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BISUREAS

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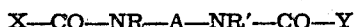
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8 Claims. (Cl. 260—247)

This invention relates to new bis-ureas which are useful as stimulants of the respiratory and vasomotor centres, having a low ratio of active dose to toxic dose, and to processes for the manufacture of the same.

It is an object of this invention to provide new bis-ureas of the general formula hereinafter set forth. A further object is to provide new chemical compounds which are useful stimulants of the respiratory and vasomotor centres. A further object is to provide such compounds having a low ratio of active dose to toxic dose. A further object is to provide processes for the manufacture of the said bis-ureas. Still further objects will appear as the description proceeds.

These objects are accomplished by the present invention which comprises new bis-ureas of the general formula—



wherein the symbols A, R, R', X and Y have the following meanings, namely:

A stands for an alkylene chain of 2 to 6 carbon atoms which may be unsubstituted or may bear one or more alkyl, alkoxy or alkoxyalkyl substituents or for a group consisting of two such alkylene chains united by an ether (—O—), sulphide (—S—) or imino (—NH— or —N.Alkyl—) linkage.

R and R', which are not necessarily alike, stand for alkyl groups which jointly contain not more than 8 carbon atoms or for alkoxyalkyl groups which jointly contain not more than 12 carbon atoms.

While X and Y, which also are not necessarily alike, each stands for the secondary amino group corresponding with an amine X—H which is a dialkylamine or heterocyclic secondary amine of molecular weight not exceeding 120, or which is of the form Alk—O—alk—NH—Alk and has a molecular weight not exceeding 160, or which is of the form (Alk—O—alk)₂NH and has a molecular weight not exceeding 220, the terms Alk and alk representing an alkyl and an alkylene radical respectively.

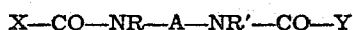
The various alternative values for A, R, R', X and Y and the limitations put upon each of them are not arbitrarily selected. On the contrary, bearing in mind that the preferred compounds are designed to be respiratory stimulants, these limitations are of the essence of the invention. Respiratory stimulants are used, as the name indicates, to stimulate those portions of the central nervous system which control the respiratory mechanism, particularly in cases where breath-

ing has stopped during an operation under anesthetic. As will be apparent, such compounds must act rapidly and accordingly they are normally administered by intravenous injection. Clearly adequate solubility in water, or more particularly in physiological saline solution is a prerequisite for such compounds. Now other factors being equal, increase in the size and weight of the various radicals A, R, R', X and Y diminishes the solubility of the bis-urea, and so limits must be set for the sizes of these various radicals, but also the limits must vary with any changes in the nature of the radicals. For instance when A has the form of a simple straight alkylene chain (which is not water-solubilising) then the maximum permissible size is a chain of 6 carbon atoms, whereas if the chain is branched or carries alkoxy or alkoxyalkyl substituents, or is broken by an ether, sulphide or imino linkage (all of which modifications tend to enhance water-solubility), then A may contain, in total, more than 6 carbon atoms. Similarly if R and R' represent alkyl groups they must not jointly contain more than 8 carbon atoms, whereas if they are alkoxyalkyl groups a greater size and weight (up to 12 carbon atoms) can be tolerated because of the enhanced solubilising effect. Again, if X and Y have the alkoxyalkyl-alkylamino or bis-alkoxyalkylamino form it can be of greater size and weight than if it is a simple dialkylamino or heterocyclic secondary amino group. Also the nature and size of the various radicals A, R, R', X and Y affect the intrinsic chemotherapeutic activity of the compound. Accordingly the particular limitations imposed on the values which can be possessed by these terms have been selected bearing in mind both the intrinsic activities and the solubilities of the compounds. All the above limitations may be expressed generically under the single rule that none of the radicals expressed by the symbols A, R, R', X and Y shall contain an uninterrupted chain of more than 6 carbon atoms, and that for each pair of corresponding symbols (that is R and R', X and Y) the average carbon content in each uninterrupted alkyl chain shall not exceed 4 atoms. These limitations are of the essence of the invention and must be observed if its object is to be achieved.

The new compounds can be made by two main synthetic methods.

In the first method the carbamyl chloride X—CO—Cl, (X, it must be remembered, is the radical of a secondary amino group as defined above and is used here as typical of the pair X

and Y) is caused to interact with the diamine $R-NH-A-NH-R'$. If two molecular proportions of the carbamyl chloride are used for each molecular proportion of the diamine, then a symmetrical bis-urea is obtained. Alternatively one may first use one molecular proportion each of the diamine and the carbamyl chloride, so forming the mono-urea $X-CO-NR-A-NHR'$ and then combine that with one molecular proportion of a different carbamyl chloride $Y-CO-Cl$, thereby obtaining the unsymmetrical bis-urea



In the second method the diamine is first combined with phosgene, forming the carbamyl chloride $Cl-CO-NR-A-NR'-CO-Cl$ which is then caused to react with the secondary amine $X-H$. Here also the reaction may be between one molecular proportion of the diamine and two molecular proportions each of, firstly phosgene, and secondly the secondary amine, whereby a symmetrical bis-urea results; or alternatively it may be carried out in stages so as to obtain the unsymmetrical compounds. Thus the diamine may be combined with one molecular proportion of phosgene, followed by one molecular proportion of the secondary amine $X-H$, whereby the mono-urea $X-CO-NR-A-NHR'$ is formed and this may then be combined with a further proportion of phosgene and then with one molecular proportion of a different secondary amine $Y-H$, whereby the unsymmetrical bis-urea

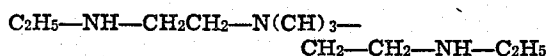


is produced.

