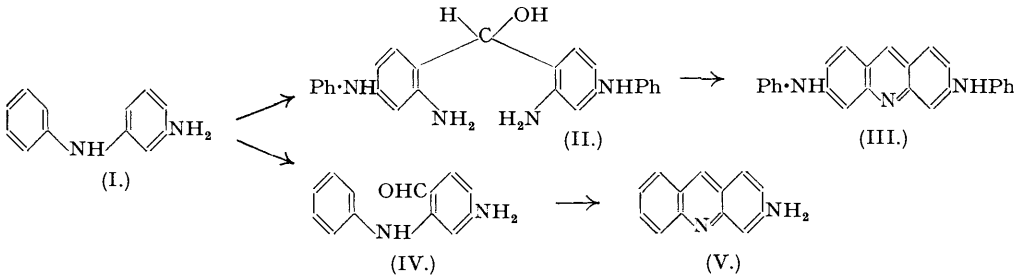
242. *Acridine Syntheses and Reactions. Part IV. A New Synthesis of Aminoacridines from Formic Acid and Diarylamines.*

By Adrien Albert.

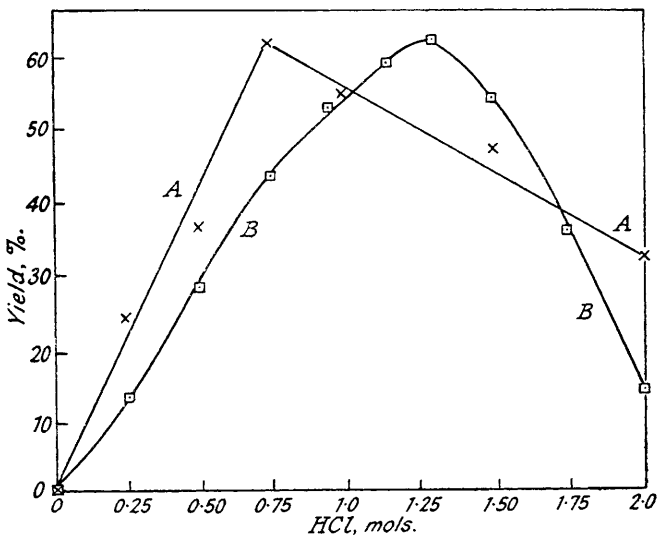
The reaction between formic acid and *N*-aryl-substituted *m*-diamines gives not only symmetrically-substituted diaminoacridines, according to the reaction described in Parts I—III (Albert, *J.*, 1941, 121, 484; 1947, 244) but also monoaminoacridines. The latter arise from a new reaction, which has a formal similarity to the Bernthsen synthesis and whose mechanism is discussed.

Experimental conditions can be regulated so that the new reaction preponderates, thus providing a useful preparative method for 2-aminoacridine and its derivatives.

It was shown (Part III) that derivatives of *m*-phenylenediamine, when heated with formic acid and hydrogen chloride, gave the corresponding derivatives of 2 : 8-diaminoacridine. For instance, *NN*-dimethyl-*m*-phenylenediamine gave 2 : 8-bisdimethylaminoacridine, and *N*-phenyl-*m*-phenylenediamine (3-aminodiphenylamine, I) gave 2 : 8-bisphenylaminoacridine (III) in 40% yield accompanied by a by-product, 2-aminoacridine (V).



By reducing the proportion of mineral acid, it has been found that progressively less (III) and more (V) were formed and a maximal yield of 2-aminoacridine (60%) was obtained when



Catalytic effect of hydrogen chloride.

(A) 2-*Aminoacridine from* 3-*aminodiphenylamine* (1 *mol.*) *and formic acid* (1 *mol.*).
(B) 2 : 7-*Diaminoacridine from* 3 : 4′-*diaminodiphenylamine* (1 *mol.*) *and formic acid* (1·25 *mols.*).

