45. *Amino-oxy-derivatives. Part II.*[1] *Some Derivatives of N-Hydroxydiguanide.*

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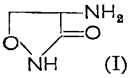
The preparation of some amino-oxyalkanes and their corresponding diguanides, together with certain arylmethyl analogues, is described. A summary of bacteriostatic activities is included.

The isolation of the tuberculostat cycloserine[2,3] (I) which may be regarded as a cyclised form of α-amino-β-amino-oxypropionic acid (II), and the fact that a number of compounds containing the amino-oxy-group are known to be of pharmacological interest, has prompted us to investigate the bacteriostatic properties of amino-oxy-containing compounds. The preceding paper[1] described some α-amino-oxy-acids and their derivatives which were, however, relatively inactive: the present communication describes further compounds containing the amino-oxy-group.



(I)

$NH_2 \cdot O \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$ (II)

$RO \cdot NH \cdot C(:NH) \cdot NH \cdot C(:NH) \cdot NH_2$ (III)

Although many amino-oxyalkanes were described by L. W. Jones and his collaborators,[4] their pharmacological properties were not examined. Andrews, King, and Walker,[5a] and Fuller and King,[5b] found significant bacteriostatic activity *in vitro* with the higher alkyl members of the series, the maximum bacteriostatic index[6] occurring at C_{12}—C_{14}; replacement of the amino- by the guanidino-group afforded alkoxyguanidines with greater activity. While the pharmacological properties of the few known alkyloxydiguanides (III; R = alkyl)[5b,7,8] have not been described, those of the analogous alkyldiguanides have been examined by several groups of workers; *e.g.*, *N*-dodecyldiguanide is said to be an effective bacteriostat,[9] and the hypoglycæmic activity of *NN*-dimethyldiguanide has been noted by several workers (cf. Slotta and Tschesche[10]). Other compounds have been used as analgesics,[11] antiviral agents,[11,12] local anæsthetics,[13] and anticholinesterases.[14]

[1] Part I, McHale, Green, and Mamalis, preceding paper.
[2] Kuel, Wolf, Trenner, Peck, Buhs, Putler, Ormond, Lyons, Chaiet, Howe, Hunnewell, Downing, Newstead, and Folkers, *J. Amer. Chem. Soc.*, 1955, **77**, 2344; Hidy, Hodge, Young, Harned, Brewer, Phillips, Runge, Stavely, Pohland, Boaz, and Sullivan, *ibid.*, p. 2345.
[3] Spencer and Payne, *Antibiotics and Chemotherapy*, 1956, **6**, 708.
[4] Jones and Oesper, *J. Amer. Chem. Soc.*, 1914, **36**, 730; Jones and Neuffer, *ibid.*, p. 2202; Neuffer and Hoffmann, *ibid.*, 1925, **47**, 1685.
[5] (*a*) Andrews, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**,29; (*b*) Fuller and King, *J.*, 1947, 963.
[6] Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **26**, 160.
[7] Nyberg and Christensen, *J. Amer. Chem. Soc.*, 1956, **78**, 781.
[8] Curd and Rose, *J.*, 1946, 729.
[9] F.P. 788,429.
[10] Slotta and Tschesche, *Ber.*, 1929, **62**, 1398.
[11] Garcia, *J. Phillipine Med. Assoc.*, 1950, **26**, 287.
[12] Sapniewski and Chrusciel, *Bull. Acad. polon. Sci., Classe II*, 1954, **2**, 29; B.P. 776,176.
[13] Jones and Major, *J. Amer. Chem. Soc.*, 1927, **49**, 1527.
[14] Palazzo, Rogers, and Marini-Bettolo, *Gazzetta*, 1954, **84**, 915.

These facts together with the known interesting pharmacological properties of aryldiguanides and aminoguanidines [15] suggested that derivatives of *N*-hydroxydiguanide might be worth study.

RO·NH·COPh	RO·NH·CO_2Et	RO·NH·CO_2·CH_2Ph
(IV)	(V)	(VI)

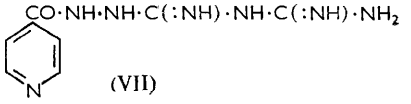
In order to be able to compare the antibacterial activities of the alkyloxydiguanides with those of Fuller and King's amino-oxy-alkanes [5b] under the same conditions, we have repeated the preparation of some of the latter compounds. Methyl-, ethyl-, and allyloxyamine were prepared by acid hydrolysis of the alkyl benzhydroxamates [16] (IV; R = alkyl): application of this method to higher homologues was unsatisfactory owing to appreciable O–N cleavage. The benzhydroxamates were, however, smoothly cleaved by hot ethanolic hydrogen chloride, affording good yields of amino-oxyalkane hydrochlorides. Whereas, for example, hydrolysis of propyl benzhydroxamate with aqueous hydrochloric acid gave benzoic acid (64%), ammonium chloride (71%), and an oil, treatment with ethanolic hydrogen chloride yielded the required amino-oxypropane hydrochloride (94%). The amino-oxyalkanes were also conveniently prepared by alkaline hydrolysis of alkyloxyurethanes (V; R = alkyl), the products being isolated as hydrochlorides. As was observed by Fuller and King,[5b] alkylation of hydroxyurethane sometimes gave the *ON*-dialkylated urethane as by-product readily separated by distillation. In a few instances *N*-benzyloxycarbonylhydroxylamine (VI; R = H) was used to prepare the alkyl intermediates (VI; R = alkyl) which were converted into amino-oxyalkanes by dry hydrogen bromide in acetic acid. Catalytic reduction of the esters (VI; R = alkyl) resulted in O–N cleavage and failed to yield the required products. Since the completion of this work, Theilacker and Ebke [17] have described the preparation of many amino-oxyalkanes by reaction of alkanols with sodium and chloramine.

The amino-oxyalkane hydrochlorides reacted readily with dicyandiamide in ethanol to afford the diguanides (III; R = alkyl), generally isolated as dihydrochlorides: as these were solids of somewhat indefinite melting point the bases were better characterised as their crystalline picrates. The encouraging bacteriostatic properties of the higher alkyloxydiguanides *in vitro* made it desirable to prepare hydroxydiguanide derivatives containing an arylalkyl group since compounds with molecular weights comparable with those of the more effective alkyloxydiguanides would thus be obtained. Certain *N*-aryldiguanides [18] and heterocyclic diguanides [19] have in fact shown some bacteriostatic and antiviral [20] properties. The required amino-oxymethyl-benzenes and -naphthalenes (of which only amino-oxymethylbenzene [21] and *p*-amino-oxymethylnitrobenzene [22] have previously been described) were prepared in good yield by alcoholysis of the corresponding benzhydroxamates. Reaction of 9-chloromethylphenanthrene with benzhydroxamic acid yielded, as well as the expected 9-benzamido-oxymethylphenanthrene, a by-product shown to be *N*-benzoyl-*ON*-di-(9-phenanthrylmethyl)hydroxylamine. From these amino-oxyhydrochlorides, the diguanides were prepared by the usual reaction with dicyandiamide. During this work the parent member of the series, *N*-hydroxydiguanide dihydrochloride, was prepared by hydrogenolysis of *N*-benzyloxydiguanide dihydrochloride.

