460. *Cytotoxic Compounds. Part II.*[1] *Some Amides of the "Nitrogen Mustard" Type.*

By M. H. Benn, A. M. Creighton, L. N. Owen, and G. R. White.

Amides, including urethanes and ureas, have been prepared from *NN*-di-2′-chloroethyl-*p*-phenylenediamine or *p*-(*NN*-di-2-chloroethylamino)phenol. *p*-(*NN*-Di-2-chloroethylamino)phenyl isocyanate is a useful reagent for some of these syntheses. Urethanes and ureas containing the carboxyl group are conveniently made by the use of methyl isocyanatoacetate or *p*-isocyanatobenzoate, followed by mild hydrolysis of the methyl ester; *p*-*NN*-diethylaminophenyl isocyanate can be used to introduce a basic group. An improved synthesis of *p*-(*NN*-di-2-chloroethylamino)phenol is described.

In continuation of studies[1] on the synthesis of detoxicated "nitrogen mustards" which might become reactivated by enzymic fission at the site of a tumour, some new derivatives of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (I) have been prepared. Carbamates are known[2] to possess cytotoxic properties, but tumours which are initially sensitive to such compounds usually soon become resistant to them. In 1954, Danielli[3] suggested that this was due to the formation of an adaptive enzyme which decomposed the urethane by fission of the ester or peptide linkage. He pointed out that such conditions, once established, should be favourable for the selective activation, at the tumour site, of a "nitrogen mustard" of type (II), in which the highly toxic parent compound (I) has been deactivated by incorporation of the electron-attracting urethane group. Several such compounds (II; Y = Me, Et, Pr^i, Ph, cholesteryl) have therefore been synthesised by one or more of the following methods: (i) reaction of the amine (I) with a chloroformate; (ii) reaction of an alcohol with the isocyanate (VI), either as such or formed *in situ* from the azide (III) or the carbamoyl chloride (IV). The azide was synthesised from the known[4] carboxylic acid *via* the hydrazide, whilst the isocyanate was obtained (though not isolated) by treatment of the amine (I) in toluene with carbonyl chloride. The latter reaction initially gave a solid which showed infrared absorption in the carbonyl region but absence of an isocyanate band; on treatment with water the compound gave two equivalents of hydrogen ion, and was therefore the carbamoyl chloride hydrochloride (IV). When stored under reduced pressure over potassium hydroxide it slowly lost one mol. of hydrogen chloride to form a product which showed only very weak carbonyl but strong isocyanate absorption and was therefore essentially the isocyanate hydrochloride (V); elimination of hydrogen chloride from carbamoyl chlorides is known[5] to occur readily. When the original reaction mixture, containing the solid salt (IV) in

[1] Part I, Benn, Owen, and Creighton, *J.*, 1958, 2800.
[2] Haddow and Sexton, *Nature*, 1946, **157**, 500.
[3] Danielli, Ciba Foundation Symposium, "Leukaemia Research," Churchill, London, 1954, p. 263.
[4] Ross, Warwick, and Roberts, *J.*, 1955, 3110.
[5] Siefken, *Annalen*, 1949, **562**, 75.

suspension, was boiled, hydrogen chloride was evolved and a clear solution of the free isocyanate (VI) was obtained. This compound, its precursors (IV) and (V), and the azide (III) can be used for reactions with various functional groups, and are thus of potential value for the attachment of a nitrogen mustard to a wide variety of other units. The

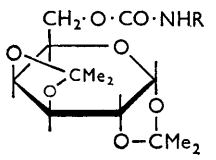
R = *p*-$(CH_2Cl\cdot CH_2)_2N\cdot C_6H_4$

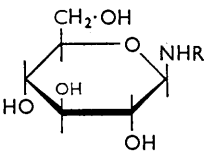
$R\cdot NH_2$ (I)	$R\cdot NH\cdot CO_2Y$ (II)	$R\cdot CON_3$ (III)	$R\cdot NH\cdot COCl,HCl$ (IV)	$R\cdot NCO,HCl$ (V)	$R\cdot NCO$ (VI)	$R\cdot NH\cdot CO\cdot NHR$ (VII)

$R\cdot NH\cdot CO\cdot NH\cdot C_2H_4\cdot NEt_2$ (VIII)	$R\cdot NH\cdot CO\cdot NH_2$ (IX)	$(CH_2Cl\cdot CH_2)_2N\cdot CO_2Y$ (X)	$R\cdot NH\cdot CO\cdot[CH_2]_n\cdot CO_2Y$ (XI; Y = Et) (XII; Y = H)	$CO_2Me\cdot CH_2\cdot NCO$ (XIII)	

$R\cdot NH\cdot CO\cdot NH\cdot CH_2\cdot CO_2Y$ (XIV; Y = Me) (XV; Y = H)	$R\cdot OH$ (XVI)	$R\cdot O\cdot CO\cdot NH\cdot CH_2\cdot CO_2H$ (XVII)	$R\cdot NH\cdot CO\cdot NH\cdot C_6H_4\cdot Y(p)$ (XVIII; Y = CO_2H) (XIX; Y = NEt_2)	$R\cdot O\cdot CO\cdot NH\cdot C_6H_4\cdot Y(p)$ (XX; Y = CO_2H) XXI; Y = NEt_2)

(XXII)





(XXIII)

ureas (VII) and (VIII) were prepared by reaction with the amine (I) and *NN*-diethylethylenediamine respectively. The monosubstituted urea (IX) was made from the amine (I) and sodium cyanate. Two of the urethanes (II; Y = Me, Pr^i) were converted into the more reactive bromo-analogues by exchange reactions with lithium bromide.

The aliphatic urethanes (X; Y = Pr^i or cholesteryl) were made from di-(2-chloroethyl)amine and the appropriate chloroformate; the cholesteryl compound was also obtained by displacement of one chloroethyl group from tri-(2-chloroethyl)amine by reaction with cholesteryl chloroformate, a method based on the reported [6] reaction of chloroformates with tertiary amines.

Some of the compounds showed promising results in animal tests,[7] but all were insoluble in water and were usually administered in oily solution or suspension, a method which has disadvantages in clinical practice. It was, therefore, desirable to obtain derivatives containing hydrophilic groups to confer water-solubility.

Reaction of the amine (I) with the ethyl ester chlorides of oxalic, malonic, and succinic acid gave the ester-anilides (XI; $n = 0$, 1, or 2). The ester group in the oxanilate was smoothly removed by brief alkaline hydrolysis, giving the acid (XII; $n = 0$) in good yield. Hydrolysis of the succinanilate was of course much slower, and was probably accompanied by some hydrolysis of the halide groups since only a poor yield of the acid (XII; $n = 2$) could be isolated; better results would probably be obtained with the methyl ester. The acid (XII; $n = 1$) could not be isolated by hydrolysis of the malonate (XI; $n = 1$). Two dianilides were prepared by reaction of the amine (I) with oxalyl and succinyl dichloride.

