58. *Respiratory Stimulants. Part I. Fully-substituted Ureas derived from αω-Alkylenediamines.*

By W. R. Boon.

Reaction of an *NN'*-disubstituted ethylene- or trimethylene-diamine with carbonyl chloride gives a mixture of the cyclic urea and the biscarbamyl chloride. The cyclic ureas show some activity as respiratory stimulants. The bis-ureas, $X{\cdot}CO{\cdot}NR{\cdot}[CH_2]_n{\cdot}NR'{\cdot}CO{\cdot}Y$ (when X and Y are secondary amine residues), obtained by reaction of the biscarbamyl chlorides with secondary amines, or preferably of a diamine with a carbamyl chloride, are in general even more potent substances. The synthesis of compounds in which R and R' are straight or branched hydrocarbon chains or are substituted by ether groups is described. Examples are given of the use of dialkylamines, cyclic bases, and dialkylamines containing ether linkages. The relationship between constitution and activity is briefly discussed.

Since Uhlmann (*Z. ges. exp. Med.*, 1924, **43**, 566) introduced pyridine-3-carboxydiethylamide (" Nikethamide ", B.P.) into medicine as a cardiac stimulant and analeptic, this substance has been widely used to combat respiratory and circulatory collapse associated with surgical emergencies. Although no conclusive evidence has ever been offered for any direct action of this substance on the heart, it is recognised that it is a powerful stimulant of the respiration, particularly if this function has been depressed by previous administration of narcotics such as morphine or the barbiturates. Nikethamide, and the other substances commonly used as analeptics, suffer from the disadvantage that the dose stimulating the respiration is very close to that causing convulsions. In addition, Das (*Quart. J. Exp. Physiol.*, 1939, **29**, 355) has shown that in cases of severe respiratory depression produced by hexobarbitone the administration of nikethamide frequently fails to stimulate the respiration and may even augment the initial depression.

There have been many attempts to obtain better respiratory stimulants among the general class of acid amides. In the pyridine series the following may be mentioned: diethylamides of pyridine-2- and -4-carboxylic acid and of 2 : 2 : 5 : 5-tetramethylpyrroline-3-carboxylic acid (Gryszkiewicz-Trochimowski, *Rocz. Chem.*, 1931, **11**, 193); pyridine-2 : 5-biscarboxydiethylamide and some complex amides of nicotinic acid (*idem*, *ibid.*, 1934, **14**, 335). Graf, Theyerl, and Purkert (*J. pr. Chem.*, 1933, **138**, 259) prepared the diethylamides of a number of nuclear-substituted nicotinic acids including pyridine-3 : 5-dicarboxylic acid; similarly F.P. 798,639 (S. C. I. Basle) claims the preparation of amides of pyridine-*o*-dicarboxylic acids as respiratory stimulants. A closely related group of substances, pyridine-3-carboxyurethanes, is described in D.R.-P. 603,733 (S. C. I. Basle).

Among other heterocyclic systems, amides (usually the diethylamides) of the following acids or groups of acids have been reported as possessing respiratory stimulant activity: pyrazinecarboxylic acid (Merck, E.P. 451,304); *iso*oxazole-, thiazole-, and pyrazole-carboxylic acids (Heffer and Reinert, *Arch. int. Pharm. Ther.*, 1937, **56**, 211; Hoffman–La Roche, E.P. 451,913); tetrazole-5-carboxylic acid (Gryszkiewicz-Trochimowski, *Rocz. Chem.*, 1933, **138**, 259); glyoxaline-4(5)-carboxylic acid (Weidenhagen and Wegner, *Ber.*, 1937, **70**, 2309); indole-3-carboxylic acid, indole-3-acetic acid, octahydroindole-3-acetic acid and thionaphthen-3-carboxylic acid; various thiazole-carboxylic acids (Erlenmeyer and von Meyenburg, *Helv. Chim. Acta*, 1937, **20**, 204; Boon, *J.*, 1945, 601) and 1 : 2-pyrone-5-carboxylic acid (J. R. Geigy A.G., E.P. 537,670).

Among carbocyclic compounds may be mentioned phthalic acid bisdiethylamide—the corresponding derivatives of *iso*- and tere-phthalic acid are said to be considerably less active (Landshoff and Meyer, E.P. 443,396)—and the dimethyl- or diethyl-amides of di- or tri-methoxy- or -ethoxy-benzoic acids (Hoffman–La Roche, E.P. 403,892).

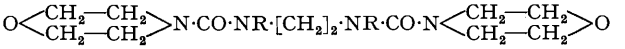
Although in most of the above publications there are statements that some or all of the products described show respiratory stimulant activity, there is a noteworthy absence of any detailed pharmacological report in nearly all cases. Only two of the many compounds described appeared to have attained to clinical use: phthalic acid bisdiethylamide has been used, mainly in Germany, under the name " Neospiran ", and 3 : 5-dimethyl*iso*oxazole-4-carboxylic acid diethylamide is used under the name " Cycliton ".

A paper by Aeschlimann (*Festschr. E. C. Barrell*, Basle, 1936, 246; *Chem. Zentr.*, 1936, III, 2944) suggested the initial experiments in the present work. In this paper it was shown that, *inter alia*, tetraethylurea and piperazine-1 : 4-biscarboxydiethylamide possessed respiratory stimulant properties. It was decided, therefore, to examine the reaction between carbonyl

chloride and some *NN'*-dialkyl-ethylene- or -trimethylene-diamines which was expected to give either a 1 : 3-dialkyliminazolidine-2-one (or the corresponding hexahydropyrimidone) or a biscarbamyl chloride. Both of these types of compound were considered to be of interest. The former may be regarded as a fully alkylated urea, and the latter as a derivative of piperazine-1 : 4-dicarboxylic acid in which one side of the ring has been broken. Both the cyclic ureas and the bisureas resulting from the reaction of the biscarbamyl chlorides with secondary amines showed respiratory stimulant activity. In general, the latter class of compound was more active; this fact, combined with the greater possibilities of chemical elaboration offered by it, led to its selection for more detailed study.

Although a detailed report on the pharmacology of these compounds will be published elsewhere, the following notes on the main conclusions to be drawn from results of their pharmacological evaluation by Dr. J. Raventos are given so that the lines of development of the chemical work may be more readily appreciated.

In the series of compounds represented by the general formula $X{\cdot}CO{\cdot}NR{\cdot}[CH_2]_n{\cdot}NR'{\cdot}CO{\cdot}Y$, lengthening the hydrocarbon chain between the diamine nitrogen atoms increases the activity if X, Y, R, and R' are kept constant, but at the same time the solubility in water is decreased and the toxicity is raised. The nature of the groups R and R' has a very pronounced effect on the activity; in general, a regular increase occurs from methyl to *n*-butyl, and branching of the chain, unsaturation, or the introduction of ether linkages reduces the activity. In the series of compounds



activity increases in the order

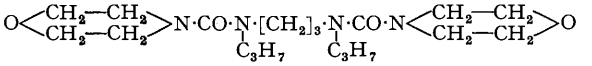
$$R = Me = CMe_3 = CHMeEt < Et < CHMe_2 < CH_2{\cdot}CH{:}CH_2 < CH_2{\cdot}CHMe_2 < n\text{-}Pr < n\text{-}Bu$$

In symmetrical compounds where X = Y the degree of activity is generally in the following order :

$$NMe{\cdot}C_2H_4{\cdot}OMe < NMe_2 < O\langle \begin{matrix} CH_2{-}CH_2 \\ CN_2{-}CN_2 \end{matrix} \rangle N < NMe{\cdot}C_2H_4{\cdot}OEt < NEt{\cdot}C_2H_4{\cdot}OMe$$
$$< NEt{\cdot}C_2H_4{\cdot}OEt < NMe{\cdot}CHMe_2 < NEt_2 < NC_5H_{10}$$

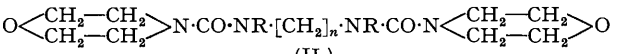
Unsymmetrical compounds, in general, possess the mean of the activities of the two related symmetrical compounds.

Although these conclusions are true in outline, there are numerous exceptions; thus NN'-*di*-n-*propyltrimethylenediamine*-NN'-*biscarboxymorpholide* (I) possesses only one-twelfth of the activity of the corresponding ethylenediamine derivative.



