2. *New Potential Chemotherapeutic Agents. Part III. Derivatives of Diphenylamine and of αα-Diphenylmethylamine.*

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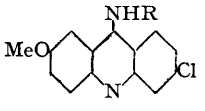
The existence in mepacrine (I, R = $CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$) of the diphenylamine and αα-diphenylmethylamine ring-systems suggested that similarly substituted derivatives of these more accessible amines might also possess antimalarial properties. Compounds of the type (II, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$) and (III, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$), including certain pyrimidine analogues, *e.g.* (VI, R = $NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$), were therefore synthesised, but neither series has afforded any substances of chemotherapeutic interest.

THE evolution of synthetic antimalarial agents was the outcome of a series of largely empirical investigations originating with the work of Guttmann and Ehrlich (*Berlin klin. Woch.*, 1891, **28**, 953). Their discovery of the antimalarial properties of methylene blue was later followed by the observation that more effective compounds were obtainable by replacing the normal substituents of the dyestuff with certain *basic* alkyl groups (Schulemann, Schönhöfer and Wingler, *Klin. Woch.*, 1932, **11**, 381). With the recognition of the importance of the amino-alkylamine side-chain as a constituent of antimalarial drugs, further developments were chiefly concerned with variations of the heterocyclic nucleus, and the discovery of pamaquin (plasmoquin) was based on the knowledge that the naturally occurring antimalarials are quinoline derivatives. Finally, in seeking a series of less toxic character, Mauss and Mietzsch (*ibid.*, 1933, **12**, 1276) found in the acridine derivative, mepacrine hydrochloride (atebrin), (I, R = $CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2,2HCl$), the most effective suppressive and prophylactic agent yet described.

Although the researches on mepacrine have led to the preparation of numerous derivatives of acridine

little attention has been given to the investigation of similarly substituted compounds of a somewhat simplified structure. In view of the many instances now known in which similar pharmacological properties persist throughout a series of compounds of comparatively superficial structural resemblance, it seemed of interest to examine certain of these mepacrine analogues. The nucleus (I) embodies the ring-systems of two relatively



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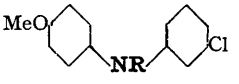

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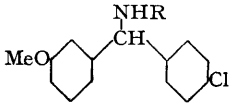

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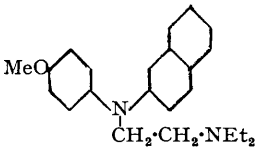

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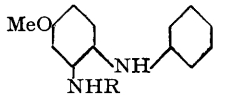

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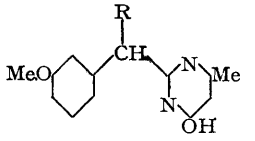

(VI.)

simple amines, *viz.*, diphenylamine and αα-diphenylmethylamine, and their derivatives, (II) and (III), in which R denotes the customary basic side-chain, are structurally analogous to mepacrine. Experiments were therefore undertaken to synthesise representative examples of these types. As in Parts I and II, instead of the normal mepacrine side-chain, we have employed the basic substituents $Et_2N{\cdot}CH_2{\cdot}CH_2{-}$ and $Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{-}$ on account of the greater accessibility of the appropriate alkylating agents.

The alkylation of diphenylamines, a necessary step in the preparation of the series represented by (II, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$), is usually effected by the action of alkyl halides on their *N*-sodio compounds (Titherley, *J.*, 1897, **71,** 465). Preliminary experiments on the preparation of *N*-β-diethylaminoethyldiphenylamine indicated that it is probably more convenient to alkylate the magnesium salt obtained from the diphenylamine and methylmagnesium iodide (cf. Oddo, *Gazzetta*, 1911, **41,** 255), and the synthesis of N-β-*diethylaminoethyl*-4-*methoxydiphenylamine* by both methods confirmed this observation. The preparation of 4-methoxydiphenylamine by the usual Ullmann method (Wieland and Wecker, *Ber.*, 1910, **43,** 708) gave a cleaner product when the monomethylnaphthalenes replaced nitrobenzene as solvent, possibly because of the oxidising properties of the latter in presence of the alkali.

The substituted diphenylamine of the required orientation (II, R = $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$) was prepared from *m*-chloronitrobenzene, which was hydrogenated in the presence of Raney nickel to the *m*-chloroaminobenzene, characterised by the p-*toluenesulphonamide*. This amine was used as a source of *m*-chloroiodobenzene which was condensed with acetyl-*p*-anisidine, and the resulting *N*-acetyldiphenylamine was hydrolysed without isolation to 3-*chloro*-4′-*methoxydiphenylamine* (II, R = H). Alkylation through the amine magnesium iodide afforded the *N*-β-diethylaminoethyl compound (II, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$) which gave a crystalline *oxalate* and *hydrochloride*. A somewhat similar compound of higher molecular weight, (IV), was prepared from 4-methoxyphenylnaphthylamine and β-chloroethyldiethylamine and was characterised by its *hydrochloride*.