Methyl isocyanatoacetate (XIII) is a reagent with obvious potentialities for the introduction of a carboxyl group. Prepared from methyl aminoacetate and carbonyl chloride (cf. ref. 5) it reacted with the amine (I) to give the urea (XIV), from which the acid (XV) was obtained by brief hydrolysis with hydrochloric acid; under more vigorous conditions of hydrolysis the corresponding hydantoin was formed. Similarly, the phenolic mustard (XVI) was converted into the urethane (XVII). Methyl *p*-isocyanatobenzoate was also used in the same way, and, although the resulting methyl arylcarboxylates were less readily hydrolysed than the above acetates, the carboxylic acids (XVIII) and

[6] Campbell, *J. Org. Chem.*, 1957, **22**, 1259.

[7] Danielli, *Ann. Reports British Empire Cancer Campaign*, 1957, **35**, 410; 1958, **36**, 527; 1959, **37**, 575.

(XX) were obtained in good yield. These acids and those described above, though not appreciably water-soluble as such, were soluble in the form of sodium salts.

The introduction of a basic tertiary amino-group, to permit the formation of a hydrochloride or quaternary salt, is another possible method of increasing aqueous solubility. The urea (XIX) and the urethane (XXI) were therefore prepared by reaction of *p*-*NN*-diethylaminophenyl isocyanate with the amine (I) and the phenol (XVI) respectively; the urethane was characterised as the quaternary methiodide, which was readily soluble in water. In contrast to the mustard isocyanate hydrochloride (V), which readily lost hydrogen chloride when heated, the hydrochloride of the much more strongly basic *p*-*NN*-diethylaminophenyl isocyanate could be sublimed; it required heating for 17 hr. in boiling toluene [compared with 10 min. for (V)] for complete conversion into the free isocyanate.

The galactose derivative (XXII) was synthesised (i) by reaction of the mustard isocyanate (VI) with 1,2:3,4-di-*O*-isopropylidene-D-galactose, and (ii) by reaction of the mustard amine (I) with 1,2:3,4-di-*O*-isopropylidene-D-galactose 6-chloroformate. Mild acid-hydrolysis removed both the isopropylidene groups in this urethane to give the 6-substituted galactose, but the hydrophilic properties of the sugar unit were insufficient to endow the product with any marked aqueous solubility. The glucosylamine (XXIII), prepared by reaction of the amine (I) with acetobromoglucose, followed by solvolytic deacetylation, was also only sparingly soluble in water.

The phenolic mustard (XVI) has hitherto been prepared, in very poor yield, by reaction of *p*-(*NN*-di-2-hydroxyethylamino)phenol with phosphorus oxychloride.[4] It seemed likely that side reactions at this stage could be avoided by prior protection of the phenolic group as the benzyl ether, the phenol (XVI) being then obtained by hydrogenolysis of the product, and this procedure has now been found to give much more satisfactory results. It has also now been possible to prepare the phenolic acetate by direct acetylation of the phenol (XVI) under mild conditions, and earlier difficulties [4] were possibly due to the ease with which this ester is hydrolysed back to the phenol. Attempts to make the trichloroacetate were fruitless, for although reaction occurred the ester presumably decomposed when being washed, only the phenol being isolated.

During this work some model compounds were made, containing the phenyl or the *p*-*NN*-diethylaminophenyl group instead of the *p*-(*NN*-di-2-chloroethylamino)phenyl moiety of a mustard. Some of these originated from exploratory experiments, but others were required as substrates for enzymic tests or for investigation as possible biological potentiators. The correctness of Danielli's original hypothesis [3] of adaptive enzyme formation has now been proved,[7] not only with urethanes but also with other compounds; pretreatment of an animal with a suitable model may thus stimulate production of an enzyme capable of hydrolysing the linkage present in the model and hence able also to activate the related nitrogen mustard which is subsequently administered.

The extent of hydrolysis of the halide groups in some of the mustards was determined

Rates of hydrolysis.

R = *p*-(*NN*-Di-2-chloroethylamino)phenyl. R′ = *p*-(*NN*-Di-2-bromoethylamino)phenyl.

Compound	Mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°	Compound	Mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min at 66°.
R·NH·CO·NH_2	0·4	42	R·NH·CO·CO_2H	0·4	19
R·NH·CO·NH·CH_2·CO_2H	0·3	50	R·NH·CO·[CH_2]$_2$·CO_2H	0·4	28
R·NH·CO_2Me	0·6	33	R·NH·(tetra-*O*-acetyl-glucosyl)	0·4	55
R·NH·CO_2Et	0·5	31	R·O·CO·NHPh	0·5	18
R·NH·CO_2Pr^i	0·5	33	R·O·CH_2Ph	0·3	55
R′·NH·CO_2Me	0·5	88	R′·O·CH_2Ph	0·3	100
R′·NH·CO_2Pr^i	0·5	94			

(Ross's method [8]) by titration of the acid produced after 30 min. in boiling 50% aqueous acetone (see Table); in some cases the amount of halide ion was also measured, and gave a similar result. The urethanes show greater deactivation than the amides, as would be expected from the relative electron-attracting capacities of, *e.g.*, the CO_2Me and the $CO{\cdot}NH_2$ group. The much higher reactivity of the bromo-analogues is apparent.

Experimental

Microanalyses were by Miss J. Cuckney and the staff of the Organic Microanalytical Laboratories.

p-(NN-*Di*-2-*chloroethylamino*)*benzhydrazide*.—*p*-(*NN*-Di-2-chloroethylamino)benzoyl chloride [4] (2·2 g.) in dry ether (50 c.c.) was shaken with pure hydrazine hydrate (7 c.c.) in ethanol (10 c.c.) for 5 min. The granular precipitate was filtered off, combined with the residue obtained by evaporation of the filtrate, and recrystallised from ethanol (charcoal) to give the *hydrazide* as prisms (1·9 g., 88%), m. p. 151° (Found: C, 48·5; H, 5·7; N, 14·5. $C_{11}H_{15}Cl_2N_3O$ requires C, 47·8; H, 5·5; N, 15·2%).

p-(NN-*Di*-2-*chloroethylamino*)*benzazide* (III).—A solution of the above hydrazide (1·6 g.) in concentrated hydrochloric acid (16 c.c.) and water (2 c.c.) was cooled to 0°, and potassium nitrite (0·8 g.) in water (2 c.c.) was added with stirring; a pale yellow solid separated, and after a further 5 min. the mixture was extracted with benzene. Evaporation of the dried extracts gave a solid (1·1 g., 66%), m. p. 110—112°, which when recrystallised from chloroform–light petroleum (b. p. 40—60°) gave the *azide*, yellow prisms, m. p. 114—115° (Found: C, 46·0; H, 4·5; N, 19·3. $C_{11}H_{12}Cl_2N_4O$ requires C, 46·0; H, 4·2; N, 19·5%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylcarbamoyl Chloride Hydrochloride* (IV) (with B. J. Johnson).—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 14 g. of the hydrochloride [9]) in dry toluene (125 c.c.) was slowly added (40 min.) to a stirred solution of liquid carbonyl chloride (50 c.c.) in toluene (125 c.c.), at *ca.* 10°, through which a slow stream of gaseous carbonyl chloride was passed. After a further 45 min., the solid product was collected, washed with dry ether, and freed from solvent under reduced pressure to give the *carbamoyl chloride hydrochloride* (16 g.) as a grey powder (Found, by addition of water and titration with alkali, Cl^-, 21·4. $C_{11}H_{14}Cl_4N_2O$ requires for $2Cl^-$, Cl^-, 21·4%), $\nu_{max.}$ (paraffin mull) 1751s, 1715w cm.$^{-1}$.

