-proton apparent triplet, $J_{3,4}$= $J_{4,5}$ = 9.2Hz, H-4), 4.61 (1-proton multiplet, $J_{1,2}$= 2.9, $J_{2,3}$= 12.0Hz, H-2), 4.31 (2-proton doublet, $J_{5,6}$= 3.4Hz, H-6's), 3.96 (1-proton pair of triplets, $J_{4,5}$= 9.2, $J_{5,6}$= 3.4Hz, H-5), 3.44 (3-proton singlet, methoxyl).

The nmr spectrum of compound 1 (pyridine-$\underline{d}_5$) gave the following data: δ 5.82 (1-proton singlet, benzylidene-H), 5.36 (1-proton doublet, $J_{1,2}$= 2.9Hz, H-1), 5.14 (1-proton apparent triplet, $J_{2,3}+J_{3,4}$= 21.4Hz, H-3), 4.66 (1-proton multiplet, $J_{1,2}$= 2.9, $J_{2,3}$= 12.0Hz, H-2) (cf. ref. 70).

The ir spectrum of compound F showed bands at 1800 (νC=O, carbonate) and 3400cm^{-1} (νO-H, broad).

Experiment 8b. Hydrogenolysis of methyl 4,6-O-benzylidene-α-D-glucopyranoside bis-(N-phenylcarbamate).

A solution of the title compound (500mg) in methanol (80cm^3) was shaken with palladium catalyst

(5% on charcoal) for 8h under hydrogen. The solution was then filtered and evaporated to yield a glass (413mg, 100%) which showed a single component (Rf 0.31) on tlc (X). The glass was crystallized from ethyl acetate:light petroleum (100-120°) to give methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (G; 172mg), mp 148-153° (lit.[154] mp 151-153°), $[\alpha]_D^{20}$+57.3° (c1.0, C_2H_5OH) (lit.[154] $[\alpha]_D^{25}$+55° in pyridine) (Found: C, 58.1; H, 5.7; N, 6.4. $C_{21}H_{28}N_2O_8$ calc: C, 58.3; H, 5.6; N, 6.5%).

Nmr data ($CDCl_3$): δ 7.4-6.9 (10-proton multiplet, phenyls), 5.40 (1-proton apparent triplet, $J_{2,3} = J_{3,4}$ = 11Hz, H-3), 5.0 (2-proton multiplet, H-1 and H-2 superimposed), 3.39 (3-proton singlet, methoxyl).

The ir spectrum showed bands at 1530 (δN-H), 1600 (C=C multiple bond stretching) and 1710cm^{-1} (ν C=O).

SECTION III

Preparations, reactions and analysis of a carbonate of starch.

Experiment 9. Preparation of a starch carbonate.

a. Preparation of the starch[97]. —— Wheat starch (R.H.M., low protein; 20g) was stirred in distilled water (600 cm^3) on a steam bath until a gel was formed, and the treatment was continued for a further 0.5h. The gel was then poured into vigorously

stirred ethanol (ca. 4l) and the agitation was continued for at least 1h. The starch was collected by filtration using gentle suction from a water pump, stirred with more ethanol ($300cm^3$), filtered off, washed with a little ether and immediately placed in a vacuum desiccator over calcium chloride (recovery, ca. 100%). A sample for analysis was dried to constant weight at 40^o under vacuum with phosphoric oxide in a pistol drier (Found: C, 43.2; H, 6.1; N, 0. $(C_6H_{10}O_5)_4 . H_2O$ calc: C, 43.4; H, 6.4%).

b. Reaction of ethyl chloroformate with starch. — Pretreated wheat starch (1.0g), prepared as described above, was stirred vigorously with dry Me_2SO ($70cm^3$) at room temperature. Dry (Na) 1,4-dioxan ($10cm^3$) and pure triethylamine ($10cm^3$) were added successively and after stirring for 1h, ethyl chloroformate ($4.0cm^3$) was added in one batch. The mixture was stirred for 5min, before being poured into dry (Na) ether ($300cm^3$) and agitated in a blender. The solid was allowed to settle, the supernatant was decanted, further dry ether ($300cm^3$) was added and the material was again subjected to vigorous blending. After collection on a filter, the solid was washed with ethanol ($2x200cm^3$) and ether ($100cm^3$) and dried in the vacuum oven at 40^o. The product (SCI; 1.2g) was a granular white material (Found: C, 45.6; H, 7.3; N, 3.6%).

A portion of SCI (62.8mg) was shaken with dry ether ($20cm^3$) for 2h, filtered off and dried under

vacuum (recovery = 60.6mg; SCIA) (Found: C, 45.2; H, 7.3; N, 1.3%). An aqueous extract of the ethereal washings turned litmus paper faintly blue.

Another portion of SCI (655mg) was dialysed against running tap water for 24h and against distilled water for 12h, and then freeze-dried (recovery= 520mg; SCIB) (Found: C, 43.1; H, 5.3; N, 0%).

The significance of the analytical data is discussed on page28.

c. Ir spectra.—— Ir spectra were recorded from Nujol and hexachlorobutadiene (HCB) suspensions and in some cases from salt (KBr) discs. Product SCI showed distinctive bands at 1750 (acyclic carbonate) and 1810cm^{-1} (cyclic carbonate), an unassigned band at 1280cm^{-1}, and bands at 810, 850 and 2300-2800cm^{-1} which were attributed to triethylamine hydrochloride by reference to the spectrum of an authentic specimen. The spectrum of product SCIA was almost identical with that of product SCI, but product SCIB showed no absorptions attributable to triethylamine hydrochloride and the ratio of cyclic (1810cm^{-1}) to acyclic carbonate (1750cm^{-1}) absorptions was lower than for product SCI (see Fig.XVII).

The ir spectra (HCB) of products SCI and SCIB and the pretreated starch showed no significant differences in the ranges 1300-1500 and 2500-3500cm^{-1}.

Experiment 10. Reaction of amines with starch carbonate.

a. Piperidine. —— Piperidine (5.0cm^3) was

added to a warmed suspension of starch carbonate (SCI; 0.20g) in Me_2SO ($15cm^3$) and the mixture was shaken vigorously. The suspension was maintained at room temperature for 1h and then poured into ether ($150cm^3$). The solid was filtered off, washed with ethanol ($100cm^3$) and ether ($50cm^3$), and dried in a vacuum desiccator to give product SCII (0.18g) (Found: C, 44.5; H, 5.8; N, 2.1%). The ir spectrum showed distinctive bands at 1680 (νC=O, carbamate) and 1750cm^{-1} (ν C=O, acyclic carbonate).

b. Cyclohexylamine. —— Cyclohexylamine ($5cm^3$) was added to a warmed suspension of starch carbonate (SCI; 0.20g) in Me_2SO ($15cm^3$), and the mixture was processed as described in a. to give product SCIII (0.18g) (Found: C, 43.5; H, 5.6; N, 0.7%). The ir spectrum showed a band at 1640-1770cm^{-1} (νC=O, carbamate and acyclic carbonate).

c. Refluxing cyclohexylamine. —— A portion (800mg) of starch carbonate (SCI) was heated for 5min with refluxing cyclohexylamine ($15cm^3$). The cooled, faintly brown suspension was poured into ethanol ($50cm^3$) and, after 3h, the ethanolic suspension was stirred with ether ($300cm^3$). A precipitate (SCIVA; 269mg) (Found: C, 49.0; H, 7.2; N, 3.0%) was filtered off and a second crop (SCIVB; 192mg) (Found: C, 49.1; H, 6.9; N, 3.0%) was collected from the solution after 24h. The filtrate was then evaporated to low volume, and stirring with ether ($100cm^3$) produced a further

precipitate (SCIVC; 265mg) (Found: C, 51.9; H, 8.5; N, 5.9%).

The ir spectrum (Nujol) of product SCIVA showed bands at 1530 (δN-H) and 1650-1770cm^{-1} (νC=O, carbamate and acyclic carbonate) (see Fig.XVII). Products SCIVB and SCIVC showed similar spectra. The ir spectrum of product SCIVA measured from a hexachlorobutadiene suspension showed bands at 2860 and 2940cm^{-1} (νC-H), and 1250-1500cm^{-1} (δC-H).

Experiment 11. Hydrolyses of carbonates.

a. Barium hydroxide/sulphuric acid. —— Samples of starch, starch carbonate and methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1) (ca. 120mg) were dried to constant weight in a pistol drier at 40° over phosphoric oxide. Each sample was placed in a two-necked flask, which had been flushed well with nitrogen gas, together with an excess of 20m$\underline{\underline{M}}$ barium hydroxide (25cm^3). The mixture was heated on a steam bath for 1h under a stream of nitrogen, phenolphthalein (1 drop) and saturated barium chloride[158] (10cm^3) were added and the remaining hydroxide was titrated with 10m$\underline{\underline{M}}$ sulphuric acid.

b. Barium hydroxide/hydrochloric acid. —— The products were treated as in Experiment 11a except that 12m$\underline{\underline{M}}$ hydrochloric acid was used as titrant.

Each titration result from Experiments 11a, 11b and 11c was used to calculate a value for the moles (M) of carbonate produced per gram of material

Table I. Results of hydrolyses of carbonates (Experiments 11a, 11b and11c).