In all the above discussion where a definite molal quantity is specified for an amine or a diamine, it will be understood that this refers to the quantity employed for actual condensation, exclusive of any additional quantity added to act as an acid-absorbing agent for HCl liberated in the process. In other words, the specified molal quantity of the amine or diamine is the minimal, theoretical quantity, to be exceeded in practice by a convenient excess for absorbing the HCl.

As will be seen, therefore, the new compounds are made from the following starting materials, namely, diamines $R-NH-A-NH-R'$, carbamyl chlorides $X-CO-Cl$ and the corresponding secondary amines $X-H$.

Then as diamines suitable for use in making the new compounds there may be mentioned, for example, N:N'-dimethylethylenediamine, N:N'-diethylethylenediamine, N:N'-dimethyltrimethylethylenediamine, N-methyl-N'-ethylethylenediamine, N:N'-di-n-propylethylenediamine, N:N'-di-n-butylethylenediamine, N:N'-dimethyl-tetramethylene diamine, N:N'-dimethylhexamethylene diamine, N:N'-dimethyl-1:2-propylene diamine, N:N'-dimethyl-1:3-butylene diamine, N:N'-dimethyl-2-methoxy-trimethylene diamine, $\beta:\beta'$ -di(ethylamino)-diethyl ether, $\beta:\beta'$ -di(ethylamino)-diethyl sulphide, $\beta:\beta'$ -di(ethylamino)-diethyl methylamine of the formula

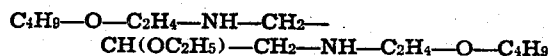


N:N'-di-n-butyl-1-ethoxymethylethylenediamine of the formula



N:N'-bis(β -methoxyethyl)-ethylene diamine, N:N'-bis(β -ethoxyethyl)-ethylene diamine, N:N'-bis(β -isopropoxyethyl)-ethylene diamine, N:N'-bis(β -ethoxyethyl)-hexamethylene dia-

mine and N:N'-bis-(β -n-butyloxyethyl)-2-ethoxy-trimethylene diamine of the formula



The following secondary amines and the carbamyl chlorides derived therefrom may be mentioned to exemplify the other classes of starting materials useful for making the new bis-ureas of this invention, for instance: dimethylamine, diethylamine, methyl ethylamine, di-n-propylamine, di-n-butylamine, methyl-n-propylamine, piperidine, morpholine, methyl methoxyethylamine, ethyl methoxyethylamine, ethyl ethoxyethylamine, di(methoxyethyl)amine and di(β -ethoxyethyl)amine.

The above starting materials are mentioned only for purposes of illustration and not for limitation of the invention. Obviously other members of the classes indicated by the definitions previously given for the radicals A, R, R', X and Y can be used in the same way. Clearly the number of compounds which can be made by combining together in the manner indicated the various starting materials is very large and the following detailed examples are given by way of illustration only (and not in limitation) of the invention.

Example 1

88 parts of diethylcarbamyl chloride dissolved in 120 parts of benzene are added with stirring to a solution of 53 parts of N:N'-dimethyltrimethylenediamine (obtainable from N:N'-dimethyl-N:N'-diphenyltrimethylenediamine by the method described—in respect of N:N'-dimethylethylenediamine—*Berichte der deutschen chemischen Gesellschaft* 1918, vol. 51, p. 738) in 450 parts of benzene. When the reaction is complete the N:N'-dimethyltrimethylenediamine dihydrochloride (which has M. P. 266° C.) is removed by filtration, and the filtrate is shaken with 100 parts of saturated potassium carbonate, dried over anhydrous potassium carbonate and distilled whereby there is obtained 67 parts of N:N'-dimethyltrimethylenediamine-N:N'-dicarboxylic acid bis-diethylamide as a colourless liquid, B. P. 238° C. at 33 mm. pressure which is miscible in all proportions with water and the common organic solvents.

In a similar manner there are obtained the following:

(a) N:N'-dimethylethylenediamine-N:N'-dicarboxylic bis-piperidide (M. P. 90° C.).

(b) N-methyl-N'-ethylethylenediamine-N:N'-dicarboxylic bis-dimethylamide (B. P. 205° C. at 22 mm. pressure).

(c) N:N'-diethylethylenediamine-N:N'-dicarboxylic bis-morpholide (M. P. 98° C.), which is a colourless crystalline solid readily soluble in water, ethanol and benzene and sparingly soluble in light petroleum. The morpholine-N-carboxylic chloride used in making this substance has B. P. 137–138° C. at 33 mm. pressure and is obtained by the action of phosgene on morpholine in accordance with the method described in respect of diethylamine in *Bulletin de la Société chimique de Paris*, 104, 3rd series, vol. 31, p. 689.

(d) N:N'-di-n-propylethylenediamine-N:N'-dicarboxylic bis-dimethylamide (B. P. 208° C. at 18 mm. pressure). The N:N'-di-n-propylethylenediamine (B. P. 189° C., dihydrochloride M. P. 300° C.) required is made by reacting di-p-toluenesulphonylethylenediamine with n-propyl bromide by the method of *Berichte*, 1895, vol. 28, p.