0·75 mol. of hydrogen chloride per mol. of amine was used (cf. Fig.). Under these conditions the yield of (III) was only 10%, and when still less mineral acid was used both reactions (I ⟶ V) and (I ⟶ II ⟶ III) were progressively suppressed. Finally, in the complete absence of hydrogen chloride, no more than a trace of acridines was produced even with a five-fold excess of formic acid.

It is evident that there are two competitive reactions. Both are catalysed by hydrogen ions, but (I ⟶ III) is favoured by a hydrogen-ion concentration which is above the optimum for (I ⟶ V). It is relevant that no less than 1·15 mols. of hydrogen chloride per mol. of *m*-phenylenediamine were required for maximal conversion of the latter into proflavine, a reaction which is the prototype of (I ⟶ III).

It was thought that reaction (I ⟶ V) was an example of the Bernthsen reaction, *i.e.*, the conversion of diphenylamines into acridines on heating with organic acids, preferably in the presence of zinc chloride, at 220—270° for 10 to 48 hours; for example, diphenylamine and acetic (or benzoic) acid give 5-methyl- (or 5-phenyl-) acridine in 50% yields (Bernthsen, *Annalen*, 1884, **224**, 3). The Bernthsen reaction, however, gives only a 7·5% yield with formic acid (Bernthsen, *loc. cit.*), whereas the new reaction gave no acridines with acetic or benzoic acids, even after heating for two hours at 185°, but gave a good yield with formic acid even after only one hour at 155°. Again, zinc chloride is prejudicial to the new reaction. These data suggest that this reaction may have a different mechanism from the Bernthsen reaction.

It is often assumed that the Bernthsen reaction proceeds through acylation of the secondary amino-group in diphenylamines. The new reaction, however, cannot proceed *via* 3-amino-*N*-formyldiphenylamine because this compound did not produce any 2-aminoacridine below 150° (whereas 3-aminodiphenylamine began to produce it at 120°), and the final yield at 175° was low (50% instead of 60%). This retarding effect of *N*-formylation is even more marked with 3 : 3′-diamino-*N*-formyldiphenylamine (see experimental section). Although 3-*formamidodiphenylamine* gave the same yields as (I) under both wet and dry conditions, it is not a likely intermediate because the reaction was applicable to 3-hydroxydiphenylamine which gave 2-hydroxyacridine. Likewise 3-*dimethylaminodiphenylamine* gave 2-*dimethylaminoacridine*. In neither case was excess of acidity (up to at least 1·5 equivs.) prejudicial to the yields, possibly because no reaction of the type (I ⟶ III) is possible.

Although no intermediate could be isolated from the reaction mixture, 3-aminodiphenylamine-6-aldehyde (IV) is the most likely intermediate in the reaction (I ⟶ V), the aldehyde group entering at the point of greatest electron density. The synthesis of aldehydes from formic acid and amines may have a precedent in that *p*-dimethylaminobenzaldehyde is almost certainly an intermediate in the formation of 4 : 4′-bisdimethylaminobenzhydrol from dimethylaniline, formic acid, and hydrochloric acid at 120° (Votoček and Kraus, *Ber.*, 1909, **42**, 1604).

Attempts to synthesise 3-aminodiphenylamine-6-aldehyde (IV), *e.g.*, through 3-*nitrodiphenylamine*-6-*carboxyhydrazide*, its p-*toluenesulphonyl* derivative, or 3-*aminodiphenylamine*-6-*carboxyhydrazide*, gave only resins. An estimate of the ease of ring closure of (IV) was obtained by the examination of *diphenylamine*-2-*aldehyde* which was prepared from ethyl diphenylamine-2-carboxylate through *diphenylamine*-2-*carboxyhydrazide* and its p-*toluenesulphonyl* derivative. This aldehyde has been obtained in an impure form by Mayer and Stein (*Ber.*, 1917, **50**, 1306) who refluxed iodobenzene, 2-aminobenzaldehyde, sodium carbonate, and copper in nitrobenzene. The nitrobenzene was removed by steam distillation, the authors apparently not realising that the new aldehyde is steam-volatile.

