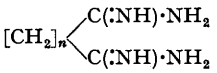
182. *Some Alkoxy- and Alkylenedioxydi-amines and Alkoxy- and Alkylenedioxydi-guanidines.*

By A. T. Fuller and Harold King.

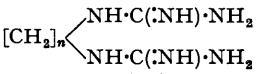
The aim of the investigation was the preparation of a series of alkoxy- and alkylenedioxydiamines (*O*-alkyl- and *OO'*-alkylene-hydroxylamines) and the corresponding alkoxy- and alkylenedioxydi-guanidines with a view to their being tested for antiprotozoal and antibacterial activity. Several representatives of all these types have been successfully made, starting from hydroxyurethane. Other methods of approach have been partly successful. Incidentally, two representatives of the hitherto undescribed class of *O*-alkoxydiguanides have been isolated.*

All these substances have been tested on a range of bacteria *in vitro*.

King, Lourie, and Yorke (*Lancet*, 1937, ii, 1360; *Ann. Trop. Med. Parasit.*, 1938, **32**, 177) discovered that diamidines (I), diguanidines (II), and di*iso*thioureas (III) had a pronounced trypanocidal action, some of the members where $n = 10$ or more being lethal to trypanosomes *in vitro* at a dilution of 1 in 250,000,000



(I.)



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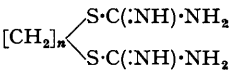
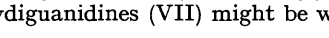


(III.)

Fuller (*Biochem. J.*, 1942, **36**, 548) examined the action of many of these bases, as salts, on a range of bacteria and found that their bacteriostatic titres were lower than their trypanocidal titres, but even so the activity was very pronounced in some of the higher members.

It seemed to us that in further exploration of the parent types the preparation of a series of alkoxyamines (IV), *N*-alkoxyguanidines (V), alkylenedioxydiamines (VI), and alkylenedioxydiguanidines (VII) might be worth undertaking.

(IV.) $CH_3 \cdot [CH_2]_n \cdot O \cdot NH_2$



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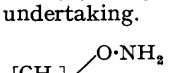

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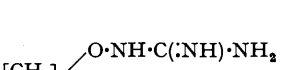
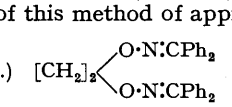
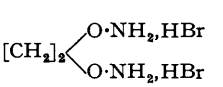


(VII.)

Direct alkylation of hydroxylamine leads to *N*-substitution, so for the preparation of *O*-substituted hydroxylamines, the amino-group must be partly or wholly protected. A number of ways of accomplishing this are described in the literature, but without preliminary exploration of these methods it was by no means certain which method would lend itself to the object we had in view.

Alkylation of oximes by methyl iodide or methyl sulphate leads, both with the aliphatic ketoximes (Dunstan and Goulding, *J.*, 1901, **79**, 628) and with the aromatic ketoximes (Semper and Lichtenstadt, *Ber.*, 1918, **51**, 928) to production of *O*- and *N*-methyl ethers. Borek and Clarke (*J. Amer. Chem. Soc.*, 1936, **58**, 2020) were, however, able to use acetoxime for the preparation of carboxymethoxyamine, $NH_2 \cdot O \cdot CH_2 \cdot CO_2H$ in 60% yield. On these lines a trial was made of the use of benzophenone oxime, which reacted in alcoholic solution with ethylene bromide and sodium ethoxide to give a single homogeneous *ethylenedibenzophenone oxime* of the probable constitution (VIII). The poor yield and slight dubiety about the structure led to the abandonment of this method of approach.

(VIII.) 

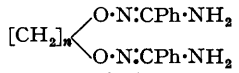


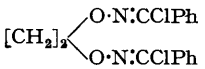
(IX.)

Luxmoore (*J.*, 1895, **67**, 1018) claimed to have prepared ethylenedioxydiamine dihydrobromide (IX) by the direct action of ethylene dibromide on hydroxylamine, but Werner and

* Curd and Rose (*J.*, 1946, 736) have, however, recently described the preparation of a member of this group of substances.

Gemeseus (*Ber.*, 1896, **29**, 1161) pointed out that Luxmoore's claim was inconsistent with the behaviour of hydroxylamine towards alkyl halides. These investigators were, however, able to prepare the corresponding dihydrochloride from the benzamidoxime ethylene ether (X, $n = 2$) of Falck (*Ber.*, 1886, **19**, 1481) which, on treatment with nitrite in the presence of hydrochloric acid, gave benzenyl chloride oxime ethylene ether (XI). The latter with sodium ethoxide furnished the ethylene ether of an ethylbenzhydroxamic acid (XII) which, without


(X.)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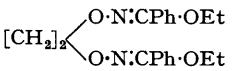
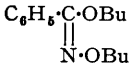

(XII.)

characterisation was hydrolysed to ethylenedioxydiamine. As this method seemed applicable to alkylenedioxydiamines, ethylene dibromide, 1 : 6-dibromohexane, and 1 : 12-dibromododecane have been condensed with benzamidoxime to give *ethylenedi*-OO′-*benzamidoxime dihydrochloride*, 1 : 6-*hexamethylenedi*-OO′-*benzamidoxime* (X, $n = 6$), and *dodecamethylenedi*-OO′-*benzamidoxime* (X, $n = 12$), respectively. In a similar way heptyl bromide was converted into O-*heptylbenzamidoxime* but all attempts to convert the latter or 1 : 6-hexamethylenedibenzamidoxime into the chloride oximes failed completely.

