## 169. *Synthetic Antimalarials. Part XIX. Dialkylaminoalkylaminodiphenylguanidines.*

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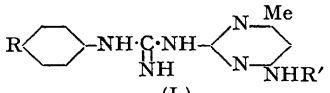
The study of the effect on antimalarial activity caused by replacing the pyrimidine by the benzene ring has been extended to include the diphenylguanidines of types (II) and (III), the former being the benzene analogues of the active 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines of type (I).

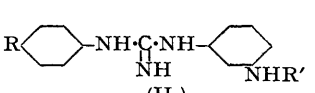
The scope of the investigation was restricted by the intractable nature of many of the products.

In Part XVIII (Mann and Porter, preceding paper) an attempt was made to ascertain whether the marked antimalarial properties of the 2-*p*-chloroanilino-4-dialkylaminoalkylamino-6-methylpyrimidines were determined primarily by their general molecular structure, or more specifically by the presence and properties of the constituent pyrimidine ring. This factor was investigated by preparing analogous compounds differing only in that the pyrimidine ring of the former compounds had now been replaced by a benzene ring. The compounds so prepared, of the general type 4′-chloro-3-dialkylaminoalkylamino-4 : 5-dimethyldiphenylamine, were found to be without antimalarial activity.

It was clearly desirable, however, that the evidence concerning this factor should not be limited to one class of pyrimidine derivative. The 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines (Curd and Rose, *J.*, 1946, 362) (I) constitute a second class of pyrimidine derivative having high antimalarial activity, and it was considered of interest,




(I.)

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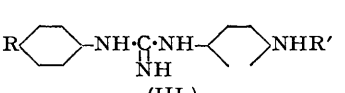
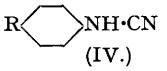



(III.)

therefore, to prepare their benzene analogues, *i.e.*, diphenylguanidines of type (II). Furthermore, in order to determine whether the position of the dialkylaminoalkylamino-

substituent relative to that of the guanidine nucleus has any marked influence on the antimalarial activity, the preparation of the *pp'*-disubstituted diphenylguanidines of type (III) was investigated.

The most convenient method for the preparation of asymmetrically disubstituted diaryl guanidines is the interaction of an aryl cyanamide with the hydrochloride of an arylamine (Heller and Bauer, *J. pr. Chem.*, 1902, **65**, 384). Thus *p*-chlorophenylcyanamide (IV, R = Cl) condensed with N-β-*diethylaminoethyl*-m-*phenylenediamine* (V, R = $CH_2 \cdot CH_2 \cdot NEt_2$) in alcoholic hydrogen chloride to afford N-p-*chlorophenyl*-N'-m-β-*diethylaminoethylaminophenylguanidine* (II, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) in moderate yield. A similar condensation between (IV, R = Cl) and N-β-*diethylaminoethyl*-p-*phenylenediamine* furnished N-p-*chlorophenyl*-N'-p-β-*diethylaminoethylaminophenylguanidine* (III, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$). Both the above guanidines were crystalline compounds.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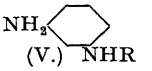
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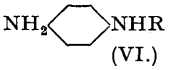
(VI.)

*N*-β-Diethylaminoethyl-*m*-phenylenediamine has previously been prepared (U.S.P. 1,757,394) by heating *m*-phenylenediamine with β-diethylaminoethyl chloride. A more convenient preparation both of this compound and of *N*-β-diethylaminoethyl-*p*-phenylenediamine consists in the condensation of β-diethylaminoethyl chloride and the corresponding nitroaniline to give the *hydrochloride* of 1-*nitro*-3-β-*diethylaminoethylamino*- and of 1-*nitro*-4-β-*diethylaminoethylamino-benzene*. Catalytic reduction of these hydrochlorides afforded good yields of the phenylenediamines (V and VI, R = $CH_2 \cdot CH_2 \cdot NEt_2$).

With the object of preparing the analogous guanidines carrying the δ-diethylamino-α-methyl-*n*-butyl side chain, N-δ-*diethylamino*-α-*methyl*-n-*butyl*-m- and -p-*phenylenediamine* (V and VI, R = $CHMe \cdot [CH_2]_3 \cdot NEt_2$) were prepared by condensing the appropriate nitroaniline with 5-diethylamino-*n*-pentan-2-one diethyl ketal and reducing the resulting anil to give the required product (cf. Mann and Porter, *loc. cit.*). Although both these substituted phenylenediamines appeared to react with (IV, R = Cl) under the usual conditions, the products proved to be intractable, deliquescent gums which could neither by crystallised nor induced to give crystalline salts. Dewar (*J.*, 1944, 534) has noted similar difficulties in attempting to crystallise *N*-dialkylaminoalkyldiarylguanidines.