This aldehyde cyclised almost quantitatively to acridine under the conditions which were used to produce (V) from (I) and also under a variety of other acidic conditions. If the ring closure of (IV) is equally facile, as seems likely, the reaction (I ⟶ IV) must be the limiting factor and it is understandable that no intermediate could be isolated. The ring closure of 2-nitrodiphenylamine-2′-aldehyde was also studied.

The new reaction (I ⟶ V) provides the easiest known synthesis of 2-aminoacridine and many of its derivatives, although symmetrically substituted acridines are more conveniently made by the reaction (I ⟶ III); *e.g.*, 2 : 8-diaminoacridine is best made from *m*-phenylenediamine and not from 3 : 3′-diaminodiphenylamine. Apart from examples already mentioned, syntheses, by the new reaction, are described for 2-*dimethylaminoacridine*, 2 : 7-diaminoacridine, 7-*amino*-2-*dimethylaminoacridine*, 8-*amino*-1 : 2-*benzacridine*, and 8-amino-3 : 4-benzacridine. The diamines require 1·3 moles of hydrochloric acid per mole for optimal yields (cf. Fig.).

The reaction was not successful when a strong electron-repelling group was absent from the 3- position (*e.g.*, diphenylamine, 4-aminodiphenylamine, 3-nitrodiphenylamine). 3 : 2′-Diaminodiphenylamine gave only a benziminazole.

No 4-aminoacridine was obtained as a by-product in reaction (I ⟶ V), and 3-amino-6-methyldiphenylamine (which could not have given a derivative of 2-aminoacridine) did not yield any 4-*amino*-1-*methylacridine*, which was prepared by an independent route for comparison. Hence the substances formed by the new reaction have all been formulated as

derivatives of 2-(and not 4-)aminoacridine. Confirmation of this orientation is derived from the relatively high basic strengths (forthcoming publication), and yellow (as distinct from violet) colours of the ions.

Experimental.*

Acridine Derivatives.

2-*Aminoacridine* (V).—3-Aminodiphenylamine (3·7 g.; 0·02 mole), glycerol (15 g.), formic acid (0·92 g. anhydrous; 0·02 mole), and hydrogen chloride (0·55 g.; 0·015 mole as 1·55 ml. of standardised acid) were raised to 155° during ½ hour, kept at 155° for ½ hour, then heated at 175° for ½ hour. When the dark red mass was cool, concentrated hydrochloric acid (0·5 ml.) and then water (40 ml.) were stirred in. The mixture was brought to the boil, hydrated sodium acetate (1 g.) was added, and the less basic by-products, including (III), were filtered off. 2-Aminoacridine was precipitated from the boiling filtrate with sodium hydroxide and recrystallised as the hydrochloride from 20 parts of 0·5N-hydrochloric acid. The base was again precipitated and recrystallised from alcohol. Yield 60%, m. p. 216°. Identity was confirmed by comparison (including mixed m. p.) with a specimen prepared by reducing 2-nitroacridone.

These conditions were optimal, even on the 100 g. scale. The yield was not improved by doubling the amount of formic acid or by longer heating at 175°, and was reduced to 40% by omission of the ½ hour's heating at 175°, to 50% by the use of substantially anhydrous conditions, and to 50% by the addition of 0·02 mole of zinc chloride. When hydrochloric acid was omitted, 3-formamidodiphenylamine, m. p. 125°, was obtained in 75% yield, the rest of the 3-aminodiphenylamine being unchanged.

The absence of 4-aminoacridine from all mother-liquors was established by concentration and precipitation with sodium hydroxide. The precipitate was washed and dissolved in 0·1N-acetic acid. The tip of a clamped strip of filter paper was then inserted. After 15 minutes, no violet band had appeared at the top of the wet area. This test will detect 1 part of the 4-isomeride in 200 parts of the 2-isomeride at a dilution of 1 in 1000.

When 3-acetamidodiphenylamine replaced 3-aminodiphenylamine in the above condensation, hydrolysis preceded condensation, as 2-aminoacridine (32% yield), but no 2-acetamidoacridine, was isolated.