(I.)

In spite of the above generalisations of the effect of changes in portions of the structure on the activity of the product, it is, nevertheless, true that the value of a compound depends more on a suitable balancing of different groups within the molecule. In general, it appears that the most active compounds are those which are distributed approximately equally between water and hydrocarbon solvents; this is most readily illustrated by the compounds of general formula (II).



(II.)

If the strongly hydrophilic morpholine residue is combined with a short-chain substituent, R = Me or Et, the products have very high water-solubility with low solubility in hydrocarbon solvents and low respiratory-stimulant activity. As R is increased to propyl or *n*-butyl the solubility in hydrocarbon solvents increases and very potent stimulants are obtained, with approximately twelve times the activity of nikethamide. Both of these substances have a prolonged period of action, longer than that of picrotoxin, which itself is some ten times longer than that of nikethamide. Unlike picrotoxin, however, these two substances stimulate the depressed respiration at doses far removed from those causing convulsions or death. Prolonged activity appears to be associated with a combination of the morpholine residue with a three- or four-carbon substituent on the diamine nitrogen. Replacing the morpholine residue by another hydrophilic grouping such as methyl-2-ethoxyethylamine, or lengthening the diamine

chain in conjunction with a morpholine residue associated with a methyl or ethyl group on the diamine nitrogen atoms, does not lead to prolonged action.

The two most interesting compounds with a short duration of action are NN′-*dimethyltrimethylenediamine*-NN′-*biscarboxydiethylamide* and NN′-*di*-n-*propylethylenediamine*-NN′-*biscarboxydimethylamide*. Both of these substances are approximately twice as active as nikethamide, but whereas the ratio of convulsant dose to stimulant dose is 7·5 in the case of the former compound compared with 2·8 for nikethamide, the latter compound is devoid of convulsant action. Both of these substances, unlike nikethamide, may be administered repeatedly without any habituation. By the continuous administration of a suitable mixture of a short-acting barbituric acid derivative, such as hexobarbitone, and either of these compounds it is possible to maintain an animal under anæsthesia with its respiratory activity at the normal conscious level.

Derivatives of ethylene- and trimethylene-diamine, reacting with carbonyl chloride, gave approximately equal yields of urea and carbamyl chloride.

Conversion of the biscarbamyl chlorides into bisureas by reaction with secondary amines proceeded smoothly in all cases; this reaction in fact was used to identify the biscarbamyl chlorides, since in most cases it was not possible to purify these substances for analysis as they were liquids which decomposed on distillation with loss of carbonyl chloride and formation of what appeared to be linear polyureas which could not be purified. In general, it was more convenient to prepare the bisurea by reaction of the diamine with a carbamyl chloride. In most cases the reaction proceeded substantially to completion, but in others appreciable quantities of amino-ureas were obtained. In general, the reactivity of the carbamyl chloride (Z·COCl) appeared to be in the following order :

$$Z = NMe_2 > NEt_2 > NC_5H_{10} > O\langle\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}\rangle N > NEt\cdot C_2H_4\cdot OEt > N(C_2H_4\cdot OEt)_2$$

The nature of the substituent on the diamine nitrogen atom also affected the result; alkoxyethyl groups, in particular, produced a marked decrease in reactivity.

Unsymmetrical bisureas of type X·CO·NR·$[CH_2]_n$·NR·CO·Y were made by reaction of a carbamyl chloride with an excess of diamine to give a monourea of type X·CO·NR·$[CH_2]_n$·NRH, which was then caused to react with a different carbamyl chloride.

Unsymmetrical bisureas of the type X·CO·NR·$[CH_2]_n$·NR′·COX were readily made by reaction of the appropriate unsymmetrical diamine with a carbamyl chloride.

The numerous diamines required in this work have been prepared by three methods, the choice of method being governed partly by convenience and partly by the unsuitability of the alternative routes in a particular case.

The most convenient method for preparing *NN′*-dimethylethylenediamine, the simplest member of the series, was by decomposition of *NN′*-di-(4-nitrosophenyl)-*NN′*-dimethylethylenediamine with sodium hydrogen sulphite, essentially according to the method of Esch and Marckwald (*Ber.*, 1900, **33**, 762). The parent *NN′*-diphenyl-*NN′*-dimethylethylenediamine was best prepared by a modification of the method of Dunlop and Jones (*J.*, 1909, **95**, 417), involving condensation of ethylene dibromide with methylaniline; the alternative method of Thorpe and Wood (*J.*, 1913, **103**, 1608), involving condensation of ethylene dibromide with dimethylaniline, consistently failed, 1 : 4-diphenylpiperazine being the only product identified. Condensation of ethylene dibromide with *iso*propylaniline did not proceed so readily, and some 1 : 4-diphenylpiperazine was formed as well as NN′-*diphenyl*-NN′-*di*iso*propylethylenediamine*; none of the former was detected when ethylene dibromide was condensed with methyl- or ethyl-aniline. The diamine derivative could not be converted into *NN′*-di*iso*propylethylenediamine.

An attempt was made to prepare *NN′*-diphenyl-*NN′*-diethyltetramethylenediamine by reaction of ethyl-2-chloroethylaniline with sodium. Although the product analysed satisfactorily for nitrogen it did not give *NN′*-diethyltetramethylenediamine on nitrosation and subsequent hydrolysis.

All of the above compounds have been converted into the corresponding disecondary amines by the action of sodium hydrogen sulphite on their nitroso-derivatives (cf. Esch and Merckwald, *loc. cit.*). None of the nitroso-compounds has been isolated in the pure state : this was usually difficult and was not necessary. Where a hydrochloride of the nitroso-compound separated, this was filtered off and decomposed by heating with sodium hydrogen sulphite solution; otherwise an excess of the latter reagent was added to the reaction mixture resulting from the nitrosation. Yields were variable, but owing to the nature of the reactions involved it is not

possible to decide the relative efficiency of the operation at different stages in any particular case.

Many disecondary diamines have been made by hydrolysis of the corresponding *p*-toluenesulphonamide derivatives with 80% sulphuric acid at 140° instead of the less convenient method (Schneider, *Ber.*, 1895, **28**, 3074) involving heating with fuming hydrochloric acid under pressure. This method failed with *di*-p-*toluenesulphonyl*-NN′-*diallylethylenediamine* which charred when it was mixed with the acid, and with *di*-p-*toluenesulphonyl*-NN′-*di*iso*propylethylenediamine*.

The requisite sulphonamides were made either by alkylating the toluenesulphonyl derivative of the primary diamine or by reaction between a sulphonamide of a primary monoamine and a suitable dihalogeno-compound. The corresponding reaction between *p*-toluenesulphonamide and a dihalogeno-compound occurs satisfactorily only with ethylene dibromide. With higher alkylene dibromides the complications resulting from ring formation render the method unworkable. For instance, from the condensation of trimethylene dibromide with *p*-toluenesulphonamide it was possible to isolate di-*p*-toluenesulphonyltrimethylenediamine in only very poor yield; *p*-toluenesulphonyltrimethyleneimine and 1 : 5-di-*p*-toluenesulphonylbistrimethylenediamine were also identified. Marckwald and v. Droste-Huelshoff (*Ber.*, 1898, **31**, 3265) identified only the last two products from a similar reaction. Usually the sulphonamide of the primary diamine was alkylated in aqueous alcoholic solution.

The condensation of the dihalogeno-compounds with the sodium salts of *p*-toluenesulphonalkylamides was carried out in boiling xylene. No reaction occurred between ethylene dibromide and *p*-toluenesulphon*iso*butylamide under these conditions; this is in agreement with Wedekind's observation (*Ber.*, 1909, **42**, 3941) that the unstable sodium salt of *p*-toluenesulphon*iso*butylamide is very unreactive.

The direct formation of a disecondary amine by reaction of a dihalide with an excess of a primary amine has been used in several cases, mainly those in which one or other of the above methods broke down, *e.g.*, in the preparation of NN′-*diallyl*- and NN′-*di*iso*propyl-ethylenediamine*, or were markedly inefficient, *e.g.*, NN′-*di*iso*butylethylenediamine*, or were judged to be inapplicable, *e.g.*, NN′-*di*-tert.-*butylethylenediamine* or NN′-*di*-(2-*ethoxyethyl*)*ethylenediamine*.

