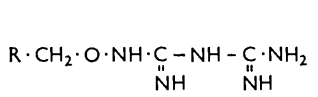
## 770. *Amino-oxy-derivatives. Part III.*[1] *Dihydrotriazines and Related Heterocycles.*

By P. MAMALIS, J. GREEN, D. J. OUTRED, and M. RIX.

A number of 1-alkyloxy-4,6-diamino- and 4,6-diamino-1-arylmethoxy-1,2-dihydro-2,2-dimethyl-1,3,5-triazines have been prepared from the corresponding diguanides and found to possess antimicrobial properties. Some related pyrimidines and 2-amino-4-arylmethylamino-1,3,5-triazines are also described.

THE broad-spectrum activity *in vitro* of a number of alkyloxy- and arylmethoxy-diguanides (I) was reported by Mamalis *et al.*;[1,2] these compounds when administered subcutaneously failed, however, to protect mice from lethal doses of *Strept. pyogenes* CN4. A search has therefore been made of new derivatives of these oxygen-containing diguanides, which might be active *in vivo* as well as *in vitro* and exhibit low toxicity.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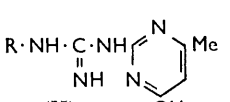
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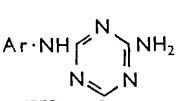
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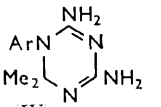
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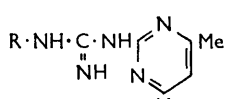
Pyrimidones (II), triazines (III), and dihydrotriazines (IV) are readily prepared from aryldiguanides. The dihydrotriazines, in particular, show a wide range of biological activity including antimalarial, antitumour, anticoccidial, and antivitamin effects.[3] Significant antibacterial activity has been reported only for the individual (IV; Ar = 3,5-$C_6H_3Cl_2$).[4]

Analogues containing C–O–N groups of all these types of compound, have now been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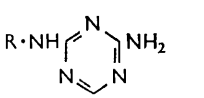
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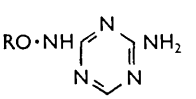
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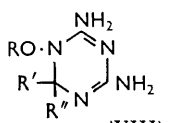

(VIII)

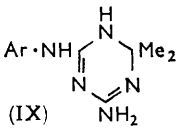
prepared and submitted for antibacterial screening both *in vitro* and *in vivo*. Condensation of alkyloxy- and arylmethoxy-diguanides[1] with ethyl acetoacetate gave the basic pyrimidones (II; R = alkyloxy or arylmethoxy), and reaction with acetylacetone gave

[1] Part II, Mamalis, Green, and McHale, *J.*, 1960, 229.
[2] Price, Mamalis, McHale, and Green, *Brit. J. Pharmacol.*, 1960, **15**, 243.
[3] Modest in " Heterocyclic Compounds," ed. Elderfield, John Wiley & Sons Inc., New York, 1961, Vol. VII, p. 717.
[4] Fisher and Doub, *Biochem. Pharmacol.*, 1959, **3**, 10; B.P. 836,958.

the corresponding guanidinodimethylpyrimidines (V). For purposes of comparison, some alkyldiguanides and 1-phenethyldiguanide were also cyclised with the same reagents. 1-Phenethyldiguanide and ethyl acetoacetate gave a secondary product, which appeared to be the triazine (VI; R = $Ph{\cdot}CH_2{\cdot}CH_2$) formed by the alternative cyclisation on the ethoxycarbonyl group (cf. Curd and Rose [5]). The triazines (VII; R = alkyl or arylmethyl) were prepared by reaction of the corresponding diguanides with ethyl formate or formic acid. They were very weak bases: thus (VII; R = $C_{10}H_{21}$) formed an unstable hydrochloride which hydrolysed in air or in water.

Cyclisation of alkyloxy- and arylmethoxy-diguanides with acetone in the presence of hydrogen chloride gave smoothly the dihydrotriazine hydrochlorides (VIII; R = alkyl or arylmethyl, R′ = R″ = Me). The ease of cyclisation appeared to depend on the strength of the acid used: acetic acid did not promote ring formation but use of formic acid gave the dihydrotriazine formate. Modest and Levine [6] have shown that, while the use of picric or nitric acid led to dihydrotriazines (IV), acetic acid gave rise to the isomeric anilinotriazine (IX) as did reaction in presence of a basic catalyst. Similar conclusions were reached by Carrington, Crowther, and Stacey.[7]

It has been reported [6-8] that careful basification of an aqueous solution of an aryldihydrotriazine hydrochloride (cf. IV) gives the relatively unstable free base, which on mild heat-treatment rearranges to the isomeric anilinodihydrotriazine (IX). Arylmethoxyhydrotriazine bases could not be obtained satisfactorily by basification of solutions of the hydrochlorides with aqueous sodium hydroxide, but percolation of an aqueous-ethanolic solution of the hydrochlorides through an ion-exchange resin such as Deacidite FF or treatment of a methanolic solution with an excess of triethylamine followed by addition of water gave good yields of the free bases.



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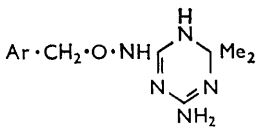

(X)

When an ethanolic solution of the unrearranged base (VIII; R = 1-naphthylmethyl, R′ = R″ = Me) was treated with ethereal hydrogen chloride, an unstable dihydrochloride was obtained, which reverted to the monohydrochloride on crystallisation from ethanol or on storage. These structures were confirmed by their infrared spectra. Like the aryldihydrotriazines,[8] arylmethoxydihydrotriazines were smoothly converted into the isomeric dihydrotriazines (X) when heated in partial aqueous suspension on the steam-bath for a few hours: heating in benzene or ethanol was equally effective. Since rearrangement also occurred rapidly at the melting point, double melting points could be observed, the higher being that of the rearranged base. The rearranged bases formed monohydrochlorides that crystallised only with difficulty.

Rearrangement could also be brought about on a small scale by heating the dihydrotriazine hydrochlorides to just above their melting points for a short time. The hydrochlorides were stable to boiling ethanol for 12 hours.

Arylmethoxydiguanides, when heated with acetone in the presence of piperidine for several hours, yielded isomeric dihydrotriazines (X) identical with those obtained by the rearrangement. Both the unrearranged and the rearranged dihydrotriazine bases were converted into salts with several organic acids.

Modest and Levine [6] and Sen and Singh [9] found that reaction of aryldiguanides with

[5] Curd and Rose, *J.*, 1946, 362.
[6] Modest and Levine, *J. Org. Chem.*, 1956, **21**, 14.
[7] Carrington, Crowther, and Stacey, *J.*, 1954, 1017.
[8] Modest, *J. Org. Chem.*, 1956, **21**, 1.
[9] Sen and Singh, *J. Indian Chem. Soc.*, 1958, **35**, 857; 1959, **36**, 260; 1960, **37**, 643; B.P. 709,906; U.S.P. 2,803,628.

aliphatic aldehydes, acetone, cyclopentanone, and cyclohexanone proceeded to completion, whereas with other ketones and benzaldehyde reaction was slower and unchanged diguanide was sometimes recovered. Although arylmethoxydiguanides reacted readily with acetone, reaction with other carbonyl compounds was less satisfactory. Thus, 1-4′-chlorobenzyloxydiguanide (I; R = 4-Cl·$C_6H_4$) with ethyl methyl ketone afforded only a very low yield of the 2-ethyl-2-methyldihydrotriazine (VIII; R = 4-Cl·$C_6H_4$·$CH_2$, R′ = Et, R″ = Me) and n-decyloxydiguanide with acetaldehyde gave a low yield of triazine (VIII; R = $C_{10}H_{21}$, R′ = H, R″ = Me). Better results were obtained by carrying out the reaction at room temperature. Attempts to prepare arylmethoxydihydrotriazines by the " three-component synthesis " of Modest,[8] *i.e.*, by reaction of an arylmethoxyamine, dicyandiamide, and acetone under acid conditions, were unsuccessful, giving rise to amidinourea hydrochloride and the isopropylidene derivative of the oxy-amine.

The new arylmethoxydiguanides required for the present series of compounds were prepared by the route reported previously.[1]

Three new 4-alkylbenzyl bromides were prepared from the corresponding alkylbenzenes by Kubiczek and Neugebauer's bromomethylation procedure.[10] Bromomethylation of ethylbenzene has been shown to give a mixture of 4- and 2-ethylbenzyl bromide [11] in the ratio 76 : 24, but the formation of an isomeric product has not been reported for the bromomethylation of t-butylbenzene.[12] Chloromethylation of alkylbenzenes has likewise been reported to give mainly *para*-substituted products.[13] Each of our benzyl bromides, although it possibly contained a proportion of the *ortho*-isomer, yielded only one crystalline benzhydroxamate. Bromomethylation of 1-bromonaphthalene proved to be the most convenient method for the preparation of 1-bromo-4-bromomethylnaphthalene, which had previously been made by bromination of 1-bromo-4-methylnaphthalene,[14] itself prepared by sulphonation of 1-methylnaphthalene followed by bromination.[15] During the preparation of certain of the arylmethoxyamine hydrochlorides required for conversion into diguanides, small amounts of by-products were isolated and found to be the *ON*-di(arylmethyl)hydroxylamines Ar·$CH_2$·O·NR·$CH_2$Ar, arising from the benzhydroxamates Ar·$CH_2$·O·NBz·$CH_2$Ar.