MATERIAL.	METHOD. (Exp't 11)	MEAN VALUE OF M FOR EACH METHOD $x10^3$.	%age OF THEOR-ETICAL CONSUMED.	OVERALL MEAN OF M $x10^3$.	DS OF CARBONATE.
methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-carbonate (1).	a.	3.25*	100		(1.0)
	b.	3.17	98		
Pretreated starch.	a.	0.07		0.09	0
	b.	0.11			
Starch carbonate SCI.	a.	3.28		3.20	0.52
	b.	3.08*			
	c.	3.02*			

* single values.

taken. The values of M for compound 1 were used to calculate the percentage of the available carbonate groups consumed, and the mean value of M for the starch carbonate was used to calculate the degree of substitution (DS) of carbonate groups per anhydroglucose unit assuming that all the acyclic carbonate was present as bis(carbohydrate) carbonate (see Table I).

c. Sodium hydroxide/hydrochloric acid. —— Starch carbonate (SCI; 152mg) was treated with excess 10m$\underline{M}$ sodium hydroxide under conditions identical with those of Experiment 11a except that hydrolysis was continued for 1.5h. The excess hydroxide was titrated with 8m$\underline{M}$ hydrochloric acid using phenolphthalein as the indicator (see Table I), and the titrated mixture was dialysed against running tap water for 30h, against frequently changed distilled water for 12h and freeze-dried. The product (SCIC; 104mg) (Found: C, 40.3; H, 5.4; N, 0%) showed a small acyclic carbonate absorption ($1750cm^{-1}$) in the ir spectrum.

d. Treatment of starch carbamate with sodium hydroxide.—— A portion (144mg) of the starch carbamate SCIVA was treated with 10m$\underline{M}$ sodium hydroxide under the conditions of Experiment 11c. The ir spectrum of the product (SCIVD; 112mg) (Found: C, 44.5; H, 5.7; N, 1.7%) obtained after dialysis and freeze-drying was substantially the same as that of product SCIVA. The nitrogen analysis of product SCIVD corresponds to a degree of substitution (DS) of $\underline{N}$-cyclohexylcarbamate of 0.2.

SECTION IV.

Preparation and some reactions of N-methyl-N-phenylcarbamates.

Experiment 12. Benzyl N-methyl-N-phenylcarbamate.

N-Methyl-N-phenylcarbamoyl chloride (2; mp 86-88°, prepared by the method of Weygand and Mitgau[114], 0.892g), benzyl alcohol (1.140g, 2mol) and dry pyridine (25cm^3) were heated together under reflux for 17h, and the resulting mixture was cooled and diluted with chloroform (150cm^3). This solution was extracted with water (2x100cm^3), ice-cold M aqueous hydrochloric acid (150cm^3) and water (100cm^3), washed with saturated aqueous sodium chloride (100cm^3) and dried. The solvent was evaporated and the brown syrupy residue was extracted with boiling light petroleum (80-100°; 3x50cm^3). The combined extracts were evaporated to yield a syrup (1.423g).

The product was chromatographed on a column (180x25mm) of silica gel (40g) using a benzene:ether (9:1) solvent mixture (30cm^3 fractions). A major fraction (615mg) was homogeneous (Rf 0.74) on examination by tlc (Y). Distillation (152°/0.5mmHg)* yielded benzyl N-methyl-N-phenylcarbamate as a faintly green syrup (477mg, 38%) (Found: C, 74.8; H, 6.3; N, 5.9. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%).

Nmr data ($CDCl_3$): δ 7.37 (10-proton multiplet, phenyl groups), 5.22 (2-proton singlet, -C$\underline{H}_2$-), 3.36

* The compound prepared by the action of benzyl chloroformate on N-methylaniline had bp 171°/1.5mmHg[159].

(3-proton singlet, N-C$\underline{H}_3$). The ir spectrum showed bands at 1600 (νC=C) and 1710cm^{-1} (νC=O), and the compound showed λ_{max} (hexane) 255nm (ε=8460).

Experiment 13a. 2,2-Dimethyl-4-(N-methyl-N-phenyl-carbamoyl)oxymethyl-1,3-dioxolan.

Sodium hydride (50% dispersion in oil; 0.301g, 1.4mol) was washed with ether (2x100cm^3), and the ethereal washings were decanted. A solution of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolan[160] (0.576g, 1.0mol) in dry ether (100cm^3) was stirred with the washed sodium hydride for 1.5h, and N-methyl-N-phenylcarbamoyl chloride (2; 0.735g, 1mol) was then added. After the solution had been maintained at room temperature for 1.5h, it was refluxed for 2h. A little ethanol was added to the cooled solution to destroy any excess sodium hydride, and the ethereal solution was then extracted with water (3x50cm^3), dried and evaporated to yield an oily product (0.847g). Examination by tlc (Y) showed the presence of three components [Rf's 0.82 (compound 2), 0.71, and 0.26]. Chromatography on a column (520x20mm) of silica gel (80g), with elution (50cm^3 fractions) by ethyl acetate: hexane mixtures of increasing polarity (commencing with 1:2), yielded two major fractions.

The first fraction (Rf 0.82) was a white solid (113mg) which was crystallized from ethanol to give compound 2, mp 85-87° and mixed mp 85-88° (compound 2

had mp 86-88°). The ir spectrum was identical with that of compound 2.

The syrupy second fraction (611mg, 53%), which was homogeneous on tlc (Y; Rf 0.26), was distilled (128°/0.4-0.5mmHg) to yield the title compound as a clear syrup (453mg) (Found: C, 63.8; H, 7.4; N, 5.5. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%).

Nmr data ($CDCl_3$): δ 7.50-7.25 (5-proton multiplet, phenyl), 3.32 (3-proton singlet, N-C$\underline{H}_3$), 1.33 (6-proton singlet, C-C$\underline{H}_3$). The ir spectrum showed bands at 1600 (ν C=C) and 1710cm^{-1} (νC=O), and the compound had λ_{max} (hexane) 235nm (ϵ=8360).

<u>Experiment 13b.</u> 5-(<u>N</u>-Methyl-<u>N</u>-phenylcarbamoyl)oxy-1,3-dioxan.

1,3-Dioxan-5-ol was prepared by the action of a catalytic amount of sodium methoxide in methanol on 5-benzoyloxy-1,3-dioxan and the product was distilled (44-45°/0.5mmHg)[161,162].

Sodium hydride (50% dispersion; 0.441g, 1.1mol) was washed with ether as in Experiment 14a and stirred with a solution of 1,3-dioxan-5-ol (0.721g, 1.0mol) in ether (60cm^3) for 2h. <u>N</u>-Methyl-<u>N</u>-phenylcarbamoyl chloride (2; 1.160g, 0.85mol) was added and the resulting mixture was stored at room temperature overnight and then maintained at reflux temperature for 5h. Excess sodium hydride was destroyed with a little ethanol, the solution was diluted with ether (50cm^3), and washed, dried and

evaporated as in Experiment 14a. The syrupy product (1.443g) was distilled (146-148°/0.8-1.0mmHg) in two portions to give the title compound as a syrup (0.952g, 59% w.r.t. compound 2) (Found: C, 60.8; H, 6.3; N, 5.8. $C_{12}H_{15}NO_4$ requires C, 60.8; H, 6.4; N, 5.9%).

Nmr data ($CDCl_3$): δ 7.5-7.3 (5-proton multiplet, phenyl), 4.86 (2-proton singlet, H-2's), 4.72 (1-proton multiplet, H-5), 3.98 (4-proton AB(X) octet, $J_{4,4'}$=12.0, $J_{4,5}$=3.4, $J_{4',5}$=4.5Hz, H-4's and H-6's), 3.37 (3-proton singlet, N-CH_3). The ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O), and the compound had λ_{max} (hexane) 235nm (ε=9120).

Experiment 13c. cis-5-(N-Methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan.

cis-2-Phenyl-1,3-dioxan-5-ol (mp 82-83°, prepared by a modification of the method of Dobinson[163], 10.0g) was treated with washed sodium hydride (50% dispersion; 3.20g, 1.2mol) in refluxing ether (500cm^3) for 0.5h. N-Methyl-N-phenylcarbamoylchloride (10.3g, 1.1mol) was then added, and the resulting solution was maintained at reflux temperature for 2.3h. After cooling, a few drops of ethanol were added and after the evolution of hydrogen had ceased the ethereal solution was extracted with water (3x200cm^3), the combined aqueous layers were washed with ether (100cm^3), and the combined ethereal solutions were dried, filtered and evaporated. Crystallization of the resulting

material from ethanol yielded two products.

Recrystallization of the first crop (15.57g, 89.5%), mp 108-111°, from ethanol gave the title compound (10.57g) as white crystals, mp 110-111° (Found: C,68.8; H, 6.3; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%). Nmr data ($CDCl_3$): δ 7.56-7.27 (10-proton multiplet, phenyls), 5.54 (1-proton singlet, H-2), 4.69 (1-proton multiplet, H-5), 4.23 (4-proton AB quartet, $J_{4,4'}$=13Hz, H-4's and H-6's), 3.39 (3-proton singlet, N-CH_3). The ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O). The compound had λ_{max} (C_2H_5OH) 235nm (ε=7450), and gave a top mass peak of m/e 312 (M^+-1).

Recrystallization of the second crop (132mg, 0.8%), mp 148-149°, from ethanol gave trans-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan (67mg), mp 151-152° (Found: C, 69.3: H, 6.4; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%). Nmr data ($CDCl_3$): δ 7.51-7.15 (10-proton multiplet, phenyls), 5.40 (1-proton singlet, H-2). 5.01 (1-proton multiplet, $J_{4,5}$=5.2Hz, H-5), 4.41 (2-proton apparent quartet, $J_{4,5}$=5.2, $J_{4,4'}$=10.3Hz, H-4' and H-6'), 3.62 (2-proton apparent triplet, $J_{4,4'}=J_{4',5}$= 10.3Hz, H-4' and H-6'), 3.32 (3-proton singlet, N-CH_3). The ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O), and the compound had λ_{max} (C_2H_5OH) 229nm (ε=7740).

Experiment 13d. 1,2:3,4-Di-O-isopropylidene-α-D-galacto-pyranose 6-(N-methyl-N-phenylcarbamate).

A solution of 1,2:3,4-di-O-isopropylidene-α-

D-galactopyranose (1.182g) in dry ether ($100cm^3$) was refluxed with washed sodium hydride (50% dispersion; 0.262g, 1mol) for 1h. N-Methyl-N-phenylcarbamoyl chloride (2; 772mg, 1.0mol) was then added and the solution was refluxed for a further 12h. The cooled solution was worked up in a similar manner to that of Experiment 13a to give a syrup (1.544g) from which crystals formed during a week in the refrigerator. The crystals were filtered off, washed with ethanol ($2x5cm^3$) and then recrystallized from ethanol to give the title compound as fine white crystals (375mg, 21%), mp 109-110°, $[\alpha]_D^{19}$-52.4° (c1.3, $CHCl_3$) (Found: C, 61.0; H, 6.9; N, 3.4. $C_{20}H_{27}NO_7$ requires C, 61.1; H, 6.9; N, 3.6%).

