168. *Synthetic Antimalarials. Part XVIII. 3-Dialkylaminoalkylaminodiphenylamines.*

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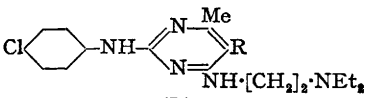
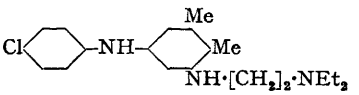
In order to determine whether the antimalarial activity of certain 2-anilino-4-dialkylaminoalkylaminopyrimidines of type (I) was determined primarily by their general structure, the corresponding compounds in which the pyrimidine ring has been replaced by a benzene ring, *i.e.*, diphenylamines of type (II), have been synthesised. The similar benzene analogues of the active 2-amino-4-dialkylaminoalkylaminopyrimidines of type (III) have also been synthesised.

All these benzene analogues proved to be devoid of antimalarial activity, however, and the activity of both the above types of pyrimidine compound must therefore be intimately associated either with the pyrimidine ring itself or with the tautomerism which this ring allows.

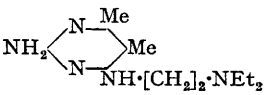
When this investigation was started, it was known that 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I, R = H) showed marked antimalarial activity against avian malaria; the corresponding *p*-methoxyanilino-compound showed lower activity, but the 5 : 6-dimethyl homologue (I, R = Me) an activity slightly greater than that of (I, R = H) (Curd and Rose, *J.*, 1945, **343**; Curd, Richardson, and Rose, *ibid.*, p. 378). Many other homologues, having similar 4-dialkylaminoalkylamino-substituents, also showed varying degrees of activity.



(I.)



(II.)



(III.)

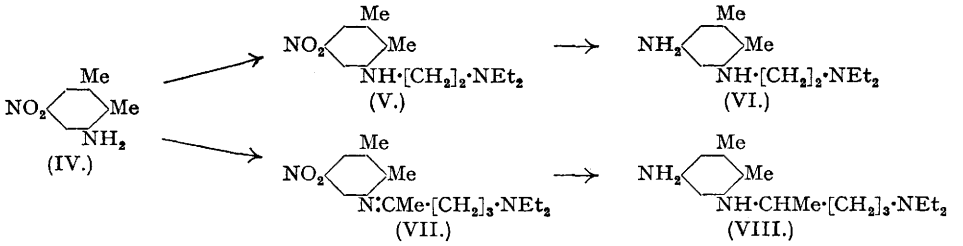
It had been suggested (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 157; Curd, Davis, and Rose, *J.*, 1946, 351) that these various anilino-pyrimidines might owe their antimalarial activity to their interference with some essential metabolic process involving riboflavin, due to the structural similarity which not only exists between riboflavin and the pyrimidines themselves, but might also exist between riboflavin and the most probable degradation products of these pyrimidines, for example, the corresponding 4-hydroxy-pyrimidines which could be formed by hydrolytic removal of the alkylamino-group from the drug. It was shown later by Madinaveitia (*Biochem. J.*, in the press) that the growth-inhibitory action of the above pyrimidines, as well as that of mepacrine and quinine, for *Lactobacillus casei* was actually antagonised by riboflavin.

It became of interest therefore to prepare diphenylamine compounds of type (II), which differed from compounds of type (I) only in that the pyrimidine ring of the latter had now been replaced by a benzene ring. If antimalarial activity is due primarily to a general structural similarity between riboflavin and the drug, compounds of type (II) should have an activity of the same order as that of their analogues of type (I); if, however, it is due primarily to a structural similarity between riboflavin and the main degradation products of the drug, then compounds of type (II), by virtue of their greater stability, might well prove inactive.

It should be noted, however, that a further factor enters here which might itself largely offset the result of any general structural similarity between the two classes of drugs. Pyrimidines of type (I) can clearly exist in several tautomeric forms (formulated in Part VIII, *J.*, 1946, 713), whereas in the benzene analogues of type (II) no such tautomerism can occur. It is noteworthy that a similar tautomerism can occur in mepacrine, and Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has suggested that the antimalarial activity of mepacrine is closely associated with this tautomerism.