The parent dihydrotriazine, 4,6-diamino-1,2-dihydro-1-hydroxy-2,2-dimethyl-1,3,5-triazine hydrochloride, was obtained by catalytic reduction of the benzyloxy-dihydrotriazine hydrochloride (VIII; R = Ph·$CH_2$, R′ = R″ = Me). The corresponding 1-hydroxytriazine base showed no tendency to rearrange in refluxing ethanol (2 hr.).

Some 1-aryldiguanides and 4,6-diamino-1-aryl-1,2-dihydro-2,2-dimethyl-1,3,5-triazine hydrochlorides were prepared by known routes for comparison with the arylmethoxy-analogues.

*Microbiological Results.*—A summary of the activities *in vitro* is given in Table 1. As with the alkyloxydiguanides,[1] the alkyloxydihydrotriazines increased in bacteriostatic activity with increasing molecular weight: the lower members were, however, more active than the corresponding diguanides. The arylmethoxydihydrotriazines were all considerably more active than the corresponding diguanides, activity reaching a maximum with the naphthylmethyl- and phenanthrylmethyl-derivatives. Significant activity was also recorded against a number of other micro-organisms, both Gram-positive and Gram-negative including strains of penicillinase-forming staphylococci. Mice infected with lethal doses of *Strept. pyogenes* CN4 were well protected when treated with certain of the dihydrotriazines orally, subcutaneously, or intramuscularly.

Interesting differences were observed when the oxygen-containing diguanides and

[10] Kubiczek and Neugebauer, *Monatsh.*, 1950, **81**, 917.
[11] Nazarov and Semenovskii, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1957, 212, 840.
[12] Krausz, *Bull. Soc. chim. France*, 1953, C51.
[13] Kosolapoff, *J. Amer. Chem. Soc.*, 1946, **68**, 1670; Benington, Marion, Clark, and Fox, *J. Org. Chem.* 1958, **23**, 1979; Freeman, *ibid.*, 1961, **26**, 212.
[14] Shoesmith, *J.*, 1927, 3098.
[15] Fieser, *J. Amer. Chem. Soc.*, 1939, **61**, 136.

TABLE 1.

Activity *in vitro* of arylmethoxytriazine hydrochlorides.

Minimum inhibitory concentrations (μg./ml.) in broth at 37° (48 hr.).

| R in (VIII; R′ = R″ = Me) | *Staph. aureus* 4163 | *E. coli* 8196 | R in (VIII; R′ = R″ = Me) | *Staph. aureus* 4163 | *E. coli* 8196 |
|---|---|---|---|---|---|
| H | >300 | >300 | 4-Butylbenzyl | 19 | 1·25 |
| Butyl | 37·5 | 37·5 | 3-Phenylpropyl | 5 | 5 |
| Hexyl | 19 | 9·5 | *p*-Chlorobenzyl | 19 | 19 |
| Octyl | 2·5 | 9·5 | 3,4-Dichlorobenzyl | 9·5 | 5 |
| Decyl | 5 | 2·5 | 1-Naphthylmethyl | 0·6 | <0·6 |
| Tetradecyl | 1·25 | 1·25 | 1-Phenanthrylmethyl | <0·6 | <0·6 |
| Benzyl | 75 | 75 | Cf. Sulphathiazole | 5 | 10 |

TABLE 2.

Comparison of activity *in vitro* of aryl- and arylmethoxy-diguanides and triazines.

Minimum inhibitory concentrations (μg./ml.) (cf. Table 1).

| | Ar·NH·C(:NH)·NH·C(:NH)·NH$_2$ | | Ar·CH$_2$·O·NH·C(:NH)·C(:NH)·NH$_2$ | |
|---|---|---|---|---|
| Ar | *S. aureus* | *E. coli* | *S. aureus* | *E. coli* |
| *p*-Tolyl | >600 | >600 | 300 | 300 |
| *p*-Chlorophenyl | 500 [16] | 1000 [16] | 75 | 75 |
| *p*-Bromophenyl | 300 | 600 | 150 | 75 |
| 3,4-Dichlorophenyl | 37·5 | 37·5 | 37·5 | 37·5 |
| 1-Naphthyl | 300 | 300 | 37·5 | 19 |
| 2-Naphthyl | 150 | 300 | 37·5 | 37·5 |
| 1-Bromo-2-naphthyl | 37·5 | 37·5 | 19 | 19 |

| | Compounds (IV) | | Compounds (IV; Ar·CH$_2$·O in place of Ar) | |
|---|---|---|---|---|
| Ar | *S. aureus* | *E. coli* | *S. aureus* | *E. coli* |
| *p*-Tolyl | 300 | 600 | 37·5 | 19 |
| *p*-Chlorophenyl | 600 | 600 | 19 | 19 |
| *p*-Bromophenyl | 150 | 300 | 19 | 9·5 |
| 3,4-Dichlorophenyl | 75 | 37·5 | 9·5 | 5 |
| 1-Naphthyl | 150 | 300 | 0·6 | <0·6 |
| 2-Naphthyl | 150 | 300 | 2·4 | 1·2 |
| 1-Bromo-2-naphthyl | 75 | 37·5 | 0·6 | <0·6 |

triazines were compared with the corresponding aryldiguanides and aryldihydrotriazines. These results are collected into Table 2, the figures having the same significance as in Table 1. Whereas the aryldihydrotriazines are no more active *in vitro* than the corresponding diguanides, the arylmethoxydihydrotriazines are considerably more active than arylmethoxydiguanides.

*Infrared Spectra.*—Infrared spectra were obtained for many of the new compounds described in the Experimental section. All the amino-oxy-hydrochlorides displayed a characteristic absorption peak at 5·0—5·15 μ which was not present in the spectra of the free bases. Considerable differences were detectable between the rearranged and the unrearranged dihydrotriazines in the 6·0—10·0 μ region and could be used for diagnostic purposes.

## EXPERIMENTAL

2-(N-*Decyloxyguanidino*)-4-*hydroxy*-6-*methylpyrimidine* (II; R = $C_{10}H_{21}O$).—1-Decyloxydiguanide [1] (1·3 g.), ethyl acetoacetate (1·65 ml.), ethanol (6 ml.), and aqueous 4N-sodium hydroxide (1·6 ml.) were heated on the steam-bath for 1½ hr., then set aside overnight. The white *product* was collected and crystallised from dimethylformamide as needles (1·2 g.), m. p. 157—158° (Found: C, 59·8; H, 9·1; N, 21·8. $C_{16}H_{29}N_5O_2$ requires C, 59·6; H, 9·1; N, 21·7%). Other *guanidinohydroxypyrimidines*, similarly prepared, are described in Table 3.

2-(*N′-Decyloxyguanidino*)-4,6-*dimethylpyrimidine* (V; R = $C_{10}H_{21}$).—1-Decyloxydiguanide (1·3 g.), acetylacetone (1·5 g.), ethanol (6 ml.), and aqueous 4N-sodium hydroxide (1·25 ml.) were

[16] Fuller, *Biochem. J.*, 1947, **41**, 403.

TABLE 3.

Substituted guanidinohydroxypyrimidines (II).

| R | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| Ethoxy | 234—235° *‡ | $C_8H_{13}N_5O_2$ | 45·0 | 6·2 | 32·7 | 45·4 | 6·2 | 33·2 |
| Butoxy | 187—188 ‡§ | $C_{10}H_{17}N_5O_2$ | 50·2 | 7·0 | 28·9 | 50·2 | 7·2 | 29·3 |
| Pentyloxy | 195—196 *§ | $C_{11}H_{19}N_5O_2$ | 52·3 | 7·1 | 27·6 | 52·2 | 7·6 | 27·6 |
| Hexyloxy | 183—184 *§ | $C_{12}H_{21}N_5O_2$ | 53·8 | 7·4 | 25·7 | 54·0 | 7·9 | 26·2 |
| Octyloxy | 170 †§ | $C_{14}H_{25}N_5O_2$ | 57·3 | 9·1 | 23·6 | 57·2 | 8·6 | 23·8 |
| Butyl | 293—294 †§ | $C_{10}H_{17}N_5O$ | 53·7 | 7·8 | 31·2 | 53·8 | 7·7 | 31·4 |
| Pentyl | 274 †§ | $C_{11}H_{19}N_5O$ | 56·3 | 7·9 | 28·8 | 55·8 | 8·1 | 29·5 |
| Hexyl | 283—285 †§‖ | $C_{12}H_{21}N_5O$ | 57·6 | 8·5 | 27·95 | 57·4 | 8·4 | 27·9 |
| Heptyl | 277—279 †§ | $C_{13}H_{23}N_5O$ | 58·6 | 8·9 | 26·1 | 59·0 | 8·7 | 26·4 |
| Benzyloxy | 217—218 †§ | $C_{13}H_{15}N_5O_2$ | 57·7 | 6·0 | 25·2 | 57·7 | 5·5 | 25·6 |
| Phenethyl | 293 †§¶ | $C_{14}H_{17}N_5O$ | 62·3 | 6·4 | 25·4 | 62·0 | 6·3 | 25·8 |
| 1-Naphthylmethoxy | 233—235 †§ | $C_{17}H_{17}N_5O_2$ | 62·8 | 5·5 | 21·8 | 63·1 | 5·3 | 21·7 |

* Prisms. † Needles. Recryst. from ‡ ethanol, § dimethylformamide. ‖ From the mother-liquors an isomer, *2-acetonyl-4-amino-6-hexylaminotriazine* (VI; R = $C_6H_{13}$), was isolated and formed needles from ethanol–light petroleum (b. p. 60—80°), m. p. 191—192° (Found: C, 57·7; H, 8·1; N, 27·9%). ¶ *2-Acetonyl-4-amino-6-phenethylaminotriazine* (VI; R = $C_6H_5{\cdot}CH_2{\cdot}CH_2$), isolated from the mother-liquors, formed prisms (from ethanol), m. p. 204—205° (Found: C, 62·1; H, 6·4; N, 25·8%).