2-*Nitro*-4-*methoxydiphenylamine* was also prepared by the Ullmann reaction for the synthesis of (V, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$), in which the substituents have the pamaquin orientation. It was necessary in this preparation to use *N*-acetyl-3-nitroanisidine, bromobenzene and activated copper; the method which Kehrmann and Havas (*Ber.*, 1913, **46,** 341) employed for 2-nitrodiphenylamine failed when applied to 4-bromo-3-nitroanisole and acetanilide, the mesomeric effect of the methoxyl on the bromine atom opposing that of the activating *o*-nitro group. Reduction of the nitrodiphenylamine in the presence of Raney nickel gave the readily oxidisable 2-*amino*-4-*methoxydiphenylamine* (V, R = H), but this could not be made to react with β-chloroethyldiethylamine under the usual conditions. An attempt to alkylate the 2-*N*-sodio compound after acetylation of the reactive secondary nitrogen atom gave 5-*methoxy*-1-*phenyl*-2-*methylbenziminazole* as the sole product. When the 2-p-*toluenesulphonyl* derivative (V, R = $p{\cdot}SO_2{\cdot}C_6H_4{\cdot}Me$) was alkylated with γ-chloropropyldiethylamine in presence of sodamide, 2-p-*toluensulphon*-(γ-*diethylaminopropyl*)-*amido*-4-*methoxydiphenylamine* was obtained as a crystalline solid. This appeared to resist the action of sulphuric acid, and when the protecting group was removed by sodium in liquid ammonia, admission of air so rapidly oxidised the product that its isolation proved impracticable.

The synthesis of (III, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$) was modelled on that of the simple N-β-*diethylaminoethyl*-αα-*diphenylmethylamine*, $Ph_2CH{\cdot}NH(CH_2)_2{\cdot}NEt_2$, which was obtained by alkylation of αα-diphenylmethylamine or of its magnesium derivative, $Ph_2CH{\cdot}NHMgI$, with β-chloroethyldiethylamine. αα-Diphenylmethylamines are conveniently prepared from the appropriate benzophenones by heating with ammonium formate (Leuckart and Bach, *Ber.*, 1886, **19,** 2129), the resulting *N*-formyl derivatives being hydrolysed with acid. The chloromethoxybenzophenone of the required orientation was obtained from 4-chloro-3′-nitrobenzophenone which was reduced by stannous chloride in alcoholic hydrochloric acid to the 3-*amino* compound, and thence converted by diazotisation and heating to 4-*chloro*-3′-*hydroxybenzophenone*. Methylation to the *methoxybenzophenone* was achieved with either methyl sulphate and sodium methoxide or methyl iodide and potassium carbonate in methanol. Application of the Leuckart reaction, using the modified conditions of Ingersoll *et al.* (*J. Amer.*

Chem. Soc., 1936, **58**, 1809), gave **4-*chloro*-3'-*methoxy*-αα-*diphenylamine*** (III, R = H), and alkylation through the Grignard compound led to the amine (III, R = $CH_2 \cdot CH_2 \cdot NEt_2$). At the same time **N-β-*diethylaminoethyl*-4-*chloro*-4'-*methoxy*-*diphenylmethylamine*** was synthesised by similar methods, the required benzophenone being obtained by the action of *p*-chlorobenzoyl chloride on anisole (Peterson, *ibid.*, 1924, **46**, 339). The ***dihydrochloride*** was highly crystalline, but the corresponding salt of the homologous γ-diethylaminopropylamine, obtained from the purified ***dioxalate***, could not be obtained in a crystalline state.

Hydrochlorides of the foregoing amines were tested against trophozoite infections of (a) *P. relictum* in canaries, at the Molteno Institute, Cambridge, and/or (b) *P. gallinaceum* in chicks, at the National Institute for Medical Research, London, but with the doubtful exception of (III, R = $CH_2 \cdot CH_2 \cdot NEt_2$), they exerted no antimalarial action. A possible explanation for their failure was that, unlike their prototype, these new derivatives did not possess a heterocyclic nucleus, and this led us to consider the synthesis of analogues containing a heterocyclic radical in place of one of the aryl groups. Of several alternatives, the pyrimidine nucleus was selected, first, because of the relative ease with which the necessary intermediates can be prepared, and secondly, in view of the widespread occurrence of pyrimidines as constituents of living cells, the introduction of a pyrimidine ring was not likely to give rise to unduly toxic compounds. The preparation by Pinner (*Ber.*, 1891, **23**, 2948) of 4-hydroxy-2-(α-hydroxybenzyl)-6-methylpyrimidine, derived from mandelonitrile by condensation of the related amidine with ethyl acetoacetate, suggested a practicable route to the desired compounds. The crude cyanohydrin from *m*-methoxybenzaldehyde was rapidly transformed by the action of hydrogen chloride in ether–methanol into the methyl imino-ester ***hydrochloride***, and this with alcoholic ammonia was converted into the amidine ***hydrochloride***; the latter, by condensation with ethyl acetoacetate in alcoholic alkali, gave **4-*hydroxy*-2-(α-*hydroxy*-m-*methoxybenzyl*)-6-*methylpyrimidine*** (VI, R = OH). Replacement of the α-hydroxy group occurred on treatment with thionyl chloride in cold chloroform to give the corresponding ***α-chloro*** compound, a crystalline solid which reacted with α-diethylaminopropylamine forming the pyrimidine (VI, R = $NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$). This was identified by its ***dipicrate*** and ***dipicrolonate***, but the amine hydrochloride obtained from the latter by treatment with the aqueous acid could not be obtained crystalline.