Dihalogeno-compounds in which the halogen atoms are separated by more than two carbon atoms usually give very poor results. In general, where free choice is possible, methods involving the degradation of a suitable tertiary or quaternary nitrogen compound are better than the direct synthesis of a disecondary amine by this last method.

The 2-alkoxyethylamines were readily obtained by catalytic reduction of the corresponding alkoxyacetonitriles in presence of Raney nickel. This method of preparation is much simpler than those reported in the literature.

A series of alkyl-alkoxyethylamines as well as *di*-(2-*ethoxyethyl*)*amine* have been prepared from the corresponding aniline derivatives by hydrolysis of the nitroso-compounds. An alternative procedure used in some cases was alkylation of an alkoxyethylamine: this is more convenient if the alkoxyethylamines are available.

Experimental.

Preparations marked by an asterisk were made by Dr. J. A. Hendry. Microanalyses are by Mr. E. S. Morton M. p.'s are corrected.

(1) *Aniline Derivatives.*—*NN′*-Diphenyl-*NN′*-dimethylethylenediamine was made by the following modification of Dunlop and Jones's method (*loc. cit.*). Ethylene dibromide (1128 g., 6 mols.), methylaniline (1819 g., 17 mols.), and anhydrous sodium carbonate were heated under reflux with stirring at 105° for 24 hours. The excess of methylaniline was then removed by steam-distillation, and the residue was cooled while stirring was continued, and filtered off. The product was washed thoroughly with cold water and air-dried; yield 1355 g. (83%), m. p. 49°, raised by crystallisation from methanol to 50°. The crude product was suitable for conversion into *NN′*-dimethylethylenediamine. The following amines were made by similar methods: *NN′*-diphenyl-*NN′*-diethylethylenediamine, m. p. 75°, yield 90%; *NN′*-diphenyl-*NN′*-dimethyltrimethylenediamine, b. p. 230°/16 mm., m. p. 46°, yield 84%; *NN′*-diphenyl-*NN′*-diethyltrimethylenediamine, b. p. 236°/20 mm., m. p. 39° (from petrol, b. p. 60—80°); yield 85%: Fröhlich (*Ber.*, 1907, **40**, 764) describes this compound as an uncrystallisable oil.

NN′-*Diphenyl*-NN′-*di*iso*propylethylenediamine*. The crude *product*, b. p. 234—239°/28 mm., contained much 1 : 4-diphenylpiperazine which was separated by crystallisation from ethanol; the residue from the evaporation of the mother-liquors was recrystallised from petrol (b. p. 60—80°); m. p. 62°, yield 21% (Found: C, 81·0; H, 9·05; N, 9·6. $C_{20}H_{28}N_2$ requires C, 81·0; H, 9·45; N, 9·45%). By heating at 120° for 17 hours under an air condenser the yield was raised to 60% with only a trace of piperazine formation.

Ethyl-2-chloroethylaniline was made by the following modification of the method given in D.R.-P. 650,259 (I.G. Farbenind. A.G.; Friedländer, Vol. 22, p. 286): To thionyl chloride (190 g., 1·6 mols.), dissolved in toluene (100 c.c.), was added with stirring below 2° a solution of ethyl-2-hydroxyethylaniline (247 g., 1·5 mols.) in toluene (650 c.c.). After being stirred at room temperature overnight, the

reaction mixture was poured on ice, basified with sodium carbonate, and the toluene layer separated. Distillation of the toluene solution after drying (Na_2SO_4) gave 235 g. (82·5%) of ethyl-2-chloroethylaniline, b. p. 163—164°/42 mm. *Ethyl-3-chloropropylaniline* was made in a similar manner from ethyl-3-hydroxypropylaniline in 64% yield; b. p. 161°/30 mm. (Found: N, 7·4. $C_{11}H_{16}NCl$ requires N, 7·1%). The *hydroxy*-compound (b. p. 168—172°/16 mm.) was made by condensation of trimethylene chlorohydrin (Gough and King, *J.*, 1928, 2439) with ethylaniline substantially according to Laun's method (*Ber.*, 1884, **17**, 677) for the preparation of ethyl-2-hydroxyethylaniline (Found: C, 73·6; H, 9·3; N, 8·0. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·5; N, 7·8%).

NN'-*Diphenyl*-N-*methyl*-N'-*ethylenediamine*. Methylaniline (870 g., 8·1 mols.) and ethyl-2-chloroethylaniline (393 g., 2·15 mols.) were heated together on the steam-bath for 16 hours. Water (500 c.c.) and 32% sodium hydroxide (175 c.c.) were then added, and the oily layer separated and distilled. The product had b. p. 226—228°/16 mm., m. p. after recrystallisation from methanol 35°; yield 450 g. (83%). NN'-*Diphenyl*-N-*methyl*-N'-*ethyltrimethylenediamine* was similarly obtained in 84% yield from methylaniline and ethyl-3-chloropropylaniline; it had b. p. 216°/16 mm. (Found: N, 10·7. $C_{18}H_{24}N_2$ requires N, 10·45%).

Ethyl-2-methoxy- and -2-ethoxy-ethylaniline were first made by condensation of the appropriate glycol ether *p*-toluenesulphonate with ethylaniline (B.P. 422,843). The following method was more convenient: Ethyl-2-hydroxyethylaniline (375 g., 2·25 mols.) was dissolved in toluene (750 c.c.) and the solution dried by distillation until a clear distillate was obtained; after it had cooled to 40°, sodium (46 g., 2 mols.) was added. When the initial reaction had subsided, the mixture was boiled for 6 hours to dissolve all the sodium. The solution of the sodium derivative was cooled to 10°, and methyl sulphate (252 g., 2 mols.) was added with stirring below 25°. After standing for 48 hours, the solution was washed with water and extracted with dilute hydrochloric acid. The oil which separated on basifying the acid solution was distilled, giving 325 g. (80%) of ethyl-2-methoxyethylaniline, b. p. 130°/11 mm.

Methyl-2-methoxyethylaniline, b. p. 125°/15 mm., and *methyl-2-ethoxyethylaniline*, b. p. 142°/23 mm. (Found: C, 73·4; H, 9·5. $C_{11}H_{17}ON$ requires C, 73·6; H, 9·0%), were made similarly.

*Di-(2-ethoxyethyl)aniline.** Di-(2-hydroxyethyl)aniline (271 g., 1·5 mols.), dissolved in toluene (500 c.c.), was added with stirring during 45 minutes to a suspension of sodium (69 g., 3 mols.) in toluene (150 c.c.) the temperature being kept at 100—110°. After a further 6 hours' heating, the temperature was lowered to 20°, and methyl sulphate (462 g., 3·66 mols.) in toluene (500 c.c.) was added so that the temperature did not rise above 30°. After 12 hours' stirring at room temperature, water (500 c.c.) was added, and the toluene layer separated and extracted with dilute hydrochloric acid. The extract was basified with sodium hydroxide, extracted with benzene, and the extract dried (Na_2SO_4). Distillation gave 140 g. (39%) of *di-(2-ethoxyethyl)aniline*, b. p. 187—189°/25 mm. (Found: C, 70·65; H, 9·45; N, 6·1. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7; N, 5·9%).

(2) *Sulphonamides.—Condensation of* p-*toluenesulphonamide and trimethylenedibromide*. *p*-Toluenesulphonamide (213 g., 1·25 mols.) was dissolved in ethanol (325 c.c.) and 32% sodium hydroxide (153 g., 1·25 mols.); trimethylene dibromide (126 g., 0·625 mol.) was added, and the whole heated under reflux for 15 hours. The alcohol was distilled off, and water added together with sufficient hydrochloric acid to make the residue acid to Congo-red. The supernatant liquid was poured off, and the residual oil triturated with an excess of 15% sodium hydroxide. The solid which separated was filtered off and fractionally crystallised from ethanol to give *p*-toluenesulphontrimethyleneimide, m. p. 120°, and 1 : 5-di-*p*-toluenesulphonylbistrimethylenediamine, m. p. 215°. By acidification of the alkaline solution, crude di-*p*-toluenesulphonyltrimethylenediamine was obtained contaminated with much *p*-toluenesulphonamide. The latter was removed by repeated boiling out with water, and the trimethylenediamine derivative purified by three crystallisations from ethanol; yield 35 g., m. p. 148°.