TABLE 4.

Substituted dimethylpyrimidines (V).

| R | M. p. | Solvent for crystn. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| Octyloxy | 58—59° | Aq.EtOH | $C_{15}H_{27}N_5O$ | 61·0 | 8·8 | 24·8 | 61·4 | 9·3 | 24·9 |
| Pentyl | 208—209 | Aq.MeOH | $C_{12}H_{21}N_5$ | 61·6 | 9·0 | 29·5 | 61·3 | 9·0 | 29·5 |
| Heptyl | 162—164 | H·CO·$NMe_2$ | $C_{14}H_{25}N_5$ | 63·9 | 9·7 | 26·7 | 64·0 | 9·6 | 26·6 |
| 1-Naphthylmethoxy | 165 | Aq.MeOH | $C_{18}H_{19}N_5O$ | 67·6 | 6·1 | 21·3 | 67·3 | 6·9 | 21·8 |

TABLE 5.

Substituted 2-amino-1,3,5-triazines (VII).

| R | M. p. | Solvent for crystn. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| Octyl | 184° | Aq.EtOH | $C_{11}H_{21}N_5O$ | 55·6 | 8·9 | 29·6 | 55·2 | 8·8 | 29·3 |
| Dodecyl | 175—177 | AcOH | $C_{15}H_{29}N_5O$ | 61·4 | 9·9 | 23·7 | 61·0 | 9·9 | 23·7 |
| 4-Chlorobenzyl | 236·5—237·5 | H·CO·$NMe_2$ | $C_{10}H_{10}ClN_5O$ | 47·8 | 4·0 | 28·3 | 47·7 | 4·0 | 28·0 |
| 4-Bromobenzyl | 230—231 | ,, | $C_{10}H_{10}BrN_5O$ | 41·2 | 3·4 | 23·7 | 40·6 | 3·4 | 23·6 |
| 1-Bromo-2-naphthylmethyl | 238—240 | ,, | $C_{14}H_{12}BrN_5O$ | 48·3 | 3·6 | 20·05 | 48·6 | 3·5 | 20·2 |

warmed at 60° for 3 hr. After cooling and addition of water the *product* was collected and crystallised from aqueous ethanol as leaflets (1·15 g.), m. p. 74—75° (Found: C, 63·7; H, 9·7; N, 22·0. $C_{17}H_{31}N_5O$ requires C, 63·5; H, 9·7; N, 21·8%). *Analogues*, similarly prepared, are described in Table 4; all formed needles.

*2-Amino-4-decyloxyamino-1,3,5-triazine* (VII; R = $C_{10}H_{21}$).—1-Decyloxydiguanide (1·0 g.) and 98% formic acid (5 ml.) were heated on the steam-bath for 4 hr. Concentration followed by addition of water precipitated the *product* that formed needles (from ethanol) (0·7 g.), m. p. 183—184° (Found: C, 58·7; H, 9·4; N, 25·7. $C_{13}H_{25}N_5O$ requires C, 58·5; H, 9·4; N, 26·2%). Use of ethyl formate in refluxing ethanol in place of formic acid resulted in lower yields of the same product. Treatment of a solution of the base in ethanol with ethereal hydrogen chloride afforded an unstable hydrochloride as needles, m. p. 148—150°; this rapidly hydrolysed in air. Other *triazines* prepared are described in Table 5; they formed needles.

O-*Substituted* 4,6-*Diamino*-1,2-*dihydro*-1-*hydroxy*-2,2-*dimethyl*-1,3,5-*triazines* (VIII; R′ = R″ = Me).—The diguanide base (0·1 mole), acetone (250 ml.), and concentrated hydrochloric acid (0·2 mole) were heated under reflux until the test for diguanide was negative, as indicated by the absence of a pink colour or precipitate on dilution with water and treatment with ammoniacal copper sulphate solution. For aromatic substituted diguanides ethanol was

usually added to increase solubility. The product often separated on cooling and was collected and recrystallised; in other cases concentration yielded the product. *Dihydrotriazines* prepared by this method are listed in Table 6.

TABLE 6.

*O*-Substituted 4,6-diamino-1,2-dihydro-1-hydroxy-2,2-dimethyl-1,3,5-triazines (VIII; R′ = R″ = Me).