From *o*-chlorobenzaldehyde the analogous series of *o*-chloro compounds has been similarly prepared, and the final product, **4-*hydroxy*-2-[α-(γ-*diethylaminopropyl*)*amino*-o-*chlorobenzyl*]-6-*methylpyrimidine*** characterised by its crystalline ***dipicrolonate*** and deliquescent ***hydrochloride***. Neither the methoxy- nor chloro-γ-diethylaminopropylaminopyrimidine hydrochlorides showed any activity against trophozoite infections of *P. gallinaceum* in chicks.

Experimental.

N-β-*Diethylaminoethyldiphenylamine*.—A solution prepared from magnesium (1 g., *ca.* 1·5 mol.), methyl iodide (6·2 g.) and ether (20 c.c.) was slowly treated in a hydrogen atmosphere with diphenylamine (5·2 g., 1 mol.) in benzene (100 c.c.) and refluxed for 30 minutes. To the boiling liquid, β-chloroethyldiethylamine (5·9 g., 1·25 mol.) dissolved in benzene (10 c.c.) was then added in 3 portions during 1 hour, and after a further 1½ hours the mixture was cooled and shaken with aqueous ammonium chloride. The 10% hydrochloric acid extract of the benzene layer was made alkaline and the liberated amine isolated by means of ether. *N*-β-Diethylaminoethyldiphenylamine, a straw-coloured oil (2 g., 31%), b. p. 145°/0·15 mm., gave a *picrate* which separated from alcohol in needles, m. p. 142—145° (Found: C, 57·6; H, 5·5. $C_{18}H_{24}N_2,C_6H_3O_7N_3$ requires C, 57·9; H, 5·4%).

N-β-*Diethylaminoethyl*-4-*methoxydiphenylamine*.—Only poor yields of discoloured product were obtained in the preparation of 4-methoxydiphenylamine from acet-*p*-anisidide, bromobenzene, potassium carbonate and copper-bronze in refluxing nitrobenzene (Wieland and Wecker, *loc. cit.*), but with α- and β-methylnaphthalenes as solvent, the methoxydiphenylamine was obtained after distillation at 160°/0·4 mm. as an orange solid (yield 75%), m. p. 105°.

The sodium salt obtained by cautiously heating a powdered mixture of 4-methoxydiphenylamine (10 g., 1 mol.) and sodamide (5 g., 2·5 mol.), finally to 200° (Titherley, *loc. cit.*), was covered with benzene (150 c.c.), and to the refluxing liquid a solution of β-chloroethyldiethylamine (8 g., *ca.* 1·2 mol.) in benzene (20 c.c.) was added. After 4 hours' heating, in a hydrogen atmosphere, the base extracted from the solvent by 10% hydrochloric acid was distilled. The *N*-alkyldiphenylamine, a pale orange oil (2·5 g., 16·7%) which darkened in air, had b. p. 180°/0·15 mm., and gave a *picrolonate* which separated from alcohol in yellow needles, m. p. 120—121° (Found: C, 61·5; H, 6·2. $C_{19}H_{26}ON_2,C_{10}H_8O_5N_4$ requires C, 61·9: H, 6·1%).

The reagent prepared from magnesium (1·6 g.), methyl iodide and ether was treated with 4-methoxydiphenylamine (13 g.) dissolved in benzene (110 c.c.) and heated for 2½ hours with β-chloroethyldiethylamine (13 g.). When the product was worked up as in the case of *N*-diethylaminoethyldiphenylamine, the 4-methoxy analogue, b. p. 145—155°/0·07 mm., was obtained and gave a *picrate* crystallising in orange prisms, m. p. 139° (Found: C, 56·5; H, 5·5. $C_{19}H_{26}ON_2,C_6H_3O_7N_3$ requires C, 56·8; H, 5·5%). The purified salt dissolved in a little alcohol was treated with concentrated hydrochloric acid, and when the picric acid had been removed with ether, the amine was recovered by addition of alkali and distillation. From a dry ethereal solution of the product hydrogen chloride precipitated the ***hydrochloride*** (2·5 g.) which crystallised from alcohol in colourless needles, m. p. 130° (Found: C, 68·5; H, 7·9. $C_{19}H_{26}ON_2,HCl$ requires C, 68·2; H, 8·1%).

m*-Chloroaniline.**—*m*-Chloronitrobenzene (30 g.) dissolved in ethanol (100 c.c.) was rapidly reduced in presence of Raney nickel (2·5 g.) at room temperature and 2—3 atm., giving the chloroaniline (24 g., 98·5%), b. p. 113°/18 mm. p-Toluenesulphon*-3-*chloroanilide*** crystallised from alcohol in colourless needles, m. p. 134° (Found: C, 55·5; H, 4·4. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·3%).