Di-*p*-toluenesulphonylhexamethylenediamine was made in practically theoretical yield from hexamethylenediamine and *p*-toluenesulphonyl chloride by the normal Schotten–Baumann procedure; m. p. 149° (from ethanol) (Found: C, 56·1; H, 7·1; N, 6·9. Calc. for $C_{20}H_{28}O_4N_2S_2$: C, 56·6; H, 6·7; N, 6·7%).

*Di-*p-*toluenesulphonyldialkyl-alkylenediamines*. (A) To the di-*p*-toluenesulphonylalkylenediamine (1 mol.), dissolved in methanol and 32% sodium hydroxide (1·1 mols.) cooled in an ice-bath, the appropriate alkyl sulphate or alkyl halide (2·25 mols.) was added during 2 hours, and after a further hour's stirring at room temperature, reaction was completed by 4 hours' heating under reflux. After cooling, the product was filtered off, washed with a little methanol, then with water and dried.

(B) To sodium (2 mols.) suspended in xylene at 105°, ethanol (3·2 mols.) was added with stirring. After cooling to 60°, the *p*-toluenesulphonalkylamide (2 mols.) was added, and the ethanol removed by distillation. The alkylene dibromide (1 mol.) was then added, and heating continued at 130—135° for 17 hours. The reaction mixture was then cooled to 20°, and the solid filtered off and washed first with methanol and then with water. Table I gives details of the compounds prepared. p-*Toluenesulphonmethyliso*propylamide, required for the preparation of methyl*iso*propylamine, was made in 89% yield by method B from *p*-toluenesulphon*iso*propylamide and methyl sulphate; b. p. 226°/40 mm., m. p. 78° (from petrol, b. p. 60—80°) (Found: C, 58·7; H, 7·1; N, 6·2. $C_{11}H_{17}O_2N_5$ requires C, 58·2; H, 7·5; N, 6·2%).

(3) *Diamines*.—The following are details of typical experiments involving the three different methods employed.

(A) *By hydrolysis of a di-*p-*toluenesulphonyl derivative*. The di-*p*-toluenesulphonyl derivative (1 mol.) was dissolved with stirring in concentrated sulphuric acid (98%, 8·2 mols.), water (9 mols.) added, and the resulting suspension heated with stirring for 7 hours at 140—145°. It was then cooled, diluted with water, and made alkaline to Clayton-yellow by addition of 32% sodium hydroxide. This solution was then steam-distilled until the distillate was only faintly alkaline to brilliant-yellow. After the distillate had been acidified to Congo-red by hydrochloric acid, it was evaporated to dryness. The free base was obtained by dissolving the dihydrochloride in a 10% excess of 32% sodium hydroxide, and the solution evaporated to dryness under reduced pressure. The distillate was then saturated with sodium hydroxide, the oily layer separated, dried over potassium hydroxide, and finally distilled from sodium.

TABLE I.

Di-p-*toluenesulphonamides*, $C_7H_7 \cdot SO_2 \cdot NR \cdot [CH_2]_n \cdot NR \cdot SO_2 \cdot C_7H_7$.

R.	*n*.	Method of prep.	Yield, %.	M. p.	Solvent.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me	2	A	85	164°	HOAc	$C_{18}H_{25}O_4N_2S_2$	54·4	6·7	7·3	54·5	6·1	7·1
Et	2	A	60	158	,,	$C_{20}H_{28}O_4N_2S_2$	56·35	6·5	6·7	56·5	6·6	6·6
Pr$^{\alpha}$	2	A	66	122	,,	$C_{22}H_{32}O_4N_2S_2$	58·8	7·4	6·2	58·3	7·2	6·2
Pr$^{\beta}$	2	A	8	221	$CH_2(OMe) \cdot CH_2 \cdot OH$	$C_{22}H_{32}O_4N_2S_2$	58·4	6·95	6·2	58·3	7·2	6·2
Allyl	2	A	75	146	HOAc	$C_{22}H_{28}O_4N_2S_2$	59·1	6·0	6·3	58·7	6·2	6·2
n-Bu	2	A	66	119	MeOH	$C_{24}H_{36}O_4N_2S_2$	59·5	7·3	5·9	59·9	7·5	5·8
iso-Bu	2	A	19	143	EtOH	$C_{24}H_{36}O_4N_2S_2$	60·1	7·9	5·5	59·9	7·5	5·8
Me	3	A	50	113	MeOH	$C_{19}H_{26}O_4N_2S_2$	56·0	6·4	6·95	55·6	6·34	6·8
Et	3	A	—	68	EtOH	$C_{21}H_{30}O_4N_2S_2$	—	—	6·2	—	—	6·4
Pr$^{\alpha}$	3	B	57	47 (b. p. 280—290°/0·1 mm.)	Petrol (b. p. 40—60°)	$C_{23}H_{34}O_4N_2S_2$	59·3	7·1	5·85	59·2	7·2	6·0
Me	4	B	88	131	EtOH	$C_{20}H_{28}O_4N_2S_2$	57·2	7·2	6·2	56·7	6·6	6·6
Me	5	B	98	61 (b. p. 285°/0·4 mm.)	,,	$C_{21}H_{30}O_4N_2S_2$	57·2	6·9	6·3	57·5	6·85	6·4
Me	6	A	84	140	HOAc	$C_{22}H_{32}O_4N_2S_2$	57·9	7·0	6·3	58·4	7·1	6·2
Et	6	A	81	115	EtOH	$C_{24}H_{36}O_4N_2S_2$	60·0	7·5	6·2	59·9	7·5	5·8

(B) *From a dianilino-derivative.* The *NN'*-diphenyl-*NN'*-dialkylalkylenediamine (1 mol.) was dissolved in concentrated hydrochloric acid (6·3 mols.) and diluted with ice (92·5 mols.). Sodium nitrite (2·22 mols.) in approximately twice its weight of water was then added with stirring during 30 minutes. After a further 30 minutes' stirring, the precipitated nitroso-compound was filtered off, pressed dry, suspended in a 20% aqueous solution of sodium hydrogen sulphite (7·5 mols.), and heated at 90—95° for 5 hours. The resulting solution was then made acid to Congo-red by addition of concentrated hydrochloric acid and concentrated to half its volume. This solution, after being made alkaline to Clayton-yellow by addition of solid sodium hydroxide, was steam-distilled, and the hydrochloride and base isolated as above.

In the preparation of *N*-methyl-*N'*-ethylethylenediamine, the hydrochloride of the nitroso-compound separated slowly and was filtered off after the reaction mixture had stood in ice for 17 hours.

(C) *By reaction of an alkylene dibromide with a primary amine.* The bromide (1 mol.), amine (5 mols.), and water (*ca.* 3 mols.) were heated under reflux for 15 hours. An excess of 32% sodium hydroxide was then added, and the excess of primary amine removed by distillation. The residual solution was then distilled to dryness under reduced pressure, and the diamine salted out from the distillate with solid sodium hydroxide, dried, and distilled in the usual way. The reaction with methyl- or *iso*propyl-amine was carried out in an autoclave. With allylamine or 2-methoxy- or 2-ethoxy-ethylamine the reaction in the early stages was vigorously exothermic. Details of the various preparations are given in Table II. None of the free bases was analysed owing to the marked tendency of most of them to take up water and carbon dioxide, but most of the *hydrochlorides* were analysed.

(4) *Carbamyl Chlorides from Secondary Amines.*—Dimethyl- and diethyl-carbamyl chlorides were prepared essentially according to the method of Lumière and Perrin (*Bull. Soc. chim.*, 1904, **31**, 689). Attention to the following points gave a consistently good yield (75%); the amine in toluene was added to an excess (*ca.* 3 mols.) of carbonyl chloride in toluene below −10°; the amine hydrochloride was best removed by washing with ice-water followed by rapid drying of the toluene solution with calcium chloride. The following were also prepared by this method: Piperidine-*N*-carboxychloride, b. p. 119°/18 mm.; *morpholine*-N-*carboxychloride*, b. p. 137—138°/33 mm. (Found: C, 40·05; H, 5·5; N, 9·1. $C_5H_8O_2NCl$ requires C, 40·2; H, 5·35; N, 9·3%); *di*-(2-*ethoxyethyl*)*carbamyl chloride*,* b. p. 165°/19 mm. (Found: C, 48·15; H, 8·4; N, 6·4. $C_9H_{18}O_5NCl$ requires C, 48·3; H, 8·05; N, 6·3%); and *ethyl*-2-*ethoxyethylcarbamyl chloride*,* b. p. 108°/20 mm. (Found: C, 47·1; H, 7·85; N, 7·5. $C_7H_{14}O_2NCl$ requires C, 46·8; H, 7·8; N, 7·8%).