Attempts were next made to prepare compounds of types (II) and (III) in which R = OMe. *p*-Methoxyphenylthiourea (Dienske, *Rec. Trav. chim.*, 1931, **50**, 407) was treated with lead hydroxide to give p-*methoxyphenylcyanamide* (IV, R = OMe). This reacted normally with each of the above four substituted phenylenediamines but no crystalline product could be isolated. Analysis of the resinous gum produced by the reaction between (IV, R = OMe) and *N*-β-diethylaminoethyl-*p*-phenylenediamine showed it to be almost certainly the required N-p-*methoxyphenyl*-N'-p-β-*diethylaminoethylaminophenylguanidine* (III, R = OMe, R' = $CH_2 \cdot CH_2 \cdot NEt_2$).

An alternative synthetic route was equally unproductive of crystalline products. *p*-Methoxyphenylcyanamide was heated in alcoholic solution with *m*-nitroaniline hydrochloride to form N-p-*methoxyphenyl*-N'-m-*nitrophenylguanidine hydrochloride* which was catalytically reduced to N-p-*methoxyphenyl*-N'-m-*aminophenylguanidine hydrochloride* (II, R = OMe, R' = H). The latter compound, however, did not condense normally with β-diethylaminoethyl chloride: a complex mixture of products, arising apparently from the rupture of the guanidino-linkage, being isolated.

Only the two crystalline guanidine derivatives (II and III, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) have been tested. Whereas the former (5220) showed significant activity (+ to ++ at 80 mg./kg.) the latter (6180) was inactive at the same dosage (highest tested). The former is the more closely related to the active 2-arylguanidino-4-dialkylaminoalkylaminopyrimidines of type (I), and the conclusion may therefore perhaps be drawn that the replacement of a pyrimidine ring by a benzene ring in an antimalarial structure based on pyrimidine does not necessarily lead to complete loss of activity despite the results given in the previous paper. In this connection it may be noted that, whereas the diphenylamines described in the previous paper do not retain any of the tautomeric possibilities characteristic of their pyrimidine analogues, the diphenylguanidine (II, R = Cl, R' = $CH_2 \cdot CH_2 \cdot NEt_2$) is not devoid of all the tautomeric possibilities existent in type (I).

## Experimental.

1-*Nitro*-3-β-*diethylaminoethylaminobenzene*.—A mixture of *m*-nitroaniline (100 g.) and β-diethylaminoethyl chloride (105 g., 1·1 mols.) in xylene (500 c.c.) was refluxed for 3 hours. The crystalline

*hydrochloride* was then collected and recrystallised from ethyl alcohol–light petroleum (b. p. 60—80°) (equal vols.); pale yellow needles, m. p. 177—178° (Found: N, 15·3; Cl, 13·2. $C_{12}H_{19}O_2N_2$,HCl requires N, 15·4; Cl, 13·0%). Yield, 140 g.; 70%.

Basification of an aqueous solution of the hydrochloride furnished the oily *base* (Found: C, 60·35; H, 8·1; N, 17·7. $C_{12}H_{19}O_2N_2$ requires C, 60·7; H, 8·1; N, 17·7%). The base readily afforded a *picrate*, orange crystals from alcohol, m. p. 149—150° (Found: N, 18·2. $C_{12}H_{19}O_2N_2,C_6H_3O_7N_3$ requires N, 18·0%).

1-*Nitro*-4-*β*-*diethylaminoethylaminobenzene hydrochloride* was similarly prepared and recrystallised; yellow needles, m. p. 159—160° (Found: C, 52·35; H, 7·6; N, 15·3. $C_{12}H_{19}O_2N_2Cl$ requires C, 52·6; H, 7·6; N, 15·4%). Yield, 72%. The *picrate*, yellow needles from ethyl alcohol, had m. p. 168—169° (Found: N, 18·5. $C_{12}H_{19}O_2N_2,C_6H_3O_7N_3$ requires N, 18·0%).