When the compound was stored at 0·5 mm. over potassium hydroxide, the alkali titre gradually diminished, and after 5 days the product was essentially p-(NN-*di*-2-*chloroethylamino*)*phenyl isocyanate hydrochloride* (V) (Found: Cl^-, 12·1. $C_{11}H_{13}Cl_3N_2O$ requires Cl^-, 12·0%), $\nu_{max.}$ (paraffin mull) 2275s (NCO), *ca.* 1748vw, *ca.* 1709vw cm.$^{-1}$.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Isocyanate* (VI).—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 10 g. of the hydrochloride) and carbonyl chloride were allowed to react in toluene as described above. The mixture was then boiled under reflux until no more hydrogen chloride was evolved (10 min.), and the resulting homogeneous solution was evaporated under reduced pressure to an oil which contained only a trace of ionic chloride. This could not be purified, but its conversion into urethanes by reaction with alcohols (see below) indicated a content of at least 80% of the isocyanate.

N-p-(NN-*Di*-2-*chloroethylamino*)*phenylcarbamates* (II).—(i) *From* NN-*di*-2′-*chloroethyl*-p-*phenylenediamine*. Methyl chloroformate (0·48 g.) in chloroform (3 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 1·35 g. of hydrochloride) in chloroform (15 c.c.) containing pyridine (0·40 g.). After the exothermic reaction had subsided, the mixture was refluxed for 30 min., cooled, washed with water, dried, and concentrated under reduced pressure to a green oil which crystallised from methanol to give *methyl* N-p-(NN-*di*-2-*chloroethylamino*)-*phenylcarbamate* (1·0 g.), needles, m. p. 99—100° (Found: C, 49·8; H, 5·8; N, 10·1. $C_{12}H_{16}Cl_2N_2O_2$ requires C, 49·5; H, 5·5; N, 9·6%), *ethyl* N-p-(NN-*di*-2-*chloroethylamino*)-*phenylcarbamate*, needles [from ethanol–light petroleum (b. p. 40—60°)], m. p. 80—81° (Found: C, 51·4; H, 6·0; N, 9·05. $C_{13}H_{18}Cl_2N_2O_2$ requires C, 51·2; H, 5·9; N, 9·2%), *isopropyl* N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, needles (from methanol), m. p. 87—88° (Found: C, 53·1; H, 6·4; N, 8·8. $C_{14}H_{20}Cl_2N_2O_2$ requires C, 52·8; H, 6·3; N, 8·8%), and *cholesteryl*

[8] Ross, *J.*, 1949, 183.
[9] Everett and Ross, *J.*, 1949, 1972.

N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, a microcrystalline powder (from acetone–methanol), m. p. 68—70°, $[\alpha]_D^{24}$ −16° (*c* 1 in $CHCl_3$) (Found: C, 70·5; H, 9·1; N, 4·2. $C_{38}H_{58}Cl_2N_2O_2$ requires C, 70·7; H, 9·05; N, 4·3%), were prepared similarly in yields of 60—70%.

(ii) *From* p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamoyl chloride hydrochloride*. A solution of the carbamoyl chloride hydrochloride (3 g.) in propan-2-ol (30 c.c.) was heated on the steam-bath for 15 min., then cooled, poured into saturated aqueous sodium hydrogen carbonate (70 c.c.), and extracted with chloroform to give isopropyl *N*-*p*-(*NN*-di-2-chloroethylamino)-phenylcarbamate, which after recrystallisation from methanol had m. p. and mixed m. p. 87—88° (yield, 2·8 g.). The methyl and ethyl esters, identical with those described above, were prepared in the same way. *Phenyl* N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, needles (from benzene–ethanol), m. p. 125° (Found: C, 57·5; H, 5·3; N, 7·8. $C_{17}H_{18}Cl_2N_2O_2$ requires C, 57·8; H, 5·1; N, 7·9%), was made by heating equimolecular quantities of the reactants at 100° for 20 min.

Cholesterol (1·0 g.) and the carbamoyl chloride hydrochloride (1·0 g.) in pyridine (30 c.c.) were heated at 100° for 30 min. The cooled solution was poured into water and extracted with chloroform. Removal of solvent under reduced pressure gave a solid residue which was extracted with boiling ethanol; concentration of this extract gave the cholesteryl ester (1·1 g.), m. p. and mixed m. p. 68°. The material insoluble in boiling ethanol was recrystallised from benzene to give needles (0·3 g.) of NN′-*di*-(NN-*di*-2-*chloroethylamino*)*phenylurea* (VII), m. p. 207° (Found: C, 51·2; H, 5·5; N, 11·2. $C_{27}H_{26}Cl_4N_4O$ requires C, 51·2; H, 5·3; N, 11·4%); this was also obtained (4·3 g.) by reaction of the carbamoyl chloride hydrochloride (4 g.) with *NN*-di-2′-chloroethyl-*p*-phenylenediamine hydrochloride (3·8 g.) in pyridine (40 c.c.) for 5 min. at 100°, precipitation of the product by addition of water, and recrystallisation from acetic acid.

(iii) *From* p-(NN-*di*-2-*chloroethylamino*)*phenyl isocyanate*. A solution of the crude isocyanate (0·45 g.) in propan-2-ol (4 c.c.) was refluxed for 15 min., then cooled, poured into water, and extracted with chloroform to give isopropyl *N*-p-(*NN*-di-2-chloroethylamino)phenyl-carbamate (0·4 g.), m. p. and mixed m. p. 88° after recrystallisation from methanol.

(iv) *From* p-(NN-*di*-2-*chloroethylamino*)*benzazide*. A solution of cholesterol (0·6 g.) and the azide (0·5 g.) in petroleum (b. p. 100—120°) (50 c.c.) was boiled under reflux for 3 hr. Removal of solvent and recrystallisation of the residue from ethanol gave cholesteryl *N*-*p*-(*NN*-di-2-chloroethylamino)phenylcarbamate, m. p. 66—68°.

Methyl N-p-(NN-*Di*-2-*bromoethylamino*)*phenylcarbamate*.—A solution of methyl *N*-*p*-(*NN*-di-2-chloroethylamino)phenylcarbamate (1·4 g.) and anhydrous lithium bromide (5 g.) in isobutyl methyl ketone (25 c.c.) was boiled under reflux for 5 hr., then cooled and poured into water. Extraction with ether gave the *dibromo-compound* (0·95 g.), needles [from chloroform–light petroleum (b. p. 60—80°)], m. p. 113° (Found: Br, 41·7; N, 7·6. $C_{12}H_{16}Br_2N_2O_2$ requires Br, 42·0; N, 7·4%).

Isopropyl N-p-(NN-*Di*-2-*bromoethylamino*)*phenylcarbamate*.—Prepared similarly, this *compound* crystallised from chloroform–light petroleum (b. p. 60—80°) in plates, m. p. 90—91° (Found: Br, 39·2; N, 6·95. $C_{14}H_{20}Br_2N_2O_2$ requires Br, 39·2; N, 6·9%).