| Subst. (R) & deriv. | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| Methyl, HCl | 227—228° [a] | $C_6H_{14}ClN_5O$ | 34·5 | 6·7 | 33·8 | 34·7 | 6·8 | 33·7 |
| Ethyl, HCl | 232—233 [a, d] | $C_7H_{16}ClN_5O$ | 38·0 | 7·2 | 31·8 | 38·0 | 7·3 | 31·7 |
| Propyl, HCl | 214 [a, c] | $C_8H_{18}ClN_5O$ | 40·3 | 7·4 | 29·7 | 40·6 | 7·6 | 29·7 |
| Butyl, HCl | 206—207 [a, c] | $C_9H_{20}ClN_5O$ | 42·9 | 8·1 | 27·9 | 43·3 | 8·1 | 28·0 |
| Hexyl, HCl | 174—176 [b, e] | $C_{11}H_{24}ClN_5O$ | 47·8 | 8·5 | 25·4 | 47·5 | 8·7 | 25·2 |
| Hexyl, picrate | 204—206 [b, c] | $C_{17}H_{26}N_8O_8$ | 43·3 | 5·1 | 24·1 | 43·2 | 5·5 | 23·8 |
| Heptyl, HCl | 201 [b, c] | $C_{12}H_{26}ClN_5O$ | 49·0 | 9·2 | 24·0 | 49·4 | 9·0 | 24·0 |
| Heptyl, picrate | 186—187 [b, c] | $C_{18}H_{28}N_8O_8$ | 44·8 | 5·7 | 23·4 | 44·5 | 5·8 | 23·1 |
| Octyl, HCl | 205—206 [a, e] | $C_{13}H_{28}ClN_5O$ | 51·7 | 9·3 | 22·7 | 51·1 | 9·2 | 22·9 |
| Nonyl, HCl | 220—222 [b, c] | $C_{14}H_{30}ClN_5O$ | 53·0 | 9·6 | 21·6 | 52·6 | 9·45 | 21·8 |
| Nonyl, picrate | 180—181 [b, d] | $C_{20}H_{32}N_8O_8$ | 47·0 | 6·2 | 21·8 | 46·8 | 6·3 | 21·8 |
| Decyl, HCl | 198—200 [b, e] | $C_{15}H_{32}ClN_5O$ | 54·0 | 9·7 | 21·0 | 54·0 | 9·7 | 21·0 |
| Decyl, picrate | 193—194 [b, d] | $C_{21}H_{34}N_8O_8$ | 47·8 | 6·5 | 21·2 | 47·8 | 6·6 | 20·9 |
| Undecyl, HCl | 195—196 [b, f] | $C_{16}H_{34}ClN_5O$ | 55·3 | 9·6 | 20·4 | 55·2 | 9·8 | 20·1 |
| Dodecyl, HCl | 200 [b, c] | $C_{17}H_{36}ClN_5O$ | 56·6 | 10·0 | 19·6 | 56·4 | 10·0 | 19·4 |
| Tetradecyl, HCl | 196—197 [b, c] | $C_{19}H_{40}ClN_5O$ | 58·7 | 10·2 | 18·0 | 58·5 | 10·3 | 18·0 |
| Hexadecyl, HCl | 187—190 [b, c] | $C_{21}H_{44}ClN_5O$ | 60·8 | 10·8 | 16·8 | 60·4 | 10·6 | 16·7 |
| Benzyl, HCl | 219—220 [a, d] | $C_{12}H_{18}ClN_5O$ | 51·0 | 6·6 | 24·9 | 50·7 | 6·4 | 24·7 |
| Benzyl, picrate | 207—208 [b, c] | $C_{18}H_{20}N_8O_8$ | 45·1 | 4·1 | 23·9 | 45·3 | 4·3 | 23·5 |
| 4-Methylbenzyl, HCl | 245 [a, g] | $C_{13}H_{20}ClN_5O$ | 52·5 | 6·8 | 23·5 | 52·5 | 6·8 | 23·6 |
| 4-Ethylbenzyl, HCl | 220—221 [b, c] | $C_{14}H_{22}ClN_5O$ | 53·6 | 6·9 | 22·8 | 53·9 | 7·1 | 22·4 |
| 3-Phenylpropyl, HCl | 199—200 [a, f] | $C_{14}H_{22}ClN_5O$ | 54·0 | 7·0 | 22·3 | 53·9 | 7·1 | 22·4 |
| 4-Isopropylbenzyl, HCl | 209 [b, f] | $C_{15}H_{24}ClN_5O$ | 55·3 | 7·5 | 21·8 | 55·3 | 7·4 | 21·5 |
| 4-Butylbenzyl, HCl | 206—207 [a, d] | $C_{16}H_{26}ClN_5O$ | 56·6 | 7·7 | 21·0 | 56·5 | 7·7 | 20·6 |
| 4-s-Butylbenzyl, HCl | 210—211 [b, f] | $C_{16}H_{26}ClN_5O$ | 56·4 | 7·7 | 20·7 | 56·5 | 7·7 | 20·6 |
| 4-t-Butylbenzyl, HCl | 231—232 [b, d] | $C_{16}H_{26}ClN_5O$ | 56·9 | 7·6 | 20·5 | 56·5 | 7·7 | 20·6 |
| 4-Methoxybenzyl, HCl | 214—215 [b, e] | $C_{13}H_{20}ClN_5O_2$ | 49·6 | 6·4 | 21·9 | 49·7 | 6·4 | 22·3 |
| 4-Chlorobenzyl, HCl | 243 [a, g] | $C_{12}H_{17}Cl_2N_5O$ | 45·0 | 5·4 | 21·9 | 45·3 | 5·4 | 22·0 |
| 4-Bromobenzyl, HCl | 239 [a, g] | $C_{12}H_{17}BrClN_5O$ | 40·1 | 4·7 | 19·2 | 39·7 | 4·7 | 19·3 |
| 2-Nitrobenzyl, HCl | 203—204 [b, c] | $C_{12}H_{17}ClN_6O_3$ | 43·4 | 5·5 | 25·1 | 43·8 | 5·2 | 25·5 |
| 4-Nitrobenzyl, HCl | 230 [a, d] | $C_{12}H_{17}ClN_6O_3$ | 44·0 | 5·5 | 26·0 | 43·8 | 5·2 | 25·5 |
| 3,4-Dichlorobenzyl, HCl | 227 [a, g] | $C_{12}H_{16}Cl_3N_5O$ | 40·5 | 5·2 | 20·1 | 40·8 | 4·6 | 19·9 |
| 1-Naphthylmethyl, HCl | 215 [b, h] | $C_{16}H_{20}ClN_5O$ | 57·0 | 6·05 | 20·6 | 57·5 | 6·05 | 20·9 |
| 2-Naphthylmethyl, HCl | 231—232 [b, c] | $C_{16}H_{20}ClN_5O$ | 57·9 | 6·4 | 20·8 | 57·5 | 6·05 | 20·9 |
| 2-Methyl-1-naphthylmethyl, HCl | 215 [b, c] | $C_{17}H_{22}ClN_5O$ | 59·4 | 6·6 | 20·4 | 58·7 | 6·4 | 20·1 |
| 1,2,3,4-Tetrahydro-6-methyl-naphthylmethyl, HCl | 219 [b, c] | $C_{16}H_{24}ClN_5O$ | 56·4 | 7·1 | 20·9 | 56·9 | 7·1 | 20·7 |
| 1-Chloro-2-naphthylmethyl, HCl | 221 [b, f] | $C_{16}H_{19}Cl_2N_5O$ | 52·0 | 5·2 | 19·3 | 52·3 | 5·2 | 19·0 |
| 1-Bromo-2-naphthylmethyl, HCl | 217 [a, c] | $C_{16}H_{19}BrClN_5O$ | 46·7 | 4·8 | 17·1 | 46·5 | 4·7 | 16·9 |
| 1-Bromo-4-naphthylmethyl, HCl | 227 [b, c] | $C_{16}H_{19}BrClN_5O$ | 46·3 | 4·7 | 17·3 | 46·5 | 4·7 | 16·9 |
| 8-(1,3-Benzodioxanyl)methyl-6-chloro, HCl | 247 [a, d] | $C_{14}H_{19}Cl_2N_5O_3$ | 45·1 | 5·3 | 18·6 | 44·6 | 5·1 | 18·6 |
| 1-Phenanthrylmethyl, HCl | 228 [b, f] | $C_{20}H_{22}ClN_5O$ | 62·0 | 5·9 | | 62·5 | 5·8 | |
| 3-Phenanthrylmethyl, HCl | 214 [b, c] | $C_{20}H_{22}ClN_5O$ | 62·1 | 5·7 | | 62·5 | 5·8 | |
| 9-Phenanthrylmethyl, HCl | 235 [a, d] | $C_{20}H_{22}ClN_5O$ | 62·5 | 6·0 | | 62·5 | 5·8 | |

[a] Prisms. [b] Needles. Recryst. from [c] ethanol–acetone, [d] ethanol, [e] acetone, [f] ethanol–ether [g] aqueous ethanol, [h] ethanol–ethyl acetate.

4,6-*Diamino*-1,2-*dihydro*-2,2-*dimethyl*-1-2′-*naphthylmethoxy*-1,3,5-*triazine formate*.—1-2′-Naphthylmethoxydiguanide [1] (0·5 g.), acetone (25 ml.), and formic acid (10 ml.) were refluxed for 8 hr. Evaporation of the clear solution and crystallisation of the residual solid from propan-2-ol–ether afforded the *product* as needles (0·4 g.), m. p. 148° (Found: C, 59·5; H, 6·3; N, 20·1. $C_{17}H_{21}N_5O_3$ requires C, 59·5; H, 6·2; N, 20·4%). When acetic acid was used in place of formic acid the only product was 1-2′-*naphthylmethoxydiguanide monoacetate*, needles (from ethanol–ether), m. p. 186° (Found: C, 56·3; H, 6·0; N, 22·1. $C_{15}H_{19}N_5O_3$ requires C, 56·8; H, 6·0; N, 22·1%).

4,6-*Diamino*-1-*benzamido*-1,2-*dihydro*-2,2-*dimethyl*-1,3,5-*triazine Hydrochloride* (IV; Ar = NHBz).—1-Benzamidodiguanide monohydrochloride [1] (1·0 g.), 4N-hydrochloric acid (1 ml.),

acetone (15 ml.), and ethanol (10 ml.) were heated under reflux for 3 hr. Removal of the solvents and crystallisation of the residual solid from ethanol yielded needles of the *triazine hydrochloride monohydrate* (0·95 g.), m. p. 214—215° (Found: C, 46·1; H, 5·8; N, 26·5. $C_{12}H_{17}ClN_6O,H_2O$ requires C, 45·8; H, 6·05; N, 26·7%).

4,6-*Diamino*-1,2-*dihydro*-1-*isonicotinoylamino*-2,2-*dimethyl*-1,3,5-*triazine Hydrochloride* (IV; Ar = $C_6H_4N{\cdot}CO{\cdot}NH$).—1-Isonicotinoylaminodiguanide dihydrochloride [1] (0·75 g.), acetone (20 ml.), and water (8 ml.) were heated on the steam-bath for 18 hr. The colourless solution was evaporated and the residual solid triturated with acetone and collected (0·68 g.; m. p. 210—212°). Several crystallisations from aqueous ethanol gave the *triazine hydrochloride* as prismatic needles (0·27 g.), m. p. 218—220° (Found: C, 44·0; H, 5·8. $C_{11}H_{16}ClN_7O$ requires C, 44·3; H, 5·4%).

4,6-*Diamino*-1,2-*dihydro*-2,2-*dimethyl*-1-1′-*naphthylmethoxy*-1,3,5-*triazine*.—(*a*) The triazine hydrochloride (1·0 g.) dissolved in 50% aqueous ethanol (30 ml. was percolated through a column of Deacidite FF, and the column then washed with a further quantity of the solvent (70 ml.). Evaporation at <40° gave the *triazine* base as leaflets (0·7 g.), m. p. 168—170°. Rapid recrystallisation from aqueous ethanol gave leaflets, m. p. 168°, solidifying and remelting at 202—203° (Found: C, 64·6; H, 6·6; N, 24·0. $C_{16}H_{19}N_5O$ requires C, 64·7; H, 6·9; N, 23·5%).

(*b*) The triazine hydrochloride (11·5 g.), dissolved in methanol (100 ml.), was treated with triethylamine (33 ml.) and after 30 min. at room temperature was diluted with water (600 ml.). After a further 1 hr. the triazine base was collected (9·6 g.; m. p. 164—166°).

Other *bases* similarly prepared are described in Table 7, together with a number of salts. The latter were prepared by brief warming of the components in ethanol to give a clear solution from which the salts usually crystallised on cooling.

TABLE 7.