3-*Chloro*-4'-*methoxydiphenylamine* (II, R = H).—A mixture of acet-*p*-anisidide (30 g., 1 mol.), *m*-chloroiodobenzene (69 g., 1·6 mol.), potassium carbonate (14 g., 1·1 mol.) and copper-bronze (0·8 g.) was heated in refluxing nitrobenzene (160 c.c.) for 32 hours with exclusion of air. Steam-distillation followed by heating the residue with hydrochloric acid (12%, 120 c.c.) gave a product which was dissolved in ether and twice passed through a charcoal column. Distillation gave the chloromethoxydiphenylamine, b. p. 190°/0·5 mm., which after two crystallisations from ethanol formed yellow prisms (10 g., 23·6%), m. p. 92°. It was characterised by the p-***toluenesulphonamide***, colourless needles from alcohol, m. p. 106·5° (Found: C, 61·6; H, 4·8. $C_{20}H_{18}O_3NClS$ requires C, 61·9; H, 4·7%).

N-β-*Diethylaminoethyl*-3-*chloro*-4'-*methoxydiphenylamine* (II, R = $CH_2 \cdot CH_2 \cdot NEt_2$).—The magnesium salt prepared from methylmagnesium iodide and 3-chloro-4'-methoxydiphenylamine (10 g.) was alkylated with β-chloroethyldiethylamine (8·5 g.) in benzene (110 c.c.) and the product isolated as before. The fraction, b. p. 185—194°/0·2 mm. (4·5 g.,

31%), gave with saturated alcoholic oxalic acid the *oxalate* of *N*-β-diethylaminoethyl-3-chloro-4′-methoxydiphenylamine which crystallised from ethyl acetate in colourless needles, m. p. 139° (Found: C, 60·1; H, 6·4. $C_{19}H_{25}ON_2Cl,H_2C_2O_4$ requires C, 59·7; H, 6·4%). The amine *hydrochloride* was a microcrystalline powder, m. p. 159—160° (Found: Cl, 19·0. $C_{19}H_{25}ON_2Cl,HCl$ requires Cl, 19·3%).

N-β-*Diethylaminoethyl*-4-*methoxyphenyl*-β-*naphthylamine* (IV).—The greenish precipitate obtained on adding 4-methoxyphenyl-β-naphthylamine (10 g.) in dry xylene (120 c.c.) to ethereal methylmagnesium iodide in a hydrogen atmosphere was heated at 100° for 1½ hours with β-chloroethyldiethylamine (9·1 g.) and cuprous bromide (1·7 g.). Isolation in the usual way gave a base distilling at 210—215°/0·15 mm. as a pale orange viscous oil (4·1 g., 29%) easily oxidised in air, giving in ether solution a stable *hydrochloride* which crystallised from ethyl acetate–ether in colourless fine needles, m. p. 184·5° (Found: C, 71·6; H, 7·6. $C_{23}H_{28}ON_2,HCl$ requires C, 71·9; H, 7·6%).

2-*Nitro*-4-*methoxydiphenylamine*.—A mixture of 3-nitro-*p*-anisidine (50 g.), bromobenzene (270 c.c.) and potassium carbonate (21 g.) containing potassium iodide (1·5 g.) and freshly reduced copper (0·9 g.) (*Organic Syntheses*, 1936, **14**, 67) was heated under reflux in a metal-bath at 180°. Further quantities of the copper catalyst (1—2 g.) were added at intervals until the reaction was complete (16 hours); the product was filtered and the excess bromobenzene removed in steam. The residue was taken up in ether, and after washing with 2N hydrochloric acid the solution was evaporated. The product solidified on trituration with ligroin–alcohol, and recrystallisation from ether gave 2-*nitro*-4-*methoxydiphenylamine* (45·8 g., 62%) in shining red oblong plates, m. p. 48° (Found: C, 63·7; H, 4·8. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9%).

2-*Amino*-4-*methoxydiphenylamine* (V, R = H).—The nitro compound (38 g.) dissolved in alcohol (40 c.c.) was hydrogenated in the presence of Raney nickel under pressure at 50—60°. 2-*Amino*-4-*methoxydiphenylamine* separated on cooling, but owing to its speedy oxidation it was more conveniently purified by distillation; the pale yellow product (21 g., 63%), b. p. 155°/0·04 mm., had m. p. 98° (Found: C, 73·1; H, 6·7. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5%).