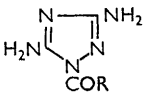
Cohn [23] has shown that free amines such as aniline do not react with dicyandiamide, so for the preparation of diguanides it is usual to employ amine salts such as hydrochlorides,

[15] Petersen and Domagk, *Naturwiss.*, 1954, **41**, 10; Petersen, Gauss, and Urbschat, *Angew. Chem.*, 1955, **67**, 217.
[16] Brady and Peakin, *J.*, 1930, 226.
[17] Theilacker and Ebke, *Angew. Chem.*, 1956, **68**, 303.
[18] Fuller, *Biochem. J.*, 1947, **41**, 403; Rose and Swain, *J.*, 1956, 4422.
[19] Sirsi, Gupta, and Rama Rao, *Current Sci.*, 1950, **19**, 292; Sirsi, Rama Rao, and De, *ibid.*, p. 317.
[20] Clark, Isaacs, and Walker, *Brit. J. Pharm. Chem.*, 1958, **13**, 424.
[21] Behrend and Leuchs, *Annalen*, 1890, **257**, 206.
[22] Brady and Klein, *J.*, 1927, 874.
[23] Cohn, *J. prakt. Chem.*, 1911, **84**, 396.

arylsulphonates,[24] or free bases in the presence of a copper salt. It was, therefore, of interest to note the claim [25] that prolonged reaction of isonicotinoylhydrazine with dicyandiamide in absence of acid yielded the diguanide (VII), a compound reported to possess tuberculostatic and bacteriostatic activity, especially since it is known that hydrazide hydrochlorides and dicyandiamide usually give rise to 1-acyl-3,5-diamino-1,2,4-triazoles



(VII)



(VIII)

(VIII).[26] As we wished to observe the effect of replacement of the CH_2·O group in our diguanides by CO·NH, the reaction of representative hydrazides with dicyandiamide was investigated. As in the patent claim,[25] isonicotinoylhydrazine was heated with dicyandiamide in methanol in the absence of acid to give a colourless crystalline substance in good yield, with a melting point close to the recorded figure. Infrared absorption showed that the substance, although giving analyses correct for (VII), was not a diguanide, its spectrum over the range 2—8 μ being very similar to that of dicyandiamide: the presence of >NH, −CN, and >CO groups was indicated and it was thus probable that the material was a simple salt or molecular complex. This was confirmed when on treatment with picric acid isonicotinoylhydrazine picrate separated. When the reaction was carried out in the presence of hydrogen chloride a product was obtained giving satisfactory analyses for the diguanide hydrochloride (VII) and possessing an infrared spectrum resembling that of other diguanides obtained in this work: there was no evidence for formation of a triazole. Similarly, benzhydrazide hydrochloride and dicyandiamide gave a diguanide with the expected properties. Although isonicotinoylhydrazine formed a salt with dicyandiamide in absence of acid, both amino-oxydecane and 8-amino-oxy-6-chloro-1,3-benzodioxan failed to do so even after prolonged heating, dicyandiamide being recovered unchanged. In a control experiment, dicyandiamide was stable to boiling methanol under the same conditions. Since the acyl-substituted diguanides were microbiologically inactive, these experiments were not pursued further.

R·CH(CO_2H)·O·NH·C(:NH)·NH·C(:NH)·NH_2 (IX)

In an attempt to improve on the slight antibacterial activity of the α-amino-oxy-acids of McHale, Green, and Mamalis,[1] the diguanide derivatives (IX; R = C_5H_{11}, C_6H_{13}, C_7H_{15}, and C_8H_{17}) were prepared by hydrolysis of the reaction product of the amino-oxy-ester hydrochloride with dicyandiamide: amino-oxy-acid hydrochlorides failed to react with dicyandiamide.

Microbiological Results.—A summary of the results (a fuller account of which will be reported elsewhere) is given in the Table, the figures representing the minimum bacteriostatic concentration *in vitro* of compound in parts per million.

While the amino-oxyalkanes exhibited a limited but approximately uniform bacteriostatic effect against the representative bacteria, the diguanides showed a sharp increase of activity with increase in size of group R. Unlike Fuller and King's derivatives, the diguanides were active against a broad range of organisms: thus, decyloxydiguanide inhibited the growth of *Strept. pyogenes*, *C. diptheriae*, *Kl. pneumoniae*, *S. typhi*, and *Ps. aeruginosa* at concentrations of *ca.* 1 p.p.m. The activity of the aryl-substituted diguanides also increased with increasing molecular weight and reached a maximum with 9-phenanthrylmethoxydiguanide. Benzamido- and isonicotinamido-diguanide were inactive. The more active compounds were bactericidal against these organisms at concentrations of 1—5 p.p.m. and also inhibited the growth of the fungi *M. canis*, *C. albicans*,

[24] Oxley and Short, *J.*, 1951, 1252.
[25] U.S.P. 2,753,354.
[26] U.S.P. 2,480,514; 2,456,090; 2,352,944.

	$RO{\cdot}NH_2$			$RO{\cdot}NH{\cdot}C(:NH){\cdot}NH{\cdot}C(:NH){\cdot}NH_2$		
R	*S. aureus* N.C.T.C.4163	*E. coli* 8196	*M. tuberculosis* 7416	*S. aureus* 4163	*E. coli* 8196	*M. tuberculosis* 7416
Hydrogen	75—150	150—300	37—75	>300	>300	
Butyl	>600	*ca.* 600		300—600	300—600	
Hexyl	300—600	>600	300—600	37—75	75—150	
Octyl	150—300	300—600	*ca.* 75	5—10	5—10	5—10
Decyl	75—150	150—300		0·6—1·2	0·6—1·2	5
Tetradecyl				1·25—2·5	6—12	2·5
Benzyl	300	600	75—150	150—300	300	
4-Chlorobenzyl				75	75	
3,4-Dichlorobenzyl				37	37	
3-Phenylpropyl				75	75	
1-Naphthylmethyl	300	300		37	19	
9-Phenanthrylmethyl				5	5	
Cf. sulphathiazole	5	10		Isoniazid		0·1—0·2

T. mentagrophytes, and *E. floccosum* at a level of 1—5 p.p.m. The carboxyl-containing diguanides were almost devoid of activity and, surprisingly, even less active than the amino-oxy-acids of McHale, Green, and Mamalis.[1]

Experimental

Light petroleum refers to the fraction b.p. 40—60°.

