293. *Respiratory Stimulants. Part II. Fully Substituted Bisureas derived from* 2 : 2′-*Diaminodiethyl Ether and* 1 : 3-*Diamino-2-alkoxypropanes.*

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The preparation is described of a number of diamines containing ether linkages of the type NHR·$[CH_2]_n$·Y·$[CH_2]_n$·NHR, where R or R′ is alkyl or alkoxyalkyl, *n* is 1 or 2, and Y is O or CH·OMe or CH·OEt. The diamines have been converted into fully substituted bisureas by reaction with dialkylcarbamyl chlorides or similar heterocyclic compounds.

In Part I (*J.*, 1947, 307) the preparation was reported of a number of bisureas (derived from αω-alkylenediamines) of the general formula, X·CO·NR·$[CH_2]_n$·NR′·COY, in which R and R′ represent alkyl or alkoxyethyl radicals and X and Y represent secondary amine residues. In the present paper the preparation of a similar series of compounds is reported, in which the central alkylene chain is interrupted by an oxygen atom or substituted by an alkoxy-group. It was thought that compounds so modified might show more useful pharmacological properties than did those reported in Part I. Apart, however, from some slight reduction in toxicity, no great advantage appeared to compensate for the greater difficulty of preparation.

The 2 : 2′-bisalkylaminodiethyl ethers required were prepared from the corresponding bisalkylanilino-compounds by hydrolysis of their nitroso-derivatives with sodium hydrogen sulphite; this procedure proved to be much less efficient than with the corresponding alkylenediamines, probably owing partly to the increased solubility of the nitrosoamine hydrochlorides and partly to the much lower volatility of the products in steam. The 2 : 2′-bisalkylanilinodiethyl ethers were first prepared, in poor yield, by condensation of 2 : 2′-dichlorodiethyl ether with the appropriate alkylaniline, the main product being 4-phenylmorpholine. During the course of this work, Brill, Webb, and Halbedel (*J. Amer. Chem. Soc.*, 1941, **63**, 971) reported the isolation only of the morpholine under similar conditions. The best method of preparing the required ethers was condensation of an alkyl-2-chloroethylaniline with the sodium derivative of an alkyl-2-hydroxyethylaniline, this having the further advantage that it was available for the preparation of unsymmetrical diamines. *Methyl* 1 : 3-*bismethylamino*-2-*propyl ether* was prepared in this way from *methyl* 1 : 3-*bismethylanilino*-2-*propyl ether*, itself obtained from the corresponding *propanol*; a more convenient method was direct interaction of methyl 1 : 3-dichloro-2-propyl ether with excess of methylamine; *ethyl* 1 : 3-*bis*-2′-n-*butoxyethylamino*-2-*propyl ether* was prepared by procedure analogous to this last method.

An alternative method for the preparation of methyl 1 : 3-bismethylamino-2-propyl ether was examined, involving the hydrolysis of its *bistoluene*-p-*sulphonyl* derivative. It was hoped that this compound could be hydrolysed under relatively mild conditions, thus avoiding the danger of possible hydrolysis of the ether group inherent in the normal methods for hydrolysing toluene-*p*-sulphonamides; in addition all products of the reaction should be volatile, thus simplifying isolation of the diamine which is only slightly volatile in steam. The toluenesulphonamide was unaffected by being heated with constant-boiling hydrochloric acid, and this line was not pursued further.

All the amines were converted smoothly into the ureas by reaction with the appropriate carbamyl chloride.

EXPERIMENTAL.

(Preparations marked by an asterisk were carried out by Dr. J. A. Hendry. Microanalyses are by Mr. E. S. Morton.)

2 : 2′-*Bismethylanilinodiethyl Ether*.—Of several conditions examined the following gave the best yield. 2 : 2′-Dichlorodiethyl ether (117 g., 0·8 mol.), methylaniline (357 g., 3·35 mols.), anhydrous potassium carbonate (170 g.), and copper powder (2 g.) were stirred for 14 hours at 100—105°. Water was added, and the oil separated and distilled under reduced pressure, giving 235 g. of material, largely recovered methylaniline, boiling below 130°/16 mm., 75 g. (55·2%) of phenylmorpholine, b. p. 158—160°/22 mm., m. p. 53° (from methanol), and 63 g. (36·3%) of 2 : 2′-*bismethylanilinodiethyl ether*, b. p. 258—260°/22 mm., m. p. 45° (from methanol) (Found : N, 10·3. $C_{18}H_{42}ON_2$ requires N, 9·9%).