Nmr data ($CDCl_3$): δ 7.41-7.28 (5-proton multiplet, phenyl), 5.57 (1-proton doublet, $J_{1,2}$=5.1Hz, H-1), 4.62 (1-proton apparent quartet, $J_{2,3}$=7.7, $J_{3,4}$=2.6Hz, H-3), 3.32 (3-proton singlet, N-CH_3), 1.49 and 1.45 (3-proton singlets,-CH_3), 1.34 (6-proton singlet,-CH_3's). The ir spectrum showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O). The compound had λ_{max} (hexane) 235nm (ε=8460) and gave a top mass peak of m/e 393 (M^+).

A second crop of crystals (312mg), mp 106-109°, was collected from ethanol and examination of the mother liquors by tlc (Y) showed the presence of compound 2 (Rf 0.82), the carbamate (Rf 0.37), the starting diacetal (Rf 0.15) and an unidentified material (Rf 0.74). Isolation of the product was completed by chromatography of the

mother liquors on a column (280x20mm) of silica gel (35g) using benzene:ether (9:1) as eluant. The carbamate was obtained from ethanol as crystals (397mg, total yield = 60.5%), mp 108-110°.

Experiment 13e. 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(N-methyl-N-phenylcarbamate).

A solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1.016g) in ether ($100cm^3$) was treated with washed sodium hydride (50% dispersion; 0.237g, 1.3mol) at room temperature for 6h. A solution of N-methyl-N-phenylcarbamoyl chloride (0.662g, 1.0mol) in dry ether ($100cm^3$) was added and the resulting mixture was refluxed for 6h and then worked up as in the previous experiments to yield a syrup (1.384g). Trituration with hexane gave a solid material (1.002g) which on crystallization from ethanol gave the title compound (622mg, 30%), mp 115-116°, $[\alpha]_D^{19}$ -52.5° (c 1.0, $CHCl_3$) (Found: C, 60.7; H, 6.6; N, 3.6. $C_{20}H_{27}NO_7$ requires C, 61.1; H, 6.9; N, 3.6%).

Nmr data ($CDCl_3$): δ 7.55-7.18 (5-proton multiplet, phenyl), 5.81 (1-proton doublet, $J_{1,2}$=3.5Hz, H-1), 5.16 (1-proton doublet, $J_{3,4}$=2.9Hz, H-3), 4.66 (1-proton doublet, $J_{1,2}$=3.5Hz, H-2), 3.32 (3-proton singlet, N-CH_3), 1.49 and 1.42 (3-proton singlets, -CH_3), 1.32 (6-proton singlet, -CH_3's). The ir spectrum showed bands at 1600 (νC=C) and 1715cm^{-1} (νC=O). The compound had λ_{max} (C_2H_5OH) 228nm (ε=7250), and gave a top mass peak of m/e 393 (M^+).

Experiment 14. Carbamoylation of cis-2-phenyl-1,3-dioxan-5-ol using sodium hydroxide.

A solution of sodium hydroxide (25g) in water ($25cm^3$) was heated to boiling with cis-2-phenyl-1,3-dioxan-5-ol (240mg). N-methyl-N-phenylcarbamoyl chloride (240mg, 1.1mol) was added, the mixture was maintained at reflux for 15min, cooled and then extracted with chloroform ($2x30cm^3$). The extracts were combined and the organic solution was washed with water ($2x30cm^3$), dried and evaporated. The residue (407mg) was applied to a column (240x20mm) of silica gel (30g) and elution ($10cm^3$ fractions) was effected with benzene:ether (9:1) to give the following fractions:-

I; 71mg, Rf (Y) 0.72 (N-methylaniline).

II; 184mg, Rf's 0.72 and 0.38.

III; 64mg, Rf's 0.72 and 0.31 (1,3-dimethyl-1,3-diphenylurea[164]).

IV; 5mg, Rf's 0.72 and 0.12 (cis-2-phenyl-1,3-dioxan-5-ol).

Fraction II was crystallized from ethanol to give cis-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan (85mg, 19%), mp 109-111°, mixed mp 109-111° (the cis-carbamate in Experiment 13c had mp 110-111°). The ir spectrum was indistinguishable from that of the cis-carbamate in Experiment 13c.

Experiment 15a. Hydrogenolysis of cis-5-(N-methyl-N-phenylcarbamoyl)oxy-2-phenyl-1,3-dioxan.

A solution of the title compound (Experiment 13c; 5.00g) in ethanol ($250cm^3$) was shaken with palladium

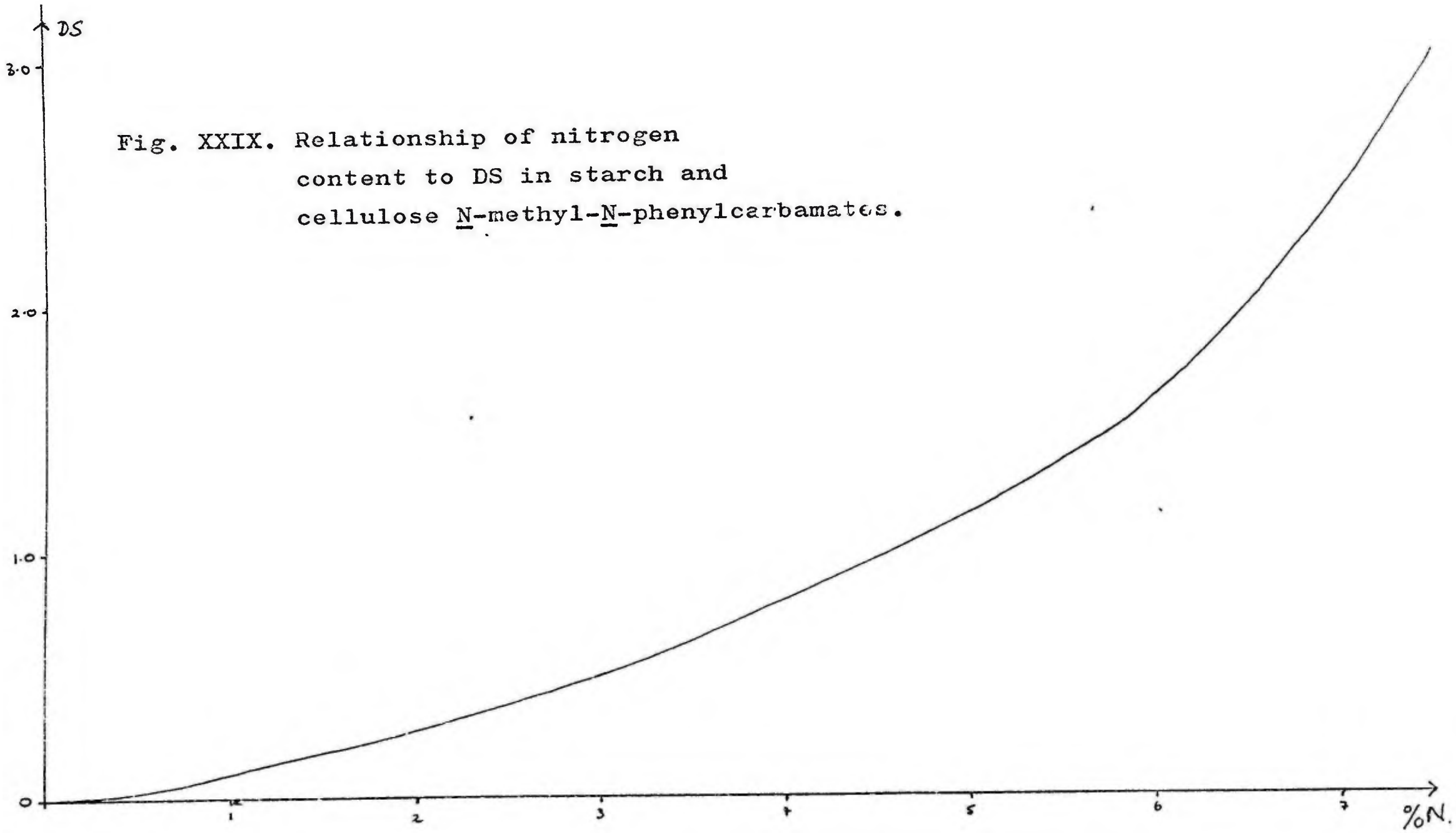
catalyst (5% on charcoal; 0.50g) under hydrogen for 4h. The mixture was then filtered through Celite and the solvent was evaporated to give a syrup which yielded pale-green crystals (3.234g), mp 44-50°, from chloroform:hexane. Recrystallization from ether:hexane gave glycerol 2-(N-methyl-N-phenylcarbamate) (2.214g, 61.5%), mp 50-52° (Found: C, 58.9; H, 6.9; N, 6.3. $C_{11}H_{15}NO_4$ requires C, 58.7; H, 6.7; N, 6.2%). Further crops were collected which had depressed melting points.

Nmr data ($CDCl_3$): δ 7.48-7.25 (5-proton multiplet, phenyl), 4.84 (1-proton multiplet, H-2), 3.75 (4-proton doublet, $-CH_2-O$), 3.33 (3-proton singlet, $N-CH_3$), 2.66 (2-proton multiplet, O-H's). The ir spectrum showed bands at 1600 (νC=C), 1700 (ν C=O) and 3340cm^{-1} (νO-H), and the compound had λ_{max}(C_2H_5OH) 232nm (ϵ=7320).

Experiment 15b. Acetylation of glycerol 2-(N-methyl-N-phenylcarbamate).