3074, to give di-p-toluenesulphonyl-di-n-propylethylenediamine of M. P. 122° C. which is then hydrolysed by heating with 80% sulphuric acid at 150° C. for 5 hours.

(e) N:N'-di-n-butylethylenediamine-N:N'-dicarboxylic bis-morpholide (B. P. 229° C. at 0.4 mm. pressure, M. P. 41-42° C.). The N:N'-di-n-butylethylene-diamine required has B. P. 226° C., its dihydrochloride melts at 300° C. with decomposition and its di-p-toluene-sulphonyl derivative at 119° C. It is made in a manner analogous to that used for making N:N'-di-n-propylethylenediamine.

(f) N:N'-dimethyltetramethylene-N:N'-dicarboxylic bis-diethylamide (B. P. 216° C. at 10 mm. pressure). The N:N'-dimethyltetramethylenediamine (B. P. 164° C., dihydrochloride M. P. 275° C.) required is made by condensing 1:4-dibromobutane with sodium p-toluenesulphonylmethylamide in xylene at 140° C. to give di-p-toluenesulphonyl-N:N'-dimethyltetramethylenediamine of M. P. 129° C. which is hydrolysed in the usual manner.

(g) N:N'-dimethylhexamethylenediamine-N:N'-dicarboxylic bis-dimethylamide (B. P. 238° C. at 17 mm. pressure).

Example 2

21 parts of N:N'-dimethylethylenediamine carbonate is suspended in 250 parts of dry chloroform and the solution is saturated with phosgene at room temperature. After it has stood for 15 hours air is blown through the mixture to remove the excess of phosgene. The mixture is then filtered to remove N:N'-dimethylethylenediamine dihydrochloride and from the filtrate the chloroform is distilled, leaving a pale yellow, mobile somewhat lachrymatory liquid which is the bis-carbamyl chloride. This is dissolved in 100 parts of ether. 20 parts of diethylamine are added. After the reaction is complete the whole is agitated with 150 parts of saturated aqueous sodium carbonate solution, the ethereal layer is separated and dried over anhydrous potassium carbonate. This dry ethereal solution is fractionally distilled to give as one fraction N:N'-dimethylethylenediamine-N:N'-dicarboxylic bis-diethylamide as a colourless liquid, B. P. 339° C. at atmospheric pressure or 224° C. at 13 mm. pressure which is miscible in all proportions with water and the commoner organic solvents.

Example 3

16 parts of N:N'-dimethylethylenediamine dihydrochloride are dissolved in 150 parts of water, and sufficient 32% aqueous caustic soda is then added to make the solution alkaline to phenolphthalein and the whole is cooled to 5° C. 25 parts of dimethylcarbamyl chloride are now added with stirring and cooling at such a rate that the temperature does not exceed 20° C., more caustic soda being added as required to keep the solution just alkaline to phenolphthalein. After stirring for 6 hours sufficient solid potassium carbonate is added to saturate the solution and the oil which separates out is dissolved up in 100 parts of benzene. The benzene solution is dried over anhydrous potassium carbonate and the benzene is then distilled off. N:N'-dimethylethylenediamine-N:N'-dicarboxylic bis-dimethylamide (B. P. 193° C. at 20 mm. pressure) is thus obtained. It is a colourless oil which gradually solidifies to a crystalline mass; it is miscible in all proportions with water and the commoner organic solvents.

Example 4

20 parts of N:N'-dimethyltrimethylenediamine are gradually added with stirring to a cooled solution of 150 parts of phosgene in 500 parts of toluene, the temperature being kept below -10° C. After the addition is complete air is blown through the reaction mixture to remove the excess of phosgene and the mixture is filtered to remove N:N'-dimethyltrimethylenediamine dihydrochloride. 34 parts of piperidine are added and after standing one hour the mixture is filtered to remove piperidine hydrochloride. The toluene is then distilled off whereby N:N'-dimethyltrimethylenediamine-N:N'-dicarboxylic bis-piperidide is obtained. It is a colourless oil of B. P. 205° C. at 0.075 mm. pressure which is readily soluble in ethanol and benzene and only slightly soluble in water.

In a similar manner there can be obtained N:N'-dimethyltrimethylenediamine-N:N'-dicarboxylic bis-(methyl-n-propylamide) and N:N'-dimethyltrimethylenediamine-N:N'-dicarboxylic bis-(ethyl- β -ethoxyethylamide).

Example 5

67 parts of diethyl carbamyl chloride dissolved in 150 parts of toluene are added with stirring to a cooled solution of 75 parts of N:N'-dimethyl trimethylenediamine in 450 parts of toluene at such a rate that the reaction temperature does not rise above 0° C. At the end of the reaction 42 parts of N:N'-dimethyltrimethylenediamine dihydrochloride are filtered off and washed with toluene. The filtrate and washings are now distilled whereby there is obtained 50 parts of N:N'-dimethyltrimethylenediamine-N'-carboxylic diethylamide, a colourless, strongly basic liquid of B. P. 141° C. at 10 mm. which is miscible in all proportions with water, ethanol, benzene and light petroleum; on further distillation a second fraction consisting of 25 parts of N:N'-dimethyltrimethylenediamine-N:N'-dicarboxylic bis-diethylamide of B. P. 210° C./10 mm. is obtained.