2 : 2′-*Bisethylanilinodiethyl ether* was obtained similarly in 13% yield, b. p. 255—256°/20 mm., m. p. 37° (from methanol) (Found : N, 9·1. $C_{20}H_{28}ON_2$ requires N, 9·0%). This compound was also prepared as follows. Ethylhydroxyethylaniline (375 g., 2·3 mols.) was dissolved in toluene (250 c.c.), and dried by distillation. After the solution had been cooled to 30°, sodium (45 g., 1·96 atoms) was added and, after the reaction had subsided, the whole was stirred under reflux for 3 hours. Ethylchloroethylaniline (350 g., 1·9 mols.) was then added, and heating continued under reflux with stirring for 15 hours. After being cooled, the mixture was washed twice with water (500 c.c. in all) and distilled under reduced pressure. Yield, 444 g. (75%).

2-*Methylanilino*-2′-*ethylanilinodiethyl ether* was prepared by the second method described above, from methyl-2-hydroxyethylaniline and ethyl-2-chloroethylaniline in 73% yield; b. p. 248—250°/13 mm. (Found : C, 76·0; H, 8·9; N, 9·6. $C_{19}H_{26}ON_2$ requires C, 76·5; H, 8·7; N, 9·4%).

1 : 3-*Bismethylanilino*-2-*propanol*.—Dichlorohydrin (903 g., 7 mols.), methylaniline (1926 g., 18 mols.), and powdered calcium carbonate were stirred at 150° for 45 hours. After the mixture had been cooled to 80°, water was added and the whole filtered through a steam-jacketed Buchner funnel. After separation of the water, the oil was distilled giving 1420 g. (75%) of 1 : 3-*bismethylanilino*-2-*propanol*, b. p. 220°/0·25 mm., m. p. 80° (from light petroleum, b. p. 60—80°) (Found : C, 75·3; H, 8·6; N, 10·5. $C_{17}H_{22}ON_2$ requires C, 75·4; H, 8·2; N, 10·4%).

Methyl-1 : 3-*bismethylanilino*-2-*propyl Ether*.—Sodium (46 g.) was added to a solution of 1 : 3-bismethylanilino-2-propanol (540 g., 2 mols.) in xylene (1 l.). After the reaction had subsided, the mixture was heated under reflux until all the sodium had dissolved. After the mixture had been cooled to 25°, methyl sulphate (252 g., 2 mols.) was added in one lot, whereupon the temperature rose to 120°. After the temperature had fallen below 100°, the whole was stirred under reflux for 10 hours. After cooling it, water was added, followed by sodium carbonate until the mixture was alkaline to brilliant-yellow. The xylene layer was separated and extracted with acid. The acid layer was basified with sodium hydroxide and extracted with benzene. Distillation of the benzene solution gave 253 g. (45%) of *methyl* 1 : 3-*bismethylanilino*-2-*propyl ether*, b. p. 185°/0·5 mm. (Found : C, 75·7; H, 8·8; N, 10·3. $C_{18}H_{24}ON_2$ requires C, 76·0; H, 8·6; N, 9·9%).

1 : 3-*Bistoluene*-p-*sulphonylmethylamido*-2-*propanol*.—Sodium (8·7 g., 0·378 atom) was broken up in hot xylene (350 c.c.), and ethanol (35 c.c.) was added, reaction being completed by stirring under reflux. After addition of toluene-p-sulphonylmethylamide (70 g., 0·378 mol.), the ethanol was distilled off, dichlorohydrin (24 g., 0·186 mol.) was added, and heating continued under reflux with stirring for 20 hours. The xylene was then removed by steam-distillation, the residue basified with sodium hydroxide, and the aqueous layer separated. The residual oil was triturated with methanol, and the resultant solid was filtered off and recrystallised from methanol, giving 48 g. (62%) of 1 : 3-*bistoluene*-p-*sulphonylmethylamido*-2-*propanol*, m. p. 118° (Found : C, 53·4; H, 5·7; N, 6·5. $C_{19}H_{26}O_5N_2S_2$ requires C, 53·4; H, 6·1; N, 6·6%).