Benzhydroxamates.—These were prepared by reaction of sodium benzhydroxamate with the alkyl or arylmethyl halide according to the general method of Brady and Peakin.[16] New benzhydroxamates are described in Table 1. The required arylmethyl bromides were made by

Table 1. *Substituted benzhydroxamates.*

			Found (%)			Reqd. (%)		
Substituent	M. p. or b. p.	Formula	C	H	N	C	H	N
n-Hexyl	138—140°/0·3 mm.	$C_{13}H_{19}O_2N$	70·1	8·7	6·4	70·5	8·7	6·2
4-*Methylbenzyl*	107—108 [a, c]	$C_{15}H_{15}O_2N$	74·8	6·3	6·3	74·7	6·3	5·8
4-*Chlorobenzyl*	162 [a, c]	$C_{14}H_{12}O_2NCl$	64·3	5·0	5·2	64·2	4·6	5·4
4-*Bromobenzyl*	176 [a, d]	$C_{14}H_{12}O_2NBr$	54·7	4·0	4·6	54·8	4·0	4·6
2-*Nitrobenzyl*	121 [a, e]	$C_{14}H_{12}O_4N_2$	61·8	4·7		61·8	4·5	
3,4-*Dichlorobenzyl*	134 [b, d]	$C_{14}H_{11}O_2NCl_2$	56·6	3·5	4·6	56·8	3·7	4·7
Cinnamyl	118—120 [b, d]	$C_{16}H_{15}O_2N$	75·5	6·0	5·5	75·9	6·0	5·5
1-*Naphthylmethyl*	140 [b, d]	$C_{18}H_{15}O_2N$	78·5	5·8	4·7	78·1	5·5	5·1
2-*Naphthylmethyl*	131 [b, c]	$C_{18}H_{15}O_2N$	77·8	5·5	4·9	78·1	5·5	5·1
2-*Methyl-1-naphthylmethyl*	150 [b, d]	$C_{19}H_{17}O_2N$	78·2	6·5	4·8	78·4	5·9	4·8
1-*Bromo-2-naphthylmethyl*...	144 [b, e]	$C_{18}H_{14}O_2NBr$	60·6	4·2		60·6	4·0	
8-*Quinolylmethyl*	133—134 [b, d]	$C_{17}H_{14}O_2N_2$	73·0	4·9	10·5	73·4	5·0	10·1
6-*Chloro*-8-(1,3-*benzodioxanylmethyl*)	131—132 [b, c]	$C_{16}H_{14}O_4NCl$	60·2	4·5	4·3	60·0	4·4	4·4

[a] Leaflets. [b] Needles. Recrystallised from (*c*) ethyl acetate–light petroleum, (*d*) ethyl acetate, (*e*) ethanole.

side-chain bromination of the toluenes and methylnaphthalenes with *N*-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide. 4-Bromobenzyl bromide, 1-bromomethylnaphthalene, and 1-bromo-2-bromomethylnaphthalene do not appear to have been made previously in this way. Bromination of 2-methylnaphthalene with *N*-bromosuccinimide afforded 2-bromomethylnaphthalene, m. p. 48°, as major product: in one run a substance of m. p. 128° was also obtained in low yield and shown to be 1-*dibromomethylnaphthalene* (Found: C, 44·2; H, 3·0; Br, 52·9. $C_{11}H_{18}Br_2$ requires C, 44·0; H, 2·7; Br, 53·3%) since with boiling water it yielded 2-naphthaldehyde as leaflets, m. p. 57—58°, characterised as the semicarbazone, needles (from acetone), m. p. 245°.[27] In addition to the bromomethyl derivatives, 1-chloromethylnaphthalene,[28] 1-chloromethyl-2-methylnaphthalene,[29] and 6-chloro-8-chloromethyl-1,3-benzodioxan [30] were prepared. The following benzhydroxamates were prepared with properties

[27] Monier-Williams, *J.*, 1906, **89**, 273.
[28] Cambron, *Canad. J. Res.*, 1939, **17***B*, 10.
[29] Darzens and Levy, *Compt. rend.*, 1936, **202**, 73.
[30] Buchler, Bass, Darling, and Lubs, *J. Amer. Chem. Soc.*, 1940, **62**, 890.

in agreement with those in the literature: methyl [31], ethyl [32], allyl [16], butyl [5b], benzyl [33], and 4-nitrobenzyl benzhydroxamate.[22]

3-Phenylpropyl Benzhydroxamate.—Cinnamyl benzhydroxamate (1·0 g.) in ethanol (15 ml.) and ethyl acetate (15 ml.) was shaken with hydrogen and 10% palladised charcoal (theoretical absorption in 3 min.). Evaporation of the filtered solution gave an oil which solidified to a white solid (0·88 g.), m. p. 42—45°, which was difficult to crystallise. Distillation in a short-path still gave the *product* as a colourless oil, b. p. 120—140° (bath)/3 × 10^{-5} mm., m. p. 45—46° (Found: C, 74·8; H, 6·5; N, 5·5. $C_{16}H_{17}O_2N$ requires C, 75·1; H, 6·7; N, 5·5%).

9-Phenanthrylmethyl Benzhydroxamate.—To benzhydroxamic acid (6·9 g.) and sodium hydroxide (2·0 g.) in ethanol (50 ml.) was added 9-chloromethylphenanthrene (11·3 g.), and the mixture was refluxed for 4 hr. Solid separated on cooling and was collected, and washed with ethanol, then with water. Crystallisation from aqueous dimethylformamide gave needles of *N-benzoyl-ON-di-(9-phenanthrylmethyl)hydroxylamine* (2·1 g.), m. p. 209—210° (Found: C, 85·8; H, 5·2; N, 2·5. $C_{33}H_{27}O_2N$ requires C, 85·7; H, 5·3; N, 2·7%). Addition of water to the original mother-liquors precipitated *9-phenanthrylmethyl benzhydroxamate* which separated from ethyl acetate as needles (8·6 g.), m. p. 160—161° (Found: C, 80·4; H, 5·6; N, 4·3. $C_{22}H_{17}O_2N$ requires C, 80·6; H, 5·3; N, 4·3%).

Alkyloxyurethanes.—Prepared by Fuller and King's method [5b] from the potassium salt of hydroxyurethane and the alkyl bromides, the alkyloxyurethanes are summarised in Table 2. They were colourless oils or low-melting solids purified by distillation or crystallisation.