In a similar manner by the interaction of 87 parts of N:N'-diethylethylenediamine with 67.7 parts of diethylcarbamyl chloride there is obtained 75 parts of N:N'-diethylethylenediamine-N'-carboxylic diethylamide as a colourless, strongly basic liquid of B. P. 126° C. at 17 mm. and 31 parts of N:N'-diethylethylenediamine N:N'-dicarboxylic bis-diethylamide, a colourless liquid of B. P. 218° C. at 19 mm. which is miscible in all proportions with ethanol and benzene and moderately soluble in water.

Example 6

20 parts of N:N'-dimethyltrimethylenediamine-N'-carboxylic diethylamide and 7.5 parts of piperidine-N-carboxylic chloride are mixed together. Reaction occurs with evolution of heat. After the reaction has ended the mixture is dissolved in 100 parts of water and solid potassium carbonate is added until the solution is saturated. The solution is warmed to 100° C. for a short time, then cooled. An oily layer is formed. 100 parts of benzene are added and the oil dissolves therein. The benzene solution is separated and dried over anhydrous potassium carbonate and then distilled whereby there are obtained, as two fractions, 9 parts of unchanged N:N'-dimethyltrimethylenediamine-N'-carboxylic diethylamide and 15 parts of N:N'-dimethyltrimethylenediamine N'-carboxylic diethylamide N-carboxylic piperidide as a colourless liquid of B. P. 245° C. at 17 mm. which is moderately soluble in water and

is miscible in all proportions with ethanol, benzene and petroleum ether.

In a similar manner by the interaction of 23 parts of N:N'-diethyl ethylene diamine-N'-carboxylic diethylamide and 14 parts of diethylcarbamylyl chloride there are obtained 29 parts of N:N'-diethylethylenediamine-N:N'-dicarboxylic bis-diethylamide of B. P. 218° C. at 19 mm. together with 10 parts of unchanged N:N'-diethylethylenediamine-N'-carboxylic diethylamide.

Example 7

94 parts of diethylcarbamylyl chloride dissolved in 300 parts of toluene are added with stirring to a cooled solution of 144 parts of N:N'-dimethylhexamethylene-diamine in 800 parts of toluene at such a rate that the reaction temperature does not rise above 0° C. By working up the reaction mixture as described in Example 5 there are obtained 90 parts of N:N'-diethyl-N'-methyl-N'-(6-methylaminohexyl)-urea, a strongly basic liquid of B. P. 182° C. at 12 mm. pressure which is moderately soluble in water, and 40 parts of N:N'-dimethylhexamethylenediamine-N:N'-dicarboxylic bis-diethylamide of B. P. 229° C. at 9 mm. pressure.

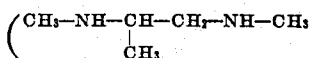
24 parts of N:N'-diethyl-N'-methyl-N'-(6-methylaminohexyl)-urea are mixed with 9 parts of morpholine-N-carboxylic chloride. When the reaction is ended 13 parts of N:N'-dimethylhexamethylenediamine-N-carboxylic diethylamide-N'-carboxylic morpholide of B. P. 248° C. at 9 mm. pressure are isolated as described in Example 6.

Example 8

40 parts of N:N'-diethyl-N'-methyl-N'-(3-methylaminopropyl)-urea dissolved in 150 parts of dry ether are gradually added, with stirring, to a cooled solution of 10 parts of phosgene in 100 parts of dry ether at such a rate that the temperature does not exceed -10° C. When the reaction is complete the N:N'-diethyl-N'-methyl-N'-(3-methylaminopropyl)-urea hydrochloride which has separated out is filtered off and washed with 50 parts of dry ether. The filtrate and washings are combined and the ether is distilled off. The residue is added to a solution of 20 parts of dimethylamine in 80 parts of benzene. Dimethylamine hydrochloride separates out and is filtered off. The benzene solution remaining is distilled whereby there are obtained 15 parts of N:N'-dimethyltrimethylenediamine-N-carboxylic diethylamide N'-carboxylic dimethylamide, which is a colourless oil of B. P. 210° C. at 9 mm. pressure, which is miscible with water.

Example 9

88 parts of diethylcarbamylyl chloride dissolved in 120 parts of benzene are added with stirring to a solution of 53 parts (an excess) of N:N'-dimethylpropylene diamine



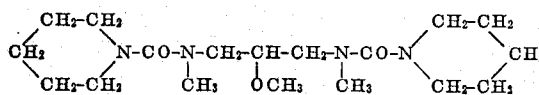
obtainable by reacting propylene diamine with an excess of 20% aqueous methylamine) in 450 parts of benzene. When the reaction is complete the N:N'-dimethylpropylene diamine hydrochloride which separates out is removed by filtration and the filtrate is shaken with 100 parts of a saturated aqueous solution of potassium carbonate. The benzene layer is separated off, dried over anhydrous potassium carbonate and distilled, whereby there are obtained 15 parts of N:N'-dimethylpropylene diamine-N:N'-dicarboxylic bis-di-

ethylamide in the form of a colourless liquid, B. P. 209° C. at 16 mm. pressure. Some 1:3:4-trimethyliminoazolid-2-one is also formed. This distills off first as it has B. P. 135° C. at 20 mm. pressure.

In a similar manner there are obtained the following:

(a) N:N'-dimethyl-1:3-butylene diamine-N:N'-dicarboxylic bis-diethylamide, B. P. 217° C. at 19 mm. pressure. No cyclic urea is formed in this case.