The title compound (200mg) was treated with refluxing pyridine (2.0cm^3) and acetic anhydride (0.7cm^3) for 4h. The mixture was then left at room temperature overnight, diluted with ethanol (100cm^3), left at room temperature for 1h, and evaporated. A solution of the brown syrupy residue in chloroform (50cm^3) was extracted with M aqueous hydrochloric acid (50cm^3) and water (50cm^3), dried and evaporated. Chromatography of the resulting syrup (427mg) on a column (110x20mm) of silca gel (15g)

Fig. XXIX. Relationship of nitrogen content to DS in starch and cellulose N-methyl-N-phenylcarbamates.



using benzene:ether (9:1) as the eluant gave as a homogeneous (tlc, Y; Rf 0.38) syrup 1,3-di-O-acetylglycerol 2-(N-methyl-N-phenylcarbamate) (266mg, 97%) (Found: C,58.3; H, 6.3; N, 4.6. $C_{15}H_{19}NO_6$ requires C, 58.3; H, 6.2; N, 4.5%).

Nmr data ($CDCl_3$): δ 7.48-7.17(5-proton multiplet, phenyl), 5.18 (1-proton multiplet, H-2), 4.23 (4-proton AB(X) octet, $J_{1,1'}=12.0$, $J_{1,2}=4.5$, $J_{1',2}=5.7$Hz, H-1's and H-3's), 3.31 (3-proton singlet, N-CH_3), 2.02 (6-proton singlet, acetyls). The ir spectrum showed bands at 1600 (νC=C) and 1710cm^{-1} (νC=O).

Distillation (160-170°/0.1mmHg) gave the product (166mg) with an identical ir spectrum. The compound had λ_{max} (cyclohexane) 234nm (ε=8030).

SECTION V.

Preparations of N-methyl-N-phenylcarbamoyl derivatives of starch and cellulose.

Experiment 16. Carbamoylation of starch in pyridine.

Dry, pretreated starch (prepared as in Experiment 9a) (150mg) was refluxed with dry pyridine (10cm^3) for 1.5h[137]. N-Methyl-N-phenylcarbamoyl chloride (395mg) was added to the gelatinous material, and the mixture was refluxed for 4h. After cooling the product was dialysed against tap water for 48h, against distilled water for 4h and freeze-dried to yield a yellow solid (MPI; 266mg, theory for DS of 1.0 =273mg) (Found: C, 56.1; H, 5.5; N, 5.8%; see Fig.XXIX). The ir spectrum

of the product showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O).

A portion of MPI (221mg) was extracted continuously with chloroform for 5h. Most of the material (181mg) was insoluble (Found: C, 53.0; H, 9.1; N, 8.7%). The chloroform solution was evaporated to give a transparent film (36mg). The ir spectra of both products were indistinguishable from that of product MPI, and an nmr spectrum ($CDCl_3$) of the extracted material showed, inter alia, absorptions at δ7.0 (phenyl) and 3.20 (N-C$\underline{H}_3$).

Experiment 17. Carbamoylation of 'alkali cellulose'.

a. In benzene:dioxan. —— Alkali cellulose* (20g; NaOH, 16%; fibrous cellulose, 33%) was stirred with a refluxing solution of N-methyl-N-phenylcarbamoyl chloride (2; 5.0g) in a mixture of benzene (200cm^3) and dioxan (200cm^3) for 1h. The fibrous material was filtered off, macerated for a few minutes with ice-cold M aqueous hydrochloric acid (300cm^3), filtered off, washed with ethanol and ether, and dried. The ir spectrum of the product (6.1g) showed no new absorptions (Found: C, 43.8; H, 6.2; N, 0%). Examination (tlc; Y) of the residue remaining on evaporation of the reaction solution showed the presence of 1,3-dimethyl-1,3-diphenylurea[164] and compound 2.

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* Kindly supplied by Courtaulds Ltd.

b. Without a solvent. —— Alkali cellulose (5.0g; as in Experiment 18a) was mixed with compound 2 (5.0g) and benzene ($50cm^3$). The benzene was removed slowly on the rotary evaporator and the remaining mixture was heated at 100^o for 0.5h on an oil bath, cooled, steeped in ethanol ($100cm^3$) for 0.5h, filtered off and then macerated in cold M aqueous hydrochloric acid ($300cm^3$). The product was collected on a filter, washed with water ($2x100cm^3$), ethanol ($2x100cm^3$) and ether ($2x100cm^3$), and then dried to give a white, fibrous, hydrophobic solid (MPII; 2.21g) (Found: C, 52.6; H, 6.1; N, 3.4%;see Fig,XXIX).The ir spectrum of product MPII showed distinctive bands at 1600 (νC=C) and $1700cm^{-1}$ (νC=O).

Examination (tlc; Y) of the residue (2.75g), obtained by evaporation of the first ethanolic extracts of the product, showed that it contained 1,3-dimethyl-1,3-diphenylurea and compound 2.

A portion (0.570g) of MPII was treated with refluxing ethanol ($120cm^3$) for 2h. The hot solution was filtered and the fibrous cake was washed with ethanol ($100cm^3$) and ether ($100cm^3$), and dried (recovery = 0.530g) (Found; C, 52.0; H, 5.8; N, 3.5%). The ir spectrum was indistinguishable from that of product MPII.

A portion (0.170g) of MPII was treated with refluxing DMF ($80cm^3$) for 14h. The hot solution was filtered and the cellulose derivative was dialysed

against running tap water for 24h and against distilled water for 8h, and freeze-dried (recovery =0.139g) (Found: C, 51.7; H, 5.6; N, 2.9%). The ir spectrum was indistinguishable from that of product MPII.

c. Blank for Experiment 17b. —— Alkali cellulose (5.0g; as in Experiment 17a) was treated as in Experiment 17b except for the absence of compound 2 (recovery =1.64g) (Found: C, 42.3; H, 6.3; N, 0%).

d. Preparation of an alkali cellulose. —— Microgranular cellulose (10.0g; Whatman CC41) (Found: C, 43.1; H, 6.1; N, 0%) was mixed thoroughly with a solution of sodium hydroxide (4.6g) in water ($16.0cm^3$) and the product was stored at -25°.

e. Second preparation of a cellulose carbamate.—— Alkali cellulose (10.0g; Experiment 17d) was treated with compound 2 (2.0g) by a method similar to that of Experiment 17b. A granular product (MPIII; 3.40g) was obtained (Found: C, 46.4; H, 5.8; N, 1.7%; see Fig.XXIX).

A portion (3.159g) of MPIII was extracted continuously with chloroform for 5h. The insoluble material (MPIIIA) was dried (recovery =2.962g) (Found: C, 45.6; H, 6.5; N, 1.5%), and the chloroform extracts were evaporated to yield a transparent film (MPIIIB; 120mg), mp 200-300° (Found; C, 57.3; H, 6.2; N, 6.0%).

The ir spectra of MPIII and MPIIIA were indistinguishable, and MPIII, MPIIIA and MPIIIB each showed strong bands at 1600 (ν C=C) and $1700cm^{-1}$ (ν C=O).

The nmr spectrum ($CDCl_3$) of product MPIIIB showed peaks at δ 7.32 (phenyl) and 3.26 (N-C$\underline{H}_3$).

Experiment 18. Carbamoylation of starch in the presence of sodium hydroxide.

A solution of sodium hydroxide (500mg) in water ($2.0cm^3$) was mixed with pretreated starch (1.100g). The resulting paste was mixed with N-methyl-N-phenyl-carbamoyl chloride (2; 3.600g) and benzene ($50cm^3$). The organic solvent was evaporated slowly at room temperature on a rotary evaporator and the residue was heated for 0.5h on an oil bath at 100°. After cooling, the pasty product was mixed thoroughly with ethanol ($50cm^3$) for 15min, filtered off, washed with ethanol ($2x50cm^3$) and then macerated in suspension in water ($300cm^3$). M Hydrochloric acid was added to the slightly alkaline solution until it remained slightly acidic after repeated maceration. The starch derivative was collected on a sintered glass filter, washed with water ($50cm^3$), ethanol ($50cm^3$) and ether ($2x50cm^3$), and dried to give a white powdery product (MPIV; 1.630g) (Found: C, 58.4; H, 5.7; N, 6.1%; see Fig.XXIX). The combined ethanolic solutions were evaporated to yield a crystalline material (1.242g) consisting (tlc; Y) of compound 2 (Rf 0.82), N-methylaniline (Rf 0.72) and 1,3-dimethyl-1,3-diphenylurea (Rf 0.31).

A portion (0.567g) of MPIV was treated with refluxing ethanol ($150cm^3$) for 2h. The hot solution was

filtered and the starch derivative was washed with ethanol ($2x20cm^3$) and ether ($2x20cm^3$), and dried to give MPIVA (0.469g) (Found: C, 56.0; H, 5.6; N, 5.5%). The combined ethanolic solutions were evaporated and examination of the residue (0.072g) by tlc (Y) showed, inter alia, spots corresponding to compound 2 (Rf 0.82), and 1,3-dimethyl-1,3-diphenylurea (Rf 0.31).

The ir spectra of products MPIV and MPIVA were identical, and showed bands at 1600 (νC=C) and 1700cm^{-1} (νC=O; broad).

Experiment 19. Attempted methanolysis of an N-methyl-N-phenylcarbamoylstarch.

A portion (100mg) of product MPIV (Experiment 18) was treated with a refluxing mixture ($15cm^3$) of concentrated hydrochloric acid ($1cm^3$) and methanol ($100cm^3$) for 27h. p-Toluenesulphonic acid (ca. 50mg) was then added and the heating was continued for 12h, followed by addition of DMF ($1cm^3$) and a final heating for 11h. The remaining solid was filtered off, washed with methanol ($5cm^3$) and ether ($5cm^3$), and dried. The ir spectrum of the undissolved material (60mg) was indistinguishable from that of MPIV.