TABLE 2. *Alkyloxyurethanes.*

			Found (%)			Reqd. (%)		
Alkyl	B. p./mm. or m. p.	Formula	C	H	N	C	H	N
Allyl	123°/28 [a]							
Isobutyl	55°/0·2	$C_7H_{15}O_3N$	52·3	9·3	9·1	52·1	9·4	8·8
Pentyl	76°/0·08	$C_8H_{17}O_3N$	54·5	9·7	8·3	54·7	9·8	8·0
Hexyl	86°/0·35 [b]							
Heptyl	93°/0·3 [c]							
Octyl	98°/0·04	$C_{11}H_{23}O_3N$	61·1	10·9	6·2	60·9	10·7	6·5
Nonyl	103—104°/0·3 [d]							
Decyl	112°/0·05 [e]	$C_{13}H_{27}O_3N$	63·5	10·9	5·9	63·6	11·1	5·7
Undecyl	130°/0·3 [f]	$C_{14}H_{29}O_3N$	64·9	11·0	5·2	64·9	11·0	5·2
2-Methyldecyl	128°/0·2 [g]	$C_{14}H_{29}O_3N$	65·2	10·8	5·5	64·9	11·0	5·2
Tetradecyl	39—40° [h]	$C_{17}H_{35}O_3N$	68·2	11·9	4·8	67·8	11·7	4·7
Hexadecyl	40·5—41·5° [h]	$C_{19}H_{39}O_3N$	69·8	12·0	4·0	69·3	11·9	4·3
Octadecyl	45—46° [h]	$C_{21}H_{43}O_3N$	71·0	12·3	3·9	71·4	12·1	3·9

[a] Lit.,[34] b. p. 108°/12·5 mm. [b] Lit.,[5b] b. p. 146—147°/16 mm. [c] Lit.,[5b] b. p. 158°/20 mm. [d] Lit.,[5b] b. p. 179°/20 mm. [e] n_D^{18} 1·4464. [f] n_D^{17} 1·4484. [g] n_D^{18} 1·4482. [h] Needles from light petroleum.

N-Decyl-N-decyloxyurethane.—Isolated as a by-product from the reaction of hydroxyurethane with decyl bromide, the disubstituted *urethane* had b. p. 154°/0·1 mm., n_D^{18} 1·4490 (Found: C, 71·0; H, 11·9; N, 3·8. $C_{23}H_{47}O_3N$ requires C, 71·5; H, 12·2; N, 3·6%).

N-Benzyloxycarbonylhydroxylamine.—To a stirred mixture of hydroxylamine hydrochloride (5·6 g.), anhydrous sodium carbonate (12·5 g.) and water (37 ml.) was added benzyl chloroformate (13·4 g.) dropwise at 15—20°. After a further 4 hours' stirring the mixture was acidified with concentrated hydrochloric acid, and the liberated oil was extracted into ether. The extracts were washed with water, dried, and evaporated to afford a white *product* (10·2 g.), which formed plates (from ether–light petroleum), m. p. 68—69° (Found: C, 57·8; H, 5·5; N, 8·0. $C_8H_9O_3N$ requires C, 57·5; H, 5·5; N, 8·4%).

Amino-oxymethane Hydrobromide.—Sodium hydroxide (0·96 g.) in ethanol (25 ml.) was treated with *N*-benzyloxycarbonylhydroxylamine (4·0 g.), the sodium salt separating. After addition of methyl iodide (3·4 g.) the mixture was refluxed for 4 hr., water added, and the oily product isolated with ether. Removal of solvent left a yellow oil (3·3 g.) which failed to solidify. The oil was left with a 20% solution (10 ml.) of hydrogen bromide in acetic acid overnight at 20°, then evaporated, and the residual solid crystallised from ethanol–ether, giving the

[31] Jacobson, *Annalen*, 1894, **281**, 186.
[32] Waldstein, *ibid.*, 1876, **181**, 384.
[33] Beckmann, *Ber.*, 1893, **26**, 2633.
[34] Kleinschmidt and Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 1929.

hydrobromide as deliquescent plates (1·5 g.), m. p. 102° (Found: C, 9·6; H, 4·8; N, 11·1. CH_6ONBr requires C, 9·4; H, 4·7; N, 10·9%).

Amino-oxymethane Hydrochloride.—Methyl benzhydroxamate (3·0 g.), concentrated hydrochloric acid (15 ml.), and water (15 ml.) were heated under reflux for 2 hr. After cooling, the benzoic acid was collected (2·1 g.) and the filtrate evaporated to dryness. The white solid remaining was crystallised from ethyl acetate–ethanol to give the hydrochloride as white plates (1·4 g.), m. p. 148—149° (lit.,[35] m. p. 149°).

Amino-oxyethane hydrochloride similarly prepared, formed plates (from ethyl acetate–ethanol), m. p. 130—132° (lit.,[36] m. p. 128°).

3-Amino-oxypropene hydrochloride, obtained from allyl benzhydroxamate, crystallised as plates, m. p. 172—174°. Brady and Peakin [16] give m. p. 172° (decomp.).

1-*Amino-oxypropane Hydrochloride.*—(*a*) The above hydrochloride (5·0 g.) in ethanol (50 ml.) was shaken with hydrogen and 10% palladised charcoal till uptake ceased. Concentration of the filtered solution and addition of ethyl acetate afforded the product as plates (4·8 g.), m. p. 150—151° (Found: C, 31·9; H, 8·9; N, 12·8. Calc. for $C_3H_{10}ONCl$: C, 32·3; H, 8·9; N, 12·6%) (lit.,[37] m. p. 140—141°,[17] m. p. 155—157°).

(*b*) Propyl benzhydroxamate (11·5 g.) and 6% ethanolic hydrogen chloride (60 ml.) were heated under reflux for 1 hr. After removal of solvent, dry ether was added; the product (6·9 g.) had m. p. 147—149°, raised to 150—151° on crystallisation (6·4 g.).

Hydrolysis of Propylbenzhydroxamate with Aqueous Acid.—Propyl benzhydroxamate (11·1 g.) and 17% hydrochloric acid (100 ml.) were heated under reflux for 2 hr.; a black oil rapidly separated. After cooling and extraction with ether, the aqueous layer was evaporated and the residual solid triturated with ethyl acetate–ethanol to yield ammonium chloride (2·35 g., 71%). The ethereal layer was extracted with aqueous sodium hydrogen carbonate from which benzoic acid (4·8 g., 64%) was recovered. Evaporation of the extracted ethereal layer afforded an oil (2·95 g.) which on acid hydrolysis gave benzoic acid (2·0 g., 26%) and a little low-boiling mobile oil, probably propan-1-ol.

1-*Amino-oxybutane Hydrochloride.*—Butyl benzhydroxamate [5b] (17 g.) and 6% ethanolic hydrogen chloride (80 ml.) were heated under reflux for 2 hr. Evaporation and addition of ether yielded the product which formed plates (from ethyl acetate–ethanol) (7·8 g.), m. p. 155—156° (Neuffer and Hoffmann [4] give m. p. 152—153°; Winternitz and Lachazette [37] give m. p. 155—156°).

1-*Amino-oxypentane Hydrochloride.*—Made as was the above compound, the *hydrochloride* separated from ethyl acetate–ethanol as plates, m. p. 148° (Found: C, 43·2; H, 10·0; N, 10·3. $C_5H_{14}ONCl$ requires C, 43·0; H, 10·0; N, 10·0%).