(b) N:N'-dimethyl-2-methoxy-trimethylene diamine-N:N'-dicarboxylic bis-piperidine, B. P. 265° C. at 15 mm.; structural formula:



The N:N'-dimethyl-2-methoxy-trimethylene diamine required as starting material is prepared by condensing glycerol dichlorohydrin with methylaniline to give 1:3-bis-(methylanilino)-propan-2-ol, converting this to its sodium salt and reacting with dimethyl sulphate to give 1:3-bis-(methylanilino)-2-methoxypropane which is then converted into N:N'-dimethyl-2-methoxy-trimethylene diamine by the method described, in respect of N:N'-dimethylethylene diamine, in *Berichte der deutschen Chemischen Gesellschaft*, 1918, vol. 51, p. 738, or alternatively by interaction of glycerol dichlorohydrin with methyl iodide and silver oxide to give methyl β : β' -dichloroisopropyl ether which is then treated with an excess of aqueous 20% methylamine solution.

(c) β : β' -di(ethylamino)-diethyl ether N:N'-dicarboxylic dimorpholide B. P. 228° C. at 0.3 mm. The β : β' -di(ethylamino)-diethyl ether is prepared as above from β : β' -di(ethylanilino)-diethyl ether which itself is prepared by reacting ethyl chloroethylaniline with the sodium derivative of ethyl hydroxyethylaniline or less advantageously by reacting β : β' -dichlorodiethyl ether with an excess of ethylaniline.

(d) β : β' -di(ethylamino)-diethyl sulphide N:N'-dicarboxylic dimorpholide B. P. 275°-276° C. at 21 mm. from β : β' -di(ethylanilino)-diethyl sulphide, itself obtained by reaction of ethyl chloroethylaniline with sodium sulphide in alcohol or aqueous alcohol.

(e) β : β' -di(ethylamino)-diethyl methylamine N:N'-dicarboxylic dimorpholide from β : β' -di(ethylanilino)-diethyl methylamine (B. P. 235°-238° C. at 8 mm.) itself obtained from ethyl chloroethylaniline and aqueous 20% methylamine solution.

(f) N:N'-di-n-butyl-1-ethoxymethyl-ethylene diamine N:N'-dicarboxylic dimorpholide from N:N'-di-n-butyl-1-ethoxymethyl-ethylene diamine (of B. P. 260° C.) itself obtained by interaction of ethyl 2:3-dibromopropyl ether with an excess of aqueous n-butylamine.

Example 10

73 parts of β -methylamino- β' -ethylamino-diethyl ether dissolved in 200 parts of dry toluene are added with stirring to a solution of 250 parts of phosgene in 1000 parts of toluene cooled to -25° C. After the addition is completed the excess of phosgene is removed by blowing with air, the amine hydrochloride which separates out is filtered off and to the filtrate there are added 73 parts of diethylamine. After filtering off the diethylamine hydrochloride which is precipitated the toluene solution is shaken with 100 parts of

saturated aqueous potassium carbonate solution. The toluene solution is separated off, dried with anhydrous potassium carbonate and distilled whereby there is obtained β -methylamino- β' -ethylamino-diethyl ether N:N'-dicarboxylic bis-diethylamide of B. P. 233° C. at 15 mm. pressure.

Example 11

81 parts of piperidine-N-carboxylic chloride dissolved in 150 parts of benzene are added with stirring to 88 parts of N:N'-bis(β -methoxyethyl)-ethylenediamine dissolved in 150 parts of benzene. After filtering off the amine hydrochloride which separates out, the benzene solution is shaken with 100 parts of a saturated aqueous potassium carbonate solution, dried over anhydrous potassium carbonate and distilled whereby there is obtained N:N'-bis-(β -methoxyethyl)-ethylenediamine-N:N'-dicarboxylic acid bis-piperidide of B. P. 285° C./11 mm.

The N:N'-bis(β -methoxyethyl)-ethylenediamine used as starting material is obtained by reacting ethylene dibromide with an excess of an aqueous solution of β -methoxyethylamine which is conveniently prepared by the catalytic hydrogenation of methoxyacetonitrile in presence of a Raney nickel catalyst.

In a similar manner there are obtained:

(a) N:N'-bis(β -methoxyethyl)-ethylenediamine-N:N'-dicarboxylic bis-diethylamide of B. P. 252° C. at 23 mm.

(b) N:N'-bis(β -ethoxyethyl)-ethylenediamine-N:N'-dicarboxylic bis-piperidide of B. P. 282° C. at 19 mm.

(c) N:N'-bis(isopropoxyethyl)-ethylenediamine-N:N'-dicarboxylic-bis-dimethylamide of B. P. 230° C. at 1 mm.

(d) N:N'-bis(isopropoxyethyl)-ethylenediamine-N:N'-dicarboxylic dimorpholide of M. P. 94° C.

Example 12

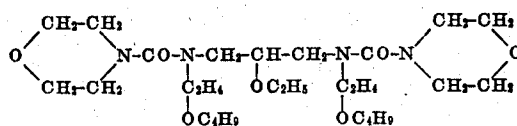
71 parts of dimethyl carbamyl chloride dissolved in 150 parts of benzene are added gradually, with stirring, to 130 parts of N:N'-bis-(β -ethoxyethyl)-hexamethylene diamine in 450 parts of benzene. The whole is then refluxed for one hour, cooled and the precipitated N:N'-bis-(β -ethoxyethyl)-hexamethylene diamine dihydrochloride removed by filtration. The benzene solution is shaken with 100 parts of a saturated aqueous potassium carbonate solution, dried over anhydrous potassium carbonate and distilled, whereby there is obtained N:N'-bis-(β -ethoxyethyl)-hexamethylene diamine-N:N'-dicarboxylic bis-dimethylamide of B. P. 268-9° C. at 11 mm.