Methyl 1 : 3-*Bistoluene*-p-*sulphonmethylamido*-2-*propyl Ether*.—To 1 : 3-bistoluene-*p*-sulphonylmethylamido-2-propanol (43 g., 0·1 mol.) in toluene (300 c.c.), sodium (2·3 g.) was added, and the whole heated under reflux until the sodium was dissolved. After cooling, methyl sulphate (13 g., 0·103 mol.) was added, whereupon the temperature rose to 40°. After 48 hours the toluene was removed by distillation in steam, and the residue crystallised twice from methanol. However, the product had an indefinite

m. p. and was further purified by crystallisation from carbon tetrachloride, which gave 10 g. of unchanged starting material. The residue obtained on evaporation of the mother-liquor gave, on crystallisation from methanol, 10 g. (25%) of *methyl* 1 : 3-*bistoluene*-p-*sulphonmethylamido*-2-*propyl ether*, m. p. 88° (mixed m. p. with starting material 76°) (Found: C, 54·9; H, 7·0; N, 6·3. $C_{20}H_{28}O_5N_4$ requires C, 54·6; H, 6·4; N, 6·4%).

Bisureas, $(X\cdot CO\cdot NR\cdot[CH_2]_n)_2Y$.

X.	R.	Y.	n.	Yield, %.	B. p.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me_2N	Me	O	2	96	254°/30 mm.	$C_{12}H_{26}O_3N_4$	52·3	9·2	20·5	52·6	9·5	20·5
Et_2N	Me	O	2	93	244/12 mm.	$C_{16}H_{34}O_3N_4$	58·4	9·9	16·7	58·2	10·3	16·9
$[CH_2]_5{>}N$	Me	O	2	68·5	286/14 mm.	$C_{18}H_{34}O_3N_4$	60·9	9·5	16·1	61·0	9·6	15·8
$O{<}[CH_2]_4{>}N$	Me	O	2	86	262/0·8 mm.	$C_{16}H_{30}O_5N_4$	53·4	8·1	—	53·6	8·4	—
Et_2N	Et	O	2	89	239/18 mm.	$C_{18}H_{38}O_3N_4$	61·1	10·6	15·7	60·9	10·6	15·7
$O{<}[CH_2]_4{>}N$	Et	O	2	74	228/0·3 mm.	$C_{18}H_{34}O_5N_4$	55·6	8·7	14·3	55·8	8·8	14·5
Et_2N	Me	CH·OMe	1	69	228/21 mm.	$C_{16}H_{34}O_3N_4$	57·8	9·8	17·2	58·1	10·3	17·0
$[CH_2]_5{>}N$	Me	CH·OMe	1	80	265/15 mm.	$C_{18}H_{34}O_3N_4$	60·6	9·6	15·9	61·0	9·7	15·8
$O{<}[CH_2]_4{>}N$	$[CH_2]_2\cdot OBu^n$	CH·OEt	1	40	256/0·4 mm.	$C_{27}H_{52}O_7N_4$	59·2	9·6	10·0	59·5	9·6	10·3