The success of Werner and Gemeseus in obtaining ethylenedioxydiamine, in unstated yield, depended essentially on a method for the preparation of the readily hydrolysable ethylene ether of ethylbenzhydroxamic acid (XII). To explore the possibility of a short route to allied compounds the direct butylation of benzhydroxamic acid was examined. When potassium benzhydroxamate was boiled with butyl bromide in alcohol in presence of potassium carbonate, equal weights of a non-acidic fraction and of an acidic fraction were obtained. The former, on fractional distillation, gave OO′-*dibutyl benzhydroximate* (XIII) as its main component and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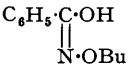
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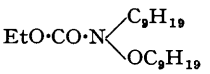
(XV.)

aniline, as a minor component, produced during the reaction by a Lossen rearrangement; (XIII) on hydrolysis with aqueous-alcoholic hydrogen chloride gave mainly ethyl benzoate and butoxyamine hydrochloride.

The acidic fraction on distillation proved to be O′-*butyl benzhydroxamate* (XIV) which on hydrolysis with hydrobromic acid gave *butoxyamine hydrobromide* and benzoic acid.

Whilst the foregoing method might prove suitable for the preparation of the alkoxyamines it would clearly lead to complications with alkylene dihalides.

Most of the above methods of approach to the synthesis of *O*-alkyl- and *OO′*-alkylenedihydroxylamines have involved compounds of oxime type where the nitrogen atom is doubly linked to carbon. Lauder W. Jones and his pupils (cf. Jones and Neuffer, *J. Amer. Chem. Soc.*, 1914, **36**, 2202) have successfully used hydroxyurethane, $OH{\cdot}NH{\cdot}CO_2Et$ for the preparation of the simplest *O*-alkylhydroxylamines. In our hands this method has proved capable of extension to the higher *O*-alkylhydroxylamines and to the *OO′*-alkylenedihydroxylamines. In the cases of the lower homologues up to heptyl no evidence was found for significant proportions of *N*-alkyl derivatives but from the products of the reaction between nonyl bromide and hydroxyurethane, *nonoxyurethane* and *nonoxynonylurethane* (XV) were obtained by fractional distillation. Similarly, alkylene dibromides have been found to give alkylenedioxydiurethanes except that with trimethylene and tetramethylene dibromides cyclisation took place with production of derivatives of *iso*oxazolidine and tetrahydro*iso*oxazine (King, *J.*, 1942, 432). For the hydrolysis of the urethanes, alkali and acid have been used successfully, but there is always some fission of ammonia.

All the hydroxylamines have been converted into alkoxyguanidines and alkylenedioxydiguanidines by use of *S*-methyl*iso*thiourea or cyanamide. Where cyanamide has been employed in excess, two representatives of the hitherto unknown *O*-alkoxydiguanides have been isolated as exemplified by *butoxydiguanide nitrate* and *hexoxydiguanide nitrate*. The former was also prepared by the action of dicyanodiamide on butoxyamine hydrochloride in boiling butyl alcohol. The parent substance hydroxydiguanide also seems to be unknown.

Finally, the complete methylation of heptoxyamine was attempted in methyl alcohol in the presence of potassium carbonate. The products were tetramethylammonium iodide and 2-*n*-heptylidene-*n*-heptaldehyde, identified as its *dinitrophenylhydrazone* :

$$C_7H_{16}ONH_2 \longrightarrow N(CH_3)_4I + CH_3{\cdot}[CH_2]_5{\cdot}CH{:}C(CHO){\cdot}[CH_2]_4{\cdot}CH_3$$

This reaction is fundamentally the same as that observed by Meisenheimer (***Annalen*, 1913, 397**, 273; cf. Jones and Major, *J. Amer. Chem. Soc.*, 1927, **49**, 1529), who found that evaporation of alcoholic solutions of ethoxy- and propoxy-trimethylammonium hydroxide led to production of acetaldehyde and propaldehyde respectively.

Antibacterial Activity.

The methods used were similar to those previously described (Fuller, *loc. cit.*). The results are summarised in the following table: the figures of inhibitory concentrations are those which prevented visible growth in 20 hours at 37° and are expressed as mg. per 100 c.c. (parts per 100,000). The sign > indicates that the drug was not active at the highest concentration tested.