Isopropyl Di-2-*chloroethylcarbamate* (X; Y = Pr^i).—Isopropyl chloroformate (10·3 g.) was added dropwise to di-(2-chloroethyl)amine (from 14·5 g. of hydrochloride) and pyridine (8 c.c.) in chloroform (150 c.c.). The mixture was then refluxed for 15 min., cooled, washed with water, dried, and distilled to give the *urethane* (15·1 g., 81%), b. p. 102—104°/2 mm., n_D^{21} 1·4634 (Found: C, 42·5; H, 6·9; Cl, 31·2. $C_8H_{15}Cl_2NO_2$ requires C, 42·1; H, 6·6; Cl, 31·1%).

Cholesteryl Di-2-*chloroethylcarbamate* (X; Y = *cholesteryl*).—(i) Similar reaction of cholesteryl chloroformate[10] (2·3 g.) with di-(2-chloroethyl)amine (from 1·9 g. of hydrochloride) in chloroform (70 c.c.) gave, after removal of solvent, a solid which was recrystallised from acetone–methanol to give the *urethane* as needles (2·25 g., 79%), m. p. 111—112°, $[\alpha]_D^{22}$ −18° (*c* 1 in $CHCl_3$) (Found: C, 69·0; H, 9·9; Cl, 13·1. $C_{32}H_{53}Cl_2NO_2$ requires C, 69·3; H, 9·6; Cl, 12·8%).

(ii) A solution of cholesteryl chloroformate (0·45 g.) and tri-(2-chloroethyl)amine (from 4 g. of hydrochloride) in benzene (45 c.c.) was refluxed for 2 hr., then cooled, washed successively with water, 2N-hydrochloric acid, and water, dried, and concentrated to an oil. Purification by

[10] Wieland, Honold, and Pascual-Vila, *Z. physiol. Chem.*, 1923, **130**, 326.

chromatography in benzene on alumina, followed by recrystallisation from acetone–methanol, gave the same urethane, m. p. and mixed m. p. 110°.

Di-p-(NN-*di*-2-*chloroethylamino*)*anilides of Dibasic Acids*.—A solution of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5·4 g. of hydrochloride) and triethylamine (2·0 g.) in chloroform (75 c.c.) was treated dropwise with oxalyl dichloride (1·3 g.) in ether (10 c.c.). The mixture was refluxed for 15 min., cooled, washed with water, dried, and concentrated to an oil, which crystallised from chloroform–ethanol to give pp′-*di*-(NN-*di*-2-*chloroethylamino*)*oxanilide*, needles (2·6 g.), m. p. 156—157° with a second m. p. 170—171° (Found: C, 50·9; H, 5·0; N, 10·7. $C_{22}H_{26}Cl_4N_4O_2$ requires C, 50·8; H, 5·0; N, 10·8%). The *derivative* of succinic acid, prepared similarly, formed needles (from chloroform–ethanol), m. p. 169° (Found: C, 52·3; H, 5·7; N, 10·2. $C_{24}H_{30}Cl_4N_4O_2$ requires C, 52·6; H, 5·5; N, 10·2%).

Ethyl Esters of p-(NN-*Di*-2-*chloroethylamino*)*anilic Acids* (XI).—Addition of ethyl succinyl chloride (1·85 g.) in chloroform (10 c.c.) to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 3 g. of hydrochloride) in chloroform (50 c.c.) containing triethylamine (1·1 g.) gave *ethyl* p-(NN-*di*-2-*chloroethylamino*)*succinanilate*, which crystallised from ethanol–light petroleum (b. p. 40—60°) in needles (2·9 g.), m. p. 111—112° (Found: C. 53·5; H, 6·6; N, 7·8. $C_{16}H_{22}Cl_2N_2O_3$ requires C, 53·2; H, 6·1; N, 7·8%). The *derivative* of malonic acid, needles (from ethanol), m. p. 87° (Found: C, 51·7; H, 5·8; N, 8·4. $C_{15}H_{20}Cl_2N_2O_3$ requires C, 51·9; H, 5·8; N, 8·1%), and the *derivative* of oxalic acid, pale yellow needles (from ethanol), m. p. 138—139° (Found: C, 50·8; H, 5·7; Cl, 21·0. $C_{14}H_{18}Cl_2N_2O_3$ requires C, 50·5; H, 5·45; Cl, 21·3%), were prepared similarly.

p-(NN-*Di*-2-*chloroethylamino*)*anilic Acids* (XII).—(i) N-Ethanolic potassium hydroxide (3 c.c.) was added to ethyl *p*-(*NN*-di-2-chloroethylamino)oxanilate (1·0 g.) in hot ethanol (30 c.c.), and the solution was heated under reflux for 5 min., concentrated to about 10 c.c., and diluted with ether (50 c.c.). The precipitated salt (0·9 g.) was collected, dissolved in water (30 c.c.), acidified with a slight excess of dilute hydrochloric acid, and extracted with ether to give a solid, which on recrystallisation from ethanol–light petroleum (b. p. 60—80°) gave p-(NN-*di*-2-*chloroethylamino*)*oxanilic acid*, yellow prisms (0·8 g., 88%), m. p. 149° (Found: C, 47·5; H, 4·8; Cl, 23·3. $C_{12}H_{14}Cl_2N_2O_3$ requires C, 47·2; H, 4·6; Cl, 23·2%).

(ii) N-Ethanolic potassium hydroxide (5·5 c.c.) was added slowly (20 min.) to ethyl *p*-(*NN*-di-2-chloroethylamino)succinanilate (2·0 g.) in boiling ethanol (30 c.c.). The solution, which was then neutral, was evaporated to dryness, and the solid residue was washed with chloroform, then dissolved in water (40 c.c.), treated with a slight excess of 2N-hydrochloric acid, and extracted with chloroform to give an oil which partly crystallised. The solid was collected and extracted with boiling ether; evaporation of this extract gave p-(NN-*di*-2-*chloroethylamino*)-*succinanilic acid* (0·2 g.), which after recrystallisation from acetone–ether had m. p. 118—120° (Found: C, 50·2; H, 5·7; N, 8·4. $C_{14}H_{18}Cl_2N_2O_3$ requires C, 50·5; H, 5·5; N, 8·4%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(2-NN-*diethylaminoethyl*)*urea* (VIII).—A solution of *NN*-diethylethylenediamine (1·1 g.) and *p*-(*NN*-di-2-chloroethylamino)phenyl isocyanate (2·6 g.) in dry ether (10 c.c.) was heated under reflux for 3 hr. Evaporation then gave the crude urea (2·8 g.) as an oil. It formed a *picrate*, m. p. 138° (from ethanol) (Found: C, 45·6; H, 5·5; Cl, 11·6. $C_{23}H_{31}Cl_2N_7O_8$ requires C, 45·7; H, 5·2; Cl, 11·7%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylurea* (IX).—To *NN*-di-2′-chloroethyl-*p*-phenylenediamine hydrochloride (6·4 g.) in acetic acid (100 c.c.), a solution of sodium cyanate (1·6 g.) in water (3 c.c.) was added. The mixture was heated on a steam-bath for 10 min., then allowed to cool and poured into water (600 c.c.). The precipitated solid, recrystallised from ethanol, gave the *urea* as needles (4·5 g., 69%), m. p. 140—141° (Found: C, 48·6; H, 5·7; N, 15·3. $C_{11}H_{13}Cl_2N_3O$ requires C, 48·8; H, 5·5; N, 15·2%).