5-*Methoxy*-1-*phenyl*-2-*methylbenziminazole*.—After heating with β-chloroethyldiethylamine and sodium acetate in alcohol under pressure at 130—135° for 16 hours, 2-amino-4-methoxydiphenylamine was recovered unchanged. The aminodiphenylamine (5 g.) was then heated in nitrogen with sodamide (1·1 g.) and toluene (110 c.c.) at 100° (4 hours), and afterwards with acetyl chloride (2·4 g.). β-Chloroethyldiethylamine (32 g.) and sodamide (1·4 g.) were added and after 1 hour at room temperature, the mixture was heated at 100° for 4 hours and finally under reflux (½ hour). When this was cold, water was added and the toluene solution extracted with hydrochloric acid (0·02 N). The base, thus isolated, was refluxed with hydrochloric acid (12%), the solution made alkaline and extracted with ether to give a yellow oil, which distilled at 0·07 mm. (bath temp. 200°) and then solidified. Crystallisation from ligroin gave 5-*methoxy*-1-*phenyl*-2-*methylbenziminazole* (0·8 g.) as colourless slender needles, m. p. 103—105°, showing no tendency to discolour in air (Found: C,75·4; H, 6·0. $C_{15}H_{14}ON_2$ requires C, 75·6; H, 5·9%).

2-p-*Toluenesulphon*-(γ-*diethylaminopropyl*)*amido*-4-*methoxydiphenylamine*.—A mixture of 2-amino-4-methoxydiphenylamine (5·7 g.), *p*-toluenesulphonyl chloride (5 g.) and pyridine heated at 100° for 3 hours and then digested with dilute acid, gave 2-p-*toluenesulphonamido*-4-*methoxydiphenylamine* (V, R = *p*-$SO_2{\cdot}C_6H_4{\cdot}Me$) (8·5 g.) crystallising from benzene–ligroin in pale pink stout prisms, m. p. 148° (Found: C, 65·3; H, 5·9; OMe, 7·7. $C_{20}H_{20}O_3N_2S$ requires C, 65·3; H, 5·4; OMe, 8·4%).

A solution of sodium (0·33 g.) in alcohol (17 c.c.) was treated with the sulphonamide (1·74 g.) and then with γ-chloropropyldiethylamine hydrochloride (1·76 g.). After refluxing for 2 hours, the filtered solution was evaporated and the residue crystallised from ligroin. The product (1·93 g., 84%), m. p. 84°, being inclined to oxidise, it was characterised as an *oxalate* which separated from alcohol–ether in long colourless prisms, m. p. 122° (Found: N, 7·2; S, 5·3. $C_{27}H_{35}O_3N_3S,C_2H_2O_4$ requires N, 7·3; S, 5·6%).

When dissolved in sulphuric acid (90%, 14 c.c.) and left at 0° for 18 hours, the aminosulphonamide (1·7 g.) was recovered unchanged. A solution of the compound (1·6 g.) in ether (20 c.c.) was dissolved in liquid ammonia to which sodium was added until a permanent blue colour appeared. Ammonium chloride was then used to remove excess sodium, and the ammonia allowed to evaporate. As this occurred, the product blackened in contact with the air. Attempts were made to isolate the amine by addition of water and precipitation of a hydrochloride from the dried ethereal extract, but the crystalline solid could not be obtained analytically pure.

N-β-*Diethylaminoethyl*-αα-*diphenylmethylamine*.—A solution of αα-diphenylmethylamine (44 g., 2 mol.) and β-chloroethyldiethylamine hydrochloride (24 g., *ca.* 1 mol.) in ethanol (50 c.c.) was heated in an autoclave at 110° for 6 hours. After evaporating the solvent and making alkaline, the product was collected in ether and distilled, the alkylated diphenylmethylamine, b. p. 200—210°/20 mm., giving a *dihydrochloride* (12 g., 23%) on treatment with concentrated hydrochloric acid. The salt crystallised from ethanol in colourless prisms, m. p. 244—245° (Found: C, 64·5; H, 7·7. $C_{19}H_{26}N_2,2HCl$ requires C, 64·2; H, 7·9%). The amine (b. p. 110—115°/0·1 mm.) was also obtained in approximately the same yield (27·5%) by alkylation of the magnesium derivative of αα-diphenylmethylamine prepared from methylmagnesium iodide (1 mol.) in the manner described for the chloromethoxy analogue below.

4-*Chloro*-3′-*aminobenzophenone*.—A solution of 4-chloro-3′-nitrobenzophenone (27 g., 1 mol.) in the minimum amount of ethanol was mixed with saturated alcoholic hydrogen chloride (350 c.c.). Hydrated stannous chloride (75 g., 3·5 mol.) was added at 0°, and after 1 hour, when solid had separated, the mixture was heated to 100° for 1 hour, and finally evaporated under diminished pressure. Treatment with concentrated sodium hydroxide solution liberated an oil which, after isolation with ether, solidified. 4-*Chloro*-3′-*aminobenzophenone* (23 g., 96%) crystallised from ethyl acetate–ligroin in pale yellow needles, m. p. 115° (Found: C, 67·4; H, 4·5. $C_{13}H_{10}ONCl$ requires C, 67·5; H, 4·3%).