	In blood.	In broth.				
	Strep. pyogenes.	*Strep. pyogenes.*	*Staph. aureus.*	*Cl. welchii.*	*E. coli.*	*B. proteus.*
Alkoxyamines (O-*Alkylhydroxylamines*).						
CH_3–	120	20	75	150	100	300
C_4H_9–	500	20	100	150	100	500
C_6H_{13}–	100	5	200	50	200	500
C_7H_{15}–	200	5	100	50	200	200
C_9H_{19}–	200	2	10	10	>20	>20
$C_{12}H_{25}$–	>5	1	>5	>5	>5	>5
Alkylenedioxydiamines (OO′-*Alkylenehydroxylamines*).						
–C_6H_{12}–	50	50	200	100	100	220
–$C_{10}H_{20}$–	100	1	100	8	>200	>200
Alkoxyguanidines.						
–C_4H_9	100	10	1000	50	1000	>1000
–C_6H_{13}	5	5	100	20	100	200
–C_7H_{15}	20	2	25	5	50	100
–C_9H_{19}	20	1	2	1·5	5	10
–$C_{12}H_{25}$	>10	0·2	0·8	1	2	5
Alkylenedioxydiguanidines.						
–C_6H_{12}–	50	10	200	200	>1000	>1000
–$C_{10}H_{20}$–	20	0·8	10	2	20	100

As is usual with basic drugs, these drugs are more active against the Gram-positive than the Gram-negative bacteria (*E. coli* and *B. proteus*). In a homologous series it is usual for activity to increase with chain length up to a point above which the activity decreases. The alkoxyguanidines, which are stronger bases than the *O*-alkylhydroxylamines, do not appear to have reached their maximum activity at C_{12}, while the *O*-alkylhydroxylamines show signs of having done so. This power of a more strongly basic group to support activity in a longer chain has been noted before (Fuller, *ibid.*).

The basicity of the compounds increases with the chain length. They are, however, such weak bases (the pH of their salts varies from pH 3 to pH 5·5) that none would be appreciably ionized at pH 7·5, so the observed differences of activity are probably not due to differences in their degrees of ionization.

The *O*-alkylhydroxylamines turned the colour of blood to brown or black, but the change was less marked with the alkoxyguanidines. Blood greatly reduced the activity of the drugs with increasing effect as the series was ascended, until the higher members retained 1% or less of the activity shown in broth.

Experimental.

Hydroxyurethane.—Hydroxylamine hydrochloride (27·8 g.; 1 mol.) was added to a solution of anhydrous sodium carbonate (62·4 g.; 1·5 mols.) in water (184 c.c.). The vigorously stirred solution, with salt in suspension, was slowly treated with ethyl chloroformate (42·4 g.), the temperature being kept approximately at that of the room. The final solution was acidified and extracted with ether in a continuous extractor. The yield of hydroxyurethane, dried over sodium sulphate, was about 94%. This method is based on Hantzsch's process (*Ber.*, 1894, **27**, 1255) and is more convenient than that of Jones (*Amer. Chem. J.*, 1898, **20**, 39).

Butoxyurethane and Butoxyamine Hydrochloride.—Hydroxyurethane (10·5 g.) and butyl iodide (18·4 g.) were added to ethyl alcohol (30 c.c.) containing dissolved potassium hydroxide (6·6 g., 85% pure) and the mixture boiled for 5 hours. The alcohol was removed, and the crude butoxyurethane recovered by ether extraction; yield 11·65 g. This urethane was boiled for one hour with potassium hydroxide (16·2 g.; 4 mols.) in water (32·4 c.c.). A solid potassium salt separated first but this quickly

disappeared and was followed by separation of an oily layer. The latter was taken up in ether, and the ethereal extract treated with slight excess of 3N-hydrochloric acid. This acid solution was evaporated to dryness, and the crystalline residue dissolved in boiling ethyl acetate. Butoxyamine hydrochloride, m. p. 156—157°, separated in glistening leaflets (5·3 g.) identical with the product obtained from the butylation of benzhydroxamic acid (see below).

Butoxyguanidine Nitrate.—Butoxyamine hydrochloride (9·3 g.) and cyanamide (6·3 g.) were boiled in absolute alcohol (50 c.c.) for six hours. The alcohol was removed, water added, and the required *nitrate* (9·8 g.) precipitated by adding excess of solid ammonium nitrate. It was twice crystallised from 1·5 vols. of water and separated in well-formed tablets, m. p. 77—78° (Found: C, 31·1; H, 7·5. $C_5H_{13}ON_3,HNO_3$ requires C, 30·9; H, 7·3%). On fractionation of the mother-liquors a by-product was obtained in small quantity which separated from water in nodules but from alcohol in clusters of feathery needles, m. p. 116—117°. This proved to be *butoxydiguanide nitrate* (Found: C, 30·9; H, 6·3; N, 34·8. $C_6H_{15}ON_5,HNO_3$ requires C, 30·5; H, 6·8; N, 35·6%). A specimen was synthesised for comparison by boiling butoxyamine hydrochloride and dicyanodiamide in butyl-alcoholic solution and conversion into the nitrate. On admixture of the above by-product with this substance there was no depression of m. p.

Hexoxyurethane.—Potassium hydroxide (16·8 g.) in boiling absolute alcohol (168 c.c.) was treated with a mixture of hydroxyurethane (31·5 g.) and hexyl bromide (49·5 g.), and the resulting solution boiled for 6 hours. After removal of potassium bromide by filtration the alcohol was distilled off, the residue dissolved in water, and the *hexoxyurethane* extracted by ether and fractionally distilled; b. p. 147—148°/16 mm.; yield 36·6 g. (Found: N, 7·3. $C_9H_{19}O_3N$ requires N, 7·4%).