(5) 2-*Alkoxyethylamines.*—These were made by reducing the following alkoxyacetonitriles over a Raney nickel catalyst; yields varied from 65 to 75%: methoxyacetonitrile (Henze and Righer, *J. Amer. Chem. Soc.*, 1934, **56**, 1350), ethoxyacetonitrile (Gautier, *Ann. Chim.*, 1909, **16**, 302), *iso*propoxy-acetonitrile (Henze *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1222), and *n*-butoxyacetonitrile (Hurd and Fowler, *ibid.*, 1939, **61**, 252). The following two amines are new. 2-*iso*Propoxyethylamine, b. p. 116—118°; *picrolonate*, from ethanol, m. p. 201—202° (Found: C, 48·6; H, 5·75; N, 19·1. $C_{15}H_{21}O_6N_5$ requires C, 49·0; H, 5·7; N, 19·1%). 2-n-*Butoxyethylamine*, b. p. 148—150°/22 mm. (Found: N, 11·4. $C_6H_{15}ON$ requires N, 11·9%); *picrolonate*, from ethanol, m. p. 172° (Found: C, 50·6; H, 5·6; N, 18·9. $C_{16}H_{23}O_6N_5$ requires C, 50·4; H, 6·0; N, 18·4%).

(6) *Secondary Monoamines containing Ether Groups.*—*Methyl*-2-*methoxyethylamine.* To methyl-2-methoxyethylaniline (165 g., 1 mol.), dissolved in concentrated hydrochloric acid (272 c.c.) and water (500 c.c.), sodium nitrite (74 g.) in water (125 c.c.) was added below 2°. After nitrosation was complete, the solution was added with stirring to a boiling solution of sodium hydroxide (275 g.) in water (5600 c.c.) in an iron pot arranged for distillation. Distillation was continued until the distillate was only faintly alkaline to brilliant-yellow paper. The total distillate was then acidified with hydrochloric acid, concentrated to 300 c.c., basified with 32% sodium hydroxide, and distilled to dryness. The amine was salted out from the distillate with sodium hydroxide, dried first over potassium hydroxide and then over sodium, and distilled; yield 45 g. (51%); b. p. 98—99°; *picrolonate*, from ethanol, m. p. 205° (Found: C, 48·3; H, 5·7; N, 20·0. $C_{14}H_{19}O_6N_5$ requires C, 47·8; H, 5·4; N, 19·8%). The following were made similarly: methyl-2-ethoxyethylamine (57%), b. p. 116—117°; ethyl-2-methoxyethylamine (64%), b. p. 117—119° [*picrolonate*, m. p. 222—223° (from ethanol) (Found: C, 49·0; H, 5·75. $C_{15}H_{21}O_6N_5$ requires C, 49·0; H, 5·7%)].

Ethyl-2-*ethoxyethylamine.* (*a*) The nitroso-compound (free base) was decomposed with sodium hydrogen sulphite as in the preparation of the diamines above; yield 20%; b. p. 129—130°. (*b*)* Ethyl bromide (109 g., 1 mol.), 2-ethoxyethylamine (220 g., 2·5 mols.), and water (50 c.c.) were heated in an autoclave at 90—100° for 24 hours; the mixture was then saturated with sodium hydroxide, and the amine isolated and distilled in the usual manner; yield 50 g., 42%; *picrolonate*, m. p. 181—182° (from ethanol) (Found: C, 50·25; H, 6·2; N, 18·9. $C_{16}H_{23}O_6N_5$ requires C, 50·3; H, 6·05; N, 18·4%).

Di-(2-*ethoxyethyl*)*amine.** (*a*) To a solution of di-(2-ethoxyethyl)aniline (116·2 g., 0·5 mol.) in concentrated hydrochloric acid (160 c.c.) and water (80 c.c.), sodium nitrite (40 g., 0·58 mol.) in water (100 c.c.) was added with stirring below 5°. Stirring was then continued for 30 minutes and concentrated aqueous ammonia was then added until the solution was alkaline to brilliant-yellow, and the nitroso-base was extracted with chloroform (100 c.c.). The extract was washed with water, dried (Na_2SO_4), and the chloroform removed by distillation under reduced pressure; 20% sodium hydrogen sulphite (2000 c.c.) was added to the residue, and the mixture was heated under reflux for 2 hours. The whole was then acidified to Congo-red with concentrated hydrochloric acid, concentrated to approximately 1500 c.c., basified with sodium hydroxide, and steam-distilled until the distillate was only faintly alkaline to brilliant-yellow. The distillate (6 l.), after being acidified with hydrochloric acid, was evaporated to dryness, and the residue was basified with sodium hydroxide and extracted with ether after saturation with solid sodium hydroxide. The ether extract after drying over potassium hydroxide was fractionated, giving 22 g. (27·5%) of di-(2-ethoxyethyl)amine, b. p. 198—200°; *picrolonate*, from ethanol, m. p. 161° (Found: C, 51·4; H, 6·55; N, 16·9. $C_{18}H_{27}O_7N_5$ requires C, 50·9; H, 6·35; N, 16·5%).

(*b*) 2-Ethoxyethyl chloride (108 g., 1 mol.), 2-ethoxyethylamine (200 g., 1·7 mols.), and water (25 c.c.) were heated under reflux for 20 hours. After cooling, the solution was saturated with sodium

TABLE II.

Alkylenediamines, NHR·[CH_2]$_n$·NHR′.

R = R′.	*n*.	Method of prepn.	Yield, %.	B. p.	M. p. of dihydrochloride.	Solvent.‡	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me	2	A	80	120°	235° (d.)								
		B	75										
		C	15										
Me (Et) [1]	2	B	44	135	235								
Et	2	A	80	151—152	266								
		B	50										
Pr$^{\alpha}$	2	A	91	186—189	300 (d.)	W–A	$C_8H_{22}N_2Cl_2$	44·4	9·6	—	44·3	10·1	—
Pr$^{\beta}$	2	A	0	169—171	250 (d.)	E–A	$C_8H_{22}N_2Cl_2$	44·8	10·1	12·6	44·3	10·1	12·8
		B	0										
		C	38										
Allyl	2	A	0	198—200	250 (d.)	EtOH	$C_8H_{18}N_2Cl_2$	44·8	8·5	13·2	45·1	8·5	13·2
		C	41										
n-Bu	2	A	80	226—228	295—300(d.)	W–A	$C_{10}H_{26}N_2Cl_2$	48·7	10·2	—	49·0	10·6	—
iso-Bu	2	A	90	212—214	285 (d.) †	EtOH	$C_{10}H_{26}N_2Cl_2$			29·1 §			29·0 §
		C	57										
sec.-Bu	2	C	51	210	187	E–A	$C_{10}H_{26}N_2Cl_2$	—	—	11·5	—	—	11·4
tert.-Bu	2	C	42	196—198	275—280 (d.)	E–A	$C_{10}H_{26}N_2Cl_2$	49·4	11·0	—	49·0	10·6	—
*cyclo*Hexyl	2	C	78	312	265	EtOH	$C_{14}H_{30}N_2Cl_2$	56·8	9·95	9·2	56·5	10·1	9·4
C_2H_4·OMe	2	C	44	240—241	196	E–A	$C_8H_{20}O_2N_2Cl_2$	38·5	8·7	—	38·5	8·8	—
C_2H_4·OEt	2	C	50	256—258	212	E–A	$C_{10}H_{26}O_2N_2Cl_2$	43·0	8·7	9·7	43·3	9·3	10·1
C_2H_4·OPr$^{\beta}$	2	C	33	—	231	E–A	$C_{12}H_{30}O_2N_2Cl_2$	47·6	9·95	9·4	47·3	9·8	9·2
Me	3	B	80	145	266	EtOH	$C_5H_{16}N_2Cl_2$	34·7	9·2	15·7	34·3	9·15	15·9
Me (Et) [1]	3	B	72	158	270	,,	$C_6H_{18}N_2Cl_2$	—	—	14·75	—	—	14·8
Et	3	B	46	170—173	>300	,,	$C_7H_{20}N_2Cl_2$	41·7	9·8	35·4 §	41·7	9·85	35·0 §
Pr$^{\alpha}$	3	A	68	212—216	300	E–A	$C_9H_{24}N_2Cl_2$	47·6	10·5	—	47·2	10·4	—
Me	4	A	70	164	275 (d.)	W–E	$C_6H_{18}N_2Cl_2$	37·9	9·5	14·4	38·1	9·5	14·8
Me	5	A	41	190	254 (d.)	E–A	$C_7H_{20}N_2Cl_2$	41·2	9·7	—	41·2	9·8	—
Me	6	A	80	205	210	E–A	$C_8H_{22}N_2Cl_2$	43·9	9·9	12·8	44·1	10·1	12·8
Et	6	A	77	228	278	EtOH	$C_{10}H_{26}N_2Cl_2$	48·6	10·9	—	48·8	10·6	—
C_2H_4·OEt	6	C	30	190—193 /18 mm.	262 (d.)	,,	$C_{14}H_{34}O_2N_2Cl_2$	50·8	10·5	8·7	50·5	10·2	8·4