The N:N'-bis-(β -ethoxyethyl)-hexamethylene diamine used as starting material is obtained by interaction of hexamethylene dibromide with an excess of an aqueous solution of β -ethoxyethylamine, which itself is conveniently prepared by the catalytic hydrogenation of ethoxyacetonitrile.

Example 13

49 parts of morpholine-N-carboxylic chloride dissolved in 75 parts of benzene are added with stirring to 80 parts of N:N'-bis-(β -n-butoxyethyl)-2-ethoxy-trimethylene diamine dissolved in 450 parts of benzene. When the reaction is completed the precipitated amine hydrochloride is removed by filtration, the filtrate refluxed for one hour with 25 parts of water and distilled to dryness. The residue is extracted with ether, the ether solution dried over anhydrous potas-

sium carbonate and fractionated, whereby there is obtained N:N'-bis-(β -n-butoxyethyl)-2-ethoxy-trimethylene diamine-N:N'-dicarboxylic dimorpholide of B. P. 258° C. at 0.4 mm. pressure. Its structure corresponds to the formula:



The N:N'-di-(β -n-butoxyethyl)-2-ethoxy-trimethylene diamine used as starting material is obtained by interaction of ethyl- β : β' -dichloroisopropyl ether (prepared by interaction of glycerol dichlorohydrin, ethyl iodide and silver oxide) with an excess of aqueous β -n-butoxyethylamine which itself is conveniently obtained by the catalytic hydrogenation of n-butoxyaceto-nitrile in presence of a Raney nickel catalyst.

Example 14

175 parts of N:N'-dimethyl-trimethylenediamine dissolved in 500 parts of toluene are added, at -15° C., with stirring, to a solution of 280 parts of phosgene in 1000 parts of toluene. After the addition is complete, air is blown through the reaction mixture to remove the excess of phosgene; N:N'-dimethyl-trimethylene diamine dihydrochloride separates out and is filtered off and washed with dry toluene. The united filtrate and washings are then distilled whereby there is obtained N:N'-dimethyl-trimethylenediamine-N:N'-dicarboxylic dichloride of B. P. 163-166° C. at 0.8 mm. pressure, together with some 1:3-dimethyl-2-ketohexahydropyrimidine B. P. 140° C. at 44 mm. pressure.

To a solution of 11 parts of N:N'-dimethyl-trimethylene diamine-N:N'-dicarboxylic dichloride in 50 parts of benzene there is added a solution of 18 parts of methyl methoxyethylamine in 50 parts of benzene. Methyl methoxyethylamine hydrochloride separates out and is filtered off and the filtrate is distilled whereby there is obtained N:N'-dimethyl-trimethylenediamine-N:N'-dicarboxylic acid bis(methylmethoxyethylamide) of B. P. 253° C. at 16 mm. pressure.

In a similar manner there are obtained:

(a) N:N'-diethyl-ethylenediamine-N:N'-dicarboxylic acid bis(ethyl methoxyethylamide) B. P. 239° C. at 17 mm. pressure.

(b) N:N'-di-n-propyl-ethylenediamine-N:N'-dicarboxylic acid bis(methyl ethoxyethylamide) of B. P. 255° C. at 20 mm. pressure.

(c) N:N'-dimethyl-trimethylenediamine-N:N'-dicarboxylic acid bis(ethyl ethoxyethylamide) of B. P. 253° C./14 mm.

Example 15

17 parts of ethyl methoxyethyl-carbamyl chloride (made from ethyl methoxyethylamine and phosgene) dissolved in 50 parts of benzene are added with stirring to a solution of 14 parts of N:N'-di-n-propyl ethylenediamine in 50 parts of benzene. N:N'-di-n-propylethylenediamine dihydrochloride separates out and is filtered off. The filtrate is shaken with 50 parts of a saturated aqueous solution of potassium carbonate, dried over anhydrous potassium carbonate and distilled whereby there is obtained N:N'-di-n-propyl-ethylene diamine-N:N'-dicarboxylic bis(ethyl methoxyethylamide) of B. P. 265° C. at 25 mm. pressure.

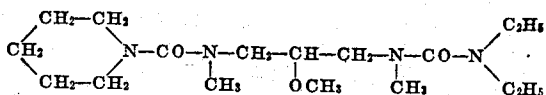
Example 16

29 parts of di-(β -ethoxyethyl) carbamyl chloride (of B. P. 165° C. at 19 mm. pressure) dissolved in 75 parts of toluene are added with stirring to 17 parts of N:N'-di-n-butyl-ethylene diamine in 50 parts of toluene and the whole is refluxed gently for 6 hours. After cooling, the precipitated amine hydrochloride is removed by filtration, the filtrate refluxed for 1/2 hour with 10 parts of water and distilled to dryness on the water bath under reduced pressure. The residue is extracted with hot 60°-80° petroleum ether and the extract fractionally distilled under reduced pressure whereby N:N'-di-n-butyl-ethylene diamine - N:N'-dicarboxylic-bis-di-(β -ethoxyethyl) amide distills over above 240° C. at 10 mm. pressure.