Dihydrotriazine bases and salts (VIII; R′ = R″ = Me).

| Subst. (R) and salt | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| Benzyl, $H_2O$ | 143° [a, d] | $C_{12}H_{17}N_5O,H_2O$ | 54·5 | 7·1 | 25·9 | 54·4 | 7·25 | 26·4 |
| 4-Chlorobenzyl, acetate | 158 [c, f] | $C_{14}H_{20}ClN_5O_3$ | 48·9 | 5·9 | | 49·0 | 5·9 | |
| 1-Naphthylmethyl | 168 [b, e, i] | $C_{16}H_{19}N_5O$ | 64·6 | 6·6 | 24·0 | 64·7 | 6·4 | 23·5 |
| 1-Naphthylmethyl acetate | 183—185 [c, f] | $C_{18}H_{23}N_5O_3$ | 60·6 | 6·3 | 19·6 | 60·5 | 6·5 | 19·6 |
| 1-Naphthylmethyl, hydrogen maleate | 202—203 [a, d] | $C_{20}H_{23}N_5O_5$ | 58·2 | 5·5 | 17·35 | 58·05 | 5·6 | 16·9 |
| 1-Naphthylmethyl, succinate | 225—226 [a, f, h] | $C_{36}H_{44}N_{10}O_6$ | 60·6 | 6·4 | 19·4 | 60·6 | 6·2 | 19·7 |
| 1-Naphthylmethyl, hydrogen phthalate | 195 [a, d] | $C_{24}H_{25}N_5O_5$ | 62·1 | 5·6 | 15·2 | 62·2 | 5·5 | 15·1 |
| 1-Naphthylmethyl, embonate | 202—204 [a, e] | $C_{55}H_{54}N_{10}O_8$ | 66·7 | 5·5 | 14·2 | 67·25 | 5·5 | 14·3 |
| 1-Naphthylmethyl, phosphate | 210—211 [a, g] | $C_{16}H_{19}N_5O,H_3PO_4$ | 48·25 | 5·5 | 18·1 | 48·6 | 5·6 | 17·7 |
| 1-Naphthylmethyl, *p*-nitrobenzoate | 230—232 [a, e] | $C_{23}H_{24}N_6O_5$ | 59·9 | 5·4 | 18·85 | 59·5 | 5·2 | 18·1 |
| 1-Naphthylmethyl, adipate | 200 [a, e] | $C_{38}H_{48}N_{10}O_6$ | 61·4 | 6·5 | 19·0 | 61·7 | 6·5 | 18·9 |
| 1-Naphthylmethyl, 5-nitro-2-furoate | 210 [a, d] | $C_{21}H_{22}N_6O_6$ | 55·5 | 4·95 | 18·7 | 55·6 | 4·7 | 18·5 |
| 2-Naphthylmethyl | 217—218 [a, e, j] | $C_{16}H_{19}N_5O$ | 64·8 | 6·8 | 23·7 | 64·7 | 6·4 | 23·5 |
| 2-Naphthylmethyl, acetate | 160 [a, g] | $C_{18}H_{23}N_5O_3$ | 60·3 | 6·9 | 19·8 | 60·5 | 6·5 | 19·6 |
| 2-Naphthylmethyl, hydrogen maleate | 195 [a, e] | $C_{20}H_{23}N_5O_5$ | 58·2 | 5·6 | 17·4 | 58·05 | 5·6 | 16·9 |
| 2-Naphthylmethyl, *p*-nitrobenzoate | 218 [a, d] | $C_{23}H_{24}N_6O_5$ | 59·1 | 5·2 | 18·6 | 59·5 | 5·2 | 18·1 |
| 1-Chloro-2-naphthylmethyl | 160 [b, e] | $C_{16}H_{18}ClN_5O$ | 58·3 | 5·4 | 21·6 | 58·0 | 5·5 | 21·1 |
| 1-Bromo-2-naphthylmethyl | 165 [a, e] | $C_{16}H_{18}BrN_5O$ | 51·0 | 4·6 | 18·65 | 51·1 | 4·8 | 18·6 |
| 1-Bromo-2-naphthylmethyl acetate | 186—187 [c, f] | $C_{18}H_{23}BrN_5O_3$ | 49·5 | 5·1 | 15·85 | 49·5 | 5·1 | 16·05 |
| 3-Phenanthrylmethyl, $H_2O$ | 170 [a, e] | $C_{20}H_{21}N_5O,H_2O$ | 66·4 | 6·4 | 19·7 | 65·9 | 6·35 | 19·2 |
| 3-Phenanthrylmethyl, acetate | 210 [a, d] | $C_{22}H_{25}N_5O_3$ | 64·4 | 6·2 | 17·0 | 64·8 | 6·2 | 17·2 |

[a] Needles. [b] Leaflets. [c] Prisms. Recryst. from [d] ethanol, [e] aqueous ethanol, [f] ethanol–ether, [g] propan-2-ol–ether. [h] A hydrogen succinate separated first (m. p. 176—178°), which on recrystallisation was converted into the neutral succinate. [i] Solidifies, then remelts at 202—203°. [j] Solidifies, then remelts at 244°.

4,6-*Diamino*-1,2-*dihydro*-2,2-*dimethyl*-1-2′-*naphthylmethoxy*-1,3,5-*triazine Dihydrochloride*.—The pure triazine base (0·5 g.) was added to an excess of 20% ethanolic hydrogen chloride, giving a clear solution to which dry ether was slowly added. Needles of the *dihydrochloride* separated and were collected, washed with ether, and dried in air (0·63 g.); they had m. p. 216—218° (Found: C, 51·8; H, 5·6; N, 19·0. $C_{16}H_{21}Cl_2N_5O$ requires C, 52·0; H, 5·7; N, 18·9%). Crystallisation from ethanol–ether gave needles, m. p. 233°, not depressed on admixture with authentic monohydrochloride. Treatment of an ethanolic suspension of the monohydrochloride with an excess of ethanolic hydrogen chloride for 15 min. gave the dihydrochloride, m. p. 217—218°.

2-*Amino*-4-*benzyloxyamino*-5,6-*dihydro*-6,6-*dimethyl*-1,3,5-*triazine* (X; Ar = Ph).—(*a*) 4,6-Diamino-1-benzyloxy-1,2-dihydro-2,2-dimethyl-1,3,5-triazine (1·0 g.) in water (10 ml.) was heated on the steam-bath for 2 hr. After cooling, the solid was collected (0·95 g.; m. p. 210—212°). Crystallisation from ethanol–ethyl acetate gave needles of the rearranged *triazine*, m. p. 220° (Found: C, 58·0; H, 6·8; N, 28·5. $C_{12}H_{17}N_5O$ requires C, 58·3; H, 6·9; N, 28·4%).

(*b*) The 1-benzyloxytriazine base (2·0 g.) when heated under reflux for 4 hr. in benzene (40 ml.) gave the same rearranged triazine (1·3 g.), m. p. 220°.

(*c*) 1-Benzyloxydiguanide (0·5 g.), ethanol (10 ml.), acetone (15 ml.), and piperidine (0·3 ml.) were heated under reflux for 6 hr. On cooling, solid separated and was collected (0·33 g.; m. p. 211—212°). The pure product, obtained by crystallisation from ethanol–ethyl acetate, had m. p. 220° not depressed on admixture with the products made by routes (*a*) and (*b*).

(*d*) The triazine hydrochloride (VIII; R = Ph·$CH_2$, R′ = R″ = Me) (0·3 g.) was heated to just above its m. p. (230°) in a metal bath for 30 sec. After cooling, the resulting glass was dissolved in water and made strongly alkaline with 4N-sodium hydroxide. The solid which separated was collected (0·2 g.). Two crystallisations from ethanol–ethyl acetate gave the rearranged triazine (0·1 g.), m. p. 217—219°.

2-*Amino*-5,6-*dihydro*-6,6-*dimethyl*-4-1′-*naphthylmethoxyamino*-1,3,5-*triazine* (X; Ar = 1-$C_{10}H_7$).—Triazine base (VIII; R = 1-$C_{10}H_7$·$CH_2$, R′ = R″ = Me) (0·3 g.) and water (20 ml.) were heated on the steam-bath for 1 hr., then cooled, giving prismatic needles (0·26 g.), m. p. 202°. The rearranged *triazine* formed needles (from aqueous ethanol), m. p. 203° (Found: C, 65·0; H, 6·4; N, 23·1. $C_{16}H_{19}N_5O$ requires C, 64·7; H, 6·4; N, 23·5%). The *monohydrochloride* crystallised with difficulty from propan-2-ol–ether as needles, m. p. 192—193° (Found: C, 56·3; H, 6·2; N, 19·9. $C_{16}H_{20}ClN_5O,0{\cdot}5H_2O$ requires C, 56·2; H, 6·2; N, 20·5%). The *acetate* formed prisms (from ethanol–ether), m. p. 163° (Found: C, 60·6; H, 6·6; N, 19·6. $C_{18}H_{23}N_5O_3$ requires C, 60·5; H, 6·5; N, 19·6%), and the *hydrogen maleate*, needles (from the same solvents), m. p. 189—190° (Found: C, 57·9; H, 5·3; N, 17·2. $C_{20}H_{23}N_5O_5$ requires C, 58·05; H, 5·6; N, 16·9%). Other rearranged *dihydrotriazines* (all needles) are described in Table 8.