1-*Amino-oxyalkanes by Alkaline Hydrolysis of the Urethanes.*—Amino-oxyisobutane hydrochloride, prepared by alkaline hydrolysis of the urethane, crystallised from ethyl acetate as leaflets, m. p. 134—135° (Found: C, 37·6; H, 9·1; N, 10·7. Calc. for $C_4H_{12}ONCl$: C, 38·0; H, 9·5; N, 11·1%), Leffler and Bothner-by [38] give m. p. 127—128°. Amino-oxyhexane hydrochloride, prepared similarly, had m. p. 151° (lit.,[5b] 150—151°). 1-*Amino-oxyheptane hydrochloride* separated as leaflets (from ethyl acetate–ethanol), m. p. 151—152° (Found: C, 50·2; H, 10·5; N, 9·0. $C_7H_{18}ONCl$ requires C, 50·2; H, 10·8; N, 8·4%). 1-Amino-oxyoctane hydrochloride formed plates, m. p. 147—149°, from the same solvents (Found: C, 52·8; H, 10·9; N, 8·2. Calc. for $C_8H_{20}ONCl$: C, 52·8; H, 11·1; N, 7·7%). Theilacker and Ebke [17] give m. p. 81—82°. 1-Amino-oxynonane hydrochloride failed to crystallise satisfactorily and the crude material was used for preparation of the diguanide; Fuller and King [5b] give m. p. 146—149° for this material. 1-*Amino-oxydecane hydrochloride* crystallised as plates (from ethyl acetate–ethanol), m. p. 145·5—146·5° (Found: C, 57·3; H, 11·2; N, 6·8. $C_{10}H_{24}ONCl$ requires C, 57·4; H, 11·6; N, 6·7%). The hydrobromide crystallised as plates (from ethyl acetate), m. p. 135—136° (lit.,[37] m. p. 125—128°) (Found: C, 47·8; H, 9·8. Calc. for $C_{10}H_{24}ONBr$: C, 47·3; H, 9·5%). When the hydrochloride (2·1 g.), salicylaldehyde (1·25 g.), sodium hydroxide in water (0·4 g. in 2 ml.), and ethanol (15 ml.) were heated under reflux for 1 hr., 1-*salicylideneamino-oxydecane* was obtained as a lemon-yellow oil (1·9 g.), b. p. 132°/0·3 mm. (Found: C, 73·5; H, 9·8; N, 4·9. $C_{17}H_{27}O_2N$ requires C, 73·5; H, 9·8; N, 5·1%). 1-*Furfurylideneamino-oxydecane*,

[35] Jones, *Amer. Chem. J.*, 1898, **20**, 39.
[36] Hecker, *ibid.*, 1913, **50**, 444.
[37] Winternitz and Lachazette, *Bull. Soc. chim. France*, 1958, 664.
[38] Leffler and Bothner-by, *J. Amer. Chem. Soc.*, 1951, **73**, 5473.

similarly prepared, was a yellow oil, b. p. 114°/0·08 mm. (Found: C, 71·3; H, 10·0; N, 5·7. $C_{15}H_{25}O_2N$ requires C, 71·8; H, 10·0; N, 5·6%). 1-*Amino-oxyundecane hydrochloride* was obtained as leaflets, m. p. 143—144° (Found: C, 59·1; H, 11·4; N, 6·0. $C_{11}H_{26}ONCl$ requires C, 59·0; H, 11·7; N, 6·2%). 2-*Amino-oxyundecane hydrochloride* crystallised similarly (m. p. 145—146°) (Found: C, 59·2; H, 11·9%). 1-*Amino-oxydodecane hydrochloride* formed plates, m. p. 140—143° (Found: C, 61·0; H, 11·9; N, 5·9; Cl, 14·6. $C_{12}H_{28}ONCl$ requires C, 60·6; H, 11·8; N, 5·9; Cl, 14·9%). 1-*Amino-oxytetradecane hydrochloride* separated as leaflets, m. p. 137—138° (Found: C, 62·9; H, 11·8; N, 5·3. $C_{14}H_{32}ONCl$ requires C, 63·2; H, 12·1; N, 5·3%). The *base* crystallised from ethyl acetate–light petroleum as leaflets, m. p. 68—70° (Found: C, 72·9; H, 13·4; N, 5·7. $C_{14}H_{31}ON$ requires C, 73·4; H, 13·7; N, 6·1%). 1-*Amino-oxyhexadecane hydrochloride* was obtained as leaflets, m. p. 133—134° (Found: C, 65·3; H, 12·3; N, 4·8. $C_{16}H_{36}ONCl$ requires C, 65·4; H, 12·4; N, 4·8%). The free *base* formed leaflets (from light petroleum), m. p. 45—47° (Found: C, 74·0; H, 13·7; N, 5·9. $C_{16}H_{35}ON$ requires C, 74·5; H, 13·7; N, 5·4%). 1-*Amino-oxyoctadecane* crystallised from light petroleum as needles, m. p. 50—52° (Found: C, 75·6; H, 13·6; N, 4·8. $C_{18}H_{39}ON$ requires C, 75·8; H, 13·7; N, 4·9%).

Amino-oxymethylbenzene Hydrochloride.—Benzyl benzhydroxamate (4·3 g.) and 6% ethanolic hydrogen chloride (30 ml.) were refluxed for 20 min. during which solid separated. The mixture was cooled and the white leaflets were collected (2·7 g., 90%; m. p. 230—232°), sufficiently pure for preparation of the diguanide. Behrend and Leuchs [21] give m. p. 230—235°.

Similar preparations gave p-*amino-oxymethyl-toluene hydrochloride* (from ethanol–water), leaflets, m. p. 233° (88%) (Found: C, 55·5; H, 7·0; N, 8·2. $C_8H_{12}ONCl$ requires C, 55·5; H, 7·0; N, 8·1%), -*chlorobenzene hydrochloride*, leaflets, m. p. 243° (Found: C, 43·1; H, 4·9; N, 7·1. $C_7H_9ONCl_2$ requires C, 43·3; H, 4·7; N, 7·2%), -*bromobenzene hydrochloride*, plates (from ethanol–ether), m. p. 246—247° (Found: C, 35·8; H, 4·0; N, 5·8. $C_7H_9ONBrCl$ requires C, 35·2; H, 3·8; N, 5·9%), and -nitrobenzene hydrochloride, as leaflets, m. p. 216° (lit.,[22] m. p. 217°), o-*amino-oxymethylnitrobenzene hydrochloride*, needles, m. p. 165—166° darkening on exposure to light (Found: C, 40·8; H, 4·8. $C_7H_9O_3N_2Cl$ requires C, 41·0; H, 4·4%), 4-*amino-oxymethyl-1,2-dichlorobenzene hydrochloride* (from ethyl acetate–ethanol), leaflets, m. p. 197° (Found: C, 36·7; H, 3·4; N, 5·7. $C_7H_8ONCl_3$ requires C, 36·7; H, 3·5; N, 6·1%), 3-*amino-oxypropylbenzene hydrochloride*, plates (from ethanol–ether), m. p. 168—169° (Found: C, 57·2; H, 7·5; N, 7·4. $C_9H_{14}ONCl$ requires C, 57·2; H, 7·5; N, 7·4%), 1-*amino-oxymethylnaphthalene hydrochloride* (from ethyl acetate containing a few drops of methanol), needles, m. p. 198° (Found: C, 63·3; H, 6·0; N, 6·9. $C_{11}H_{12}ONCl$ requires C, 63·0; H, 5·8; N, 6·7%), the 2-*amino-oxymethyl-isomer*, much less soluble, leaflets (from aqueous ethanol), m. p. 247° (Found: C, 63·5; H, 5·5; N, 6·9%) [N-*benzyloxycarbonyl derivative*, leaflets (from ethyl acetate–light petroleum), m. p. 93—94° (Found: C, 74·6; H, 5·8. $C_{19}H_{17}O_3N$ requires C, 74·3; N, 5·6%), from which the amino-oxymethyl hydrobromide could readily be obtained by treatment with dry hydrogen bromide in acetic acid], 1-*amino-oxymethyl-2-methylnaphthalene hydrochloride monohydrate*, needles (from ethanol–ether), m. p. 192—193° (Found: C, 59·2; H, 6·6; N, 6·2; Cl, 15·0. $C_{12}H_{14}ONCl,H_2O$ requires C, 59·3; H, 6·7; N, 5·8; Cl, 14·7%), 2-*amino-oxymethyl-1-bromonaphthalene hydrochloride*, needles (from ethanol–water), m. p. 199° (Found: C, 45·7; H, 4·3. $C_{11}H_{11}ONBrCl$ requires C, 45·7; H, 3·9%), 9-*amino-oxymethylphenanthrene hydrochloride*, needles (from ethanol), m. p. 216—217° (Found: C, 69·3; H, 5·6; N, 5·4. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4; N, 5·4%), and the 1-isomer, needles, m. p. 184—186°, used without further purification.