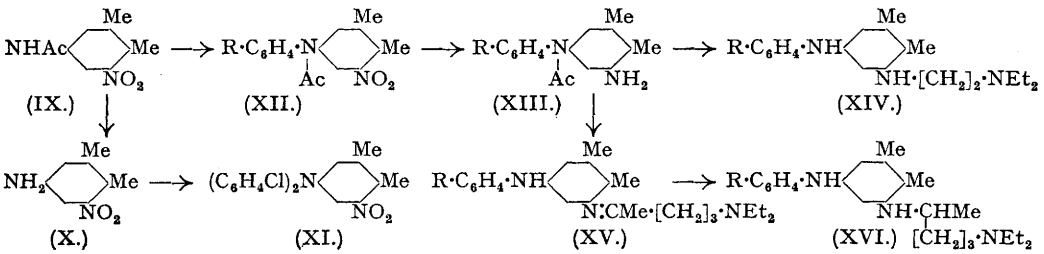
It is clear, however, that even if this structural-similarity factor is the underlying cause of the antimalarial activity of certain types of drug, it cannot apply to all types. For example, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1945, 357) have shown that 2-amino-4-β-diethylaminoethylamino-5 : 6-dimethylpyrimidine (III), which does not show this structural similarity with riboflavin, has an activity of approximately the same value as that of (I, R = Me). It is significant that Madinaveitia (*loc. cit.*) has found that the action of pyrimidines of type (III) is not antagonised by riboflavin. The additional object of the present investigation therefore was to prepare the benzene analogues of (III), in order to determine whether in this class of drug also the pyrimidine ring, with its accompanying tautomerism, was essential for antimalarial activity. The synthesis of these simpler monocyclic compounds is conveniently described before that of the more complex diphenylamine derivatives.

Condensation of 5-nitro-3-amino-*o*-xylene (IV) with β-diethylaminoethyl chloride furnished the *hydrochloride* of *5-nitro-3-β-diethylaminoethylamino-o-xylene* (V). Catalytic reduction followed by basification then gave *5-amino-3-β-diethylaminoethylamino-o-xylene* (VI). Many



attempts were then made to condense the amine (IV) with δ-bromo-α-diethylamino-*n*-pentane, $CHMeBr\cdot[CH_2]_3\cdot NEt_2$, in order ultimately to make (VIII), *i.e.*, the analogue of (VI) containing the basic side chain of mepacrine. All such attempts failed, however, in spite of a variety of conditions employed. Ultimately success was achieved by utilising the method developed by Ashley and Grove (*J.*, 1945, 768) for introducing this side chain into the aminopyridines. For this purpose, methyl 3-diethylamino-*n*-propyl ketone was converted into the diethyl ketal, $CMe(OEt)_2\cdot[CH_2]_3\cdot NEt_2$, which was readily condensed with the amine (IV) to give the anil (VII). This compound on catalytic reduction furnished *5-amino-3-δ-diethylamino-α-methyl-n-butylamino-o-xylene* (VIII).

For the preparation of the corresponding diphenylamines, 4-amino-*o*-xylene was acetylated and then nitrated to furnish 3-nitro-5-acetamido-*o*-xylene (IX) (cf. Crossley and Morrell, *J.*, 1911, **99**, 2350), hydrolysis then giving 3-nitro-5-amino-*o*-xylene (X). This amine was subjected to an Ullmann condensation with *p*-chloroiodobenzene in the presence of copper, but



in spite of a wide variety of conditions the main product isolated was always *4′ : 4″-dichloro-3-nitro-4 : 5-dimethyltriphenylamine* (XI), and it was clear that the initial production of the diphenylamine must have been a slow process compared with its conversion into the triphenylamine derivative. It should be noted that this preferential formation of a tertiary amine by the Ullmann reaction is rare but not unique : Wibaut and La Bastide (*Rec. Trav. chim.*, 1933, **52**, 493) have shown that 2-iodopyridine and 2-aminopyridine, when heated with potassium carbonate and copper, furnish the tri-2-pyridylamine.