2-*Hydroxyacridine*.—3-Hydroxydiphenylamine was condensed as above. The melt was boiled with water (20 ml.) and filtered hot. The extract and washings were precipitated at 90° with ammonia and filtered. The cake was washed with boiling water, and dissolved in hydrochloric acid. The solution was refrigerated, and the sparingly soluble hydrochloride collected, dissolved in boiling water, and precipitated with ammonia. The free base was dissolved in boiling alcohol (200 ml.) and concentrated until crystals began to separate. On cooling, orange crystals of 2-hydroxyacridine were obtained in 35% yield, m. p. 283° (sealed), undepressed by a specimen, m. p. 285°, synthesised by the method of Albert and Ritchie (*J.*, 1943, 458).

2-*Dimethylaminoacridine*.—3-Dimethylaminodiphenylamine was condensed and worked up, exactly as 3-aminodiphenylamine. The filtrate from the sodium acetate treatment was precipitated with sodium hydroxide and boiled until the oily base turned to a solid which was recrystallised from a little alcohol and then from benzene–light petroleum. 2-*Dimethylaminoacridine* (60% yield) formed orange crystals, m. p. 183°, sparingly soluble in water, very soluble in alcohol with a yellow colour and strong green fluorescence (Found: C, 81·0; H, 6·3; N, 12·6. $C_{15}H_{14}N_2$ requires C, 81·0; H, 6·35; N, 12·6%).

The scarlet sulphate is very soluble in water, and the scarlet hydrochloride is not salted out by hydrochloric acid. The orange aqueous solutions are fluorescent (orange) only when dilute.

2 : 8-*Diaminoacridine*.—3 : 3′-Diaminodiphenylamine (Albert and Linnell, *J.*, 1936, 89) was condensed in the same way as its isomeride. The melt was boiled with excess of N-sodium hydroxide. The base was filtered off and extracted with N-acetic acid. The 2 : 8-diaminoacridine was precipitated from the filtrate and recrystallised from 55 parts of alcohol, giving a 55% yield of yellow crystals, m. p. (sealed) 276°, which did not depress the m. p. of a specimen prepared as in Part I. When the diaminodiphenylamine was replaced by 3 : 3′-diamino-*N*- formyldiphenylamine, the yield fell to 30% (cf. Part II).

2 : 7-*Diaminoacridine*.—3 : 4′-Diaminodiphenylamine (4·0 g.; 0·02 mole) was condensed in the same way as 3-aminodiphenylamine except that 0·026 mole (1·3 equivs.) of hydrochloric acid was used. The melt was digested at 90—100° for 5 minutes with sulphuric acid (8 ml. of 30% w/v), diluted to 80 ml. with water, and kept on ice for an hour. The acid sulphate of 2 : 7-diaminoacridine was filtered off, washed with water (10 ml.), then boiled with N-sodium hydroxide (25 ml.). The crystalline base was triturated with pyridine trihydrate (b. p. 93°; 10 ml.), filtered, and the residue recrystallised from about 100 parts of this solvent, giving 2 : 7-diaminoacridine in 60% yield, m. p. (sealed) 350° (long-stem), 355° (short-stem), approx. 365° (corr.). The results of varying the mineral acidity are shown in the Figure.

The base is soluble *ca.* 1 in 3,000 in boiling water, moderately soluble in nitrobenzene but without temperature gradient, and can be recrystallised from aniline, or from carbitol neutralised with morpholine. The monohydrochloride was formed by mixing the base (2·09 g.) with boiling 0·5N-hydrochloric acid (20 ml.), cooling to 50°, adding boiling acetone (40 ml.), and chilling (80% recovery). It is soluble in *ca.* 200 parts of cold water but is much more soluble (*e.g.*, 1 in 10) if a trace of hydrochloric acid is added. The acid sulphate, $C_{13}H_{11}N_3,H_2SO_4$, is soluble in 600 parts of boiling and 2,000 parts of cold water and is less soluble in the presence of excess of sulphuric acid.