6-*Amino-oxymethyltetralin Hydrochloride.*—Chloromethylation of tetralin [39] yielded a mixture, b. p. 143—148°/15 mm., of some 5- with 6-chloromethyltetralin. The mixture with sodium benzhydroxamate gave the mixed benzamido-oxymethyltetralins as a thick yellow oil. This (18 g.) was heated with 6% ethanolic hydrogen chloride (150 ml.) under reflux for 3 hr. and evaporated to afford a solid (11·5 g.), m. p. 130—150°. Fractional crystallisation from ethanol furnished the *product* as needles (6·8 g.), m. p. 190—191° (Found: C, 62·2; H, 7·6; N, 7·0. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·5; N, 6·6%).

8-*Amino-oxymethyl-6-chloro-1,3-benzodioxan Hydrochloride.*—Prepared by alcoholysis of the benzhydroxamate this *salt* crystallised from ethanol–ether as needles, m. p. 204—205° (Found: C, 42·6; H, 4·7; N, 5·9. $C_9H_{11}O_3NCl_2$ requires C, 42·8; H, 4·4; N, 5·6%).

8-*Amino-oxymethylquinoline Dihydrochloride.*—Treatment of the benzhydroxamate (3·2 g.)

[39] Darzens and Levy, *Compt. rend.*, 1935, **201**, 902.

with ethanolic hydrogen chloride afforded the *product* (2·3 g.) as needles, m. p. 193° (Found: C, 48·3; H, 5·2; N, 11·8. $C_{10}H_{12}ON_2Cl_2$ requires C, 48·7; H, 4·9; N, 11·3%).

Alkyloxydiguanides.—The amino-oxy-hydrochloride (0·1 mole), dicyandiamide (0·1 mole), and ethanol (70 ml.) were heated under reflux for 2—4 hr. After filtration if necessary from solid, the mixture was evaporated, then treated with alcoholic hydrogen chloride (*ca.* 0·15 mole) and dry ether. The diguanide dihydrochloride usually crystallised and was collected and recrystallised. The dihydrochlorides were often deliquescent and this precluded analytical results' being obtained in some cases: these compounds were, therefore, characterised by conversion into the picrates.

TABLE 3. *Alkoxydiguanides* $RO{\cdot}NH{\cdot}C(:NH){\cdot}NH{\cdot}C(:NH){\cdot}NH_2$.

Substituent (R) and derivative	M. p.	Formula	Found (%) C	H	N	Reqd. (%) C	H	N
Methyl, 2HCl	183—184° [a, d]	$C_3H_{11}ON_5Cl_2$	17·4	5·4	34·2	17·6	5·4	34·3
Ethyl, 2HCl	180—181 [b, e]	$C_4H_{13}ON_5Cl_2$	22·4	6·2	32·3	22·2	6·1	32·4
Ethyl, picrate	235—236 [a, f]	$C_{10}H_{14}O_8N_8$	32·2	4·0	29·6	32·1	3·8	30·0
Propyl, 2HCl	142—147 [i]							
Propyl, picrate	219—220 [a, g]	$C_{11}H_{16}O_8N_8$	33·6	3·9	28·8	34·0	4·2	28·9
Butyl, 2HCl	135—136 [b, e]	$C_6H_{17}ON_5Cl_2$	29·4	7·1	28·0	29·5	7·0	28·6
Isobutyl, 2HCl	142—144 [i]							
Isobutyl, picrate	225 [a, f]	$C_{12}H_{18}O_8N_8$	35·8	4·5	27·8	35·8	4·5	27·8
Pentyl, 2HCl	129—133 [i]							
Pentyl	95—96 [c, h]	$C_7H_{17}ON_5$	44·4	9·0	37·0	44·9	9·2	37·4
Pentyl, picrate	204—205 [a, f]	$C_{13}H_{20}O_8N_8$	37·1	4·7	27·0	37·5	4·8	26·9
Hexyl, 2HCl	138—141 [i]							
Hexyl, picrate	204—205 [a, f]	$C_{14}H_{22}O_8N_8$	39·4	5·0	25·8	39·2	5·1	26·0
Hexyl	102—103 [c, h]	$C_8H_{19}ON_5$	47·3	9·4	35·2	47·7	9·5	34·8
Heptyl, 2HCl	135—137 [i]							
Heptyl, picrate	210 [a, f]	$C_{15}H_{24}O_8N_8$	40·7	5·2	25·0	40·6	5·4	25·2
Octyl	99—100 [a, f]	$C_{10}H_{23}ON_5$	52·6	9·8	30·0	52·5	10·1	30·6
Octyl, picrate	209 [a, f]	$C_{16}H_{26}O_8N_8$	41·6	5·6	24·4	41·9	5·7	24·4
Nonyl, 2HCl	148—152 [i]							
Nonyl, picrate	200 [a, f]	$C_{17}H_{28}O_8N_8$	42·8	5·8	23·8	43·1	6·0	23·7
Decyl, 2HCl	123—130 [i]							
Decyl	100—101 [a, f]	$C_{12}H_{27}ON_5$	55·8	10·3	26·8	56·0	10·5	27·2
Decyl, picrate	204—205 [a, f]	$C_{18}H_{30}O_8N_8$	44·1	5·8	22·6	44·4	6·2	23·0
Undecyl, 2HCl	145—148 [a, d]	$C_{13}H_{31}ON_5Cl_2$	45·6	8·9	20·2	45·3	9·1	20·4
2-*Methyldecyl*, 2HCl	108—111 [a, e]	$C_{13}H_{31}ON_5Cl_2$	45·7	9·4	20·1	45·3	9·1	20·4
Dodecyl, 2HCl	162—164 [a, f, j]	$C_{14}H_{33}ON_5Cl_2$	46·5	9·3	20·2	46·9	9·3	19·6
Dodecyl, picrate	207—208 [a, f]	$C_{20}H_{34}O_8N_8$	46·5	6·9	22·0	46·7	6·7	21·8
Tetradecyl, HCl	140 [a, e, k]	$C_{16}H_{36}ON_5Cl$	54·9	10·0	19·7	55·0	10·3	20·0
Tetradecyl, picrate	210—212 [a, f]	$C_{22}H_{38}O_8N_8$	49·5	7·6	21·0	48·8	7·1	20·7
Hexadecyl	101—103 [a, f]	$C_{18}H_{39}ON_5$	63·9	11·5	20·8	63·5	11·7	20·5