Acid hydrolysis. The foregoing urethane (18 g.) was boiled for two hours with constant-boiling hydrobromic acid solution (40 c.c.). On cooling, an oily layer separated which soon crystallised. It was collected, well pressed, and then washed with a little light petroleum to remove an oil; yield 7·9 g. On crystallisation of the dried solid from ethyl acetate, *hexoxyamine hydrobromide* separated in pearly flakes, m. p. 141° (Found: C, 36·7; H, 8·2. $C_6H_{15}ON,HBr$ requires C, 36·4; H, 8·2%). The hydrobromic acid mother-liquor after extraction with ether to remove non-basic material, mainly hexyl bromide, was basified and again extracted with ether. In this way a small quantity (2 g.) of the *base* was obtained, b. p. 159°/750 mm. (Found: C, 61·7; H, 13·0; N, 11·9. $C_6H_{15}ON$ requires C, 61·5; H, 12·8; N, 12·0%).

Alkaline hydrolysis. The urethane (36·4 g.) was boiled with potassium hydroxide (43 g.; 4 mols.) in water (215 c.c.) for 3·5 hours. The oily layer was taken up in ether, and the ethereal extracts combined and extracted with 2N-hydrochloric acid (150 c.c.). The acid extract was evaporated to dryness with absolute alcohol, dissolved in a small volume of dry ethyl acetate, and kept at 0°.

Hexoxyamine hydrochloride separated in pearly scales, and a further quantity was obtained from the mother-liquor by addition of dry ether, total yield 20·4 g. The ethereal extract (above) was evaporated and gave unchanged urethane (5·8 g.). The hydrochloride is sparingly soluble in boiling ethyl acetate and melts at 150—151° (Found: C, 46·9; H, 10·6. $C_6H_{15}ON,HCl$ requires C, 46·9; H, 10·5%).

Hexoxyguanidine Nitrate.—(1) *From methylisothiourea.* Hexoxyamine (3·5 g.; 1 mol.) in alcohol (20 c.c.) was treated with methyl*iso*thiourea sulphate (4·2 g.), and the solution boiled gently for 1 hour and then evaporated to a small volume; on keeping, it deposited methyl*iso*thiourea sulphate (0·7 g.). The residue obtained on evaporation to dryness was dissolved in water, and excess of ammonium nitrate added. Crude *hexoxyguanidine nitrate* (4·7 g.) gradually crystallised. It separated from water on recrystallisation in tablets, m. p. 72—73° (Found: C, 38·2; H, 8·5; N, 24·8. $C_7H_{17}ON_3,HNO_3$ requires C, 37·8; H, 8·2; N, 25·2%).

(2) *From cyanamide.* Hexoxyamine hydrochloride (7·68 g.) and cyanamide (4·4 g.; 2 mols.) were boiled in alcohol (25 c.c.) for 6 hours. The solvent was removed, water added, and then excess of ammonium nitrate. The oil which separated gradually solidified and after a tedious fractional crystallisation from water gave hexoxyguanidine nitrate (4·1 g.), identical with the above, and *hexoxydiguanide nitrate* (0·6 g.), m. p. 115—116°, which separated from water or alcohol in tiny plates (Found: C, 36·8; H, 7·5; N, 31·8. $C_8H_{19}ON_5,HNO_3$ requires C, 36·3; H, 7·6; N, 31·8%).

O-*Hexylcholestenone Oxime.*—Equimolecular quantities (M/1000) of cholestenone and hexoxyamine were boiled in ethyl alcohol (5 c.c.) for an hour. The crystalline *oxime* which separated was recrystallised three times from ethyl alcohol and separated in plates, m. p. 70° (Found: C, 81·4; H, 11·8. $C_{33}H_{57}ON$ requires C, 81·9; H, 11·9%).

In a similar way O-*hexylcholestanone oxime*, m. p. 51°, was obtained, crystallising in flattened prisms from alcohol (Found: C, 81·9; H, 12·2. $C_{33}H_{59}ON$ requires C, 81·6; H, 12·3%).

Heptoxyurethane.—This was prepared in the same way as the lower homologue, the yield of product, b. p. 158°/20 mm., being 47% (Found: N, 6·8, 6·9. $C_{10}H_{21}O_3N$ requires N, 7·0%).

Heptoxyamine Hydrobromide.—This salt was prepared by acid hydrolysis as described for its lower homologue, the yield of *hydrobromide*, m. p. 142°, from 38·4 g. of heptoxyurethane being 34·5 g. On crystallisation from ethyl acetate it separated in plates, m. p. 143° (Found: C, 39·7; H, 8·8. $C_7H_{17}ON,HBr$ requires C, 39·6; H, 8·6%). The hydrobromic acid mother-liquors on extraction with ether gave heptyl bromide (1·8 g.), b. p. 170—180°/749 mm.; and after the mother-liquors had been made alkaline, ether extraction gave O-*heptoxyamine*, 0·9 g. This base was prepared in larger quantity from its salt and had b. p. 179°/761 mm. (Found: C, 64·7; H, 13·2. $C_7H_{17}ON$ requires C, 64·1; H, 13·1%).