7-*Amino*-2-*dimethylaminoacridine*.—4-Amino-3′-dimethylaminodiphenylamine was condensed exactly as 3 : 4′-diaminodiphenylamine. The melt was poured directly into sodium hydroxide solution and the oily base was collected and extracted with N-acetic acid, which left a tar. The extract was poured into

* Most of this work was carried out in 1941 but publication was delayed by a National Security Order, now revoked. Accordingly the data were filed at the Patent Office by the University of Sydney and the author. Australian and British Serial Nos. are respectively 115,480 (1941) and 572,766 (1945).

boiling N-sodium hydroxide and the base filtered off. A 1 in 5, hot solution of the neutral hydrochloride was then made and precipitated with an equal volume of acetone. The regenerated base was recrystallised from 7 parts of pyridine trihydrate and from 30 parts of 25% alcohol. 7-*Amino*-2-*dimethylaminoacridine* (70% yield) formed orange needles, m. p. (sealed) 242° (249° corr.), very soluble in alcohol and methanol, less in acetone, slightly soluble in toluene and water, in all cases without temperature gradients. The orange solution in alcohol has a green fluorescence (intense yellow by ultra-violet light) (Found: C, 76·4; H, 6·3; N, 17·4. $C_{15}H_{15}N_3$ requires C, 75·9; H, 6·4; N, 17·6%).

The monohydrochloride gives intense bluish-red solutions with orange fluorescence, best seen under ultra-violet light. The dihydrochloride gives an orange solution with yellow fluorescence. Diazotisation is readily effected.

4-*Amino*-1-*methylacridine*.—4-Amino-1-methylacridan (Clemo, Perkin, and Robinson, *J.*, 1924, 1774) was suspended in boiling 50% alcoholic sodium hydroxide solution (N) and gently aerated for an hour. The oxidation was quantitative, although the solid acridan is not affected by long exposure at 20°. 4-*Amino*-1-*methylacridine* forms scarlet solvated needles, from dilute alcohol or benzene, which fall to a scarlet powder at 120°; m. p. 128—129°. Unlike 4-aminoacridine, it does not turn yellow on hydration. The orange solution in alcohol has a slight orange fluorescence (Found: C, 80·8; H, 5·85; N, 13·5. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·5%). The acetate and monohydrochloride are violet and their solutions do not fluoresce; the latter is precipitated from the solution of the base in 0·1N-hydrochloric acid by half saturation with sodium chloride. The dihydrochloride is formed in 2N-hydrochloric acid and is yellow. The yellow diazonium solution couples with β-naphthol (scarlet).

8-*Amino*-1 : 2-*benzacridine*.—α-Naphthyl-*m*-phenylenediamine hydrochloride (2·7 g.), formic acid (0·46 g.), water (0·8 ml.), and glycerol (9·4 g.) were condensed as before. The melt was repeatedly extracted with boiling water. The filtrate was basified and the precipitate extracted with N-acetic acid. The extract was treated with sodium acetate crystals (0·5 g.), filtered from weak bases, and precipitated with sodium hydroxide. The solid was dissolved in 50 parts of boiling alcohol, filtered, and concentrated to 10 parts. Recrystallisation from toluene gave 8-*amino*-1 : 2-*benzacridine* (40% yield) as bright yellow crystals with a bronze reflex when large; m. p. (sealed) 200°. The alcoholic solution has a brilliant green fluorescence (Found: C, 83·4; H, 4·9; N, 11·45. $C_{17}H_{12}N_2$ requires C, 83·6; H, 5·0; N, 11·5%).

When 0·75 or 1·25, instead of 1·0 equiv. of hydrochloric acid was used, the yield fell to 30%.

The red hydrochloride is readily salted out by chloride ions. Its orange solution in water develops a green fluorescence on dilution, gives no colour change on diazotisation, but couples with β-naphthol (deep red).

Attempted synthesis of 8-amino-1 : 2-benzacridine from α-naphthol, 2 : 4-dinitrobenzyl chloride, and stannous chloride by the general method of Baezner and Gueorguieff for the β-isomeride (*Ber.*, 1906, **37**, 3082) gave a yield of only 1%.