The combined filtrate and washings were evaporated to dryness and a solution of the residue in pyridine ($10cm^3$) was slowly evaporated to azeotrope any residual water. A small crop of crystals (pyridinium

salts) was collected from a refrigerated solution of the residue in pyridine ($10cm^3$), and the solution was then diluted with pyridine ($5cm^3$) and treated with acetic anhydride ($5cm^3$) for 20h at room temperature. Evaporation gave a thick syrup from which an amorphous solid (15mg) was obtained by refrigeration with ethanol ($10cm^3$). The ir spectrum of this material showed bands at 1600 (νC=C), 1710 (ν C=O, carbamate) and 1750cm^{-1} (ν C=O, acetate), and showed no absorption in the region 3000-4000cm^{-1}.

Examination of the amorphous acetate by tlc suggested that the material was inhomogeneous (X, Rf 0.37-0; Y, Rf 0.18-0), and tlc (Y) of the ethanolic mother liquors showed the presence of at least four components [Rf's 0.22 (corresponds to methyl α-D-glucopyranoside 2,3,4,6-tetra-acetate), 0.18, 0.06 and 0] .

SECTION VI.

Reactions of amino-1,3,5-triazines with carbonyl chloride.

Experiment 20a. Reaction of carbonyl chloride with 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3).

Compound 3 (trietazine*) was recrystallized from acetic acid:water (yield ca. 90%), mp 101-103° (lit.[165] 100-102°, from propanol).

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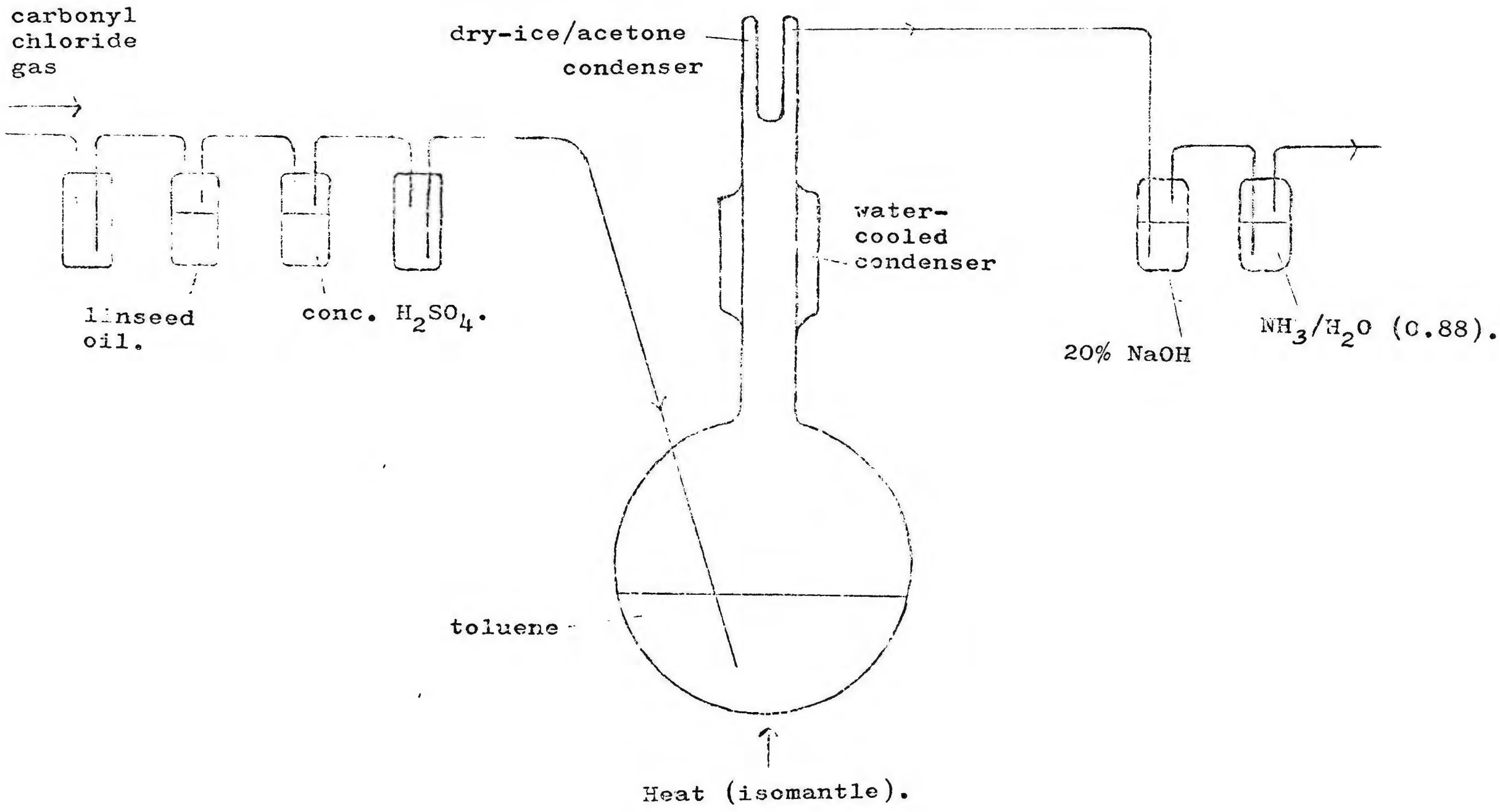
* Trietazine was kindly supplied by Fisons Limited, Agrochemical Division.

Fig.XXX. Schematic diagram of apparatus for Experiments 20 and21.



Carbonyl chloride gas was purified by passage through linseed oil[166] and concentrated sulphuric acid. It was then passed into a solution of compound 3 (5.00g) in refluxing toluene ($200cm^3$) and refluxed from a dry-ice/acetone condenser which was placed above the water-cooled condenser as shown in Fig.XXX. Hydrogen chloride and excess carbonyl chloride were removed from the exhausting gas stream by traps containing sodium hydroxide and ammonia solutions. After 6h the supply of carbonyl chloride was stopped, the reaction mixture was cooled and the reflux condensers were replaced by a distillation apparatus connected to traps to absorb the expelled gases. When all the solvent had been removed the residual syrup was distilled (140-150°/0.3mmHg) to give N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride (4) as a colourless liquid (6.05g, 95%) (Found: C, 41.4; H, 5.4; N, 23.9; Cl, 24.5. $C_{10}H_{15}Cl_2N_5O$ requires C, 41.1; H, 5.2; N, 24.0; Cl, 24.3%).

Nmr data ($CDCl_3$): δ 4.09, 3.66 and 3.62 (each a 2-proton quartet, J=7.2Hz,-$C\underline{H}_2$-), 1.32, 1.23 and 1.21 (each a 3-proton triplet, J=7.2Hz, -$C\underline{H}_3$). The ir spectrum showed bands at 1580 (νC=N) and 1750cm^{-1} (νC=O), and the compound had λ_{max} (cyclohexane) 242nm (ℓ=35,100). The mass spectrum showed a top mass peak at m/e 291 (M^+).

When a solution of the product in dry hexane ($100cm^3$) was stored for some months in a flask sealed

with a serum cap, a small crop of crystals formed. This product (153mg), mp 116-118°, had spectral properties identical with those of 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine hydrochloride (Experiment 20c).

Experiment 20b. Preparation of compound 4 on a larger scale.

A solution of compound 3 (80.0g) in toluene ($500cm^3$) at reflux temperature was treated with carbonyl chloride, as in Experiment 20a, for 7h. An ir spectrum of the syrupy product showed the presence of some compound 3. Distillation yielded two fractions.

The lower-boiling compound (4; 60.7g, 60%) had spectral properties identical with those of compound 4 (Experiment 20a). The product (60.0g) was stored as a solution in dry hexane ($300cm^3$) contained in a flask sealed with a serum cap.

The higher-boiling compound (22.8g) was crystallized from hexane to give 1,3-di(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-1,3-diethylurea (17.79g, 21%), mp 70-72°, as colourless crystals. After recrystallization the product had mp 71-73° (Found: C, 46.9; H, 5.8. $C_{19}H_{30}N_{10}Cl_2O$ requires C, 47.0; H, 6.2%). Nmr data ($CDCl_3$): δ 4.13 (4-proton multiplet, $-C\underline{H}_2-$) 3.56 (8-proton quartet, J=7.0Hz. $-C\underline{H}_2-$), 1.36 (6-proton triplet, J=7.0Hz, $-C\underline{H}_3$), 1.15 (12-proton triplet, J=7.0Hz-$C\underline{H}_3$). The ir spectrum showed bands at 1570 (νC=N) and 1680cm^{-1} (νC=O)

and the compound had λ_{max} (cyclohexane) 241nm (ϵ=43,500). The mass spectrum showed a top mass peak at $^{m}/_{e}$ 483 (M^{+}-1).

Experiment 20c. Preparation of 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine hydrochloride.

Dry hydrogen chloride gas was passed into a solution of compound 3 (1.00g) in dry ether (10.0cm^3). The precipitate which formed initially dissolved after the gas had been passing for ca. 20min. The ethereal solution was concentrated and addition of hexane (5cm^3) caused a precipitate to form slowly. 2-Chloro-4-diethylamino-6-ethylamino-1,3,5-triazine hydrochloride (1.09g, 94%) was filtered off and washed with dry hexane in a dry box; mp 128-131° (Found: C, 40.8; H, 6.2; N, 26.3; Cl, 26.3. $C_9H_{17}N_5Cl_2$ requires C, 40.6; H, 6.4; N, 26.3; Cl, 26.6%).

Nmr data ($CDCl_3$): δ 4.0-3.4 (6-proton multiplet, $-C\underline{H}_2-$), 1.5-1.2 (9-proton multiplet, $-C\underline{H}_3$). The ir spectrum showed bands at 1500-1700cm^{-1} (νC=N and δN-H) and at 2650cm^{-1} (νN-H, broad), and the compound had λ_{max} (C_2H_5OH) 227nm (ϵ=37,600) (compound 3 had ϵ=37,500 at λ_{max} 227nm in C_2H_5OH).

Experiment 21. Reaction of carbonyl chloride with 2-chloro-4,6-bis(ethylamino)-1,3,5-triazine.