This difficulty was overcome by employing the acetamido-compound (IX), which in the presence of copper bronze and potassium iodide readily combined with *p*-chloroiodobenzene to form *4′-chloro-3-nitro-N-aceto-4 : 5-dimethyldiphenylamide* (XII, R = *p*-Cl). The latter was then reduced to the *3-amino*-derivative (XIII, R = Cl) which, after condensation with β-2-diethylaminoethyl chloride and subsequent hydrolysis, furnished *4′-chloro-3-β-diethylaminoethylamino-4 : 5-dimethyldiphenylamine* (XIV, R = Cl).

When the acetyl group in (XIII) was removed, the resulting *amine* readily condensed with the above diethyl ketal to give the anil (XV, R = Cl), which on catalytic reduction gave *4′-chloro-3-(δ-diethylamino-α-methyl-n-butylamino)-4 : 5-dimethyldiphenylamine* (XVI, R = Cl).

Attempts were then made to prepare compounds of type (XIV) and (XVI) in which R = *p*-MeO, as this group has considerable significance in many antimalarial compounds. *p*-Bromoanisole was successfully condensed with the acetamido-compound (IX), but the acetodiphenylamide could not readily be isolated : consequently the crude product was hydrolysed and the pure *3-nitro-4′-methoxy-4 : 5-dimethyldiphenylamine* thus obtained. This compound was reduced to the *3-amino*-derivative, which condensed with β-diethylaminoethyl chloride to give *3-β-diethylaminoethylamino-4′-methoxy-4 : 5-dimethyldiphenylamine* (XIV,

R = MeO). The 3-amino-derivative also gave the anil (XV, R = MeO) which on hydrogenation furnished **3-δ-*diethylamino*-α-*methyl*-n-*butylamino*-4′-*methoxy*-4 : 5-*dimethyldiphenylamine*** (XVI, R = MeO). It should be noted that, whereas the constitution of the last compound is beyond doubt, that of (XIV, R = MeO) is not absolutely certain, since the ethyl chloride might conceivably condense with the secondary amino-group: the reactivity of the 3-amino-group is so very much greater, however, that this possibility can be ignored.

The two xylene derivatives (VI) and (VIII) and the four diphenylamine derivatives (XIV, R = Cl and MeO) and (XVI, R = Cl and MeO) have been tested against *P. gallinaceum* in chicks and found to be inactive not only against the blood forms but also prophylactically. It is clear, therefore, that the marked antimalarial activity of the two types of pyrimidine derivative (I) and (III) must be intimately associated either with the pyrimidine ring as such, or with the tautomerism which this ring allows, and that a superficial structural similarity with riboflavin which ignores this tautomerism, as in the diphenylamine derivatives, is insufficient to produce activity.

Experimental.

5-Nitro-3-amino-o-xylene (IV). This compound, prepared according to Noelting, Braun, and Thesmar (*Ber.*, 1901, **34**, 2242), was obtained in 35% yield as yellow needles, m. p. 111—112°.

5-Nitro-3-β-diethylaminoethylamino-o-xylene (V).—A solution of 5-nitro-3-amino-*o*-xylene (12 g.) in xylene (50 c.c.) was refluxed with 2-diethylaminoethyl chloride (45 c.c. of a 30% xylene solution; 1·1 mols.) for 4 hours. On cooling, the product, which had separated during the heating, solidified; it was collected, and recrystallised from ethyl alcohol–petrol (equal vols., 400 c.c.), furnishing pale yellow plates of the *hydrochloride* of the diethylamino-compound (V), m. p. 182—183° (Found: C, 55·8; H, 8·1. $C_{14}H_{23}O_2N_3$,HCl requires C, 55·7; H, 8·0%) (15 g., 70%). This compound formed a *picrate*, yellow needles from aqueous acetone containing a slight excess of picric acid, m. p. 164—165° (Found: C, 48·3; H, 5·5. $C_{14}H_{23}O_2N_3$,$C_6H_3O_7N_3$ requires C, 48·5; H, 5·3%).