N-*β*-*Diethylaminoethyl*-m-*phenylenediamine* (V, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—A solution of 1-nitro-3-*β*-diethylaminoethylaminobenzene hydrochloride (140 g.) in 90% aqueous ethyl alcohol (350 c.c.) was hydrogenated (Adams's catalyst, 0·3 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated and then basified with aqueous sodium hydroxide. The product was extracted with ether and the dried extract fractionally distilled. The pure *amine* had b. p. 154°/0·05 mm. (Found: C, 69·2; H, 10·4; N, 19·9. $C_{12}H_{21}N_3$ requires C, 69·5; H, 10·3; N, 20·3%). Yield, 106 g.; 85%.

N-*β*-*Diethylaminoethyl*-p-*phenylenediamine* (VI, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$) was similarly prepared as a hygroscopic oil, b. p. 156°/0·02 mm. (Found: C, 69·1; H, 10·8; N, 21·0%).

p-*Chlorophenylcyanamide* (IV, R = Cl).—This compound was prepared from *p*-chlorophenylthiourea and obtained as colourless needles, m. p. 103° (Found: N, 18·4. Calc. for $C_7H_5N_2Cl$: N, 18·3%).

N-p-*Chlorophenyl*-N′-m-*β*-*diethylaminoethylaminophenylguanidine* (II, R = Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—A solution of (IV, R = Cl) (10 g.) and *N*-*β*-diethylamino-*m*-phenylenediamine (13 g., 1 mol.) in ethyl alcohol (50 c.c.) containing hydrogen chloride (2·5 g., 2 mols.) was refluxed for 20 hours. The whole was then poured into 5% acetic acid (300 c.c.) and filtered, and the filtrate was slowly run into an excess of ice-cold 10% aqueous sodium hydroxide. The sticky white solid which separated was collected and dried. Prolonged extraction (Soxhlet) with light petroleum (b. p. 60—80°) afforded the crude product, which readily separated from the hot solution. Recrystallisation from light petroleum gave the pure *guanidine*, m. p. 112—113° (Found: C, 63·8; H, 6·9; N, 19·5. $C_{19}H_{26}N_5Cl$ requires C, 63·4; H, 7·3; N, 19·5%). Yield, 3·8 g.; 17%.

N-p-*Chlorophenyl*-N′-p-*β*-*diethylaminoethylaminophenylguanidine* (III, R = Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—A solution of (IV, R = Cl) (11·8 g.) and *N*-*β*-diethylamino-*p*-phenylenediamine (16·4 g., 1 mol.) in ethyl alcohol (55 c.c.) containing hydrogen chloride (2·85 g., 2 mols.) was refluxed for 24 hours. The solution was then evaporated and the residue was triturated with a slight excess of 5% aqueous ammonia. The resulting gum was washed by stirring with water and dried. Repeated extraction with light petroleum (b. p. 40—60°) afforded the *guanidine* which was once recrystallised from light petroleum; colourless plates, m. p. 102—103° (Found: C, 63·5; H, 7·5; N, 19·0%). Yield, 5 g.; 18%.

N-*δ*-*Diethylamino*-*α*-*methyl*-n-*butyl*-m-*phenylenediamine* (V, R = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).—*m*-Nitroaniline (50 g.), 5-diethylamino-*n*-pentan-2-one diethyl ketal (88 g.), and ammonium chloride (0·05 g.) were heated together for 2 hours, initially at 170° and later at 210°. The excess of ketal was removed under reduced pressure and the residual anil was dissolved in alcohol (200 c.c.) and hydrogenated (Adams's catalyst, 0·2 g.) at 60° and 100 atmospheres during 3 hours. The filtered solution was evaporated and the residue refluxed with 15% hydrochloric acid (400 c.c.) for ½ hour. The cold solution was basified (sodium hydroxide) and extracted with ether, and the dried extract was distilled. The *amine* was obtained as a colourless oil, b. p. 168°/0·01 mm. (Found: C, 72·1; H, 11·1; N, 17·0. $C_{15}H_{27}N_3$ requires C, 72·3; H, 10·8; N, 16·9%). Yield, 50 g.; 55%.