8-*Amino*-3 : 4-*benzacridine*.—This was prepared similarly from β-naphthyl-*m*-phenylenediamine in 45% yield. After repeated recrystallisation from dilute alcohol and toluene the m. p. (sealed) remained at 264—265°; which was also the highest m. p. obtainable from material synthesised, in 10% yield, by the method of Baezner and Gueorguieff (*loc. cit.*), and a mixed m. p. showed no depression. It would seem that the m. p. (270°) quoted by these authors had been corrected.

On acetylation with acetic anhydride, specimens obtained by either method gave 8-acetamido-3 : 4-benzacridine quantitatively. The m. p. and mixed m. p.s of the crude products were 269°, and repeated recrystallisation from dilute alcohol did not change this figure. The above authors give m. p. 267° from nitrobenzene, but the base tends to decompose in this solvent.

The solubilities, colours, and fluorescences of base and acetyl derivative were as described by these authors.

Ring Closure of Diphenylamine-2-aldehyde.—(*a*) The aldehyde (0·55 g.), glycerol (2·0 g.), and standardised hydrochloric acid (0·26 ml. = 0·10 g. HCl = 1 equiv.), heated at 155° for 5 minutes, gave 95% of acridine, m. p. 110° (highest published m. p. is 111°). (*b*) Heating at 130° for 30 minutes gave 88%. (*c*) Heating at 130° for 5 minutes gave 26% of acridine and 67% of unchanged aldehyde. (*d*) The aldehyde (0·3 g.) in glacial acetic acid (1 ml.), heated with sulphuric acid (0·15 ml.; 4 equivs.) at 100° for 5 minutes, gave a 93% yield, m. p. 110° (for this cyclising method cf. Jensen and Rethwisch, *J. Amer. Chem. Soc.*, 1928, **50**, 1144). (*e*) The aldehyde (0·3 g.), heated with sulphuric acid (1·2 ml.) at 100° for ½ hour, gave a 98% yield of acridine, m. p. 110° (cf. Mayer and Stein, *loc. cit.*).

Ring Closure of 2-Nitrodiphenylamine-2′-aldehyde.—This substance (Albert and Ritchie, *J.*, 1943, 458) was investigated similarly. Method (*a*) gave a 36% yield of 1-nitroacridine, m. p. *ca.* 157°; (*d*) gave a 50% yield, m. p. 165°; and (*e*) gave a 98% yield, m. p. 165° (the m. p. of pure 1-nitroacridine is 167°). In each case the product was diluted with hot 0·5N-hydrochloric acid and filtered from unchanged aldehyde before precipitation of the base.

Diphenylamine Derivatives.

3-*Aminodiphenylamine*.—3-Nitrodiphenylamine (50 g.), Raney nickel (9 g.), and alcohol (250 ml.) were shaken with hydrogen at atmospheric temperature and pressure until the absorption was theoretical (2 hours). The catalyst was filtered off and was active through 3 more runs. The alcohol was recovered from the filtrate and the solid was distilled, giving 3-aminodiphenylamine, b. p. 190°/2 mm., m. p. 75°, in 90% yield. This substance was often obtained as a gum which turned to white crystals if stored at 50°. This amine (7·4 g.) and formic acid (2·6 ml.; 50% excess) were heated at 97° for an hour, cooled, diluted with water, and filtered. The damp precipitate was recrystallised from a little alcohol until the m. p. became constant, then dried in a vacuum, giving white crystals of 3-*formamidodiphenylamine* in 75% yield, m. p. 135—136°, moderately soluble in benzene with a temperature gradient (Found: C, 73·1; H, 5·6. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7%). Unlike the isomeric 3-amino-*N*-formyldiphenylamine, m. p. 130—131° (Part II), it is insoluble in dilute hydrochloric acid and does not diazotise. A mixture of the isomerides began to melt at 100°.