5-Amino-3-β-diethylaminoethylamino-o-xylene (VI) (6048).—A solution of the above hydrochloride (9 g.) in 95% ethyl alcohol (150 c.c.) was rapidly hydrogenated in the presence of Adams's platinum catalyst (0·2 g.) at room temperature and pressure. The filtered solution was evaporated to dryness under reduced pressure, and the deliquescent crystalline residue dissolved in water and basified with aqueous sodium carbonate. The crude 5-*amino*-compound (VI) which separated was collected, dried, and crystallised from petrol (b. p. 40—60°); colourless needles, m. p. 75—76° (Found: C, 71·5; H, 10·4; N, 18·0. $C_{14}H_{25}N_3$ requires C, 71·5; H, 10·6; N, 17·9%).

When dry hydrogen chloride was passed into a solution of the amine in warm petrol, the deliquescent *trihydrochloride* rapidly crystallised, m. p. 170° (decomp.) (Found: N, 12·25. $C_{14}H_{25}N_3$,3HCl requires N, 12·2%). When the amine was refluxed with acetic acid–acetic anhydride, and the product poured into water and basified with sodium carbonate, the *diacetyl* derivative slowly crystallised; needles from very dilute aqueous alcohol, m. p. 140—141° (Found: C, 67·2; H, 9·4; N, 13·0. $C_{18}H_{29}O_2N_3$ requires C, 67·6; H, 9·1; N, 13·1%).

α-Diethylamino-n-pentan-δ-one Diethyl Ketal (cf. van Schelven, B.P. 388,087).—A solution of the amino-ketone (90 g.) in a slight excess of dilute hydrochloric acid was evaporated to dryness under reduced pressure, the residual hydrochloride dissolved in alcohol (100 c.c.) containing dry hydrogen chloride (1 g.), ethyl orthoformate (100 g., 1·2 mols.) added, and the mixture set aside for 8 days. The solution was then partly neutralised by addition of sodium ethoxide (from 12 g. of sodium), filtered from sodium chloride, and shaken with an excess of silver oxide. The filtered solution was fractionally distilled, and the ketal obtained as a colourless liquid, b. p. 116—118°/14 mm. (110 g., 85%).

5-Amino-3-(δ-diethylamino-α-methyl-n-butylamino)-o-xylene (VIII) (6049).—A mixture of the 5-nitro-compound (IV) (10 g.), the diethyl ketal (15·5 g., 1·1 mols.), and ammonium chloride (0·05 g.) was heated in a small distilling flask by means of a metal-bath. As the temperature reached 160° a brisk reaction set in with evolution of ethyl alcohol; when this subsided the temperature was increased to 210° and maintained there for 0·5 hour. The excess of ketal was removed under reduced pressure, and the residual anil dissolved in ethyl alcohol (100 c.c.) and hydrogenated in the presence of Adams's catalyst (0·2 g.) at 60° under a pressure of 90 atm., the almost theoretical absorption of hydrogen (4 mols.) taking 4 hours. The alcohol was then evaporated from the filtered solution, the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour to hydrolyse any traces of unchanged anil, and the solution cooled, basified with sodium carbonate, and extracted with ether, dried, and distilled. A small initial fraction of 3 : 5-diamino-*o*-xylene, b. p. 130°/0·05 mm., was followed by the main fraction, b. p. 170—175°/0·05 mm. This on redistillation gave the *amine* (VIII) as a pale brown syrup, b. p. 172—174°/0·01 mm. (Found: C, 73·3; H, 11·6; N, 15·3. $C_{17}H_{31}N_3$ requires C, 73·6; H, 11·2; N, 15·2%). The amine slowly darkens on exposure to light. No crystalline salts could be obtained; those prepared were all intractable gums which rapidly darkened when exposed to light.

4-Acetamido-o-xylene.—A solution of 4-amino-*o*-xylene (50 g.) in cold acetic acid (50 c.c.) was diluted with water (200 c.c.) and continuously agitated whilst acetic anhydride (50 g., 1·1 mols.) was slowly added. The acetamido-compound readily crystallised and, after the product had been poured into water (2 l.), was collected, washed and dried; m. p. 94—95° (65 g., 97%). Jacobsen (*Ber.*, 1884, **17**, 161) acetylated the amine both with acetic acid alone and with acetic acid–acetyl chloride; we find that the use of acetic acid–acetic anhydride gives a syrupy product containing much diacetyl derivative.