The di-(β -ethoxyethyl)-carbamyl chloride used as starting material is made from phosgene and di- β -ethoxyethylamine, which itself is obtained by interaction of β -ethoxyethyl chloride with an excess of aqueous β -ethoxyethylamine, or, less advantageously, by condensing aniline with ethylene chlorhydrin to give di-(β -hydroxyethyl)-aniline, converting this to its sodium salt and reacting with diethyl sulphate to give di-(β -ethoxyethyl)-aniline which is then converted into di-(β -ethoxyethyl) amine by the method described in respect of N:N'-dimethyl ethylene diamine, in *Berichte der deutschen Chemischen Gesellschaft*, 1918, vol. 51, p. 738.

Example 17

21.5 parts of N-methyl-N':N'-diethyl-N-(3-methyl-amino-2-methoxypropyl)urea and 7.5 parts of piperidine-N-carboxylic chloride are mixed together. Reaction occurs with the evolution of heat. After the reaction has ended the mixture is dissolved in 100 parts of water and crystalline potassium carbonate is added until the solution is saturated. The solution is warmed to 100° C. for 10 minutes, then cooled and the oily layer is extracted with ether. After drying over anhydrous potassium carbonate the ether solution is distilled whereby there is obtained N:N'-dimethyl-2-methoxytrimethylenediamine-N-carboxylic acid diethylamide-N'-carboxylic acid piperidide of B. P. 228° C. at 8 mm. pressure. Its structure corresponds to the formula:



The N-methyl-N':N'-diethyl-N-(3-methylamino-2-methoxypropyl)-urea used as starting material is made as follows. 67 parts of diethyl carbamyl chloride dissolved in 150 parts of toluene are added with stirring to a cooled solution of 96 parts of N:N'-dimethyl-2-methoxytrimethylenediamine in 450 parts of toluene at such a rate that the reaction temperature does not rise above 0° C. N:N'-dimethyl-2-methoxytrimethylenediamine dihydrochloride separates out and is filtered off. The filtrate is then distilled whereby there is obtained N-methyl-N':N'-diethyl-N-(3-methylamino-2-methoxypropyl)-urea of B. P. 151°-152° C. at 12 mm. pressure together with a small proportion of N:N'-dimethyl-2-methoxytrimethylene diamine N:N'-dicarboxylic bis-diethylamide of B. P. 210° C. at 12 mm. pressure.

Example 18

31.5 parts of N:N'-di(β -ethoxyethyl)-ethylenediamine-N-carboxylic acid piperidide are mixed with 6 parts of dimethylcarbamyl chloride and

the mixture is heated at 100° C. for 12 hours. The reaction mixture is cooled, shaken with 100 parts of a saturated aqueous solution of potassium carbonate and then extracted with ether. After drying over anhydrous potassium carbonate the ethereal extract is distilled whereby there is obtained N:N'-di-(β -ethoxyethyl) ethylenediamine-N-carboxylic acid piperidide-N'-carboxylic acid dimethylamide of B. P. 230° C. at 10 mm. pressure.

The N:N'-di-(β -ethoxyethyl)-ethylenediamine-N-carboxylic acid piperidine used as starting material is made as follows. 74 parts of piperidine-N-carboxylic chloride dissolved in 150 parts of benzene are added, with stirring, at a temperature below 10° C. to a solution of 150 parts of N:N'-di-(β -ethoxyethyl)-ethylenediamine in 500 parts of benzene. After the addition is complete the whole is stirred for 5 hours at ordinary temperature. N:N'-di-(β -ethoxyethyl)-ethylenediamine hydrochloride separates out and is filtered off and the filtrate is then distilled whereby there is obtained N:N'-di-(β -ethoxyethyl)-ethylenediamine - N - carboxylic acid piperidide of B. P. 180° C. at 15 mm. pressure, together with a small proportion of N:N'-di-(β -ethoxyethyl)-ethylene diamine N:N'-dicarboxylic acid bis piperidide of B. P. 276°-277° C. at 15 mm. pressure.

Example 19

10 parts of ethyl β -ethoxyethyl carbamyl chloride are added to 31.5 parts of N:N'-di-(β -ethoxyethyl)-ethylenediamine-N-carboxylic acid piperidide (prepared as described in Example 18 above) and the mixture is heated to 120° C. for 8 hours. It is then cooled, shaken with 80 parts of a saturated aqueous solution of potassium carbonate and extracted with ether. After drying over anhydrous potassium carbonate the ether solution is distilled, whereby there is obtained N:N'-di-(β -ethoxyethyl)-ethylenediamine-N-carboxylic acid piperidide-N-carboxylic acid ethyl (β -ethoxyethyl) amide which distills above 245° C. at 10 mms. pressure.

The ethyl β -ethoxyethyl carbamyl chloride used as starting material is made from phosgene and ethyl β -ethoxyethyl amine which is itself conveniently made by interaction of ethyl bromide with an excess of aqueous β -ethoxyethylamine.

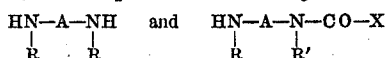
Whereas the above examples illustrate many widely divergent embodiments of the invention it will be apparent to those skilled in the art that many others may be devised without departing from the spirit and scope thereof, and accordingly the invention is not to be regarded as in any way limited thereby but only as defined in the following claims.