The following di-secondary amines were prepared from the corresponding anilino-derivatives by the general method given in Part I (*loc. cit.*, p. 313): 2 : 2′-bismethylaminodiethyl ether, b. p. 180—182° [*picrate*, m. p. 87° (from water) (Found: C, 36·9; H, 3·7; N, 19·3. $C_{18}H_{22}O_{15}N_8$ requires C, 36·6; H, 3·7; N, 19·0%)]; 2-methylamino-2′-ethylaminodiethyl ether, b. p. 196—197° (no salt satisfactory for analysis was prepared); 2 : 2′-bisethylaminodiethyl ether, b. p. 204° [*picrate* (from water), m. p. 125—126° (Found: C, 38·9; H, 4·2; N, 18·0. $C_{20}H_{26}O_{15}N_8$ requires C, 38·9; H, 4·3; N, 18·2%)]. Methyl 1 : 3-bismethylamino-2-propyl ether, b. p. 175° [*picrate* (from water), m. p. 169° (Found: C, 36·7; H, 3·7; N, 19·1. $C_{18}H_{22}O_{15}N_8$ requires C, 36·6; H, 3·7; N, 19·0%). The last compound was also prepared as follows. Methyl 1 : 3-dichloro-2-propyl ether (Hess and Fink, *Ber.*, 1915, **48**, 2003) (143 g., 1 mol.) and 20% aqueous methylamine (1400 g., 9·3 mols.) were heated in an autoclave at 100° for 12 hours and then at 105—110° for a further 36 hours. The mixture was made alkaline to Clayton-yellow with sodium hydroxide, and the excess of methylamine distilled off. After acidification, the residue was concentrated to 400 c.c., filtered, basified with sodium hydroxide, and distilled to dryness under reduced pressure. Sodium hydroxide (400 g.) was added to the distillate, and the amine layer was separated, dried (KOH), and distilled; b. p. 176—179° yield; 60 g. (45·5%).

Ethyl 1 : 3-bis-2′-*n*-butoxyethylamino-2-propyl ether, b. p. 197—199°/12 mm. [*dihydrochloride*, m. p. 274—275° (Found: C, 52·3; H, 10·0; N, 7·0. $C_{17}H_{38}O_3N_2,2HCl$ requires C, 52·2; H, 10·2; N, 7·2%)], was obtained in 52% yield by the method last described.

The symmetrical bisureas listed in the Table were made by treating equimolecular proportions of a diamine with the appropriate carbamyl chloride in an inert solvent; usually the reaction was complete at room temperature, but in a few cases heating on the steam-bath for 3—5 hours was required. The diamine hydrochloride was then filtered off, and the urea isolated by shaking the filtrate with a saturated solution of potassium carbonate, drying (K_2CO_3), and distilling.

2-*Methylamino*-2′-*ethylaminodiethyl ether* NN′-*di*(*carboxydiethyl*)*amide*, prepared in 91% yield by the above method from 2-methylamino-2′-ethylaminodiethyl ether and diethylcarbamyl chloride, had b. p. 232°/15 mm. (Found: C, 59·6; H, 10·5; N, 16·3. $C_{17}H_{36}O_3N_4$ requires C, 59·2; H, 10·5; N, 16·3%).

N-*Methyl*-N′N′-*diethyl*-N-(3-*methylamino*-2-*methoxypropyl*)*urea*.—Diethylcarbamyl chloride (22 g., 0·16 mol.) in toluene (50 c.c.) was added, with stirring, to methyl 1 : 3-bismethylamino-2-propyl ether (32 g., 0·24 mol.) in toluene (150 c.c.) at —5°. After 16 hours at room temperature, the amine hydrochloride was removed by filtration, and N-*methyl*-N′N′-*diethyl*-N-(3-*methylamino*-2-*methoxypropyl*)*urea* isolated by distillation; yield, 13 g. (35%); b. p. 150—152°/12 mm. (Found: C, 57·1; H, 10·3; N, 18·0. $C_{11}H_{25}O_2N_3$ requires C, 57·2; H, 10·2; N, 18·2%). 6 G. of the bisurea, b. p. 210°/12 mm., were also obtained.

Methyl 1 : 3-*Bismethylamino*-2-*propyl Ether* N-*Carboxydiethylamide* N′-*Carboxypiperidide*.—*N*-Methyl-*N′N′*-diethyl-*N*-(3-methylamino-2-methoxypropyl)urea (13 g., 0·56 mol.) and piperidine-1-carboxyl chloride (4·5 g., 0·33 mol.) were mixed, and, after the initial heat evolution had ceased, were heated at 100° for 1 hour. Saturated potassium carbonate solution (50 c.c.) was then added, and the whole heated under reflux for 10 minutes. After the mixture had been cooled, the oil was extracted with ether, and the extract dried (K_2CO_3) and distilled, giving 7 g. (72%) of the *bisurea*, b. p. 228°/8 mm. (Found: C, 59·3; H, 10·2; N, 16·2. $C_{17}H_{34}O_3N_4$ requires C, 59·7; H, 9·9; N, 16·4%).

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