Methylation of *Heptoxyamine.*—The amine (1·31 g.) and methyl iodide (3·1 c.c.) in methyl alcohol (25 c.c.) were boiled with anhydrous potassium carbonate (4·1 g.) for 3 hours. The solvent was removed, the residue treated with a little water and ether and filtered from some well-formed prisms (0·7 g.), which were crystallised from methyl alcohol (90 c.c.) and were unmelted at 360°. This substance proved to be tetramethylammonium iodide (picrate, m. p. 312° undepressed by an authentic specimen).

The ethereal extract of the aqueous liquor on distillation left an oil with a strong sweet odour with the reactions of an aldehyde. It readily gave a *dinitrophenylhydrazone*, red needles (0·1 g.), m. p. 129°, from alcohol. This on analysis proved to be derived from 2-*n*-heptylidene-*n*-heptaldehyde (Found: C, 61·6; H, 7·8; N, 14·5. $C_{20}H_{30}O_4N_4$ requires C, 61·5; H, 7·8; N, 14·4%).

Heptoxyguanidine Nitrate.—This salt was prepared in a similar way to the lower homologue, the yield of crude *nitrate* from 3·9 g. of heptoxyamine being 4 g. It crystallised from water in prisms, m. p. 72° (Found : C, 41·6; H, 8·6; N, 24·1. $C_8H_{19}ON_3,HNO_3$ requires C, 40·7; H, 8·5; N, 23·7%).

Heptoxy-3 : 5-dinitrobenzamide.—Heptoxyamine (1·31 g.) in pyridine (5 c.c.) was heated with 3 : 5-dinitrobenzoyl chloride (1 mol.) at 100° for 30 minutes. On cooling and adding excess of hydrochloric acid, the *product* crystallised (2·6 g.). It was purified by grinding with sodium bicarbonate solution and could then be crystallised from ether as pale yellow needles, m. p. 83—84° (Found : C, 52·1, 52·1; H, 6·0, 5·9; N, 12·7. $C_{14}H_{19}O_6N_3$ requires C, 51·7; H, 5·8; N, 12·9%).

Nonoxyurethane.—The crude alkylated urethane prepared in the usual manner from hydroxyurethane (8·4 g.) and nonyl bromide (16·5 g.) was fractionally distilled and gave *nonoxyurethane* (8·4 g.), b. p. 179°/20 mm. (Found : N, 6·1. $C_{12}H_{25}O_3N$ requires N, 6·1%), and a higher-boiling fraction of *nonoxynonylurethane* (3·0 g.), b. p. 189°/2 mm. (Found : N, 3·9. $C_{21}H_{43}O_3N$ requires N, 3·9%).

Nonoxyamine Hydrobromide.—The urethane (8·4 g.) was boiled with constant-boiling hydrobromic acid (25 c.c.) for 2 hours. On cooling, the oily layer which separated gradually crystallised. It was collected, washed with a little 48% hydrobromic acid, and finally with a few drops of ether; yield 5·3 g. It was crystallised from ethyl acetate (20 c.c.) and separated in flakes, m. p. 138°; yield 4·1 g. (Found : C, 44·2; H, 9·4. $C_9H_{21}ON,HBr$ requires C, 44·9; H, 9·2%). The hydrobromic acid mother-liquor on extraction with ether gave nonyl bromide (3·0 g.), b. p. 215—220°/756 mm.

Nonoxyamine Hydrochloride.—The urethane (33·2 g.) was boiled with 16% hydrochloric acid (100 c.c.) for 24 hours. The *hydrochloride* separated in needles (10·6 g.), m. p. 146—149° (Found : C, 55·2; H, 11·3; Cl, 18·4. $C_9H_{21}ON,HCl$ requires C, 55·6; H, 11·5; Cl, 18·2%).

Nonoxyguanidine Nitrate.—Nonoxyamine hydrochloride (3·9 g.) was dissolved in N-sodium hydroxide (20 c.c.), and methyl*iso*thiourea sulphate (2·78 g.) in alcohol (15 c.c.) added. After boiling gently for 1 hour, the solution was evaporated to dryness, the residue dissolved in absolute alcohol, and the sodium chloride removed. The solution was again evaporated to dryness, the residue dissolved in water, and ammonium nitrate added in excess. The *nitrate* was collected (4·8 g.) and crystallised from water, separating in needles, m. p. 61—62° (Found : N, 20·9. $C_{10}H_{23}ON_3,HNO_3$ requires N, 21·2%).

Dodecoxyurethane.—From lauryl bromide (37 g.) the crude urethane (39·0 g.) was obtained in the usual way. As it could not be distilled without some decomposition, it was hydrolysed without further purification.