3-Nitro-5-acetamido-o-xylene (IX).—Crossley and Morrell (*loc. cit.*) give no detailed directions for this preparation. The previous compound (100 g.) was added with stirring to concentrated sulphuric acid (500 c.c.) maintained at − 10°, and the resulting solution continuously stirred and kept below − 7° whilst a solution of nitric acid (40 c.c., *d* 1·42, 1·05 mols.) in concentrated sulphuric acid (100 c.c.) was

slowly added. The product was poured on crushed ice (*ca.* 10 kg.), and the solid nitro-compound collected, washed with water, and dried. Recrystallisation from alcohol gave colourless needles, m. p. 207—208° (Found: C, 58·0; H, 6·1. Calc. for $C_{10}H_{12}O_3N_2$: C, 57·7; H, 5·8%).

3-*Nitro*-5-*amino*-o-*xylene* (X).—The acetyl compound was refluxed with 70% sulphuric acid (5 parts) for 30 minutes, and the solution poured on ice and made alkaline with ammonia. The precipitated 5-amino-compound, collected and recrystallised from aqueous alcohol, gave deep orange needles, m. p. 74—75° (Found: C, 57·8; H, 5·9. Calc. for $C_8H_{10}O_2N_2$: C, 57·9; H, 6·0%). This compound has previously been prepared only by the reduction of the 3 : 5-dinitro-derivative (Noelting *et al.*, *loc. cit.*).

4′ : 4″-*Dichloro*-3-*nitro*-4 : 5-*dimethyltriphenylamine* (XI).—A mixture of 3-nitro-5-amino-*o*-xylene (X) (10·5 g.), *p*-chloroiodobenzene (16 g., 1·1 mols.), anhydrous potassium carbonate (5 g., 1·2 mols.), copper powder (0·2 g.), potassium iodide (0·05 g.), and dry nitrobenzene (50 c.c.) was gently refluxed with occasional shaking for 7 hours. The product was steam-distilled to remove nitrobenzene and *p*-chloroiodobenzene, and the tarry residue dried and extracted (Soxhlet) with petrol (b. p. 40—60°; 250 c.c.). The extract on cooling deposited a reddish-yellow solid, which on crystallisation from alcohol furnished the *triphenylamine* (XI), pale yellow crystals, m. p. 146—147° (Found: N, 7·3; Cl, 18·1. $C_{20}H_{16}O_2N_2Cl_2$ requires N, 7·2; Cl, 18·3%) (5 g., 20%).

Aqueous dilution of the alcoholic mother-liquor precipitated a red solid, which, crystallised from methyl alcohol, furnished 4′-chloro-3-nitro-4 : 5-dimethyldiphenylamine (see later); m. p. 120—121°. Similar dilution of the methyl-alcoholic mother-liquor gave unchanged (X) (1·5 g.).

4′-*Chloro*-3-*nitro*-N-*aceto*-4 : 5-*dimethyldiphenylamide* (XII, R = Cl).—A mixture of (IX) (30 g.), *p*-chloroiodobenzene (170 g.), anhydrous potassium carbonate (15 g.), copper powder (1 g.), and potassium iodide (0·5 g.) was heated with continuous stirring in a metal-bath at 240° for 4 hours. The cool product was poured into petrol (b. p. 60—80°, 1 l.), and the mixture boiled, filtered, and cooled. The *acetodiphenylamide* (XII, R = Cl) which separated was once recrystallised from petrol; pale yellow needles, m. p. 121—122° (Found: C, 60·7; H, 4·8; N, 8·9. $C_{16}H_{15}O_3N_2Cl$ requires C, 60·3; H, 4·7; N, 8·8%) (30 g., 70%).

4′-*Chloro*-3-*nitro*-4 : 5-*dimethyldiphenylamine*.—The previous compound was refluxed with 70% sulphuric acid (10 parts) for 30 minutes, and the solution cooled, poured into water, and basified with ammonia. The precipitated *diphenylamine* was collected and recrystallised from methyl alcohol; orange-red needles, m. p. 121—122° (Found: C, 61·2; H, 4·7; N, 10·3. $C_{14}H_{13}O_2N_2Cl$ requires C, 60·8; H, 4·7; N, 10·1%).