[1] In these two compounds R = Me, R′ = Et.
† Rameau (*Rec. Trav. chim.*, 1938, **57**, 206) gives m. p. 130° for this hydrochloride.
‡ W–A = Water–acetone; E–A = ethanol–acetone; W–E = water–ethanol.
§ These data refer to Cl.

hydroxide, and the base layer separted, dried over potassium hydroxide, and distilled, giving 98 g. (61%) of di-(2-ethoxyethyl)amine.

(7) *Biscarbamyl Chlorides and Cyclic Ureas.*—The experiments in this section, in which a diamine was treated with carbonyl chloride, were designed to give the biscarbamyl chlorides as well as the cyclic ureas.

1 : 3-*Dimethyliminazolid-2-one and* NN′-*dimethylethylenediamine-*NN′-*dicarboxychloride.* To a solution of carbonyl chloride (170 g.) in toluene (1000 c.c.), a solution of *NN′*-dimethylethylenediamine (145 g.) in toluene (500 c.c.) was added with stirring below — 15°. The excess of carbonyl chloride was then removed by a stream of dry air, and the amine hydrochloride was filtered off and washed with chloroform. The combined filtrate and washings were then distilled, giving 30 g. of crude 1 : 3-dimethyliminazolid-2-one, b. p. 129°/39 mm., and an undistillable residue of *NN′*-dimethylethylenediamine-*NN′*-dicarboxychloride. The first fraction was dissolved in water (100 c.c.), and the solution saturated with potassium carbonate and extracted with chloroform. After drying (K_2CO_3), the extract was distilled, giving 24 g. of 1 : 3-*dimethyliminazolid-2-one,* b. p. 104°/15 mm. (Found: C, 52·4; H, 8·55; N, 24·4. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·5%).

The following were made similarly: 1 : 3-*diethyliminazolid-2-one,* b. p. 122°/22 mm. (Found: C, 58·9; H, 10·2; N, 19·4. $C_7H_{14}ON_2$ requires C, 59·1; H, 9·9; N, 19·7%), and *NN′*-diethylethylenediamine-*NN′*-dicarboxychloride from *NN′*-diethylethylenediamine; 1 : 3-*di*-n-*propyliminazolid*-2-*one,* b. p. 148°/23 mm. (Found: C, 63·4; H, 10·7; N, 16·2. $C_9H_{18}ON_2$ requires C, 63·5; H, 10·6; N, 16·4%), and the dicarboxychloride from *NN′*-di-*n*-propylethylenediamine; the iso*propylurea,* b. p. 130°/15 mm. (Found: C, 63·45; H, 10·1. $C_9H_{18}ON_2$ requires C, 63·5; H, 10·6%), and NN′-*diisopropylethylenediamine*-NN′-*dicarboxychloride,* m. p. 110° (from petrol, b. p. 60—80°) (Found: C, 45·0; H, 6·45. $C_{10}H_{18}O_2N_2Cl_2$ requires C, 44·7; H, 6·7%), from *NN′*-di*iso*propylethylenediamine; 1 : 3-*dimethylhexahydropyrimid*-2-*one,* b. p. 146°/44 mm. (Found: C, 55·9; H, 9·1; N, 21·4. $C_6H_{12}ON_2$ requires C, 56·2; H, 9·3; N, 21·8%), and *NN′*-dimethyltrimethylenediamine-*NN′*-dicarboxychloride, b. p. 163—166°/0·8 mm. (decomp.), from *NN′*-dimethyltrimethylenediamine.

(8) *Ureas of Type* X·CO·NR·$[CH_2]_n$·NHR, *where* X *is a Secondary Amine Residue.*—*Triethyl*-2-*ethylaminoethylurea and* NN′-*diethylethylenediamine*-NN′-*biscarboxydiethylamide.* To *NN′*-diethylethylenediamine (48 g., 0·4 mol.) in toluene (450 c.c.), diethylcarbamyl chloride (50 g., 0·41 mol.) in toluene (300 c.c.) was added below 0° with stirring which was continued for 1 hour after addition was complete. The diamine dihydrochloride was filtered off, and the filtrate shaken with saturated potassium carbonate (200 c.c.). After drying (K_2CO_3), the toluene solution was distilled, giving 23 g. of crude *triethyl*-2-*ethylaminoethylurea* [which redistilled giving 14 g., b. p. 126—8°/17 mm. (Found: N, 19·0. $C_{11}H_{25}ON_3$ requires N, 19·5%)] and 38 g. of NN′-*diethylethylenediamine*-NN′-*biscarboxydiethylamide,* b. p. 218°/19 mm. (Found: C, 61·7; H, 11·0; N, 17·7. $C_{16}H_{34}O_2N_4$ requires C, 61·2; H, 10·8; N, 17·8%).

The following were obtained by a similar procedure: N-*Methyl*-N′N′-*diethyl*-N-3-*methylaminopropylurea,* b. p. 141°/10 mm. (Found: N, 20·5. $C_{10}H_{23}ON_3$ requires N, 20·9%), and NN′-*dimethyltrimethylenediamine*-NN′-*biscarboxydiethylamide,* b. p. 210°/10 mm., 160°/0·7 mm. (Found: C, 60·2; H, 10·45; N, 18·4. $C_{15}H_{32}O_2N_4$ requires C, 60·0; H, 10·65; N, 18·6%), from *NN′*-dimethyltrimethylenediamine and diethylcarbamyl chloride; N-*methyl*-N′N′-*diethyl*-N-6-*methylamino*-n-*hexylurea,* b. p. 182°/12 mm. (Found: C, 63·7; H, 11·75; N, 17·1. $C_{13}H_{29}ON_3$ requires C, 64·2; H, 11·8; N, 17·3%), and NN′-*dimethylhexamethylenediamine*-NN′-*biscarboxydiethylamide,* b. p. 229—230°/9 mm. (Found: C, 63·05; H, 10·9. $C_{18}H_{38}O_2N_4$ requires C, 63·1; H, 11·1%), from *NN′*-dimethylhexamethylenediamine and diethylcarbamyl chloride; NN-*pentamethylene*-N′-2-*ethoxyethyl*-N′-(2-*ethoxyethylaminoethyl*)*urea,* b. p. 180°/15 mm. (Found: C, 60·6; H, 10·3; N, 12·9. $C_{16}H_{33}O_3N_3$ requires C, 60·95; H, 10·5; N, 13·3%), and *NN′*-di-(2-ethoxyethyl)ethylenediamine-*NN′*-biscarboxypiperidide, b. p. 275—278°/15 mm. (the yield of bis-urea was much smaller in the last case).