Dodecoxyamine Hydrobromide.—The urethane (20 g.) was boiled with constant-boiling hydrobromic acid (40 c.c.) for 3 hours; on cooling, the oily upper layer crystallised. It was collected by filtration, well pressed, and then washed with ether to remove adhering oil. The *hydrobromide* (9·1 g.) was recrystallised from ethyl acetate, separating in pearly plates, m. p. 133° (Found : C, 51·0; H, 9·9. $C_{12}H_{27}ON,HBr$ requires C, 51·0; H, 10·0%). The hydrobromic acid filtrate was extracted with ether, and the extract on fractional distillation gave lauryl bromide (9·9 g.), b. p. 138—144°/18 mm.

Dodecoxyguanidine Nitrate.—The preceding hydrobromide (5·64 g.) was dissolved in N-sodium hydroxide solution (20 c.c.) and methyl*iso*thiourea sulphate (2·78 g.) in alcohol (15 c.c.) added. The reaction mixture was worked up as described for the corresponding nonyl derivative. The yield of crude *nitrate* was 4·1 g., and on crystallisation from water (100 c.c.) it separated in leaflets, m. p. 79° (Found : C, 50·9; H, 9·6; N, 18·0. $C_{13}H_{29}ON_3,HNO_3$ requires C,50·9; H, 9·9; N, 18·3%).

1 : 6-*Hexamethylenedioxydiurethane.*—Hexamethylene dibromide (24·4 g.), hydroxyurethane (21 g.), and potassium hydroxide (11·2 g.) were boiled together in absolute alcohol (100 c.c.) for 6 hours. The alcohol was removed and an ethereal extract made of the residue when diluted by water. Removal of the ether left the crude urethane (28·7 g.), which could not be distilled at 1 mm. without decomposition.

1 : 6-*Hexamethylenedioxydiamine Dihydrochloride.*—The preceding urethane was boiled for 2·5 hours with potassium hydroxide (40 g.) in water (80 c.c.), during which period there was some evolution of ammonia. The oily layer was taken up in ether and distilled, the fraction, b. p. 90—120°/1 mm. (9·8 g.), being collected and redistilled, b. p. 112°/1 mm. (7·5 g.). It was treated with the calculated amount of N-hydrochloric acid, and the *dihydrochloride* was recrystallised twice from spirit. It separated in tiny leaflets, m. p. 220° (Found : C, 32·7; H, 8·1. $C_6H_{16}O_2N_2,2HCl$ requires C, 32·6; H, 8·2%).

Attempts to hydrolyse the urethane with constant-boiling hydrobromic acid or 16% hydrochloric acid gave very poor yields of base. For instance, the diurethane (14 g.) was boiled for 1·5 hours with 16% hydrochloric acid (50 c.c.) and gave a basic fraction (0·7 g.). A portion of this was converted into the *dipicrolonate* by mixing the calculated amounts of the components in alcohol. It was very sparingly soluble in boiling absolute alcohol and crystallised in minute needles, m. p. 229° (Found : C, 45·9; H, 4·7. $C_6H_{16}O_2N_2,2C_{10}H_8O_5N_4$ requires C, 46·4; H, 4·8%).

1 : 6-*Hexamethylenedioxydiguanidine Dinitrate.*—The preceding dihydrochloride (2·21 g.) was boiled in alcohol (20 c.c.) with cyanamide (1·68 g.) for 6 hours. The solvent was removed, and a small volume of water added, followed by excess of ammonium nitrate. An oil separated which eventually crystallised. It was collected, dried, and recrystallised from absolute alcohol or water, separating in pointed prisms, m. p. 123° (efferv.). The behaviour of the solid on heating in a capillary is variable : no melting takes place and the point of effervescence may occur at any temperature between 121° and 125° (Found : C, 27·2; H, 5·9; N, 30·7. $C_8H_{20}O_2N_6,2HNO_3$ requires C, 26·8; H, 6·2; N, 31·3%).

1 : 10-*Decamethylenedioxydiurethane.*—Dibromodecane (15 g.) and hydroxyurethane (10·5 g.) were boiled in absolute alcohol (60 c.c.) containing potassium hydroxide (5·6 g.) for 6 hours. The alcohol was removed by distillation and replaced by water, and the diurethane extracted with ether. On removal of the ether, the residue (15·9 g.) crystallised on cooling to 0°. A portion was crystallised from ether–light petroleum and gave the *urethane*, m. p. 53—55° (Found : C, 55·6; H, 9·3. $C_{16}H_{32}O_6N_2$ requires C, 55·1; H, 9·3%). Attempts to hydrolyse the main bulk of diurethane by acid were unsuccessful.

1 : 10-*Decamethylenedioxydiamine Dihydrochloride.*—The crude urethane from 15·0 g. of dibromodecane was boiled for 1 hour with potassium hydroxide (20·2 g.) in water (40·6 c.c.). A potassium salt separated at first but was soon replaced by an oily layer. During the hydrolysis some ammonia was given off. The oil was taken up in ether, the ether removed, and the residue distilled; yield 3·9 g.,

b. p. 144—145°/1 mm. The undistilled residue could be again hydrolysed to give a further quantity of base. The pure distilled base which readily solidified was converted into the *dihydrochloride* which could be crystallised from alcohol but preferably from 3N-hydrochloric acid, separating in tiny needles, m. p. 220° (Found : C, 43·1; H, 9·2. $C_{10}H_{24}O_2N_2,2HCl$ requires C, 43·3; H, 9·4%).