4′-*Chloro*-3-*amino*-N-*aceto*-4 : 5-*dimethyldiphenylamide* (XIII, R = Cl).—A solution of (XII, R = Cl) (15·5 g.) in alcohol (250 c.c.) was hydrogenated (Adams's catalyst, 0·2 g.) at 50° and 50 atm., theoretical absorption occurring in 3 hours. The filtered solution was evaporated under reduced pressure, and the crystalline residue extracted (Soxhlet) with petrol (b. p. 60—80°, 1 l.). The *acetamide* (XIII, R = Cl) separated from the extract as colourless crystals, m. p. 118—119° (Found: C, 66·4; H, 6·2. $C_{16}H_{17}ON_2Cl$ requires C, 66·5; H, 5·9%). When hydrogen chloride was passed into an ethereal solution of this amine, the *hydrochloride* readily crystallised, m. p. 210—212° (decomp.) (Found: C, 58·6; H, 5·7; N, 8·3. $C_{16}H_{17}ON_2Cl,HCl$ requires C, 59·0; H, 5·7; N, 8·6%). The amine also readily afforded a *picrate*, yellow needles from aqueous alcohol, m. p. 198—199° (decomp.) (Found: C, 51·2; H, 4·2. $C_{16}H_{17}ON_2Cl,C_6H_3O_7N_3$ requires C, 51·0; H, 3·9%).

When the amine was refluxed with dilute hydrochloric acid, the *hydrochloride* of 4′-*chloro*-3-*amino*-4 : 5-*dimethyldiphenylamine* (6050) separated during the heating in almost theoretical yield; pale pink needles from aqueous alcohol, m. p. 236—237° (decomp.) (Found: C, 59·5; H, 5·8; N, 9·8. $C_{14}H_{15}N_2Cl,HCl$ requires C, 59·3; H, 5·6; N, 9·9%). Addition of aqueous ammonia to a warm aqueous-alcoholic solution of the hydrochloride precipitated the free *amine*, colourless needles from petrol, m. p. 98—99° (Found: C, 67·6; H, 6·1; N, 11·4. $C_{14}H_{15}N_2Cl$ requires C, 68·1; H, 6·1; N, 11·3%).

When the acetyl derivative (XIII) was hydrolysed with 70% sulphuric acid and the resulting solution poured into water, the *sulphate monohydrate* separated; colourless needles from alcohol, m. p. 173—174° [Found: C, 55·1; H, 5·6; N, 9·2. $(C_{14}H_{15}N_2Cl)_2,H_2SO_4,H_2O$ requires C, 55·1; H, 5·9; N, 8·8%]. The yield, however, was now only 40%.

4′-*Chloro*-3-*β*-*diethylaminoethylamino*-4 : 5-*dimethyldiphenylamine* (XIV, R = Cl) (6051).—A solution of (XIII, R = Cl) (6 g.) in xylene and a solution of *β*-diethylaminoethyl chloride (1·1 mols.) in xylene (14 c.c., of 30% concentration) were refluxed together for 12 hours, the condensation product separating meanwhile as a heavy oil. The cold mixture was then extracted with 10% aqueous hydrochloric acid (50 c.c.), and the extract refluxed for 1 hour to hydrolyse the acetamido-group. The cold extract was basified with ammonia, the oily deposit extracted with ether, and the dried ethereal extract then distilled. The *diphenylamine* (XIV, R = Cl) was obtained as a viscous syrup, b. p. 222—223°/0·002 mm. (Found: C, 70·0; H, 8·4; N, 12·4. $C_{20}H_{28}N_3Cl$ requires C, 69·5; H, 8·1; N, 12·15%) (5 g., 70%).

When acetone solutions of this amine and of *p*-toluenesulphonic acid were mixed, the *di*-p-*toluenesulphonate* crystallised, m. p. 201° (preliminary softening and darkening) (Found: C, 58·9; H, 6·5; N, 6·1. $C_{20}H_{28}N_3Cl,2C_7H_8O_3S$ requires C, 59·2; H, 6·4; N, 6·1%). This was the only crystalline salt of the base isolated.