Methyl Isocyanatoacetate.—A solution of carbonyl chloride (110 g.) in toluene (270 c.c.) was added at 25° to a stirred suspension of methyl aminoacetate hydrochloride (68·5 g.) in toluene (210 c.c.), and the mixture was then stirred and refluxed in a stream of carbonyl chloride for 7 hr. After being cooled, it was filtered and concentrated to an oil which on distillation gave *methyl isocyanatoacetate* (37·3 g., 59%), b. p. 73°/19 mm., n_D^{21} 1·4286 (Found: C, 41·3; H, 4·4; N, 11·9. $C_4H_5NO_3$ requires C, 41·7; H, 4·4; N, 12·2%).

Ethyl p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetate*.—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 5·4 g. of the hydrochloride) in ether (120 c.c.) was added to ethyl isocyanatoacetate [5] (2·6 g.) in ether (10 c.c.), and the mixture, in which a white precipitate was formed, was refluxed for 20 min. and then cooled. The solid, on recrystallisation from methanol, gave

the *ureidoacetate* (6·5 g., 90%), m. p. 130° (Found: C, 50·2; H, 5·9; Cl, 20·0. $C_{15}H_{21}Cl_2N_3O_3$ requires C, 49·7; H, 5·8; Cl, 19·6%).

Methyl p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetate* (XIV).—Similar reaction of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 10 g. of hydrochloride) and methyl isocyanatoacetate (4·5 g.) gave, on recrystallisation from methanol, the *ureidoacetate* (10·0 g., 77%), m. p. 124° (Found: Cl, 19·4. $C_{14}H_{19}Cl_2N_3O_3$ requires Cl, 20·3%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetic Acid* (XV).—(i) A suspension of ethyl *p*-(*NN*-di-2-chloroethylamino)phenylureidoacetate (3·1 g.) in N-hydrochloric acid (85 c.c.) was refluxed for 12 min. to give a homogeneous solution. The cooled (0°) reaction mixture was partly neutralised (to pH 4) with 2N-sodium hydroxide, and the solid was collected and crystallised from ethanol–light petroleum (b. p. 40—60°) to give the *acid* as the *monoethanolate* (1·6 g., 56%), m. p. 81—82° (Found: C, 46·6; H, 5·8; Cl, 18·5%; equiv., 380. $C_{13}H_{17}Cl_2N_3O_3$,EtOH requires C, 47·4; H, 6·1; Cl, 18·65%; equiv., 380).

(ii) The methyl ester (10 g.) was hydrolysed in 3 min. in boiling N-hydrochloric acid (140 c.c.) to give the acid, which after recrystallisation as above gave the same ethanolate (6·7 g., 61%), m. p. 81—82°.

3-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*hydantoin*.—A solution of ethyl *p*-(*NN*-di-2-chloroethylamino)phenylureidoacetate (0·7 g.) in acetic acid–concentrated hydrochloric acid (1 : 1; 5 c.c.) was boiled for 3 min. and then cooled to 0°. Ice-water (5 c.c.) was added and the precipitate was collected, dried, and recrystallised from benzene to give the *hydantoin* (0·4 g.), m. p. 180° (Found: C, 49·9; H, 4·65; Cl, 22·1. $C_{13}H_{15}Cl_2N_3O_2$ requires C, 49·4; H, 4·8; Cl, 22·4%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*carbamate*.—*p*-(*NN*-Di-2-chloroethylamino)phenol (from 9·6 g. of hydrochloride) and methyl isocyanatoacetate (4·1 g.) were heated together at 100—110° for 15 hr. in a sealed tube and then cooled. The oil crystallised on trituration with ether, and recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) gave the *urethane* (6·5 g., 45%), m. p. 102° (Found: Cl, 20·2; N, 8·0. $C_{14}H_{18}Cl_2N_2O_4$ requires Cl, 20·3; N, 8·0%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Carboxymethyl*)*carbamate* (XVII).—A solution of *p*-(*NN*-di-2-chloroethylamino)phenyl *N*-(methoxycarbonylmethyl)carbamate (4·0 g.) in acetic acid–concentrated hydrochloric acid (1 : 1; 25 c.c.) was boiled for 3 min., then cooled, diluted with water, and brought to pH 4 with 2N-sodium hydroxide. Extraction with chloroform gave the acid as an oil, which was characterised as the S-*benzylthiouronium salt*, m. p. 143° (from nitromethane) (Found: C, 50·8; H, 5·4. $C_{21}H_{26}Cl_2N_4O_4S$ requires C, 50·3; H, 5·2%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-[p-(*methoxycarbonyl*)*phenyl*]*urea*.—Methyl *p*-isocyanatobenzoate [5] (3·5 g.) in dry ether (50 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5·3 g. of hydrochloride) in ether (85 c.c.). The mixture was refluxed for 30 min., then cooled, and the white precipitate was recrystallised from methanol to give needles of the *urea* (7·5 g., 92%), m. p. 179—180° (Found: C, 55·8; H, 5·3; Cl, 17·1. $C_{19}H_{21}Cl_2N_3O_3$ requires C, 55·6; H, 5·2; Cl, 17·3%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(p-*carboxyphenyl*)*urea* (XVIII).—The above methyl ester (0·4 g.) was boiled with acetic acid–concentrated hydrochloric acid (1 : 1; 5 c.c.) under reflux for 35 min., then cooled and diluted with water (10 c.c.). The precipitated product could not be satisfactorily recrystallised; after precipitation from ethanol with light petroleum (b. p. 40—60°) the acid (0·3 g.) had m. p. >300° (decomp.). It gave an S-*benzylthiouronium salt*, m. p. 163° (from acetonitrile) (Found: C, 55·0; H, 5·3; Cl, 12·4. $C_{26}H_{29}Cl_2N_5O_3S$ requires C, 55·5; H, 5·2; Cl, 12·6%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*carbamate*.—A mixture of *p*-(*NN*-di-2-chloroethylamino)phenol (4·7 g.), methyl *p*-isocyanatobenzoate (3·55 g.), and pyridine (0·1 g.) was heated at 100° for 2 hr. in a sealed tube. Recrystallisation of the solid product from nitromethane gave the *urethane* (5·0 g., 61%), m. p. 164° (Found: C, 55·3; H, 4·8; Cl, 17·0. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55·5; H, 4·9; Cl, 17·2%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Carboxyphenyl*)*carbamate* (XX).—Hydrolysis of the above methyl ester (4·4 g.), as described for the corresponding urea, gave the *acid*, which was purified by precipitation from ethyl acetate with light petroleum (b. p. 40—60°), then forming a white powder (4·0 g., 94%), m. p. 207° (Found: C, 54·5; H, 4·9; Cl, 18·0. $C_{18}H_{18}Cl_2N_2O_4$ requires C, 54·4; H, 4·6; Cl, 17·85%).