N-*δ*-*Diethylamino*-*α*-*methyl*-n-*butyl*-p-*phenylenediamine* (VI, R = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$) was similarly prepared, except that the temperature during anil formation was not raised above 180°, since a higher temperature caused spontaneous decomposition. This *amine*, a colourless oil, had b. p. 174°/0·05 mm. (Found: C, 71·9; H, 10·7; N, 16·9%). Yield, 20 g.; 23%.

p-*Methoxyphenylcyanamide* (IV, R = OMe).—*p*-Methoxyphenylthiourea (30 g.), potassium hydroxide (43 g.), lead acetate (85 g.), and water (430 c.c.) were stirred during heating on a steam-bath for 15 minutes. The lead sulphide was then collected, and the filtrate acidified with 10% acetic acid and cooled. The crude product was filtered off, dissolved in 5% sodium hydroxide (150 c.c.), and cautiously reprecipitated by the addition of 5% acetic acid. Careful neutralisation resulted in the almost complete separation of a pale yellow amorphous material (*ca.* 1 g.) which was collected; acidification of the filtrate then caused the required product to separate in short needles. A second similar purification gave the *cyanamide* as colourless needles, m. p. 86—87° (Found: C, 64·8; H, 5·6. $C_8H_8ON_2$ requires C, 64·8; H, 5·4%): 10 g., 40%.

N-p-*Methoxyphenyl*-N′-m-*nitrophenylguanidine*.—*p*-Methoxyphenylcyanamide (7 g.) and *m*-nitroaniline hydrochloride (8·5 g., 1 mol.) were dissolved in alcohol (35 c.c.) and heated under reflux for 24 hours. The whole was then poured into 2% acetic acid (1 l.) and filtered. The filtrate was basified (sodium hydroxide) and the crude product collected. Two recrystallisations from 50% aqueous alcohol gave the pure *guanidine*, orange-red needles, m. p. 142° (Found: C, 58·3; H, 5·2; N, 19·6. $C_{14}H_{14}O_3N_4$ requires C, 58·7; H, 4·9; N, 19·6%): 8 g., 55%. The hydrochloride formed colourless needles, m. p. 128—136° (Found: C, 52·5; H, 4·6; N, 17·2. $C_{14}H_{14}O_3N_4$,HCl requires C, 52·1; H, 4·7; N, 17·4%).

N-p-*Methoxyphenyl*-N′-m-*aminophenylguanidine Hydrochloride* (II, R = OMe, R′ = H).—A solution of the above hydrochloride (8 g.) in alcohol (200 c.c.) was hydrogenated (Adams's catalyst, 0·2 g.) at room temperature and atmospheric pressure. The filtered solution was evaporated to *ca.* 50 c.c. and, on cooling, the *amino-guanidine hydrochloride* crystallised. Recrystallisation from alcohol gave small crystals, m. p. 212° (Found: C, 57·8; H, 6·0; N, 20·1. $C_{14}H_{16}ON_4$,HCl requires C, 57·4; H, 5·9; N, 20·05%). Yield, 5 g.; 70%.

N-p-*Methoxyphenyl*-N′-p-*β*-*diethylaminoethylaminophenylguanidine* (III, R = OMe, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—*p*-Methoxyphenylcyanamide (7·5 g.) and *N*-*β*-diethylaminoethyl-*p*-phenylenediamine

(10·5 g.) were dissolved together in ethyl alcohol (35 c.c.) containing hydrogen chloride (2·9 g.) and refluxed for 36 hours. Evaporation followed by trituration of the residue with 5% aqueous ammonia gave a brown gum which was washed and dried. Repeated extraction with hot light petroleum (b. p. 40—60°) afforded, on cooling, a pale brown gum (1 g.). This was shaken with ether (20 c.c.), the ethereal solution evaporated, and the residue re-extracted with hot light petroleum. On cooling, the *guanidine* separated as a pale brown gum which was almost pure (Found : C, 68·3; H, 8·7; N, 19·1. $C_{20}H_{29}ON_5$ requires C, 67·6; H, 8·2; N, 19·7%). Yield, 0·7 g.; 4%. Neither the base nor any salts could be obtained crystalline.

This research was carried out on behalf of the Medical Research Council under a wartime collaborative agreement on antimalarial research between the Medical Research Council and Imperial Chemical Industries Ltd. We are greatly indebted to the Council for grants (F. T. N., J. W. G. P.) and to Imperial Chemical Industries Ltd., both for materials and for carrying out the antimalarial tests.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 30th,* 1946.]