[a] Needles. [b] Prisms. [c] Leaflets. Recrystallised from [d] ethyl acetate–ethanol, [e] ethanol–ether, [f] ethanol, [g] 2-ethoxyethanol, [h] ether–light petroleum. [i] Deliquescent. [j] Shrinks at 70°. [k] Shrinks at 75—80°.

Benzyloxydiguanide Dihydrochloride.—The *salt* crystallised from ethanol–ethyl acetate as needles, m. p. 150—151° (Found: C, 39·1; H, 5·6; N, 25·5; Cl, 25·0. $C_9H_{15}ON_5Cl_2$ requires C, 38·6; H, 5·4; N, 25·0; Cl, 25·3%). The *base* formed plates (from water), m. p. 111° (Found: C, 51·8; H, 6·3; N, 34·2. $C_9H_{13}ON_5$ requires C, 52·1; H, 6·3; N, 33·8%), and the *picrate*, leaflets (from ethanol–acetone), m. p. 226—227° (Found: C, 41·5; H, 3·8; N, 26·1. $C_{15}H_{16}O_8N_8$ requires C, 41·3; H, 3·7; N, 25·8%).

Hydroxydiguanide Dihydrochloride.—The preceding dihydrochloride (1·4 g.) in ethanol (15 ml.) was shaken with hydrogen and 10% palladised charcoal for 15 min., then uptake ceased (110 ml.). The filtered solution was evaporated to dryness, leaving a stiff gum which soldified on trituration with dry ether [0·87 g.; m. p. 130—131° (decomp.)]. The *product* was recrystallised by dissolution in hot ethanol and addition of dry ether, forming prismatic needles, m. p. 139—140° (Found: C, 13·0; H, 5·0; N, 37·0; Cl, 37·0. $C_2H_9ON_5Cl_2$ requires C, 12·6; H, 4·8; N, 36·8; Cl, 37·4%). In a second experiment, the filtered hydrogenation solution was seeded and yielded the pure material directly. Treatment of an aqueous solution of the hydrochloride with aqueous lithium picrate afforded a picrate which after crystallisation from hot water formed yellow prisms, darkening from 250° but melting at >300°. This appeared to be

guanylurea picrate [40] (Found: C, 29·5; H, 2·9; N, 30·1. Calc. for $C_8H_9O_8N_7$: C, 29·0; H, 2·7; N, 29·6%). On prolonged storage, hydroxydiguanide hydrochloride decomposed to give guanylurea hydrochloride, m. p. 173—174° (lit.,[41] m. p. 172—174° for hemihydrate) (Found: C, 17·7; H, 5·1; Cl, 25·1. Calc. for $C_2H_7ON_4Cl$: C, 17·3; H, 5·1; Cl, 25·6%).

Aryloxydiguanides.—*4-Methylbenzyloxydiguanide.* *p*-Amino-oxymethyltoluene hydrochloride (8·5 g.), dicyandiamide (4·1 g.), and ethanol (50 ml.) were heated under reflux for 2 hr., evaporated and treated with ethanolic hydrogen chloride and dry ether. The dihydrochloride which separated was collected (8·0 g.; m. p. 144—145°), dissolved in the minimum amount of hot water, and basified with N-sodium hydroxide. The base crystallised from ethyl acetate–ethanol as leaflets, m. p. 177° (Found: C, 54·3; H, 7·1; N, 31·3. $C_{10}H_{15}ON_5$ requires C, 54·3; H, 6·9; N, 31·7%).

TABLE 4. *Arylmethoxydiguanides*, $RO{\cdot}NH{\cdot}C(:NH){\cdot}NH{\cdot}C(:NH){\cdot}NH_2$.

Substituent (R) and derivative	M. p.	Formula	Found (%) C	H	N	Reqd. (%) C	H	N
p-*Chlorobenzyl*	175° [a, h]	$C_9H_{12}ON_5Cl$	44·8	5·1	29·0	44·7	5·0	29·0
p-*Bromobenzyl*	188 [a, d]	$C_9H_{12}ON_5Br$	38·5	4·4	24·0	37·8	4·2	24·4
p-*Nitrobenzyl*, HCl	216 [c, e]	$C_9H_{13}O_3N_6Cl$	36·8	4·7		37·4	4·5	
o-*Nitrobenzyl*, HCl	179 [b, f]	$C_9H_{13}O_3N_6Cl$	36·7	4·8	28·6	37·4	4·5	29·0
3,4-*Dichlorobenzyl*, 2HCl	171 [b, f]	$C_9H_{13}ON_5Cl_4$	30·8	4·0	19·7	31·0	3·8	20·1
3-*Phenylpropyl*, 2HCl, EtOH	153—155 [c, e]	$C_{11}H_{19}ON_5Cl_2,C_2H_6O$	44·1	7·2	20·3	44·1	7·1	19·8
1-*Naphthylmethyl*	145 [b, d]	$C_{13}H_{15}ON_5$	60·5	5·6	26·5	60·7	5·9	27·2
2-*Naphthylmethyl*	213 [a, d]	$C_{13}H_{15}ON_5$	61·0	6·0	27·0	60·7	5·9	27·2
1-*Methyl-2-naphthylmethyl*	165 [b, d]	$C_{14}H_{17}ON_5$	62·7	6·7	26·3	62·0	6·3	25·8
1-*Bromo-2-naphthylmethyl*	158—160 [b, g]	$C_{13}H_{14}ON_5Br$	46·6	4·2		46·2	4·2	
9-*Phenanthrylmethyl*, H_2O	107—108 [a, i]	$C_{17}H_{17}ON_5,H_2O$	63·0	6·0		62·8	5·9	
9-*Phenanthrylmethyl*	95—98 [j]	$C_{17}H_{17}ON_5$	66·3	5·7		66·5	5·6	
1-*Phenanthrylmethyl*, H_2O	190 [b, i]	$C_{17}H_{17}ON_5,H_2O$	62·8	6·0		62·8	5·9	
6-Tetralylmethyl, 2HCl...	138—141 [k]							
6-*Tetralylmethyl*	157—158 [c, d]	$C_{13}H_{19}ON_5$	60·0	6·8	27·2	59·8	7·3	26·8
6-*Chloro*-8-(1,3-*benzodioxanyl*)*methyl*	191—192 [b, i]	$C_{11}H_{14}O_3N_5Cl$	44·7	5·2	23·8	44·1	4·7	23·4

[a] Leaflets. [b] Needles. [c] Plates. Recrystallised from [d] ethyl acetate, [e] ethanol, [f] ethanol–ether, [g] ethanol–light petroleum, [h] ethyl acetate–ethanol, [i] aqueous ethanol. [j] After being dried at 80°/15 mm. for 4 hr. [k] Deliquescent.