4-*Chloro*-3′-*hydroxybenzophenone*.—A solution of the chloroaminobenzophenone (5 g.) in water (30 c.c.) and sulphuric acid (8 c.c.) treated below 0° with sodium nitrite (1·5 g.) in water (10 c.c.) gave the sparingly soluble diazonium salt. The suspension was slowly added to boiling copper sulphate solution, and the resulting brown solid taken up in ether. From the ethereal solution extraction with aqueous sodium hydroxide removed the crude 4-*chloro*-3′-*hydroxybenzophenone* (4·2 g., 84%), m. p. *ca.* 148°, which after 2 crystallisations from benzene formed colourless needles, m. p. 154—155° (Found: C, 67·3; H, 4·0. $C_{13}H_9O_2Cl$ requires C, 67·1; H, 3·9%).

4-*Chloro*-3′-*methoxybenzophenone*.—Methylation of the chlorohydroxybenzophenone with methyl sulphate in aqueous alkali gave poor yields, and two other methods were used. (i) A solution of the phenol (4 g.) in methanol (60 c.c.) containing sodium (0·8 g.) was treated with methyl sulphate (9 g.) and refluxed for 2 hours. The addition of ether and water, after evaporation of the solvent, gave an ethereal extract from which aqueous alkali removed unchanged hydroxyketone (1·3 g.) leaving the methoxy compound (1·65 g., 57·5%), b. p. 140—145°/0·01 mm. The *ketoxime*, crystallising in slender needles from aqueous alcohol, had m. p. 138° (Found: C, 64·4; H, 4·7. $C_{14}H_{12}O_2NCl$ requires C, 64·2; H, 4·6%). (ii) A methanol solution (50 c.c.) of the hydroxy compound (4 g.) was refluxed with methyl iodide (15 g.) and potassium carbonate (15 g.) for 10 hours and then filtered and evaporated. Isolation as in method (i) gave 4-chloro-3′-methoxybenzophenone as an oil (2·8 g., 66%) which solidified after distillation, crystallising from ligroin in prisms, m. p. 38°, and which was identified by the oxime, m. p. 138°.

4-*Chloro*-3′-*methoxy*-αα-*diphenylmethylamine* (III, R = H).—To ammonium formate which had been heated at 165° for 1 hour, 4-chloro-3′-methoxybenzophenone (5·4 g.) was added, and the mixture heated at 180—190° for 4 hours The

viscous product was heated under reflux for an hour with water (60 c.c.) and concentrated hydrochloric acid (150 c.c.), and on cooling the diphenylmethylamine hydrochloride (4·5 g., 72·5%) separated. Crystallised from ethanol–*cyclo*hexane, it had m. p. 175°, and gave with alkali the free base, of which the *picrate* crystallised from *cyclo*hexane in fine yellow needles, m. p. 199° (Found: C, 50·5; H, 3·8. $C_{14}H_{14}ONCl,C_6H_3O_7N_3$ requires C, 50·4; H, 3·6%).

N-*β-Diethylaminoethyl-4-chloro-3′-methoxy-αα-diphenylmethylamine* (III, R = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—A solution of the Grignard reagent prepared from magnesium (0·29 g., 1 mol.) and methyl iodide (1·7 g.) in ether (120 c.c.), and containing 4-chloro-3′-methoxydiphenylmethylamine (3 g., 1 mol.) after standing for 3 hours was heated to boiling for ½ hour. Heating was continued for 2 hours with β-chloroethyldiethylamine (1·6 g., 1 mol.) and cuprous bromide (0·5 g.) and, after evaporation of the solvent, for 2 hours at 100°. The product was isolated by adding saturated aqueous ammonium chloride and dissolving the brown gummy solid in benzene, from which hydrochloric acid (15%) extracted the required amine. When precipitated with alkali and distilled, *N*-β-diethylaminoethyl-4-chloro-3′-methoxy-αα-diphenylmethylamine was a pale yellow syrup (1·92 g., 47%) giving a crystalline but highly deliquescent hydrochloride. Accordingly the *dipicrate* which crystallised from ethyl acetate in fine yellow needles, m. p. 182°, was prepared for analysis (Found: C, 48·0; H, 4·0. $C_{20}H_{27}ON_2Cl,2C_6H_3O_7N_3$ requires C, 47·7; H, 4·1%).

4-Chloro-4′-methoxy-αα-diphenylmethylamine.—The product obtained by heating 4-chloro-4′-methoxybenzophenone (23 g.) (Peterson, *loc. cit.*) with ammonium formate (33 g.) as described in the preparation of (III, R = H) was hydrolysed by boiling with hydrochloric acid (320 c.c. of 27%) for 1 hour. The amine *hydrochloride*, which separated in the cold, crystallised from hydrochloric acid in colourless needles (20 g., 87%), m. p. 234—235° (Found: C, 58·9; H, 5·3. $C_{14}H_{14}ONCl,HCl$ requires C, 59·2; H, 5·3%).