The triazine (10.0g) was treated with carbonyl chloride by the method of Experiment 20a. Evaporation of the solvent from the reaction mixture yielded a syrup (13.0g,99%),

a portion (ca. 0.5g) of which was distilled (200-210°/ 0.05mm) before the remainder solidified (product PS).

Overnight, the distillate turned to a solid, mp 50-54° (Found: C, 36.3; H, 4.3, N; 26.7; Cl, 26.7. $C_8H_{11}Cl_2N_2O$ calc: C, 36.4; H, 4.2; N, 26.5; Cl, 26.8%). Nmr data ($CDCl_3$): δ 4.08 (2-proton quartet superimposed on a small multiplet, J=7.0Hz, $-C\underline{H}_2-$), 3.5 (broad-line multiplet, $-C\underline{H}_2-$), 1.26 and 1.19 (each a 3-proton triplet overlying some small signals, J=7.0Hz, $-C\underline{H}_3$). The ir spectrum showed bands in the range 1500-1650cm^{-1} (νC=N) at 1770 (νC=O, carbamoyl chloride) and at 3150 and 3260cm^{-1} (νN-H).

Product PS (Total material recovered = ca. 7.0g) was extracted with chloroform (3x10cm^3) and the combined chloroform solutions were evaporated to give a faintly yellow solid (PSI; 4.28g), mp 90-115° (Found: C, 41.3; H, 5.6; N, 27.1 Cl, 12.3%). The extracted residue (PSII; 2.67g) had mp $>$300° (Found: C, 41.4; H, 4.3; N, 36.1; Cl, 16.2%). The nmr spectra of PSII (pyridine-d_5) andPSI ($CDCl_3$) showed broad peaks at δ 4.3 and 3.6 (methylenes) and 1.3 (methyls). The ir spectra of the products showed broad bands in the region 1500-1800cm^{-1}.

SECTION VII.

Reactions of N-(2-chloro-4-diethylamino-1,3,5-triazin-6-yl)-N-ethylcarbamoyl chloride (4).

Experiment 22a. Reaction with cis-2-phenyl-1,3-dioxan-5-ol using sodium hydride.

Sodium hydride (50% dispersion; 44mg, 1.3mol) was washed with ether, and then mixed with a solution of cis-2-phenyl-1,3-dioxan-5-ol (131mg, 1.0mol) in refluxing ether ($20cm^3$) for 1h. A solution of compound 4 (267mg, 1.3mol) in ether ($5.0cm^3$) was added by means of a syringe, and the mixture was refluxed for 0.5h. After cooling, the organic solution was washed with water ($2x20cm^3$), dried and evaporated. Crystallization of the residue from chloroform:hexane gave 2-chloro-4-diethylamino-6-[N-ethyl-N-(cis-2-phenyl-1,3-dioxan-5-yl)oxycarbonyl]amino-1,3,5-triazine (TRI) as colourless crystals (88mg, 28%), mp 100-101°, (Found: C, 55.4; H, 5.9; N, 16.0; Cl, 8.8. $C_{20}H_{26}ClN_5O_4$ requires C, 55.1; H, 6.0; N, 16.1; Cl, 8.1%). Further crops (18mg), mp 99-101° were collected.

Nmr data ($CDCl_3$): δ 7.60-7.32 (5-proton multiplet, phenyl), 5.56 (1-proton singlet, dioxan H-2), 4.81 (1-proton multiplet, dioxan H-5), 4.31 (4-proton AB quartet, $J_{4,4'}$=13Hz, H-4's and H-6's), 4.09, 3.60 and 3.56 (each a 2-proton quartet, J=6.9Hz, ethyl $-CH_2-$), 1.35, 1.21 and 1.18 (each a 3-proton triplet, J=6.9Hz, $-CH_3$). The ir spectrum showed bands at 1580 (νC=N) and 1710cm^{-1} (νC=O), and the compound had λ_{max} (C_2H_5OH)

238nm (ε=42,600). The mass spectrum showed a top mass peak at $^{m}/_{e}$ 434 (M^{+}-1).

Experiment 22b. Reaction with cis-2-phenyl-1,3-dioxan-5-ol using sodium hydroxide.

Compound 4 (267mg), cis-2-phenyl-1,3-dioxan-5-ol (131mg) and sodium hydroxide (120mg) were reacted together in solution in a mixture of 1,4-dioxan (10cm^3), water (1cm^3) and DMF (ca.0.5cm^3) for 5h at room temperature. The mixture was then partitioned between ether (100cm^3) and water (100cm^3) and the ether layer was washed with water (100cm^3), dried and evaporated. Examination of the residue by tlc (Y) showed the presence of at least four components [Rf's 0.74 (compound 3), 0.3, 0.2 (cis-2-phenyl-1,3-dioxan-5-ol) and 0.1]. Compound TRI (Rf 0.54) was not observed.

Experiment 22c. Reaction with cis-2-phenyl-1,3-dioxan-5-ol using sodium carbonate.

An ethereal solution (200cm^3) of a mixture of cis-2-phenyl-1,3-dioxan-5-ol (3.65g, 1.0mol) and compound 4 (7.40g, 1.25mol) was shaken with anhydrous sodium carbonate (5.0g) for 22h at room temperature, and then maintained at reflux temperature for a total of 26h. The solution was washed with water (2x100cm^3), dried and evaporated to give a syrup (11.05g). Chromatography on a column (600x40mm) of silica gel (300g) using elution (100cm^3 fractions) with benzene:ether

(9:1) gave the following fractions:-

I; 0.84g of a syrup. The ir spectrum and Rf value (Y; 0.85) were identical with those of compound 4.

II; 2.78g of a solid, Rf's (Y) 0.74 and 0.69. Crystallization from ether:hexane gave 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3; 0.59g) followed by TRI (0.25g), mp and mixed mp 101-103° (TRI, Experiment 22a had mp 100-101°).

III; 6.16g of a solid, Rf's 0.69 (faint) and 0.54. Crystallization from ether:hexane gave a product (3.75g, 42.5%), mp 99-101°, having spectral properties and Rf value (0.54) identical with those of TRI (Experiment 22a). A further crystallization gave a product having mp 101-103° and mixed mp 100-101°.

IV; 0.08g, Rf's 0.69, 0.54 and 0.37. This was not examined further.

Experiment 22d. Reaction with cis-2-phenyl-1,3-dioxan-5-ol using pyridine.

A solution of cis-2-phenyl-1,3-dioxan-5-ol (131mg, 1.0mol) and compound 4 (267mg, 1.3mol) in a mixture of dry (Na)1,4-dioxan (5.0cm^3) and dry pyridine (2.0cm^3) was shaken at room temperature for 18h. The two-phase mixture was partitioned between ether (100cm^3) and water (100cm^3), and the ether layer was extracted briefly with $\underline{\underline{M}}$ aqueous hydrochloric acid (2x50cm^3), dried and evaporated. Trituration of the resulting yellow syrup with hexane gave faintly yellow crystals

(59mg), mp 99-101°. An ethereal solution ($20cm^3$) of the product was shaken with silica gel (200mg) for 5min, filtered and evaporated and the residue was crystallized from ether:hexane to give TRI (42mg, 13%), mp 100-101°, mixed mp 98-100° (TRI, Experiment 22a had mp 100-101°). The ir spectrum of the product was identical with that of compound TRI (Experiment 22a).

Experiment 23. Reaction with starch.

a. Pretreating with pyridine.——— Pretreated starch (3.20g, see Experiment 9a) was treated with dry refluxing pyridine ($100cm^3$) for 4h[137]. A solution of compound 4 (3.00g) in hexane ($15cm^3$) was added to the gelatinous suspension, the hexane was evaporated, and the resulting mixture was shaken at room temperature for 3h. The starch derivative was precipitated by pouring the mixture into vigorously stirred ethanol ($400cm^3$). After it had settled overnight the product was filtered off, washed with ether ($2x20cm^3$), ethanol ($2x20cm^3$) and more ether ($3x20cm^3$) and dried. The starch derivative (TRPI; 4.19g) showed absorptions in the range 1500-1650cm^{-1} (νC=N and δN-H) and at 1730cm^{-1} (νC=O).

A portion (3.00g) of this material was extracted continuously with chloroform for 18h, and the insoluble material was dried (recovery = 2.98g) (Found: C, 43.9; H, 6.0; N, 7.8; Cl, 7.0%). It was then dialysed against running tap water for 60h and

against frequently changed distilled water for 24h and freeze-dried (recovery =2.73g) (Found: C, 42.4; H, 5.6; N, 6.8; Cl, 2.2%). The ir spectrum of this product was almost indistinguishable from that of the original precipitated product.

The chloroform solution was evaporated to give a faintly green syrup (32mg), the identity of which could not be established by ir, uv or nmr spectroscopy.

b. Without pyridine pretreatment. —— Dry pretreated starch (200mg) was treated with compound 4 in a mixture of dry 1,4-dioxan ($10cm^3$) and dry pyridine ($1cm^3$) for 18h at room temperature. The polymer was recovered by dialysis and freeze-drying (recovery = 140mg), and the ir spectrum showed no significant absorption in the region $1500-1750cm^{-1}$.

c. In the presence of DMF.—— Experiment 23b was repeated except that the 1,4-dioxan was replaced by DMF ($10cm^3$). The ir spectrum of the dialysed and freeze-dried product showed some weak bands in the region $1500-1750cm^{-1}$.

SECTION VIII.

Reactions of alcohols with 2-chloro-4-diethylamino-6-ethylamino-1,3,5-triazine (3).

Experiment 24a. Reaction with sodium methoxide[167].