1 : 10-*Decamethylenedioxydiguanidine Dinitrate.*—The preceding dihydrochloride (1·4 g.) was boiled in alcoholic solution (10 c.c.) with cyanamide (0·84 g.) for 6 hours. The alcohol was removed, and the residue dissolved in water and treated with ammonium nitrate. The required *dinitrate* (2·2 g.) readily separated as a crystalline solid which was recrystallised from spirit (5 c.c.) and separated in rosettes of compact crystals, m. p. 135° (efferv.). The point of effervescence, like that observed for the corresponding hexamethylene derivative, is very variable, values as high as 147° being observed (Found : C, 35·1; H, 7·2; N, 26·5. $C_{12}H_{28}O_2N_6,2HNO_3$ requires C, 34·8; H, 7·3; N, 27·0%).

Butylation of Benzhydroxamic Acid.—Potassium benzhydroxamate (46·7 g.), spirit (225 c.c.), butyl bromide (41·1 g.), and excess of potassium carbonate were boiled for 15 hours, the alcohol removed by distillation, and the residue diluted with water and ether and filtered from unchanged potassium benzhydroxamate (5·6 g.). The combined ethereal extracts were treated with 7 successive portions of 2N-sodium hydroxide (98 c.c. in all) to remove acidic substances. The residual ethereal solution on evaporation left non-acidic substances (*A*, 23·6 g.). The alkaline extract on acidification and extraction with ether gave an acidic fraction (*B*, 23·9 g.).

Fraction (*A*), on fractional distillation, gave aniline (3·0 g.) and a main fraction (16·2 g.), b. p. 175—180°/13 mm., which on redistillation gave *OO'-dibutyl benzhydroximate*, b. p. 175—180°/13 mm. (Found : C, 72·2; N, 9·1; N, 5·5. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·2; N, 5·6%). The dibutyl derivative was boiled with a mixture of absolute alcohol (100 c.c.) and hydrochloric acid (25 c.c., *d* 1·16) for 4 hours. The resultant solution was diluted with 2 vols. of water and extracted with ether. Washing of the latter with aqueous sodium bicarbonate removed benzoic acid (0·72 g.), and fractional distillation gave ethyl benzoate (8·35 g.), b. p. 213°, with no higher fraction. The main hydrochloric acid mother-liquor was evaporated to dryness under reduced pressure, finally with alcohol, and a small crop of ammonium chloride removed. On re-evaporation to dryness and solution in dry ether, butoxyamine hydrochloride separated as leaflets, m. p. 154°, undepressed by an authentic specimen (Found : Cl, 28·6. Calc. : Cl, 28·2%).

The acidic fraction (*B*), on distillation at 15 mm., had b. p. 182° and was much more viscous than the dibutyl compound; yield 17·0 g. Analysis showed it to be *O'-butyl benzhydroxamate* (Found : C, 68·1; H, 8·0; N, 7·6. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·2%). It was hydrolysed by boiling with constant-boiling hydrobromic acid for 6·5 hours. The solution was diluted with an equal volume of water, and ether extraction removed benzoic acid in quantitative yield. The hydrobromic acid solution was evaporated to small volume under reduced pressure with two additions of water, and the *butoxyamine hydrobromide* (4·8 g.) collected. It was crystallised from ethyl acetate and separated in pearly leaflets, m. p. 159—160° (Found : Br, 47·2. $C_4H_{11}ON,HBr$ requires Br, 47·0%). It was converted in aqueous solution by treatment with silver chloride into butoxyamine hydrochloride which, unlike the hydrobromide, is very sparingly soluble in boiling ethyl acetate. It crystallised in pearly leaflets, m. p. 156—157° (Found : Cl, 28·4. Calc. : Cl, 28·2%). Neuffer and Hoffman (*J. Amer. Chem. Soc.*, 1925, **47**, 1686) gave m. p. 152—153°.

O-*Heptylbenzamidoxime.*—Sodium (9·2 g.) was dissolved in absolute alcohol (150 c.c.) and, after addition of benzamidoxime hydrobromide (43·4 g.) and heptyl bromide (35·8 g.), was boiled for 6 hours. The alcohol was removed, and the residue treated with water and ether. The ethereal extract on distillation left a crystalline solid (42·7 g.) which distilled at 192°/11 mm. O-*Heptylbenzamidoxime* crystallised from ether in needles, m. p. 49—50° (Found : C, 71·9; H, 9·5. $C_{14}H_{22}ON_2$ requires C, 71·6; H, 9·5%). Attempts to convert this amidoxime into benzenyl chloride oxime *O*-heptyl ether by the action of nitrite in hydrochloric acid solution were unsuccessful. The amidoxime forms a sparingly soluble, oily hydrochloride which is not attacked by the nitrite, and an attempt to circumvent this by carrying out the reaction in glacial acetic acid with amyl nitrite and hydrochloric acid was also unsuccessful.