N-*β-Diethylaminoethyl-4-chloro-4′-methoxy-αα-diphenylmethylamine.*—The hydrochlorides of the foregoing diphenylmethylamine (5 g.) and of β-chloroethyldiethylamine (4·5 g.) were heated with fused sodium acetate (3·6 g.) in ethanol (25 c.c.) in a sealed tube for 17 hours at 120°. The base (2·7 g., 44%) isolated by distillation of the filtered solution had b. p. 175—180°/0·05 mm., and gave a *hydrochloride* crystallising from ethanol–ether in colourless tablets (1·6 g., 21%), m. p. 183° (Found: C, 54·8; H, 7·1; N, 7·0. $C_{20}H_{27}ON_2Cl,2HCl,H_2O$ requires C, 54·8; H, 7·1; N, 6·4%. Found after drying to constant weight: loss, 3·3; Cl, 25·0. $C_{20}H_{27}ON_2Cl,2HCl$ requires H_2O, 4·1; Cl, 25·4%).

N-*γ-Diethylaminopropyl-4-chloro-4′-methoxy-αα-diphenylmethylamine.*—Under the conditions of the preceding experiment, 4-chloro-4′-methoxydiphenylmethylamine reacted with γ-chloropropyldiethylamine to give the *N*-γ-diethylaminopropyl derivative (yield 79%), as a partly crystalline viscous mass, b. p. 180—185°/0·07 mm., characterised by a *dioxalate* crystallising from ethanol–ether in colourless needles, m. p. 142—145° (Found: C, 55·5; H, 6·4; N, 4·7. $C_{21}H_{29}ON_2Cl,2H_2C_2O_4$ requires C, 55·5; H, 6·1; N, 5·2%). The hydrochloride of the base obtained from the purified oxalate was an uncrystallisable syrup.

*Methyl α-Hydroxy-α-*m*-methoxyphenylacetiminate.*—*m*-Methoxybenzaldehyde (40 g.) was converted into the cyanohydrin by the standard method (cf. *Organic Syntheses*, 1926, **6**, 58), and its ethereal solution (*ca.* 200 c.c.) dried over potassium carbonate. Absolute methanol (7 g.) and dry hydrogen chloride (21 g.) were then added at −5°, and after 24 hours the crystalline *hydrochloride* (36 g.) was collected. The salt separated in colourless long thin prisms, m. p. 105° (efferv.) (Found: C, 51·8; H, 6·3; N, 6·1. $C_{10}H_{13}O_3N,HCl$ requires C, 51·8; H, 6·1; N, 6·1%).

*α-Hydroxy-α-*m*-methoxyphenylacetamidine.*—The imino-ester hydrochloride (36 g.) was added to a solution of anhydrous ammonia (25 g.) in methanol at −5° and left overnight. Concentrating the filtered liquid under reduced pressure to 75 c.c. and treating with ethyl acetate (150 c.c.) precipitated the amidine *hydrochloride* (27 g., 80%) which after recrystallisation from ethanol–ether formed colourless plates, m. p. 190° (Found: N, 13·1. $C_9H_{12}O_2N_2,HCl$ requires N, 12·9%).

*4-Hydroxy-2-(α-hydroxy-*m*-methoxybenzyl)-6-methylpyrimidine* (VI, R = OH).—The amidine hydrochloride (30 g.) and ethyl acetoacetate (18·2 g.) were dissolved in a solution of sodium hydroxide (11·2 g.) in water (20 c.c.) and ethanol (100 c.c.), and left at room temperature for 24 hours. Water (400 c.c.) was then added, the solution filtered and made slightly acid with hydrochloric acid. The precipitated solid (23 g., 68%) was collected and crystallised from water, from which it separated in colourless long thin prisms, m. p. 207°, very sparingly soluble in cold water and organic solvents (Found: C, 63·3; H, 5·8. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7%).

*2-(α-Chloro-*m*-methoxybenzyl)-4-hydroxy-6-methylpyrimidine* (VI, R = Cl).—A suspension of the pyrimidine (VI, R = OH) (17 g.) in chloroform (50 c.c.) at −10° was treated with thionyl chloride added in 15 minutes and then left at 0° for 12 hours. Evaporation of the clear solution yielded a pale yellow gum which gave a colourless solid (14·7 g., 81%). When recrystallised from a small volume of ethanol the *chloropyrimidine* was obtained as needles, m. p. 159—160° (Found: C, 58·9; H, 5·2; Cl, 13·0. $C_{13}H_{13}O_2N_2Cl$ requires C, 59·0; H, 4·9; Cl, 13·4%).