TABLE 8.

" Rearranged " dihydrotriazines (X).

| Ar | M. p. | Solvent for crystn. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 2-Naphthyl | 244° | EtOH | $C_{16}H_{19}N_5O$ | 64·8 | 6·8 | 23·1 | 64·7 | 6·4 | 23·5 |
| 2-Naphthyl, HCl | 202 | $Pr^iOH$–$Et_2O$ | $C_{16}H_{20}ClN_5O$ | 57·6 | 6·2 | 20·6 | 57·5 | 6·05 | 20·9 |
| 1-Chloro-2-naphthyl | 226 | EtOH | $C_{16}H_{18}ClN_5O$ | 57·5 | 5·4 | 21·5 | 58·0 | 5·5 | 21·1 |
| 1-Bromo-2-naphthyl | 228—229 | ,, | $C_{16}H_{18}BrN_5O$ | 51·0 | 4·8 | 19·0 | 51·1 | 4·8 | 18·6 |
| 8-(1,3-Benzodioxanyl)-6-chloro | 181 | * | $C_{14}H_{18}ClN_5O_3$ | 49·0 | 5·4 | 20·4 | 49·4 | 5·3 | 20·5 |
| 3-Phenanthryl | 222—223 | EtOH | $C_{20}H_{21}N_5O$ | 69·0 | 6·4 | 20·1 | 69·2 | 6·1 | 20·2 |

* From ethanol–light petroleum (b. p. 40—60°).

4,6-*Diamino*-1-*decyloxy*-1,2-*dihydro*-2-*methyl*-1,3,5-*triazine* (VIII; R = $C_{10}H_{21}$, R′ = H, R″ = Me).—1-Decyloxydiguanide (0·64 g.), ethanol (10 ml.), concentrated hydrochloric acid (0·4 ml.), and acetaldehyde (1·3 ml.) were heated on the steam-bath for 2 hr. More acetaldehyde (0·5 ml.) was added and heating continued for 4 hr. Evaporation of the solvents and trituration of the residual gummy solid with ethanol–ether gave needles (0·32 g.), m. p. 205—206°. Satisfactory analytical figures for this triazine hydrochloride could not be obtained. It was therefore converted into the *picrate* which formed prismatic yellow needles (from

ethanol), m. p. 178—179° (Found: C, 46·0; H, 5·9; N, 21·9. $C_{19}H_{30}N_8O_8$ requires C, 45·8; H, 6·1; N, 22·5%).

4,6-*Diamino*-1-*decyloxy*-1,2-*dihydro*-1,3,5-*triazine*-2-*spirocyclohexane Hydrochloride* (VIII; R = $C_{10}H_{21}$, R′R″ = $-[CH_2]_5$).—A mixture of 1-decyloxydiguanide dihydrochloride (0·5 g.), cyclohexanone (2·0 ml.), and ethanol (5 ml.) was refluxed for 4 hr. After cooling, ether was added and the solid collected (0·25 g.). Crystallisation from ethanol–ether gave the *triazine hydrochloride* as leaflets, m. p. 217—218° (Found: C, 57·1; H, 10·4; N, 18·3. $C_{18}H_{38}ClN_5O$ requires C, 57·5; H, 10·2; N, 18·6%).

4,6-*Diamino*-1,4′-*chlorobenzyloxy*-2-*ethyl*-1,2-*dihydro*-2-*methyl*-1,3,5-*triazine Hydrochloride* (VIII; R = 4-Cl·$C_6H_4$·$CH_2$, R′ = Me, R″ = Et).—1-4′-Chlorobenzyloxydiguanide dihydrochloride (2·1 g.), ethyl methyl ketone (20 ml.), ethanol (30 ml.), and benzene (40 ml.) were heated under reflux for 5 hr., the condensate passing through a Soxhlet extractor charged with anhydrous magnesium sulphate. The solution was evaporated and stirred with ethyl methyl ketone, giving a solid (0·93 g.), m. p. 162—163°. Several crystallisations from ethanol–ether gave prisms of the required *triazine hydrochloride*, m. p. 214—215° (Found: C, 44·2; H, 5·9; N, 22·2. $C_{12}H_{19}Cl_2N_5O$ requires C, 44·6; H, 6·0; N, 21·9%). The *saccharin salt* formed prisms (from ethanol), m. p. 183—184° (Found: C, 50·3; H, 4·8; N, 17·9. $C_{20}H_{23}ClN_6O_4S$ requires C, 50·1; H, 4·8; N, 17·55%).

4,6-*Diamino*-1-*benzyloxy*-1,2-*dihydro*-2-*phenyl*-1,3,5-*triazine Hydrochloride* (VIII; R = Ph·$CH_2$, R′ = Ph, R″ = H).—1-Benzyloxydiguanide (2·1 g.), ethanol (10 ml.), concentrated hydrochloric acid (1·9 ml.), and benzaldehyde (2·0 g.) were left at room temperature for 72 hr. during which solid separated (2·5 g.). Crystallisation from aqueous ethanol gave the *product* as prismatic needles, m. p. 249—250° (Found: C, 58·8; H, 5·5; N, 20·9. $C_{16}H_{18}ClN_5O$ requires C, 58·0; H, 5·5; N, 21·1%). Similarly were prepared 4,6-*diamino*-1-(1-*bromo*-2-*naphthylmethoxy*)-2-*ethyl*-1,2-*dihydro*-2-*methyl*-1,3,5-*triazine hydrochloride* (VIII; R = 1-bromo-2-naphthylmethyl, R′ = Me, R″ = Et) which formed needles, m. p. 170—172°, of the monohydrate from aqueous ethanol (Found: C, 45·8; H, 5·4; N, 15·5. $C_{17}H_{21}BrClN_5O,H_2O$ requires C, 46·0; H, 5·2; N, 15·7%), and 4,6-*diamino*-1-*benzyloxy*-1,2-*dihydro*-2-p-*methoxyphenyl*-1,3,5-*triazine hydrochloride* (VIII; R = Ph·$CH_2$, R′ = *p*-MeO·$C_6H_4$, R″ = H), needles (from aqueous methanol), m. p. 258—259° (Found: C, 56·5; H, 5·8; N, 19·1. $C_{17}H_{20}ClN_5O_2$ requires C, 56·5; H, 5·6; N, 19·4%).

*Reaction of Amino-oxymethylbenzene, Dicyandiamide, and Acetone.*—Amino-oxymethylbenzene hydrochloride (2·5 g.), powdered dicyandiamide (1·3 g.), acetone (40 ml.), ethanol (10 ml.), and concentrated hydrochloric acid (0·5 ml.) were stirred at 20° for 7 hr. The mixture cleared after 15 min. and solid began to separate after 4 hr. At no time was a positive diguanide reaction obtained (ammoniacal copper sulphate). Next morning the solid was collected (1·12 g.; m. p. 160—166°) and shown to be amidinourea hydrochloride. Evaporation of the filtrate gave amidinourea hydrochloride (0·1 g.) and an oil, b. p. 102—104°/13 mm. (1·9 g.). Analysis indicated that the oil was *isopropylidenebenzyloxyamine* (Found: C, 73·6; H, 8·3; N, 9·2. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·0; N, 8·6%). This was confirmed by comparison of its infrared spectrum with that of an authentic sample prepared by reaction of amino-oxymethylbenzene with acetone.

*Arylmethyl Bromides.*—The following illustrates the method used: Ethylbenzene (68 g.), paraformaldehyde (21·5 g.), sodium bromide (80 g.), and acetic acid (30 ml.) were stirred at 80° while a mixture of acetic acid (70 ml.) and concentrated sulphuric acid (70 ml.) was added in 3 hr. Heating was continued for a further 4 hr., and the mixture then cooled, diluted with water, and extracted with ether. The extracts were washed with aqueous sodium carbonate and water, then dried and distilled. 4-Ethylbenzyl bromide was obtained as a colourless oil, b. p. 70°/0·1 mm. (56 g.) (Found: C, 53·8; H, 5·8. Calc. for $C_9H_{11}Br$: C, 54·3; H, 5·6%) (lit.,[11] b. p. 101—104°/10 mm.). In a similar manner were prepared 4-propyl-, b. p. 130—140°/15 mm., 4-*isopropyl*-, b. p. 119°/15 mm. (Found: C, 56·1; H, 6·0. $C_{10}H_{13}Br$ requires C, 56·5; H, 6·1%), 4-*butyl*-, b. p. 144°/17 mm. (Found: C, 58·4; H, 6·6. $C_{11}H_{15}Br$ requires C, 58·2; H, 6·6%), 4-*s*-*butyl*-, b. p. 78°/0·1 mm. (Found: C, 57·8; H, 6·8%), and 4-t-butylbenzyl bromide, b. p. 135—140°/15 mm. (lit.,[12] b. p. 133°/17 mm.). 1-Bromo-4-bromomethylnaphthalene was also prepared by this route and had m. p. 103—104° (lit.,[14] 103—104°). *Di*-(4-*bromo*-1-*naphthyl*)*methane*, isolated as a by-product, formed needles (from ethyl acetate), m. p. 193—194° (Found: C, 59·6; H, 3·3. $C_{21}H_{14}Br_2$ requires C, 59·1; H, 3·3%).