3-*Acetamidodiphenylamine*.—3-Aminodiphenylamine (3·7 g.), acetic anhydride (3 ml.), and pyridine

(5 ml.) were mixed at − 5°. The mixture was left overnight at 20° and then poured into water (80 ml.). The precipitate was recrystallised from alcohol until the m. p. became constant, giving white crystals of 3-*acetamidodiphenylamine*, m. p. 131° (95% yield), only moderately soluble in benzene and light petroleum (Found: C, 73·9; H, 6·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%). The cold alcoholic solution gave a green colour with ferric chloride, in contrast to 3-amino-*N*-acetyldiphenylamine.

3-Aminodiphenylamine (7·6 g.) and acetic anhydride (15 g.) were heated for 15 minutes at 100°, cooled, and treated with benzene–light petroleum (2 : 1). The lower layer, when stirred with ether, gave a white solid (4·3 g.; m. p. 149—150°). The m. p. was not changed by recrystallisation from 10% alcohol or from water. The residues were taken to dryness and re-acetylated as above, giving altogether a 70% yield of 3-*acetamido*-N-*acetyldiphenylamine*, soluble in 200 parts of boiling water, readily soluble in alcohol, less soluble in cold benzene, and almost insoluble in light petroleum (Found: N, 10·50. $C_{16}H_{16}O_2N_2$ requires N, 10·45%). Cold ferric chloride solution gave no coloration. No acridines were formed on heating with formic and hydrochloric acids in glycerol at 175°.

3-*Amino*-N-*acetyldiphenylamine*.—3-Nitrodiphenylamine (70 g.) was refluxed with acetic anhydride (100 ml.) and one drop of sulphuric acid for 2 hours. The greater part of the acetic anhydride was removed by distillation and the rest by refluxing with alcohol (100 ml.) for 2 hours. The alcohol was distilled off and the residue recrystallised from a little methanol giving white crystals of 3-*nitro*-N-*acetyldiphenylamine*, m. p. 71°, in 90% yield (Found: C, 65·4; H, 4·9. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7%).

Reduction as for 3-nitrodiphenylamine, followed by recrystallisation from alcohol, gave white crystals of 3-*amino*-N-*acetyldiphenylamine*, m. p. 124°, in 95% yield, recrystallising well from benzene and almost insoluble in light petroleum (Found: C, 73·8; H, 6·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%). The cold alcoholic solution gave no colour with ferric chloride.

3-*Dimethylaminodiphenylamine*.—3-Amino-*N*-acetyldiphenylamine (17 g.), methyl iodide (25 g.; slight excess), methanol (80 ml.), and dried calcium carbonate (8 g.) were heated under reflux for 5 hours in a bath maintained at 40°; during the next 10 hours the temperature was gradually raised to 60°. The product was filtered and the solvent recovered. The residual oil was shaken for 2 hours with *p*-toluenesulphonyl chloride (7·5 g.), ether (20 ml.), and sodium hydroxide (60 ml. of 3N). The alkaline layer (representing primary amine) was run off, counter-extracted with a little ether, and discarded. The combined ethereal fractions were repeatedly extracted with 0·5N-hydrochloric acid. The combined aqueous layers were made alkaline and shaken out thrice with ether. The ether extracts were dried (Na_2SO_4) and taken to dryness. The yield was 5 g. of a pale orange solid which became white on recrystallisation from 40 parts of light petroleum (b. p. 60—90°). The 3-*dimethylamino*-N-*acetyldiphenylamine*, m. p. 97—98° was moderately soluble in boiling water, with gradient, and very soluble in alcohol, acetone, and benzene (Found: C, 75·3; H, 7·1; N, 11·1. $C_{16}H_{18}ON_2$ requires C, 75·6; H, 7·1; N, 11·0%).