*4-Hydroxy-2-[α-(γ-diethylaminopropyl)amino-*m*-methoxybenzyl]-6-methylpyrimidine* (VI, R = $NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$).—The chloropyrimidine (VI, R = Cl) (5·8 g., 1 mol.) and γ-diethylaminopropylamine (5·7 g., 2 mol.) were heated in refluxing ethanol (50 c.c.) for 9 hours. The solvent was then evaporated, the residue treated with excess aqueous sodium carbonate and extracted with chloroform. The chloroform solution was shaken 3 times with aqueous sodium hydroxide (0·5N), the combined extracts strongly acidified, and unchanged chloropyrimidine (1·7 g.) removed by chloroform. The aqueous acid solution was then made alkaline with sodium carbonate and the liberated amine taken up in chloroform. Evaporation gave a dark amber gum (3·5 g., 64%) which yielded deliquescent products with hydrogen chloride and oxalic acid, but a crystalline *dipicrate* separated on mixing methanolic solutions of the base and picric acid. It crystallised from acetone–ether in minute yellow tablets, m. p. 170—171° (Found: C, 46·9; H, 4·8. $C_{20}H_{30}O_3N_4,2C_6H_3O_7N_3$ requires C, 47·1; H, 4·4). The sparingly soluble *dipicrolonate*, prepared in methanol–acetone and crystallised from *cyclo*hexanone–ether, consisted of minute needles, m. p. 215° (decomp.) (Found: C, 53·1; H, 5·2; N, 18·5. $C_{20}H_{30}O_2N_4,2C_{10}H_8O_5N_4,H_2O$ requires C, 53·3: H, 5·3; N, 19·0%).

*α-Hydroxy-α-*o*-chlorophenylacetamidine.*—The crude cyanohydrin of *o*-chlorobenzaldehyde (70 g.) dissolved in ether containing methanol and hydrogen chloride very rapidly deposited *methyl α-hydroxy-α-*o*-chlorophenylacetiminate hydrochloride* (88 g.) in colourless needles, m. p. 128° (Found: 45·7; H, 4·6. $C_9H_{10}O_2NCl,HCl$ requires C, 45·8; H, 4·7%). Alcoholic ammonia converted the salt into the amidine *hydrochloride* crystallising from ethanol–ethyl acetate in microscopic plates, m. p. 171° (Found: C, 43·1; H, 4·7. $C_8H_{10}ON_2Cl_2$ requires C, 43·4; H, 4·5%).

*4-Hydroxy-2-(α-chloro-*o*-chlorobenzyl)-6-methylpyrimidine.*—Condensation of the *o*-chlorophenacetamidine with ethyl acetoacetate in aqueous alcoholic alkali gave *4-hydroxy-2-(α-hydroxy-*o*-chlorobenzyl)-6-methylpyrimidine* (69%) which separated from water in colourless cubes, m. p. 195—196° (Found: C, 57·5; H, 4·5; N, 11·1. $C_{13}H_{11}O_2N_2Cl$ requires C, 57·5; H, 4·4; N, 11·2%). As with the pyrimidine (VI, R = OH), cold thionyl chloride gave the chloropyrimidine (97%), and the pure product crystallised from aqueous alcohol in long prisms, m. p. 197° (Found: C, 53·7; H, 3·9. $C_{12}H_{10}ON_2Cl_2$ requires C, 53·6; H, 3·7%).

*4-Hydroxy-2-[α-(γ-diethylaminopropyl)amino-*o*-chlorobenzyl]-6-methylpyrimidine.*—Alkylation of the foregoing pyrimidine with γ-diethylaminopropylamine was effected exactly as with its *m*-methoxy analogue, and gave a 65% yield of the crude amine. The salts of this product, *e.g.*, hydrochloride, sulphate, oxalate, picrate, styphnate, trinitrobenzoate and meconate, showed great reluctance to crystallise. Eventually the amine was characterised by a *dipicrolonate* crystallising from ethanol–ether in pale yellow leaflets, m. p. 197° (decomp.) (Found: C, 52·1; H, 5·0; Cl, 4·1. $C_{19}H_{27}ON_4Cl,2C_{10}H_8O_5N_4$ requires C, 52·5; H, 4·8; Cl, 4·0%). By decomposition of the purified picrolonate with hydro-

chloric acid the *trihydrochloride* was obtained. The product, a straw-coloured gum, was analysed after several precipitations from methanol–ethyl acetate (Found: C, 48·7; H, 6·4; N, 11·8. $C_{19}H_{27}ON_4Cl,3HCl$ requires C, 48·3; H, 6·4; N, 11·9%).

The diethylaminoalkylamino-quinoxalines and -benzcinnolines of Parts I and II (*J.*, 1945, 791, 824) also have been tested against *P. gallinaceum* infections in chicks, and with the exception of (V, R = $-CH_2\cdot CH_2\cdot NEt_2$) of Part I, against *P. relictum* in canaries. It is now possible to state that all are devoid of antimalarial activity.

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