4-Methoxybenzyl bromide, b. p. 130—132°/13 mm., was obtained by the action of hydrogen

bromide in benzene on the alcohol (lit.,[17] b. p. 129°/6 mm.) and was characterised as the *isothiouronium bromide*, needles (from ethanol–ether), m. p. 143—145° (Found: C, 39·5; H, 5·0; N, 10·3. $C_9H_{13}BrN_2OS$ requires C, 39·0; H, 4·7; N, 10·1%). 3-Bromomethylphenanthrene, made by the action of *N*-bromosuccinimide on 3-methylphenanthrene, had m. p. 112—113°, and 2-bromomethylphenanthrene, similarly prepared, had m. p. 108—109°.

*Benzhydroxamates.*—Made as previously described,[1] the new *derivatives* are described in Table 9.

TABLE 9.

Substituted benzhydroxamates Ar·$CH_2$·O·NH·COPh.

| | | | | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| Ar | M. p. | Form | Formula | C | H | N | C | H | N |
| *p*-Ethylphenyl ..... | 81° | Needles * | $C_{16}H_{17}NO_2$ | 75·0 | 6·9 | 5·8 | 75·3 | 6·7 | 5·5 |
| *p*-Propylphenyl ..... | 97—98 | Prisms * | $C_{17}H_{19}NO_2$ | 75·2 | 7·0 | 5·7 | 75·8 | 7·1 | 5·2 |
| *p*-Isopropylphenyl ... | 100 | Needles * | $C_{17}H_{19}NO_2$ | 76·3 | 7·4 | 5·2 | 75·8 | 7·1 | 5·2 |
| *p*-Butylphenyl ..... | 99—100 | ,, † | $C_{18}H_{21}NO_2$ | 76·0 | 7·4 | 4·9 | 76·4 | 7·5 | 4·95 |
| *p*-t-Butylphenyl ..... | 87—88 | Prisms ‡ | $C_{18}H_{21}NO_2$ | 75·8 | 7·7 | 5·3 | 76·4 | 7·5 | 4·95 |
| 1-Methyl-4-naphthyl | 143 | Needles * | $C_{19}H_{17}NO_2$ | 78·75 | 5·9 | 4·8 | 78·4 | 5·9 | 4·8 |
| 1-Chloro-2-naphthyl | 145—146 | ,, | $C_{18}H_{14}ClNO_2$ | 69·5 | 4·8 | 4·5 | 69·3 | 4·5 | 4·5 |
| 1-Bromo-4-naphthyl | 160—161 | ,, § | $C_{18}H_{14}BrNO_2$ | 60·9 | 4·2 | 3·85 | 60·7 | 4·0 | 4·0 |
| 2-Phenanthryl ..... | 165—166 | ,, | $C_{22}H_{17}NO_2$ | 80·3 | 5·4 | 4·4 | 80·7 | 5·2 | 4·3 |
| 3-Phenanthryl ..... | 126 | ,, | $C_{22}H_{17}NO_2$ | 81·1 | 5·6 | 4·7 | 80·7 | 5·2 | 4·3 |

Recryst. from * ethyl acetate–light petroleum (b. p. 60—80°), † aqueous ethanol, ‡ light petroleum (b. p. 80—100°), § ethyl acetate.

4-*Methoxybenzyl benzhydroxamate.* A suspension of sodium benzhydroxamate [from benzhydroxamic acid (11·8 g.) and sodium hydroxide (3·46 g.)] in ethanol (90 ml.) was treated with 4-methoxybenzyl bromide (17·5 g.) and stirred at room temperature for 2 hr. Next morning the ethanol was removed and the residual oil treated with water and extracted with ethyl acetate. Evaporation of the ethyl acetate gave a solid (7·7 g.), m. p. 110—115°, and an oil (12·3 g.). By extraction with hot water, the solid was separated into two fractions, the more soluble of which (3·0 g.) was benzhydroxamic acid, m. p. 126—127°: the less soluble, 4-*methoxybenzyl benzhydroxamate* formed needles (4·2 g.), m. p. 121—122° (Found: C, 70·5; H, 6·1; N, 5·6. $C_{15}H_{15}NO_3$ requires C, 70·1; H, 5·9; N, 5·45%). Distillation of the oil afforded *ethyl 4-methoxybenzyl ether* (8·0 g.), b. p. 90—92°/4 mm., $n_D^{22}$ 1·5052 (Found: C, 72·0; H, 8·4. $C_{10}H_{14}O_2$ requires C, 72·2; H, 8·5%). An improved yield was obtained when the reaction was carried out in dimethylformamide at 100° rather than in ethanol.

*Amino-oxymethyl Hydrochlorides.*—These were prepared by ethanolysis of the benzhydroxamates,[1] to give the *compounds* listed in Table 10.

TABLE 10.

Substituted amino-oxy-hydrochlorides, Ar·$CH_2$·O·$NH_2$,HCl.

| | | | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|---|
| Ar | M. p.‡ | Formula | C | H | N | C | H | N |
| *p*-Ethylphenyl ..... | 222° * | $C_9H_{14}ClNO$ | 57·7 | 7·6 | 7·8 | 57·5 | 7·5 | 7·5 |
| *p*-Isopropylphenyl ..... | 191—192 † | $C_{10}H_{16}ClNO$ | 59·5 | 8·1 | 7·4 | 59·55 | 8·0 | 6·95 |
| *p*-Butylphenyl ..... | 209—210 * | $C_{11}H_{18}ClNO$ | 61·5 | 8·7 | 6·5 | 61·2 | 8·4 | 6·5 |
| *p*-s-Butylphenyl ..... | 164—165 † | $C_{11}H_{18}ClNO$ | 60·9 | 8·3 | 6·6 | 61·2 | 8·4 | 6·5 |
| *p*-t-Butylphenyl ..... | 180—181 * | $C_{11}H_{18}ClNO$ | 60·8 | 8·1 | 6·8 | 61·2 | 8·4 | 6·5 |
| *p*-Methoxyphenyl ..... | 190—192 *§ | $C_8H_{12}ClNO_2$ | 50·2 | 6·0 | 7·1 | 50·6 | 6·4 | 7·4 |
| 1-Methyl-4-naphthyl ..... | 177 * | $C_{12}H_{14}ClNO$ | 64·5 | 6·2 | 6·55 | 64·5 | 6·3 | 6·3 |
| 1-Chloro-2-naphthyl ..... | 206—207 * | $C_{11}H_{11}Cl_2NO$ | 54·6 | 4·7 | 5·8 | 54·1 | 4·6 | 5·75 |
| 1-Bromo-4-naphthyl ..... | 188 † | $C_{11}H_{11}BrClNO$ | 46·1 | 4·5 | 4·4 | 45·7 | 3·9 | 4·8 |
| 2-Phenanthryl ..... | 237 * | $C_{15}H_{14}ClNO$ | 70·0 | 5·7 | 5·2 | 69·5 | 5·45 | 5·4 |
| 3-Phenanthryl ..... | 202 * | $C_{15}H_{14}ClNO$ | 69·7 | 5·5 | 5·7 | 69·5 | 5·45 | 5·4 |

Recryst. from * ethanol or † ethanol–ether. ‡ Needles, except § leaflets.

ON-*Di(arylmethyl)hydroxyamines.*—During working up of the preparations of amino-oxymethyl hydrochlorides, by-products were isolated in a number of cases, in yields from low to 25%: details of individual *compounds* are collected in Table 11.

[17] Tiffeneau, *Bull. Soc. chim. France*, 1911, **9**, 826.

*Arylmethoxydiguanides.*—A number of new *diguanides* were prepared by the usual procedure:[1] details are given in Table 12.

TABLE 11.

*ON*-Di(arylmethyl)hydroxylamines, $Ar{\cdot}CH_2{\cdot}O{\cdot}NH{\cdot}CH_2{\cdot}Ar$.

| | | | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|---|
| Ar | M. p.* | Formula | C | H | N | C | H | N |
| *p*-Chlorophenyl | 111—112° | $C_{14}H_{13}Cl_2NO$ | 59·8 | 4·9 | 5·1 | 59·5 | 4·6 | 5·0 |
| *p*-Bromophenyl | 128—130 | $C_{14}H_{13}Br_2NO$ | 45·3 | 2·8 | 3·8 | 45·3 | 3·5 | 3·8 |
| 2-Naphthyl | 150—151 † | $C_{22}H_{19}NO$ | 84·65 | 5·8 | 4·45 | 84·5 | 5·8 | 4·5 |
| 1-Chloro-2-naphthyl | 192—193 ‡ | $C_{22}H_{17}Cl_2NO$ | 69·4 | 4·0 | 3·7 | 69·1 | 4·5 | 3·7 |
| 1-Bromo-2-naphthyl | 211—212 | $C_{22}H_{17}Br_2NO$ | 56·45 | 3·95 | 2·7 | 56·5 | 3·6 | 3·0 |
| 8-(1,3-Benzodioxanyl)-6-chloro | 208—209 ‡ | $C_{18}H_{17}Cl_2NO_5$ | 54·4 | 3·8 | 3·7 | 54·3 | 4·3 | 3·5 |

* Needles from EtOH, except † leaflets and ‡ from benzene.