Reaction of Isonicotinoylhydrazine with Dicyandiamide.—The hydrazine (1·35 g.), dicyandiamide (0·84 g.), and methanol (15 ml.) were heated under reflux for 24 hr. On cooling, cream prisms separated (1·92 g.; m. p. 138—142°), which were soluble in cold water and did not give a violet precipitate with ammoniacal copper sulphate: crystallisation from ethanol afforded needles of a substance, m. p. 138—139° (lit.,[24] 145°) (Found: C, 43·3; H, 5·3; N, 44·0. Calc. for $C_8H_{11}ON_7$: C, 43·5; H, 5·0; N, 44·3%). This substance in water was treated with ethanolic picric acid, a picrate separating as felted yellow needles, m. p. 190—191° (decomp.), not depressed on admixture with authentic *isonicotinoylhydrazine dipicrate monohydrate*, m. p. 190—191° (decomp.) (Found: C, 35·3; H, 2·7. $C_{18}H_{13}O_{15}N_9,H_2O$ requires C, 35·3; H, 2·5%). Attempted crystallisation from ethanol–acetone gave the *isopropylidene derivative picrate*, needles, m. p. 204—205° (Found: C, 44·3; H, 3·7. $C_{15}H_{14}O_8N_6$ requires C, 44·4; H, 3·5%).

Isonicotinamidodiguanide Dihydrochloride.—Isonicotinoylhydrazine (1·35 g.), dicyandiamide (0·84 g.), methanol (15 ml.), and concentrated hydrochloric acid (1·0 ml.) were heated under reflux for 1 hr., a yellow solid separating from the hot solution. After cooling, the solid was collected (1·86 g.), m. p. 205—207°. Crystallisation from water gave soft yellow needles of the *product*, m. p. 200° (Found: C, 33·3; H, 5·0; N, 33·0. $C_8H_{13}ON_7Cl_2$ requires C, 33·0; H, 4·5; N, 33·6%), which gave a dirty violet precipitate with ammoniacal copper sulphate

Benzamidodiguanide Monohydrochloride.—Benzhydrazide (20 g.), dicyandiamide (12·5 g.), and ethanol (100 ml.) containing dry hydrogen chloride (5·1 g.) were heated under reflux for 3 hr. during which time solid separated. After cooling and dilution with acetone, the solid was collected (26·9 g.). Crystallisation from ethanol containing a little water gave the *product* as needles, m. p. 169—170° (Found: C, 42·5; H, 5·0; N, 31·9. $C_9H_{13}ON_6Cl$ requires C, 42·1; H, 5·1; N, 32·7%).

[40] Bamberger and Seeberger, *Ber.*, 1893, **26**, 1587.
[41] Jona, *Gazzetta*, 1907, **37**, ii, 561.

Attempted Reactions with Dicyandiamide.—(*a*) 1-Amino-oxydecane (1·32 g., from the hydrochloride), dicyandiamide (0·64 g.), and ethanol (10 ml.) were heated under reflux for 20 hr. Cooling gave unchanged dicyandiamide (0·60 g.), m. p. 215—216°, identified by mixed m. p. and infrared absorption. 1-Amino-oxydecane (1·2 g.) was recovered from the mother-liquors.

(*b*) 8-Amino-oxymethyl-6-chloro-1,3-benzodioxan (1·24 g.), dicyandiamide (0·48 g.), and methanol (10 ml.) were refluxed for 20 hr. Only unchanged materials were isolated on working up.

(*c*) Dicyandiamide was recovered unchanged when refluxed in methanol for 24 hr.

1-*Carboxyhexyloxydiguanide.*—α-Amino-oxyheptanoic acid hydrochloride [1] (2·0 g.) was refluxed for 1 hr. with 5% methanolic hydrogen chloride (20 ml.). Evaporation gave a gum which was refluxed for 2 hr. with dicyandiamide (0·84 g.) and ethanol (20 ml.); N-sodium hydroxide (25 ml.) was added and refluxing continued for 2 hr. The solvent was evaporated, and the product taken up in water and brought to pH 6 with acetic acid. The resulting solid was collected and crystallised from aqueous ethanol to give a *monohydrate* (1·5 g.), m. p. 127—128° (Found: C, 41·3; H, 8·0; N, 27·0. $C_9H_{19}O_3N_5,H_2O$ requires C, 41·3; H, 8·0; N, 26·6%). Distillation with xylene gave, as residue, 1-*carboxyhexyloxydiguanide*, m. p. 194° (Found: C, 43·9; H, 7·6. $C_9H_{19}O_3N_5$ requires C, 44·0; H, 7·8%).

1-*Carboxyheptyloxydiguanide.*—α-Amino-oxyoctanoic acid [1] (1 g.) was suspended in methanol (20 ml.), saturated with hydrogen chloride, and then refluxed for 2 hr. Evaporation gave a gum which was refluxed for 2 hr. with dicyandiamide (0·48 g.) and ethanol (10 ml.). Hydrolysis and isolation as above gave 1-*carboxyheptyloxydiguanide monohydrate* (0·5 g.) (from aqueous ethanol), m. p. 129—131° (Found: C, 43·7; H, 8·3. $C_{10}H_{21}O_3N_5,H_2O$ requires C, 43·3; H, 8·4%).

1-*Carboxyoctyloxydiguanide.*—α-Amino-oxynonanoic acid [1] (0·8 g.), treated as above, gave 1-*carboxyoctyloxydiguanide monohydrate* (0·3 g.) (from aqueous ethanol), m. p. 128—129° (Found: C, 45·9; H, 8·4; N, 23·9. $C_{11}H_{23}O_3N_5,H_2O$ requires C, 45·3; H, 8·6; N, 24·0%).

1-*Carboxynonyloxydiguanide.*—α-Amino-oxydecanoic acid [1] (1 g.), treated as above, gave 1-*carboxynonyloxydiguanide monohydrate* (1·1 g.) (from aqueous ethanol), m. p. 122—125° (Found: C, 47·5; H, 8·7; N, 23·4. $C_{12}H_{25}O_3N_5,H_2O$ requires C, 47·2; H, 8·9; N, 23·0%), and thence by use of xylene gave 1-*carboxynonyloxydiguanide*, m. p. 187—188° (Found: C, 49·9; H, 8·6; N, 24·0. $C_{12}H_{25}O_3N_5$ requires C, 50·1; H, 8·8; N, 24·4%).

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