A solution of compound 3 (1.30g; mp 100-102°) and sodium hydroxide (0.80g) in dry methanol ($100cm^3$) was

maintained at its reflux temperature for 2.5h. After cooling, the mixture was partitioned between ether ($250cm^3$) and water ($50cm^3$), and the ethereal solution was extracted with water ($50cm^3$), dried and evaporated. The crystalline residue (0.938g, 73.5%), mp 104-106°, was recrystallized from methanol:water to give 2-diethylamino-4-ethylamino-6-methoxy-1,3,5-triazine (TRII; 831mg), mp 106-107° (lit.[168] mp107-109°, iso-octane)

Nmr data ($CDCl_3$): δ 3.86 (3-proton singlet, O-$C\underline{H}_3$), 3.57 (4-proton quartet, J=7.0Hz, -$C\underline{H}_2$-), 3.45 (2-proton multiplet, -$C\underline{H}_2$-), 1.18 (3-proton triplet, J=7.0Hz, -$C\underline{H}_3$) 1.16 (6-proton triplet, J=7.0Hz, -$C\underline{H}_3$).

Experiment 24b. Reaction with cis-2-phenyl-1,3-dioxan-5-ol using sodium.

A solution of cis-2-phenyl-1,3-dioxan-5-ol (5.0g; mp 78-84°) in refluxing toluene was allowed to react with sodium (0.77g, 1.2mol) during 8h. Compound 3 (6.37g, 1.0mol) was added and the mixture was maintained at its reflux temperature for 6h. After cooling, the mixture was diluted with chloroform ($100cm^3$) and the resulting solution was washed with water ($2x150cm^3$), dried and evaporated to yield a faintly brown solid. Crystallization from ethanol yielded 2-diethylamino-4-ethylamino-6-(cis-2-phenyl-1,3-dioxan-5-yl)oxy-1,3,5-triazine (TRIII; 3.75g) as fine needles, mp 165-167°; a second crop (1.92g, total yield =55%), mp 165-167°,

was obtained as platelets. After recrystallization from ethanol, TRIII had mp 169-170° (Found: C, 60.9; H, 7.0; N, 18.6. $C_{19}H_{27}N_5O_3$ requires C, 61.1; H, 7.3; N, 18.8%).

Nmr data ($CDCl_3$): δ 7.64-7.28 (5-proton multiplet, phenyl), 5.58 (1-proton singlet, dioxan H-2), 4.87 (1-proton multiplet, dioxan H-5), 4.34 (4-proton AB quartet, $J_{4,4'}=12.5H_z$, H-4's and H-6's), 3.56 (4-proton quartet, J=7.1Hz, N-CH_2-), 3.5 (2-proton multiplet, N-CH_2-), 1.17 (3-proton triplet, J=7.1Hz, -CH_3), 1.15 (6-proton triplet, J=7.1Hz, -CH_3). The ir spectrum showed bands in the regions 1500-1650 (νC=N and δN-H) and 3050-3300cm^{-1} (νN-H). The compound did not show a λ_{max} in the region 200-450nm. The mass spectrum showed a top mass peak at $^m/_e$ 373 (M^+).

Further crops of crystals from the product mixture were combined and recrystallized from acetic acid:water to give compound 3 (1.05g), mp 99-100°.

Experiment 24c. Reaction with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose using sodium hydride.

Sodium hydride (50% dispersion; 0.927g, 1.2mol) was washed with dry 1,4-dioxan (2x50cm^3), and then treated with a refluxing solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (5.00g) in dry distilled 1,4-dioxan (150cm^3) for 3.5h. Compound 3 (4.44g, 1.0mol) was added and the resulting solution

was refluxed for 1h, cooled and diluted with chloroform ($100cm^3$). The chloroform solution was washed with water ($2x150cm^3$), dried and evaporated, and distillation ($200-220^\circ/0.1mmHg$) of the syrupy residue gave a faintly green glass (3.86g). A solution of the product in ether ($200cm^3$) was stirred with silica gel (6.0g) for 6h, filtered and evaporated, and the resulting colourless glass was distilled to give 1,2:5,6-di-O-isopropylidene-3-O-(2-diethylamino-4-ethylamino-1,3,5-triazin-6-yl)-α-D-glucofuranose (TRIV; 2.72g, 31 %), mp $50-60^\circ$, $[\alpha]_D^{25}-11.8^\circ$ (c1.0, $CHCl_3$) (Found:C, 56.0; H, 8.0; N, 15.2. $C_{21}H_{35}N_5O_6$ requires C, 55.7; H, 7.7; N, 15.5%).

Nmr data ($CDCl_3$): δ 5.91 (1-proton doublet, $J_{1,2}$=3.5Hz, H-1), 5.51 (1-proton multiplet, H-3), 4.69 (1-proton doublet, $J_{1,2}$=3.5Hz, H-2), 3.72-3.27 (6-proton multiplet, N-CH_2-), 1.56 and 1.43 (each a 3-proton singlet, isopropylidene-CH_3), 1.32 (6-proton singlet, isopropylidene-CH_3), 1.20 (9-proton triplet, J=6.9Hz, -CH_2-CH_3). The ir spectrum showed bands at 1500-1620 (νC=N and δN-H) and 3100-3460cm^{-1} (νN-H) and the compound had λ_{max} (C_2H_5OH) 224nm (ε=33,300). The mass spectrum showed a top mass peak at m/e 453 (M^+).

Experiment 25a. Reaction with methanol using pyridine.

A solution of compound 3 (400mg) in a mixture of dry methanol ($1.0cm^3$), dry pyridine ($1.0cm^3$) and dry 1,4-dioxan ($10cm^3$) was maintained at its reflux temperature for 3h. Evaporation of the solvent gave

a brown syrup which was partitioned between chloroform ($40cm^3$) and water ($40cm^3$), and the chloroform layer was extracted with M hydrochloric acid ($50cm^3$) and water ($50cm^3$), dried and evaporated. Crystallization of the syrupy residue from methanol:water gave compound 3 (329mg, 82%), mp and mixed mp 100-101°.

Examination (tlc; toluene:acetone, 17:3) of the residue (33mg) from evaporation of the mother liquors showed the presence, inter alia, of compound 3 (Rf 0.74) and 2-diethylamino-4-ethylamino-6-methoxy-1,3,5-triazine (Rf 0.50; Experiment 24a).

Experiment 25b. Treatment with cis-2-phenyl-1,3-dioxan-5-ol in the presence of pyridine.

A solution of compound 3 (100mg) and cis-2-phenyl-1,3-dioxan-5-ol (79mg) in a mixture of dry 1,4-dioxan ($10cm^3$) and dry pyridine ($1cm^3$) was shaken at room temperature for 24h. The mixture was then dissolved in ether ($100cm^3$) and extracted with M hydrochloric acid ($2x100cm^3$), and the ethereal solution was dried and evaporated. Examination of the residue by tlc (Y) showed the presence of starting materials (Rf's 0.74 and 0.10) and two components in minor proportions (Rf's 0.75 and 0.91). No 2-diethylamino-4-ethylamino-6-(cis-2-phenyl-1,3-dioxan-5-yl)oxy-1,3,5-triazine (Experiment 24b) was detected. A solution of the residue in propanol:water yielded crystals of compound 3 (73mg), mp and mixed mp 99-101°, and a second crop (21mg) having mp 94-96°.

Experiment 26a. Treatment of alkali cellulose with compound 3 (cf. Experiments 17b and 17c).

Alkali cellulose (10.0g) was prepared by the procedure of Experiment 17d, mixed thoroughly with a solution of compound 3 (2.0g) in chloroform ($30cm^3$) and the chloroform was then evaporated slowly. The residue was heated at 100^o for 0.5h and then cooled and the product was isolated by steeping in ethanol and maceration with aqueous acid by the method of Experiment 17b. The product (TRPII; 2.5g) showed no significant bands in the region 1500-1700cm^{-1} of its ir spectrum (Found: C, 44.0; H, 6.1; N, 0%).

The ethanolic solution was evaporated to give a white solid (3.25g) which showed $\lambda_{max}(C_2H_5OH)$ 225nm. The ir spectrum showed significant similarities with that of compound 3. Examination by tlc (Y) showed the presence of compound 3 (Rf 0.74) and at least two other components (Rf's 0.49 and0).

Experiment 26b. Treatment of starch with compound 3 in the presence of sodium hydroxide (cf. Experiment 18).

A paste of wheat starch (200mg, pretreated as in Experiment 9a) with a solution of sodium hydroxide (100mg) in water ($0.4cm^3$) was mixed thoroughly with powdered compound 3 (200mg) and benzene ($10cm^3$). The solvent was removed slowly at room temperature and the resulting paste was then heated at 100^o for 0.5h. After

cooling, the faintly brown solid was steeped in ethanol ($10cm^3$), filtered off, washed with ether ($3x10cm^3$), dialysed against tap water for 48h and against distilled water for 4h, and freeze-dried to give a white solid (TRPIII, 195mg) (Found: C, 40.6; H, 5.7; N, 8.2%). An ir spectrum of TRPIII showed great similarity to that of compound 3. The ethanolic filtrate was evaporated and the residue gave crystals of compound 3 (156mg), mp 100-102° (propanol:water), mixed mp 99-100°.

Product TRPIII (110mg) was treated with refluxing 'spectroscopic' grade ethanol for 20h, filtered off and then extracted continuously with chloroform for 4h. A uv spectrum of the ethanolic extracts (8mg) was indistinguishable from that of compound 3. The material (16mg) which had been extracted with chloroform could not be identified, but showed a band at $1580cm^{-1}$ in its ir spectrum and had λ_{max} 227nm.

The extracted starch derivative (TPIIIA; 42mg after some loss) showed an ir spectrum similar to that of starch (Found: C, 39.9; H, 6.3; N, 0.9%).

Experiment 27a. Reaction with cellulose in the presence of pyridine.

Cellulose (5.00g; Whatman CC41) was treated with refluxing dry pyridine for 0.5h, and the solvent was then evaporated to give a thick paste which was

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dispersed in a solution of compound 3 (2.50g) in dry 1,4-dioxan (80cm^3). The mixture was maintained at reflux temperature for 3h and the dark suspension was cooled, poured into ethanol (400cm^3) and allowed to settle. The cellulosic material was filtered off, washed with ethanol (5x20cm^3) and ether (3x20cm^3), dried and extracted continuously with chloroform for 18h to give a faintly green product (TPIV; 4.52g) (Found: C, 43.1; H, 6.5; N, 1.0%). Evaporation of the chloroform solution gave a residue (47mg) which showed bands in the region 1500-1650cm^{-1} in its ir spectrum, but could not be identified.