(9) *Preparation of Bisureas of Type* X·CO·NR·$[CH_2]_n$·NR′·COX *in which* R *and* R′ *are Alkyl, Alkenyl, or Alkoxyethyl Groups and* X *is a Secondary Amine Residue.*[1]—(A) *Reaction of a biscarbamyl chloride* COCl·NR·$[CH_2]_n$·NR′·COCl *with a secondary amine.* To the biscarbamyl chloride (1 mol.) dissolved in dry benzene the secondary amine (5 mols.) was added with shaking and cooling. After standing overnight, the precipitated amine hydrochloride was filtered off, and the filtrate shaken with saturated aqueous potassium carbonate, dried (K_2CO_3), and distilled.

(B) *Reaction of a diamine* NHR·$[CH_2]_n$·NHR′ *with a carbamyl chloride.* To the diamine (1 mol.) in benzene the carbamyl chloride (1·1 mols.) was added. Precipitation of the diamine hydrochloride began almost immediately and was accompanied by a rise in temperature. After standing overnight, the diamine hydrochloride was filtered off and the bisurea isolated as above.

Details of the various preparations are given in Table III. The solvent used for crystallisation of solids was usually petrol (b. p. 60—80°), but in a few cases that of b. p. 40—60° was used.

(10) *Bisureas of Type* X·CO·NR·$[CH_2]_n$·NR·COY.—These substances were made by reaction of a monourea of type X·CO·NR·$[CH_2]_n$·NHR (see above) with the appropriate carbamyl chloride, either without a solvent or in a solvent heated under reflux. Details of the preparation of NN′-*dimethyltrimethylenediamine*-N-*carboxydiethylamide*-N′-*carboxypiperidide* are given in illustration: *N*-Methyl-*NN′*-diethyl-*N*-3-methylaminopropylurea (25 g., 1·25 mols.) and piperidine-*N*-carboxychloride (10 g., 0·68 mol.) were mixed; much heat was evolved and when the temperature had fallen to 30° the mixture was heated for 2 hours on the boiling water-bath, poured into water, the aqueous solution saturated with potassium carbonate, and extracted with benzene. After being dried (K_2CO_3), the benzene solution was distilled, giving 6 g. of unchanged monourea and 15 g. (78%) of the *bisurea,* b. p. 245°/17 mm. (Found: C, 61·4; H, 10·3; N, 18·0. $C_{16}H_{32}O_2N_4$ requires C, 61·5; H, 10·3; N, 18·15%), as a pale yellow oil soluble to the extent of about 25% in water.

The following were prepared similarly: NN′-*Dimethylhexamethylenediamine*-N-*carboxydiethylamide*-

[1] The preparation of bisureas is covered by B.PP. 548,625, 548,626, 560,681, 560,699, 560,700, and 560,701.

TABLE III.

Bisureas X·CO·NR·$[CH_2]_n$·NR′·CO·X.

X.	R.	R′.	*n*.	Method of prepn.	Yield, %.	M. p.[1]	S.†	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me_2N	Me	Me	2	B	48	(193—195°/20 mm.)	Misc.	$C_{10}H_{12}O_2N_4$	52·1	9·6	23·95	52·1	9·56	24·2
Et_2N	Me	Me	2	A B	90	339° (224°/13 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·2	10·35	19·7	58·6	10·5	19·6
O<$[CH_2]_4$>N	Me	Me	2	B	75	164°	>50%	$C_{14}H_{26}O_4N_4$	53·55	8·3	—	53·5	8·3	—
Me_2N	Me	Et	2	B	72	(204—205°/22 mm.)	Misc.	$C_{11}H_{24}O_2N_4$	53·95	9·5	23·2	54·0	9·8	22·9
Et_2N	Me	Et	2	B	67	(204°/10 mm.)	Misc.	$C_{15}H_{32}O_2N_4$	59·8	10·3	18·8	60·0	10·6	18·7
$[CH_2]_5$>N	Me	Et	2	B	83	(252—254°/6 mm.)	2%	$C_{17}H_{32}O_2N_4$	62·9	10·0	17·6	62·9	9·9	17·3
O<$[CH_2]_4$>N	Me	Et	2	B	50	76°	>50%	$C_{15}H_{28}O_4N_4$	54·5	8·2	16·75	54·8	8·5	17·0
Me_2N	Et	Et	2	B	85	(203—205°/23 mm.)	Misc.	$C_{12}H_{26}O_2N_2$	55·9	10·15	—	55·8	10·1	—
Et_2N	Et	Et	2	B	85	(226—228°/29 mm.)	20%	$C_{16}H_{34}O_2N_4$	61·4	11·0	17·7	61·2	10·8	17·8
$[CH_2]_5$>N	Et	Et	2	B	50	65°	< 5%	$C_{18}H_{34}O_2N_4$	63·7	9·85	16·2	63·7	10·0	16·6
O<$[CH_2]_4$>N	Et	Et	2	B	68	98°	>50%	$C_{16}H_{34}O_4N_4$	56·3	8·8	16·2	56·1	8·8	16·4
NEt·C_2H_4·OMe	Et	Et	2	A	75	(239—240°/17 mm.)	Misc.	$C_{18}H_{38}O_4N_4$	57·3	9·9	15·2	57·6	10·15	15·0
Me_2N	Pr$^\alpha$	Pr$^\alpha$	2	B	65	(208—209°/18 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·4	10·1	19·55	58·7	10·5	19·7
O<$[CH_2]_4$>N	Pr$^\alpha$	Pr$^\alpha$	2	B	33	86°	>50%	$C_{18}H_{34}O_4N_4$	58·7	9·25	15·15	58·3	9·2	15·15
NMe·C_2H_4·OEt	Pr$^\alpha$	Pr$^\alpha$	2	A	46	(255°/20 mm.)	>50%	$C_{20}H_{42}O_4N_4$	59·3	10·3	13·8	59·6	10·4	13·9
NEt·C_2H_4·OMe	Pr$^\alpha$	Pr$^\alpha$	2	A	58	(265°/20 mm.)	50%	$C_{20}H_{42}O_4N_4$	59·4	10·3	13·8	59·6	10·4	13·9
Me_2N	Pr$^\beta$	Pr$^\beta$	2	B	40	100°(202°/17 mm)	50%	$C_{14}H_{30}O_2N_4$	58·6	10·4	19·7	58·7	10·5	19·7
O<$[CH_2]_4$>N	Pr$^\beta$	Pr$^\beta$	2	B	29	126°	>50%	$C_{18}H_{34}O_4N_4$	57·8	9·1	15·1	58·3	9·2	15·15
Me_2N	Allyl	Allyl	2	B	80	(220°/20 mm.)	Misc.	$C_{14}H_{26}O_2N_4$	59·55	9·15	19·9	59·6	9·2	19·9
O<$CH_2]_4$>N	Allyl	Allyl	2	B	77	85°	>50%	$C_{18}H_{30}O_4N_4$	59·0	7·9	15·7	59·0	8·2	15·3
Me_2N	*n*-Bu	*n*-Bu	2	B	68	(222—224°/18 mm.)	10%	$C_{16}H_{34}O_2N_4$	61·16	10·75	17·85	61·1	10·8	17·8
O<$[CH_2]_4$>N	*n*-Bu	*n*-Bu	2	B	60	41°	50%	$C_{20}H_{38}O_4N_4$	60·3	9·55	13·9	60·3	9·55	14·1
$(EtO·C_2H_4)_2N$*	*n*-Bu	*n*-Bu	2	B	—	(240—245°/12 mm.)	>50%	$C_{28}H_{58}O_6N_4$	61·9	11·0	10·4	61·5	10·6	10·3
Me_2N	*iso*-Bu	*iso*-Bu	2	B	97	(220°/30 mm.)	10%	$C_{16}H_{34}O_2N_4$	61·5	10·6	17·7	61·1	10·8	17·8
O<$[CH_2]_4$>N	*iso*-Bu	*iso*-Bu	2	B	56	(270—275°/15 mm.)	20%	$C_{20}H_{38}O_4N_4$	60·7	9·55	—	60·3	9·55	—
Me_2N	*sec.*-Bu	*sec.*-Bu	2	B	38	105° (232—234°/40 mm.)	<10%	$C_{16}H_{34}O_2N_4$	61·35	10·4	17·4	61·1	10·8	17·8
O<$[CH_2]_4$>N	*sec.*-Bu	*sec.*-Bu	2	B	30	135°	10%	$C_{20}H_{38}O_4N_4$	—	—	13·6	—	—	14·1