In the claims below where a radical such as alkyl, alkylene or alkoxy is preceded by the qualification "lower" the latter shall be understood as limiting said radical to a chain length of not more than 6 carbon atoms.

I claim:

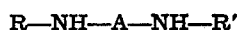
1. In the process of producing a bis-urea of the formula $\text{X}-\text{CO}-\text{NR}-\text{A}-\text{NR}'-\text{CO}-\text{Y}$, wherein A stands for an alkylene radical having from 2 to 6 carbon atoms and having one of its hydrogen atoms replaced by a radical selected from the group consisting of alkyl and alkoxy; wherein R and R' are monovalent aliphatic radicals selected from the group consisting of lower alkyl and lower alkoxy-alkyl; and wherein X and Y are the imino radicals of secondary amines selected from the group consisting of lower dialkyl amines,

lower alkoxy substituted dialkyl amines and secondary heterocyclic amines, the step which consists of reacting with a carbamyl chloride of the formula $Y-CO-Cl$, wherein Y has the same meaning as above, upon a diamine of the group



A , R , R' and X having the same significance as above, whereby at least one of the imine hydrogens of said diamine is replaced by the radical $CO-Y$, with elimination of one mole of HCl .

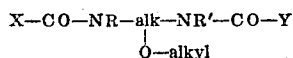
2. In the process of producing a bis-urea of the formula $X-CO-NR-A-NR'-CO-Y$, wherein A stands for an alkylene radical having from 2 to 6 carbon atoms and having one of its hydrogen atoms replaced by a radical selected from the group consisting of alkyl and alkoxy; wherein R and R' are monovalent aliphatic radicals selected from the group consisting of lower alkyl and lower alkoxy-alkyl; and wherein X and Y are the imino radicals of secondary amines selected from the group consisting of lower dialkyl amines, lower alkoxy substituted dialkyl amines and secondary heterocyclic amines, the step which consists of reacting upon a diamine of formula



wherein A , R and R' have the same meaning as above, with a carbamyl chloride of formula $X-CO-Cl$, X having the same meaning as above, whereby at least one of the imine hydrogens of said diamine is replaced by the radical $CO-X$, with elimination of one mole of HCl .

3. As new compounds, the bis-ureas of the general formula $X-CO-NR-A-NR'-CO-Y$, wherein A stands for an alkylene radical having from 2 to 6 carbon atoms and having one of its hydrogen atoms replaced by a radical selected from the group consisting of alkyl and alkoxy; R and R' are monovalent aliphatic radicals selected from the group consisting of lower alkyl and lower alkoxy-alkyl; and X and Y are the imino radicals of secondary amines selected from the group consisting of lower dialkyl amines, lower alkoxy substituted dialkyl amines and secondary heterocyclic amines.

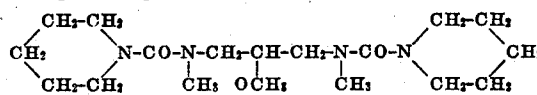
4. As new compounds, the bis-ureas of the general formula



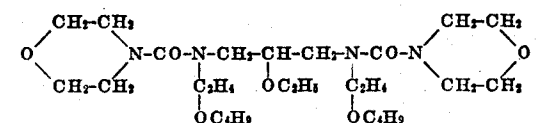
wherein "alk" designates an alkylene radical having from 2 to 6 carbon atoms; R and R' are monovalent aliphatic radicals selected from the group consisting of lower alkyl and lower alkoxy-alkyl,

but containing jointly not more than 12 carbon atoms; and X and Y are the imino radicals of secondary amines selected from the group consisting of lower dialkyl amines, lower alkoxy substituted dialkyl amines and secondary heterocyclic amines, the atomic weight of the secondary amine being less than 220.

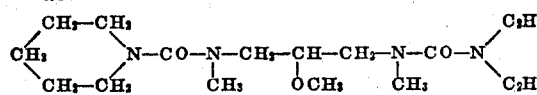
5. $N:N'$ -dimethyl-2-methoxy-trimethylene-diamine- $N:N'$ -dicarboxylic bis-piperidide, the same being a compound of the structural formula:



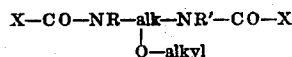
6. $N:N'$ -bis(β -n-butoxyethyl)-2-ethoxy-trimethylene-diamine- $N:N'$ -dicarboxylic dimorpholide, the same being a compound of the structural formula:



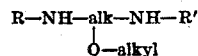
7. $N:N'$ -dimethyl-2-methoxy-trimethylene-diamine- N -carboxylic-diethylamide- N' -carboxylic piperidide, the same being a compound of the structural formula:



8. A process of producing a bis-urea of the formula



wherein "alk" designates an alkylene radical having from 2 to 6 carbon atoms; R and R' are monovalent aliphatic radicals selected from the group consisting of lower alkyl and lower alkoxy-alkyl; and wherein X , X are the imino radicals of secondary amines selected from the group consisting of lower dialkyl amines, lower alkoxy substituted dialkyl amines and secondary heterocyclic amines, which comprises reacting a carbamyl chloride of formula $X-CO-Cl$, X having the same meaning as above, in an inert organic solvent, upon an excess of a diamine of the formula



wherein "alk," R and R' have the same meanings as above, removing the precipitated amine-hydrochloride, and recovering the principal reaction product as formulated above.

WILLIAM ROBERT BOON.