A portion (3.00g) of TPIV was dialysed against tap water for 60h and against distilled water for 24h, and freeze-dried (recovery =2.96g; TPIVA) (Found: C, 44.5; H, 5.9; N, 2.1% and C, 43.6; H, 6.0; N, 0%). The ir spectra of products TPIV and TPIVA were almost indistinguishable from the spectrum of cellulose.

Experiment 27b. Treatment of starch with compound 3 in the presence of pyridine (cf. Experiment 16).

Pretreated wheat starch (150mg, prepared as in Experiment 9a) was treated with refluxing dry pyridine (10cm^3) for 4h. Compound 3 (200mg) was added to the cooled suspension and the resulting mixture was shaken for 14h at room temperature. The

entire mixture was then dialysed against running tap water for 72h and against distilled water for 5h, and freeze-dried to give a solid product (TPV; 327mg) which was extracted continuously with chloroform for 5h. The chloroform solution was evaporated to give a residue (179mg) which was identified by its ir spectrum as compound 3. The insoluble material (TPVA; 116mg) (Found: C, 40.3; H, 6.7; N, 1.4%) did not show any significant bands in the region 1500-1800cm^{-1} of its ir spectrum.

A similar experiment, in which compound 3 was heated with starch in pyridine, gave a black, intractable product.

APPENDIX.

RESULTS OF BIOLOGICAL TESTS.

The first set of results was obtained by the National Vegetable Research Station.

Key to compounds:-

No. 1. methyl α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (Experiment 8b).

No. 2. 1,3-diphenylurea.

No. 3. methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-bis(N-phenylcarbamate) (E) (Experiment 3c).

No. 4. methyl 4,6-O-benzylidene-α-D-glucopyranoside 2-(N-phenylcarbamate) (A6) (Experiment 3b).

1. Root and Shoot Growth Assay.

Solutions were prepared by dissolving each compound in 2 ml of the appropriate solvent and making to 1 litre with distilled water.

Compound	Solvent	Concentration
1	acetone	20 ppm
2	ether	15 ppm
3	acetone	10 ppm
4	acetone	10 ppm

Standard solutions of Chlorpropham (5 ppm) and Pronamide (5 ppm) prepared for comparative purposes.

Petri-dishes prepared with double filter paper in base moistened with 5 ml solutions of compounds 1-4, 5 ml chlorpropham or pronamide, or 5 ml distilled water. Six pre-germinated wheat, buckwheat or sorghum seeds placed in separate dishes for each compound, and positioned about 1 cm from the outside of the dish with the radicle touching the moist filter paper. All dishes incubated at 23°C for 4 days, after which time the lengths of the roots and shoots were measured. The results, expressed as a percentage of the growth in distilled water, are shown in Table II.

Comments. A very marked effect from compound No 3, with typical symptoms of carbamate herbicides on both wheat and buckwheat. Very prominent swelling of both root and shoot tips - typical of inhibition of cell division.

The other compounds, in terms of the figures in Table II have shown slight effects, but no visual symptoms recognised.

Table II.

The effect of several compounds on the root and shoot lengths of wheat buckwheat and sorghum after 4 days growth at 23°C.

Compound	Growth as % of control		
	wheat	buckwheat	sorghum
a. Roots			
1	92	72	119
2	76	68	113
3	17	11	106
4	67	89	82
Chlorpropham	10	7	25
Pronamide	14	11	26
b. Shoots			
1	87	95	104
2	111	80	71
3	57	48	101
4	86	99	78
Chlorpropham	14	10	11
Pronamide	15	10	13

2. Soil Effects

Separate 4 Kg amounts of air-dried soil (1.2 % carbon, 18 % clay) were treated with 10 ml solution of each compound in the appropriate solvent, and the solvent was allowed to evaporate. The solutions were of sufficient concentration to give a concentration in soil of 16.0 ppm. (approximately 10 lb/acre-2 in). The soils were rewetted to 8 % moisture by adding the required amount of water and passing several times through a 2 mm sieve to give thorough incorporation of the compound into the soil.

The soils were then transferred to seed trays (14" x 9" x 2"), and a single row of several plant species was sown across each tray. Chlorpropham and Pronamide were again included as internal standards, together with an untreated control. The plants were allowed to grow for 28 days in the glasshouse, when shoot fresh weights were determined after cutting off at soil level.

The results, expressed as a percentage of the control are shown in Table III.

Table III.

The effect of experimental compounds on the growth of several plant species grown in soil.

Plant Species	Shoot Fresh Weights as Percent of Control with Compound					
	1	2	3	4	Chlorpropham	Pronamide
Lettuce	94	108	99	116	25	12
Radish	114	116	95	79	15	0
Turnip	107	75	134	93	10	0
Ryegrass	94	78	93	119	0	0
Buckwheat	131	96	97	125	0	0
Sorghum	107	96	115	96	15	19
Wheat	132	104	92	78	0	0
Mean	111	96	104	102	9	4

Comments No effects from any of the experimental compounds - a slight depression recorded with certain combinations in Table III but no visual symptoms recorded.

3. Post-emergence activity

Single white mustard seedlings grown in sand culture with complete nutrient (Hewitt's solution) until two true leaves. Suspensions of the various compounds prepared at 500 ppm by dissolving the required amount of each compound in a minimum volume of the appropriate organic solvent and dispersing in distilled water. A suspension of phenmedipham prepared similarly as an internal standard. Sufficient Decon 75 surface active agent added to each solution to give a concentration of 0.5 % v/v. The aerial parts of three mustard plants emersed in the solutions for 15 seconds, and then grown on for 14 days. After this time, the fresh weight of the new growth - above the first two leaves - was recorded and is expressed as a percentage of the control in Table IV.

Table IV.

The effect of post-emergence treatment of white mustard seedlings with experimental compounds

Compound	Growth as percent of control
1	104
2	96
3	135
4	89
Phenmedipham	42

Comments No visual effects from any of the compounds at this concentration. Quite marked effects from phenmedipham.

The second set of results was obtained by Fisons Agrochemical Division, Chesterford Park Research Station.

Key to compounds:-

Fisons No.

14150 cis-5-(N-methyl-N-phenylcarbamoyl)-oxy-2-phenyl-1,3-dioxan (Experiment 13c, see Fig. XIX).

14229 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-(N-methyl-N-phenyl-carbamate (Experiment 13e, see Fig. XX).

14230 N-methyl-N-phenylcarbamoylcellulose (MPIIIA, Experiment 17e).

14231 2-diethylamino-4-ethylamino-6-(cis-2-phenyl-1,3-dioxan-5-yl)oxy-1,3,5-triazine (TRIII, Experiment 24b, see Fig. XXVIII).

14232 cellulose derivative (TRPII, Experiment 26a).

Table V. Results of herbicidal tests at a dose rate equivalent to 2.8kg per hectare.

Cpd. No.	Dose rate in kg/ha	Herbicidal index: species					
		Peas	Mustard	Linseed	Ryegrass	Oat	Sugarbeet
14150	2.8	1	1	1	0	0	1
14229	2.8	0	1	1	0	0	1
14230	2.8	0	0	1	0	0	0
14231	2.8	0	1	1	0	0	1
14232	2.8	0	0	1	0	0	0

Table VI. Results of herbicidal tests at a dose rate equivalent to 11.2kg per hectare.

Cpd. No.	Dose rate in kg/ha	Herbicidal index: species					
		Peas	Mustard	Linseed	Ryegrass	Oat	Maize
14150	11.2	0	0	0	0	0	0
14229	11.2	0	0	0	0	0	0
14230	11.2	0	0	0	0	0	0
14231	11.2	0	0	0	0	0	0
14232	11.2	0	0	0	0	0	0

Table VII. Results of insecticidal tests.

Cpd. No.	LC50 level in ppm									in mg/ft^2	
	Mv	Ta	Te	Tc	Ls	Pm	Pc	By	TUK	Md	Bg
14150	+	+	+	+	+	+	+	+	+	+	>50
14229	+	+	+	+	+	+	+	+	+	+	>50
14230	+	+	+	+	+	+	+	+	+	+	>50

+ = >1000

Mv = Megoura viciae (vetch aphid)

Ta = adult spider mite (Tetranychus telarius)

Te = eggs of spider mite (Tetranychus telarius)

Tc = adult flour beetle (Tribolium confusum)

Ls = larvae of sheep blowfly (Lucilia sericata)

Pm = caterpillar of diamond back moth (Plutella maculipennis)

Pc = larvae of mustard beetle (Phaedon cochleariae)

By = nymphs of cattle tick (Boophilus microplus)

TUK= resistant adult hop mites (Tetranychus urticae)

Md = adult houseflies (Musca domestica)

Bg = nymphs of german cockroach (Blatella germanica)

Table VIII. Results of *in vitro* fungicidal and bactericidal tests.

Species	NC 14229			NC 14230		
Fungi	IG50	IG95	MLD	IG50	IG95	MLD
Fusarium oxysporium	+	+	+	+	+	+
Verticillium albo-atrum	+	+	+	+	+	+
Lenzites trabea	+	+	+	+	+	+
Aspergillus niger	+	+	+	+	+	+
Cladosporium herbarum	+	+	+	+	+	+
Penicillium digitatum	+	+	+	+	+	+
Bacteria	B/static		B/cide	B/static		B/cide
Xanthomonas malvacearum	1000		>200	>1000		>1000
Corynebacterium michiganense	1000		>200	>1000		>1000

Table IX. Results of *in vivo* fungicidal tests.

Species/host	dose	% disease control 14150	14229	14230
Phytophthora infestans on potato (late blight)	500 ppm	0	35	35
Botrytis fabae on field bean (chocolate spot)	500 ppm	0	0	0
Erysiphe cichoracearum on cucumber (powdery mildew)	500 ppm	0	0	0
Uromyces phaseoli on french bean (rust)	500 ppm	40	0	0

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