$O<[CH_2]_4>N$	*tert.*-Bu	*tert.*-Bu	2	B	9	132°	10%	$C_{20}H_{38}O_4N_4$	—	—	14·5	—	—	14·1
$O<[CH_2]_4>N$	*cyclo*Hexyl	*cyclo*Hexyl	2	B	25	148°	<10%	$C_{24}H_{42}O_4N_4$	—	—	12·6	—	—	12·4
Et_2N	2-MeO·C_2H_4	2-MeO·C_2H_4	2	B	50	(252°/23 mm.)	20%	$C_{18}H_{38}O_4N_4$	57·5	10·4	14·75	57·8	10·15	14·95
$[CH_2]_5>N$	2-MeO·C_2H_4	2-MeO·C_2H_4	2	B	54	(285°/17 mm.)	<10%	$C_{20}H_{38}O_4N_4$	60·7	9·55	13·92	60·3	9·55	14·05
$O<[CH_2]_4>N$	2-Pr$^\beta$O·C_2H_4	2-Pr$^\beta$O·C_2H_4	2	B	53	94°	50%	$C_{22}H_{42}O_6N_8$	57·8	9·1	—	57·8	9·2	—
Me_2N	Me	Me	3	B	56	(213°/24 mm.)	Misc.	$C_{11}H_{24}O_2N_4$	54·1	9·6	22·85	54·1	9·8	22·9
Et_2N	Me	Me	3	B	88	(160°/0·7 mm.; 225°/21 mm.)	Misc.	$C_{15}H_{32}O_2N_4$	60·2	10·45	18·4	60·0	10·7	18·6
NMePr$^\alpha$	Me	Me	3	A	57	(225°/16 mm.)	10%	$C_{15}H_{32}O_2N_4$	59·0	10·3	18·6	60·0	10·7	18·6
NMePr$^\beta$	Me	Me	3	A	60	(218°/15 mm.)	5%	$C_{15}H_{32}O_2N_4$	60·35	10·85	18·1	60·0	10·7	18·6
$[CH_2]_5>N$	Me	Me	3	B	73	(205°/0·75 mm.)	< 5%	$C_{17}H_{32}O_2N_4$	62·5	10·2	17·3	62·8	9·9	17·3
$O<[CH_2]_4>N$	Me	Me	3	B	60	93°	>50%	$C_{15}H_{28}O_4N_4$	55·3	8·4	17·0	55·0	8·5	17·1
NMe·C_2H_4·OMe ...	Me	Me	3	A	61	(253°/16 mm.)	Misc.	$C_{15}H_{32}O_4N_4$	54·45	9·55	16·95	54·2	9·6	16·9
NMe·C_2H_4·OEt ...	Me	Me	3	A	61	(258°/15 mm.)	>50%	$C_{17}H_{36}O_4N_4$	57·0	10·4	15·65	56·7	10·0	15·6
NEt·C_2H_4·OMe ...	Me	Me	3	A	61	(254°/19 mm.)	Misc.	$C_{17}H_{36}O_4N_4$	56·2	9·95	15·9	56·7	10·0	15·6
NEt·C_2H_4·OEt ...	Me	Me	3	A	49	(253°/14 mm.)	>50%	$C_{19}H_{40}O_4N_4$	58·5	10·15	14·55	58·7	10·3	14·45
Me_2N	Me	Et	3	B	84	(219°/21 mm.)	Misc.	$C_{12}H_{26}O_2N_4$	55·45	9·8	21·65	55·7	10·05	21·7
Et_2N	Me	Et	3	B	75	(219°/12 mm.)	10%	$C_{16}H_{34}O_2N_4$	60·9	10·5	18·1	61·1	10·8	17·8
$[CH_2]_5>N$	Me	Et	3	B	51	(256°/14 mm.)	< 5%	$C_{18}H_{34}O_2N_4$	63·6	10·5	—	63·8	10·1	—
$O<CH_2]_4>N$	Me	Et	3	B	52	(236—238°/1·7 mm.)	Misc.	$C_{16}H_{30}O_4N_4$	56·1	8·65	16·1	56·1	8·8	16·3
Et_2N	Et	Et	3	B	56	(244—246°/40 mm.)	<10%	$C_{17}H_{36}O_2N_4$	62·4	10·8	16·6	62·2	11·0	17·0
$[CH_2]_5>N$	Et	Et	3	B	50	(223—225°/0·6 mm.)	< 5%	$C_{19}H_{36}O_2N_4$	64·5	10·1	15·95	64·6	10·2	15·9
$O<[CH_2]_4>N$	Et	Et	3	B	56	(238—240°/0·7 mm.)	10%	$C_{17}H_{32}O_4N_4$	56·8	9·15	15·2	57·2	9·0	15·9
Me_2N	Pr$^\alpha$	Pr$^\alpha$	3	B	30	(220°/16 mm.)	5%	$C_{15}H_{32}O_2N_4$	60·1	10·4	—	60·0	10·65	—
$O<[CH_2]_4>N$	Pr$^\alpha$	Pr$^\alpha$	3	B	40	(287°/18 mm.)	5%	$C_{19}H_{36}O_4N_4$	59·2	9·45	14·2	59·3	9·1	14·6
Et_2N	Me	Me	4	B	90	(216°/10 mm.)	>50%	$C_{16}H_{34}O_2N_4$	61·6	11·3	18·0	61·1	10·9	17·9
Et_2N	Me	Me	5	B	75	(270—275°/50 mm.)	50%	$C_{17}H_{36}O_2N_4$	61·95	10·65	17·35	62·1	10·95	17·1
Me_2N	Me	Me	6	B	28	(238—240°/17 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·5	9·9	19·8	58·7	10·4	19·7
Et_2N	Me	Me	6	B	61	(252—254°/18 mm.)	50%	$C_{18}H_{38}O_2N_4$	63·1	10·9	—	63·1	11·1	—
$O<[CH_2]_4>N$	Me	Me	6	B	50	93—94°	50%	$C_{18}H_{34}O_4N_4$	57·8	9·7	14·8	58·3	9·2	15·1
Me_2N	Et	Et	6	B	90	(242—244°/2 mm.)	50%	$C_{16}H_{34}O_2N_4$	61·2	10·5	17·95	61·2	10·8	17·85
$O<[CH_2]_4>N$	Et	Et	6	B	83	(315°/24 mm.)	>50%	$C_{20}H_{38}O_4N_4$	—	—	13·7	—	—	14·0
Me_2N *	2-EtO·C_2H_4	2-EtO·C_2H_4	6	B	60	(268—269°/11 mm.)	Misc.	$C_{20}H_{42}O_4N_4$	60·0	10·6	14·1	59·7	10·5	14·0

[1] B. p.'s are given in parentheses.
† S = Solubility (approx.) in water (Misc. = miscible in all proportions).

N′-*carboxymorpholide*, b. p. 248°/9 mm., yield 75%, miscible with water (Found : C, 61·1; H, 9·95; N, 15·9. $C_{18}H_{36}O_3N_4$ requires C, 60·7; H, 10·1; N, 15·7%) from *N*-methyl-*N′N′*-diethyl-*N*-6-methylaminohexylurea and morpholine-*N*-carboxychloride; NN′-*di*-(2-*ethoxyethyl*)*ethylenediamine*-N-*carboxydimethylamide*-N′-*carboxypiperidide*, b. p. 230°/10 mm., yield 47%, solubility in water >50% (Found: C, 58·8; H, 9·75; N, 14·8. $C_{19}H_{38}O_4N_4$ requires C, 59·1; H, 9·8; N, 14·5%), and NN′-*di*-(2-*ethoxyethyl*)-*ethylenediamine*-N-*carboxy*(*ethyl*-2-*ethoxyethyl*)*amide*-N′-*carboxypiperidide*,* b. p. 245—247°/10 mm., 21% yield, miscible with water (Found : C, 59·9; H, 10·0; N, 11·95. $C_{23}H_{46}O_5N_4$ requires C, 60·25; H, 10·0; N, 12·2%), from *NN*-pentamethylene-*N′*-2-ethoxyethyl-*N′*-2-(2-ethoxyethylamino)ethylurea and dimethylcarbamyl chloride and ethyl-(2-ethoxyethyl)carbamyl chloride, respectively.

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