p-NN-*Diethylaminophenyl Isocyanate*.—*p*-*NN*-Diethylaminoaniline (from 50 g. of hydrochloride) in toluene (200 c.c.) was added to a stirred solution of carbonyl chloride (79 g.) in

toluene (200 c.c.), a stream of carbonyl chloride being passed through and maintained whilst the stirred mixture was refluxed for 2 hr. A portion of the supernatant solution was decanted from the oil and cooled to deposit needles, which on recrystallisation from benzene–light petroleum (b. p. 40—60°) followed by vacuum-sublimation at 130—160°/10^{-4} mm. gave p-NN-*diethylaminophenyl isocyanate hydrochloride*, m. p. 133—135°, $\nu_{max.}$ (paraffin mull) 2269 and 2381 $cm.^{-1}$ (NCO) (Found: C, 58·0; H, 6·7; N, 12·0. $C_{11}H_{15}ClN_2O$ requires C, 58·3; H, 6·6; N, 12·4%).

The main bulk of the reaction mixture was refluxed in a slow stream of nitrogen for 17 hr.; a homogeneous solution resulted. This was concentrated under reduced pressure to an oil which on distillation gave p-NN-*diethylaminophenyl isocyanate* (23·5 g., 49%), b. p. 104°/10^{-2} mm., n_D^{22} 1·5692 (Found: C, 69·6; H, 7·8; N, 14·2. $C_{11}H_{14}N_2O$ requires C, 69·4; H, 7·4; N, 14·7%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(p-NN-*diethylaminophenyl*)*urea* (XIX).—*p-NN*-Diethylaminophenyl isocyanate (0·9 g.) in ether (5 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 1·35 g. of hydrochloride) in ether (45 c.c.). After 30 min. the precipitate was filtered off and recrystallised from methanol to give needles of the *urea* (1·7 g., 68%), m. p. 165° (Found: C, 60·1; H, 6·9; Cl, 17·0. $C_{21}H_{28}Cl_2N_4O$ requires C, 59·6; H, 6·7; Cl, 16·75%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-NN-*Diethylaminophenyl*)*carbamate* (XXI).—*p*-(*NN*-Di-2-chloroethylamino)phenol (from 5·4 g. of hydrochloride) and *p-NN*-diethylaminophenyl isocyanate (3·7 g.) were heated together at 125° for 26 hr. in a sealed tube and then cooled. The oil solidified when shaken with ether to give the urethane (4·7 g., 56%), m. p. 95—105°, which could not be satisfactorily recrystallised. On reaction for 24 hr. with boiling methyl iodide it gave the *methiodide*, m. p. 168—170° (from methanol–ether) (Found: C, 47·1; H, 5·6. $C_{22}H_{30}Cl_2IN_3O_2$ requires C, 46·65; H, 5·3%).

1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-{N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*carbamate*} (XXII).—(i) 1,2:3,4-Di-*O*-isopropylidene-D-galactose 6-chloroformate [11] (6·0 g.) in chloroform (30 c.c.) was added to a solution of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5 g. of hydrochloride) and pyridine (3 c.c.) in chloroform (120 c.c.). The solution was set aside for 30 min., then washed with water, dried, and concentrated to an oil, which was purified by chromatography in benzene on alumina. Evaporation of the earlier fractions of the eluate left a glass, which crystallised from pentane to give the slightly impure *urethane* (0·6 g.), m. p. 58°, $[\alpha]_D^{22}$ −41° (*c* 4 in $CHCl_3$) (Found: C, 52·2; H, 6·4; Cl, 13·65. $C_{23}H_{32}Cl_2N_2O_7$ requires C, 53·2; H, 6·2; Cl, 12·9%).

(ii) *p*-(*NN*-Di-2-chloroethylamino)phenyl isocyanate (4·4 g.) and 1,2:3,4-di-*O*-isopropylidene-D-galactose [12] (4·4 g.) were heated in a sealed tube at 100° for 15 hr. The oil was purified by chromatography, as described above, and after recrystallisation from pentane gave, in very poor yield, the same carbamate, m. p. 58—59°.

D-*Galactose* 6-{N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*carbamate*}.—The above di-*O*-isopropylidene compound (0·20 g.) in acetic acid (10·0 c.c.) showed (1 dm. tube) α_D^{24} −0·57°. After addition of concentrated hydrochloric acid (10·0 c.c.) this became α_D^{24} +0·32°, unchanged after 1 hr. Evaporation under reduced pressure below 45° gave a glass which was purified by precipitation from methanol with ether to give the amorphous *carbamate* (0·12 g.) (Found: C, 45·9; H, 5·3; Cl, 17·1. $C_{17}H_{24}Cl_2N_2O_7$ requires C, 46·5; H, 5·5; Cl, 16·1%). It was only sparingly soluble in water.

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucosylamine*.—A solution of α-acetobromoglucose (26 g.) in chloroform (150 c.c.) containing *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 17 g. of hydrochloride) was left at room temperature overnight, then washed with water, dried, and concentrated to a syrup which crystallised on trituration with ethanol–light petroleum (b. p. 40—60°). Recrystallisation from ethanol gave the *tetra*-O-*acetyl*-β-D-*glucosyl derivative* as needles (12 g., 68%), m. p. 158—159°, $[\alpha]_D^{19}$ −17° (*c* 2 in $CHCl_3$) (Found: C, 51·3; H, 5·9. $C_{24}H_{32}Cl_2N_2O_9$ requires C, 51·1; H, 5·7%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-β-D-*glucosylamine* (XXIII).—The tetra-acetyl compound (2·0 g.) was suspended in dry methanol (30 c.c.) and a trace of sodium (*ca.* 5 mg.) was added. The mixture was shaken until homogeneous, stored overnight at 0°, then saturated with carbon dioxide and evaporated to dryness. The residue was taken up in hot ethanol

[11] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.
[12] Raymond and Schroeder, *J. Amer. Chem. Soc.*, 1948, **70**, 2785.

(50 c.c.), filtered, and again evaporated to yield the *glucosylamine* as a glass (1·25 g., 89%) (Found: C, 48·3; H, 6·3. $C_{14}H_{24}Cl_2N_2O_5$ requires C, 48·6; H, 6·1%).

Benzyl p-(NN-*Di*-2-*hydroxyethylamino*)*phenyl Ether*.—*p*-(*NN*-Di-2-hydroxyethylamino)-phenol [4] (50·0 g.), potassium hydroxide (14·2 g.), benzyl bromide (43·4 g.), and ethanol (350 c.c.) were heated together under reflux for 2 hr., then concentrated and poured into water. The precipitate (61·5 g., 85%), m. p. 86—89°, on recrystallisation from ethanol–light petroleum (b. p. 60—80°) gave the *ether* as needles, m. p. 93—94° (Found: C, 70·8; H, 7·5. $C_{17}H_{21}NO_3$ requires C, 71·0; H, 7·4%).