4′-*Chloro*-3-(*δ*-*diethylamino*-*α*-*methyl*-n-*butylamino*)-4 : 5-*dimethyldiphenylamine* (XVI, R = Cl) (6052).—4′-Chloro-3-amino-4 : 5-dimethyldiphenylamine (11 g.), the diethyl ketal (12 g., 1·1 mols.), 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 dissolved in alcohol (70 c.c.) and hydrogenated (Adams's catalyst, 0·2 g.) at 60° and 100 atm. for 3 hours. The alcohol was then evaporated from the cold filtered solution, and the residue refluxed with 15% hydrochloric acid (60 c.c.) for 1 hour. The cold solution was basified (sodium hydroxide), extracted with ether, and the dried extract then distilled; the *diphenylamine* (XVI, R = Cl) was obtained as a pale yellow oil, b. p. 240—242°/0·07 mm. (Found: C, 71·4; H, 8·8; N, 11·0; Cl, 9·2. $C_{23}H_{34}N_3Cl$ requires C, 71·2; H, 8·8; N, 10·8; Cl, 9·2%). No crystalline salts of this amine could be isolated.

3-*Nitro*-4'-*methoxy*-4 : 5-*dimethyldiphenylamine*.—A mixture of (IX) (35 g.), *p*-bromoanisole (180 g.), potassium carbonate (17 g.), copper powder (1 g.), and potassium iodide (0·7 g.) was heated with stirring at 240° for 6 hours in an apparatus so arranged that water formed by slight decomposition could distil away. The cool product was then poured into hot petrol (b. p. 60—80°, 800 c.c.), and the mixture boiled, filtered, evaporated to *ca.* 250 c.c., and then steam-distilled until free from *p*-bromoanisole. The oily residue was then refluxed with 12% hydrochloric acid (120 c.c.) for 1 hour, cooled, and repeatedly extracted with ether until the extracts were colourless. The united, dried extracts on distillation gave the above *diphenylamine* as a viscous red syrup, b. p. 238—240°/0·01 mm. (30 g., 64%); trituration with methyl alcohol induced crystallisation, and the compound then crystallised from *cyclo*hexane in orange-yellow plates, m. p. 122—123° (Found: C, 66·5; H, 6·3; N, 10·1. $C_{15}H_{16}O_3N_2$ requires C, 66·2; H, 5·9; N, 10·3%).

3-*Amino*-4'-*methoxy*-4 : 5-*dimethyldiphenylamine* (6053).—A solution of the above compound (30 g.) in alcohol (250 c.c.) was hydrogenated as usual at 50° and 50 atm. for 5 hours. Fractional distillation ultimately gave this *diphenylamine* as a colourless oil, b. p. 220°/0·01 mm., which set to a brittle deliquescent glass, which could not be crystallised (Found: N, 11·3. $C_{15}H_{18}ON_2$ requires N, 11·6%) (22 g., 87%). This compound formed a *picrate* which, recrystallised from very dilute aqueous picric acid, formed fine yellow needles, m. p. 183° (decomp.) (Found: C, 53·25; H, 4·7. $C_{15}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 53·5; H, 4·5%).

3-β-*Diethylaminoethylamino*-4'-*methoxy*-4 : 5-*dimethyldiphenylamine* (XIV, R = MeO) (6054).—This was prepared precisely similarly to the 4'-chloro-analogue but by using the unacetylated diphenylamine, and obtained initially as a crude fraction, b. p. 235—240°/0·06 mm., which on refractionation gave the pure *diphenylamine* as a colourless oil, b. p. 238°/0·01 mm. (Found: N, 12·6. $C_{21}H_{31}ON_3$ requires N, 12·3%) (60%).

3-δ-*Diethylamino*-α-*methyl*-n-*butylamino*-4'-*methoxy*-4 : 5-*dimethyldiphenylamine* (XVI, R = MeO) (6055).—This *compound* was also prepared precisely similarly to the 4'-chloro-analogue and obtained as a pale green oil, b. p. 210°/0·002 mm. (Found: C, 74·8; H, 9·3; N, 11·3. $C_{24}H_{37}ON_3$ requires C, 75·2; H, 9·7; N, 11·0%): 58% of the theoretical.

No crystalline salts of the last two amines could be isolated.

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