TABLE 12.

Arylmethoxydiguanides (I).

| | | | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|---|
| Subst. (R) & deriv. | M. p.* | Formula | C | H | N | C | H | N |
| *p*-Tolyl,2HCl | 159—160° | $C_{10}H_{17}Cl_2N_5O$ | 40·7 | 6·0 | 24·4 | 40·8 | 5·8 | 23·8 |
| *p*-Ethylphenyl,2HCl | 148—149 | $C_{11}H_{19}Cl_2N_5O$ | 43·2 | 6·3 | 22·1 | 42·9 | 6·2 | 22·7 |
| *p*-Isopropylphenyl | 106 †‡ | $C_{12}H_{19}N_5O$ | 57·2 | 8·0 | 27·7 | 57·9 | 7·65 | 28·1 |
| *p*-Butylphenyl | 140—141 †‡ | $C_{13}H_{21}N_5O$ | 58·7 | 8·1 | 26·4 | 59·3 | 8·05 | 26·6 |
| *p*-s-Butylphenyl, picrate | 200 § | $C_{19}H_{24}N_8O_8$ | 46·1 | 4·9 | 23·0 | 46·4 | 4·9 | 22·8 |
| *p*-t-Butylphenyl,2HCl | 153—155 § | $C_{13}H_{23}Cl_2N_5O$ | 46·4 | 7·0 | 20·9 | 46·5 | 6·9 | 20·8 |
| *p*-Chlorophenyl,2HCl | 178 | $C_9H_{14}Cl_3N_5O$ | 33·9 | 4·6 | 25·2 | 34·4 | 4·5 | 25·2 |
| *p*-Bromophenyl,2HCl | 163—164 | $C_9H_{14}BrCl_2N_5O$ | 30·8 | 3·9 | 20·1 | 30·2 | 3·9 | 19·5 |
| 2-Naphthyl, acetate | 186 | $C_{15}H_{19}N_5O_3$ | 56·3 | 6·0 | 22·1 | 56·8 | 6·0 | 22·1 |
| 1-Chloro-2-naphthyl | 171—172 ¶ | $C_{13}H_{14}ClN_5O$ | 53·0 | 4·9 | 24·1 | 53·5 | 4·8 | 24·0 |
| 1-Bromo-4-naphthyl,2HCl | 164 | $C_{13}H_{16}BrCl_2N_5O$ | 38·2 | 3·6 | 16·9 | 38·2 | 3·9 | 17·1 |
| 3-Phenanthryl | 190—191 †‡ | $C_{17}H_{17}N_5O$ | 66·3 | 5·5 | 22·4 | 66·5 | 5·6 | 22·8 |

* Needles from EtOH–$Et_2O$, except † leaflets and from ‡ aq.EtOH, § EtOH, or ¶ ethyl acetate–light petroleum (b. p. 60—80°).

4,6-*Diamino*-1-*hydroxy*-1,2-*dihydro*-2,2-*dimethyl*-1,3,5-*triazine Hydrochloride* (VIII; R = H R′ = R″ = Me).—(*a*) 4,6-Diamino-1-benzyloxy-1,2-dihydro-2,2-dimethyl-1,3,5-triazine hydrochloride (1·1 g.) in 70% ethanol (30 ml.) was shaken with hydrogen and 10% palladised charcoal until uptake ceased (87 ml.). The catalyst was removed and the clear solution evaporated, giving needles (0·7 g.). Crystallisation from ethanol–ether gave the *product* as needles, m. p. 237° (Found: C, 30·8; H, 6·2; Cl, 18·2; N, 36·2. $C_5H_{12}ClN_5O$ requires C, 30·9; H, 6·2; Cl, 18·3; N, 36·1%).

(*b*) 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-4′-nitrobenzyloxy-1,3,5-triazine hydrochloride (1 g.), dissolved in 70% aqueous ethanol (20 ml.), was treated with reduced iron powder (3 g.) and concentrated hydrochloric acid (4 drops) and refluxed for 2 hr. The hot mixture was filtered and evaporated, giving, after treatment with ethanolic hydrogen chloride and ether, a light brown solid (0·55 g.). Crystallisation from ethanol–acetone gave cream needles, m. p. 238° (Found: C, 30·65; H, 6·35%).

4,6-*Diamino*-1,2-*dihydro*-1-*hydroxy*-2,2-*dimethyl*-1,3,5-*triazine* (base), prepared by hydrogenation of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-1′-naphthylmethoxy-1,3,5-triazine in ethanol, formed prisms [from ethanol–light petroleum (b. p. 60—80°)], m. p. 197—198° (Found: C, 37·7; H, 7·2; N, 43·9. $C_5H_{11}N_5O$ requires C, 38·2; H, 7·0; N, 44·5%).

1-*Aryldiguanides.*—These were prepared by standard methods from arylamine hydrochlorides and dicyandiamide.[5,6,8,18] *Diguanides* which have not previously been described are given in Table 13.

4,6-*Diamino*-1-*aryl*-1,2-*dihydro*-2,2-*dimethyl*-1,3,5-*triazines* (IV).—These were obtained either by reaction of the diguanide dihydrochloride with acetone (route A) or by interaction of an arylamine hydrochloride, dicyandiamide, and acetone [8] (route B). New *compounds* are described in Table 14.

[18] King and Tonkin, *J.*, 1946, 1063.

TABLE 13.

Aryldiguanides Ar·NH·C(:NH)·NH·C(:NH)·$NH_2$.

| Subst. & deriv. | M. p.† | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 2,4,5-Trichlorophenyl,HCl ... | 228—230° ‡ | $C_8H_9Cl_4N_5$ | 30·3 | 3·1 | 22·4 | 30·3 | 2·9 | 22·7 |
| 2-Naphthyl,HCl ..... | 239 § | $C_{12}H_{14}ClN_5$ | 54·2 | 5·6 | 27·0 | 54·6 | 5·3 | 26·5 |
| 1-Bromo-2-naphthyl ..... | 173 ‡ | $C_{13}H_{12}BrN_5$ | 46·9 | 4·15 | 22·4 | 47·1 | 4·0 | 22·9 |
| 1,2,3,4-Tetrahydro-2-naphthyl,2HCl,$H_2O$ * ..... | 224—230 § | $C_{12}H_{19}Cl_2N_5,H_2O$ | 44·7 | 6·6 | 21·3 | 44·7 | 6·6 | 21·7 |
| 1,2,3,4-Tetrahydro-6-naphthyl,HCl ..... | 234—235 | $C_{12}H_{18}ClN_5$ | 53·5 | 6·7 | 26·1 | 53·8 | 6·8 | 26·1 |
| 2-Biphenyl,HCl ..... | 268—270 | $C_{14}H_{16}ClN_5$ | 58·3 | 5·7 | 23·8 | 58·0 | 5·6 | 24·2 |
| 4-Biphenylyl,HCl ..... | 247 | $C_{14}H_{16}ClN_5$ | 58·3 | 5·6 | 23·6 | 58·0 | 5·6 | 24·2 |

* Prepared by fusion of 1,2,3,4-tetrahydro-2-naphthylamine hydrochloride and dicyandiamide at 140° for 2 hr. † Needles from aq. EtOH, except ‡ leaflets and § from EtOH.

TABLE 14.

Aryldihydrotriazine hydrochlorides (IV).

| Ar | Route | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 2,4,5-$C_6H_2Cl_3$ ..... | A, B | 234—235° *§ | $C_{11}H_{13}Cl_4N_5$ | 36·7 | 3·9 | 19·5 | 37·0 | 3·6 | 19·6 |
| 1-Naphthyl ..... | A, B | 226—227 *¶ | $C_{15}H_{18}ClN_5$ | 58·9 | 6·3 | 22·8 | 59·3 | 6·0 | 23·1 |
| 2-Naphthyl ..... | A | 211—212 †§ | $C_{15}H_{18}ClN_5,0·5H_2O$ | 57·7 | 6·1 | 22·8 | 57·7 | 6·1 | 22·4 |
| 1-Bromo-2-naphthyl | B | 242—244 ‡¶ | $C_{15}H_{17}BrClN_5$ | 47·5 | 4·8 | 17·8 | 47·0 | 4·5 | 18·3 |
| 2-Biphenylyl ..... | A, B | 212—213 †§ | $C_{17}H_{20}ClN_5,H_2O$ | 58·4 | 6·6 | 19·4 | 58·7 | 6·4 | 20·1 |
| 4-Biphenylyl ..... | A, B | 227—228 †¶ | $C_{17}H_{20}ClN_5,0·5H_2O$ | 60·3 | 6·6 | 20·5 | 60·2 | 6·3 | 20·6 |

* Prisms. † Needles. ‡ Leaflets. Recryst. from § EtOH or ¶ aq. EtOH.

The authors are grateful to Miss J. Mallion for the microanalyses and to Mr. P. R. Watt for the infrared spectra.

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[*Received, January 16th*, 1962.]