Benzyl p-(NN-*Di*-2-*chloroethylamino*)*phenyl Ether*.—The above dihydroxy-ether (3·0 g.) in chloroform (20 c.c.) was treated with phosphorus pentachloride (4·9 g.). When the vigorous reaction had subsided, the solution was heated under reflux for 90 min. and then cooled and poured into water. The chloroform layer was separated, washed with aqueous sodium carbonate, dried, and concentrated to an oil, which was passed in benzene through a column of alumina. Concentration of the eluates gave colourless plates of *benzyl* p-(NN-*di*-2-*chloroethylamino*)*phenyl ether* (2·4 g., 70%), m. p. 72—73° [from ethanol–light petroleum (b. p. 60—80°)] (Found: C, 63·0; H, 6·05; Cl, 22·1. $C_{17}H_{19}Cl_2NO$ requires C, 63·0; H, 5·9; Cl, 21·9%). Subsequent preparations had m. p. 105—106°, undepressed on admixture with the lower-melting variety. After being set aside for a few weeks, however, the original sample also melted at 105—106°.

p-(NN-*Di*-2-*chloroethylamino*)*phenol Hydrochloride*.—A suspension of the above dichloro-ether (23 g.) in methanol (250 c.c.) was saturated with hydrogen chloride until complete dissolution occurred, then concentrated until solid began to separate. Addition of ether gave prisms of the hydrochloride (22 g.), m. p. 135—136°. On storage, it lost hydrogen chloride and reverted to the free base after 2 days.

The freshly prepared hydrochloride (20·0 g.) was suspended in ethanol (200 c.c.) containing 2½% palladised charcoal (1·0 g.) and hydrogenated for 7 hr. at atmospheric pressure to give, after filtration and concentration, *p*-(*NN*-di-2-chloroethylamino)phenol hydrochloride (14 g., 93%), m. p. 170—173° (lit.,[4] m. p. 168°). The free base, liberated from the hydrochloride, reacted with phenyl isocyanate at 100° for 2 hr. to give p-(NN-*di*-2-*chloroethylamino*)*phenyl* N-*phenylcarbamate*, m. p. 136° (from benzene–ethanol) (Found: C, 58·0; H, 5·3; N, 7·8; Cl, 19·9. $C_{17}H_{18}Cl_2N_2O_2$ requires C, 57·8; H, 5·1; N, 7·9; Cl, 20·1%).

Benzyl p-(NN-*Di*-2-*bromoethylamino*)*phenyl Ether*.—Prepared from the dichloro-analogue (4·0 g.) and lithium bromide (5 g.) in boiling isobutyl methyl ketone for 6 hr., the *dibromide* formed rhombs, m. p. 106° [from chloroform–light petroleum (b. p. 60—80°)] (Found: Br, 38·9. $C_{17}H_{19}Br_2NO$ requires Br, 38·7%).

p-(NN-*Di*-2-*hydroxyethylamino*)*phenyl* 4-*Nitrobenzyl Ether*.—Prepared from *p*-(*NN*-di-2-hydroxyethylamino)phenol and 4-nitrobenzyl bromide in the same way as described above for the benzyl ether, the 4-*nitrobenzyl ether* formed orange needles, m. p. 125—126° (from ethanol) (Found: C, 61·4; H, 6·2. $C_{17}H_{20}N_2O_5$ requires C, 61·4; H, 6·1%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* 4-*Nitrobenzyl Ether*.—Reaction of the above diol with phosphorus pentachloride in chloroform gave the *dichloro-ether* as yellow needles, m. p. 73° (from ethanol) (Found: C, 55·3; H, 5·0; Cl, 19·2. $C_{17}H_{18}Cl_2N_2O_3$ requires C, 55·3; H, 4·9; Cl, 19·2%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Acetate*.—*p*-(*NN*-Di-2-chloroethylamino)phenol hydrochloride (2·7 g.) in pyridine (20 c.c.) was added during 5 min. to acetyl chloride (0·7 c.c.) in pyridine (5 c.c.) at −8°. The mixture was kept for a further 5 min. at −8°, then diluted with ice-water (15 c.c.) and extracted with chloroform (3 × 10 c.c.). The extracts were quickly washed with dilute hydrochloric acid at 0°, then dried and evaporated to give the acetyl derivative as an oil (2·2 g., 80%), $\nu_{max.}$ (liquid film) 1757 (C=O in phenyl acetate), 1209 $cm.^{-1}$ (C–O in phenyl acetate) (Found: Cl, 25·1. Calc. for $C_{12}H_{15}Cl_2NO_2$: Cl, 25·7%).

ω-*Fluoroacetanilide*.—Prepared by reaction of aniline with fluoroacetyl chloride in ether, the *compound* crystallised from aqueous ethanol in flakes, m. p. 74—75° (Found: C, 62·4; H, 5·4; N, 9·4. C_8H_8FNO requires C, 62·8; H, 5·3; N, 9·15%).

p-NN-*Diethylaminobenzoic Acid*.—*p*-Bromo-*NN*-diethylaniline (56 g.) in dry tetrahydrofuran (200 c.c.) was added dropwise (30 min.) to magnesium turnings (6 g.), a trace of iodine, and dry tetrahydrofuran (50 c.c.). The mixture was refluxed for 30 min. (during which almost all the magnesium dissolved), then cooled and transferred to an autoclave containing crushed solid carbon dioxide (*ca.* 500 g.). The autoclave was sealed, warmed to 50° for 2 hr., and allowed to cool overnight, stirring being maintained throughout. The mixture was then

treated with saturated ammonium chloride solution (250 c.c.) and made alkaline with ammonia. It was extracted with ether (2 × 100 c.c.) (the extracts being rejected), and the aqueous solution adjusted to pH 6 with 6N-hydrochloric acid. The precipitated acid was taken up in ether (4 × 100 c.c.), in which it is rather sparingly soluble, and this solution was dried and evaporated to a residue which on recrystallisation from ethanol gave *p-NN*-diethylaminobenzoic acid, m. p. 193° (lit.,[13] m. p. 193°). A further quantity of acid was obtained from the aqueous mother-liquors by concentration. The total yield was 17 g. (38%). The S-*benzylthiouronium salt* crystallised from ethanol in needles, m. p. 187—188° (Found: C, 63·2; H, 7·2. $C_{19}H_{25}N_3O_2S$ requires C, 63·5; H, 7·0%).

Methyl p-NN-*Diethylaminobenzoate*.—Prepared in quantitative yield by reaction of the acid with ethereal diazomethane, this *methyl ester* formed prisms (from methanol), m. p. 46—47° (Found: C, 69·4; H, 8·4. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3%).

p-NN-*Diethylaminobenzhydrazide*.—A mixture of methyl *p-NN*-diethylaminobenzoate (14 g.) and 90% hydrazine hydrate (10 c.c.) was refluxed for 18 hr. Evaporation under reduced pressure gave the hydrazide as a glass which was characterised by condensation with benzaldehyde, to give the *benzylidene derivative*, pale yellow needles (from ethanol), m. p. 218° (Found: C, 73·2; H, 7·5. $C_{18}H_{21}NO_3$ requires C, 73·2; H, 7·2%).

p-NN-*Diethylaminobenzazide*.—A solution of the crude hydrazide (6·0 g.) in 3N-hydrochloric acid (100 c.c.) was cooled to 0° and potassium nitrite (4·8 g.) in water (20 c.c.) was added dropwise with stirring and cooling. The solution was kept at 0° for 10 min., then poured into saturated aqueous sodium acetate solution at 0°, and the precipitated *azide* was collected, dried, and recrystallised from light petroleum (b. p. 40—60°) as pale yellow needles (4·2 g., 67%), m. p. 50° (Found: C, 60·7; H, 6·4. $C_{11}H_{14}N_4O$ requires C, 60·5; H, 6·5%).