Ethylenedi-O-*benzamidoxime Dihydrochloride.*—Ethylene bromide (4·7 g.), benzamidoxime (6·8 g.), and absolute alcohol (20 c.c., which had reacted with sodium, 1·2 g.) were boiled together for 4 hours. The alcohol was removed by distillation, and the residue dissolved in water and made alkaline by addition of excess of 2N-sodium hydroxide solution. The solid which separated was dissolved in 3N-hydrochloric acid and readily crystallised in needles; yield 1·1 g., m. p. 234—235° (Found : C, 51·8; H, 5·7. $C_{16}H_{18}O_2N_4,2HCl$ requires C, 51·7; H, 5·4%). The hydrochloric acid mother-liquor on basification gave a further 0·25 g., m. p. 161°, of ethylenedibenzamidoxime base. No yields for this reaction are quoted by Falck (*Ber.*, 1886, **19**, 1485) or by Werner and Gemeseus (*ibid.*, 1896, **29**, 1162).

1 : 6-*Hexamethylenedi*-O-*benzamidoxime.*—Sodium (4·6 g.) was dissolved in absolute alcohol (100 c.c.), and benzamidoxime hydrobromide (21·7 g.), dissolved in warm absolute alcohol (20 c.c.), was added; a sodium salt separated. Hexamethylene bromide (12·15 g.) was then added, and the solution boiled for 6 hours. The alcohol was removed, and the residue treated with water. *Hexamethylenedibenzamidoxime* separated as an oil which soon solidified (14·7 g.). When crystallised from 70% alcohol and then from absolute alcohol it had m. p. 106° (Found : C, 67·2; H, 7·6; N, 15·5. $C_{20}H_{26}O_2N_4$ requires C, 67·7; H, 7·4; N, 15·8%). Attempts to convert this substance into hexamethylenedi-*O*-benzenyl chloride oxime were not successful.

1 : 12-*Dodecamethylenedi*-O-*benzamidoxime.*—Sodium (8·2 g.) was dissolved in absolute alcohol (250 c.c.), and benzamidoxime (21·7 g.) and dodecamethylene bromide (16·35 g.) added. The solution was boiled for 4 hours, the alcohol removed by distillation, and the residue made alkaline with N-sodium hydroxide solution. The oil which separated rapidly crystallised; yield 18 g. The crude *oxime* was very soluble in methyl alcohol but could best be crystallised from this solvent. It separated in broad short needles, m. p. 105—106° (Found : C, 71·4; H, 8·6. $C_{26}H_{38}O_2N_4$ requires C, 71·2; H, 8·7%). With 3N-hydrochloric acid it forms an oily hydrochloride.

Ethylenedi-O-*benzophenone Oxime.*—Benzophenone oxime (9·85 g.) and ethylene bromide (4·7 g.) were added to sodium ethoxide solution prepared from absolute alcohol (25 c.c.) and sodium (1·15 g.).

On boiling, sodium bromide rapidly separated; heating was continued for 6 hours. When cold, the sodium bromide and admixed needles were collected and the former removed by water, leaving the *oxime* (1·7 g.), which crystallised from absolute alcohol (60 c.c.) in pearly leaflets, m. p. 123—124° (Found: C, 80·3; H, 5·4; N, 6·4. $C_{28}H_{24}O_2N_2$ requires C, 80·0; H, 5·6; N, 6·7%). There was no evidence for the presence of any isomeric ether, the alcoholic mother-liquors giving only unchanged benzophenone oxime.

Preparation of Benzamidoxime Hydrobromide. Isolation of 2 : 4-Diphenyl-1 : 3 : 5-oxadiazole.—Phenyl cyanide (103 g.), hydroxylamine hydrochloride (69·5 g.), and anhydrous sodium carbonate (53 g.) were treated with water (150 c.c.), and ethyl alcohol added until the solution was homogeneous. The solution was boiled for 18 hours, the alcohol removed by distillation, and the aqueous residue extracted with ether. The ethereal extract was shaken with 24% aqueous hydrobromic acid (400 c.c.), and the latter on concentration gave a 76% yield of *benzamidoxime hydrobromide*, crystallising in prisms, m. p. 183° (Found: C, 39·0; H, 4·7. $C_7H_8ON_2,HBr$ requires C, 38·7; H, 4·2%). The ethereal solution on fractional distillation gave phenyl cyanide (9·5 g.) and a non-volatile crystalline residue (2·35 g.). The latter on crystallisation from methyl alcohol separated in long silky needles, m. p. 107°, which proved to be 2 : 4-diphenyl-1 : 3 : 5-oxadiazole (Found: C, 75·4; H, 4·8. Calc. for $C_{14}H_{10}ON_2$: C, 75·7; H, 4·5%). The final hydrobromic acid mother-liquor contained benzamide (4·0 g.).

Wolf (*Ber.*, 1898, **31**, 2111) gives m. p. 168° for benzamidoxime hydrochloride. In our hands this salt crystallised from alcohol and ether in stout prisms, m. p. 203° (Found: C, 48·9; H, 5·3; Cl, 20·5. Calc. for $C_7H_8ON_2,HCl$: C, 48·7; H, 5·3; Cl, 20·5%).

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