Urethanes derived from p-NN-*Diethylaminobenzazide*.—(i) A solution of the azide (0·2 g.) and phenol (0·1 g.) in dry benzene (5 c.c.), when refluxed for 4 hr. and then evaporated, gave *phenyl* N-(p-NN-*diethylaminophenyl*)*carbamate*, needles (from methanol), m. p. 125—126° (Found: C, 71·5; H, 7·2. $C_{17}H_{20}N_2O_2$ requires C, 71·8; H, 7·1%).

(ii) *Cholesteryl* N-(p-NN-*diethylaminophenyl*)*carbamate*, prepared similarly, crystallised from ethanol in needles, m. p. 133°, $[\alpha]_D^{20}$ −19·6° (*c* 1·6 in $CHCl_3$) (Found: C, 79·1; H, 10·5. $C_{38}H_{60}N_2O_2$ requires C, 79·1; H, 10·5%).

N-(p-NN-*Diethylaminophenyl*)-N′-*phenylurea*, prepared by heating *p-NN*-diethylaminobenzazide with aniline in dry benzene, formed needles, m. p. 182—183° (from ethanol) (Found: C, 72·0; H, 7·5. $C_{17}H_{21}N_3O$ requires C, 72·05; H, 7·5%).

Isopropyl N-(p-NN-*Diethylaminophenyl*)*carbamate*.—Isopropyl chloroformate was treated with *p-NN*-diethylaminoaniline as described above for the reaction with *NN*-di-2′-chloroethyl-*p*-phenylenediamine. Distillation of the product gave the *urethane*, b. p. 148—150°/10^{-4} mm. (Found: C, 67·0; H, 8·7; N, 11·3. $C_{14}H_{22}N_2O_2$ requires C, 67·2; H, 8·9; N, 11·2%).

N-(p-NN-*Diethylaminophenyl*)-2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucosylamine*.—α-Acetobromoglucose was treated with *p-NN*-diethylaminoaniline, as described above for the reaction with *NN*-di-2′-chloroethyl-*p*-phenylenediamine, to give the *tetra*-O-*acetylglucosylamine*, needles (from ethanol), m. p. 135°, $[\alpha]_D^{20}$ −31° (*c* 2 in $CHCl_3$) (Found: C, 58·4; H, 7·1; N, 5·7. $C_{24}H_{34}N_2O_9$ requires C, 58·3; H, 6·9; N, 5·7%).

N-(2-NN-*Diethylaminoethyl*)-N′-*phenylurea*.—Reaction of *NN*-diethylethylenediamine with phenyl isocyanate gave the *urea*, b. p. 171°/10^{-2} mm. (Found: C, 66·5; H, 9·15; N, 17·5. $C_{13}H_{21}N_3O$ requires C, 66·3; H, 9·0; N, 17·9%). When triturated with concentrated hydrochloric acid it was rapidly converted into diphenylurea, m. p. 243°.

p-NN-*Diethylaminoacetanilide*, prepared by acetylation of the free base with acetic anhydride, had m. p. 104° after recrystallisation from aqueous ethanol (Found: C, 69·7; H, 8·8. $C_{12}H_{18}N_2O$ requires C, 69·9; H, 8·8%).

N-(p-NN-*Diethylaminophenyl*)-N′-p-*hydroxyphenylurea*.—Reaction of equimolecular proportions of *p*-aminophenol and *p-NN*-diethylaminophenyl isocyanate in boiling tetrahydrofuran gave the *urea*, m. p. 185° (from aqueous methanol) (Found: C, 68·1; H, 7·0; N, 13·85. $C_{17}H_{21}N_3O_2$ requires C, 68·2; H, 7·1; N, 14·0%).

N-p-*Aminophenyl*-N′-(p-NN-*diethylaminophenyl*)*urea*.—Similar reaction of equimolecular proportions of *p*-phenylenediamine and *p-NN*-diethylaminophenyl isocyanate gave the *urea*, m. p. 174—175° (from benzene) (Found: C, 68·7; H, 7·3; N, 18·45. $C_{17}H_{22}N_4O$ requires C, 68·4; H, 7·4; N, 18·8%).

[13] Kumler, *J. Amer. Chem. Soc.*, 1946, **68**, 1184.

1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-[N-(p-NN-*Diethylaminophenyl*)*carbamate*].—*p-NN*-Diethylaminophenyl isocyanate (4·3 g.) and 1,2:3,4-di-*O*-isopropylidene-D-galactose (6·0 g.) were heated together in a sealed tube at 100° for 20 hr. Recrystallisation of the product from light petroleum (b. p. 30—40°) at −30° gave the *carbamate* as a low-melting solid, which became a glass at room temperature (Found: C, 60·7; H, 7·6; N, 6·4. $C_{23}H_{34}N_2O_7$ requires C, 61·3; H, 7·6; N, 6·2%).

D-*Galactose* 6-[N-(p-NN-*Diethylaminophenyl*)*carbamate*].—A solution of the above di-*O*-isopropylidene compound (0·495 g.) in acetic acid (10·0 c.c.) showed α_D^{22} −1·79° (1 dm.). After addition of concentrated hydrochloric acid (10·0 c.c.) the value changed to +0·92° and became constant at +1·09° after 2 hr. The solution was then evaporated under reduced pressure to a glass, which was purified by treatment in ethanol with charcoal, followed by filtration and evaporation, to give the *carbamate hydrochloride* (Found: C, 50·2; H, 7·2; N, 6·3; Cl, 8·7. $C_{17}H_{27}ClN_2O_7$ requires C, 50·2; H, 6·7; N, 6·9; Cl, 8·7%).

Phenyl N-(p-*Carboxyphenyl*)*carbamate* (with B. J. JOHNSON).—A mixture of phenol (3·8 g.), pyridine (0·1 g.) and methyl *p*-isocyanatobenzoate (7·1 g.), heated for 2 hr. at 100°, gave *phenyl* N-(p-*methoxycarbonylphenyl*)*carbamate* (10·2 g.), m. p. 164—165° (from ethanol) (Found: C, 66·5; H, 4·8. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8%). This ester (6·0 g.) was boiled under reflux for 24 hr. in acetic acid (90 c.c.) and concentrated hydrochloric acid (30 c.c.), and the cooled solution was then diluted with water. The precipitated *acid* formed a microcrystalline powder (3·5 g.) (from acetone), m. p. >300° (Found: C, 64·9; H, 4·5; N, 5·5. $C_{14}H_{11}NO_4$ requires C, 65·35; H, 4·3; N, 5·45%).

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