This acetyl compound (5 g.) and hydrochloric acid (60 ml. of 7N) were heated for 2 hours at 100°, made alkaline, and refrigerated. The precipitate was powdered and washed well with water, dried in a vacuum, and recrystallised from light petroleum (b. p. 60—90°), the first orange oily drops which separated on cooling being rejected. The 3-*dimethylaminodiphenylamine* was obtained in 95% yield as white crystals, m. p. 65—66°, sparingly soluble in water and very soluble in all common organic solvents (Found: C, 78·9; H, 7·6; N, 13·3. $C_{14}H_{16}N_2$ requires, C, 79·2; H, 7·6; N, 13·2%).

This substance gives a pink colour, deepening to purple, with a mixture of equal parts of 3% hydrogen peroxide and 5N-sulphuric acid containing a trace of ferrous sulphate. The *N*-acetyl derivative does not react.

3-*Hydroxydiphenylamine*.—This has not previously been prepared from a diphenylamine derivative. 3-Amino-*N*-formyldiphenylamine (1·46 g.; Part II) was dissolved in sulphuric acid (40 ml. of 70% v/v) and a solution of sodium nitrite (0·48 g.) in water (7 ml.) added during 17 minutes. Urea (0·1 g.) was then added, and the mixture was kept in a boiling water-bath until effervescence was complete (about 15 minutes), made neutral with sodium hydroxide, and filtered. The solid was extracted with boiling N-sodium hydroxide. The extract was decolorised with carbon, acidified with acetic acid, and refrigerated, giving white crystals of 3-hydroxydiphenylamine, m. p. 81° (lit. 82°), in 35% yield.

3 : 4′-*Diaminodiphenylamine*.—The following sulphonation of *p*-chloronitrobenzene is preferred to that of Ullmann (*Ber.*, 1909, **42**, 1077) which often becomes violent. *p*-Chloronitrobenzene (210 g.) was heated, in a 1-litre three-necked ground-glass jointed flask provided with thermometer, stirrer, and condenser guarded by a calcium chloride tube, with fuming sulphuric acid (270 ml.; 10% oleum), in an oil-bath kept at 120° for 10 hours. The internal temperature quickly rose to 135° but soon returned to 115°. The yield of 2-chloro-5-nitrobenzenesulphonic acid monohydrate was 297 g. (87% yield), m. p. 165° (sealed). It was converted, by the method of Ullmann and Dahmen (*Ber.*, 1908, **41**, 3746), into 4-nitro-3′-aminodiphenylamine. The more direct synthesis of this from *m*-aminoacetanilide and *p*-bromonitrobenzene gave poor yields. 4-Nitro-3′-aminodiphenylamine was dissolved in alcohol (32 parts), filtered, and reduced with Raney nickel and hydrogen at atmospheric pressure and 70°. The product was filtered by gravity in an atmosphere of carbon dioxide, the alcohol recovered, and the residue distilled, giving 3 : 4′-*diaminodiphenylamine* as a white solid in 90% yield, b. p. 251°/2·5 mm. (uncorr.), m. p. 97° (Found: N, 20·9. $C_{12}H_{13}N_3$ requires N, 21·1%).

4-*Amino*-3′-*dimethylaminodiphenylamine*.—*m*-Aminodimethylaniline (27 g.), 2-chloro-5-nitrobenzenesulphonic acid monohydrate (51 g.; 1 mol.), sodium carbonate (10·6 g.), and water (400 ml.) were boiled for a few minutes, then calcium carbonate (10 g.) was added and the whole refluxed for 18 hours. The product was precipitated with hydrochloric acid, washed, recrystallised three times from large volumes of water, and dried at 130°, giving 4-*nitro*-3′-*dimethylaminodiphenylamine*-2-*sulphonic acid hemihydrate* as yellow-brown crystals in 50% yield, m. p. *ca.* 240° (eff., decomp., sealed) (Found: C, 48·1; H, 4·6; N, 12·0. $C_{14}H_{15}O_5N_3S,\frac{1}{2}H_2O$ requires C, 48·5; H, 4·65; N, 12·1%).

This acid (18 g.) was warmed with sulphuric acid (126 ml.; 70% v/v) for 2 hours in a boiling water-bath. The product was cooled, diluted with 3 vols. of water, refrigerated, and the sulphate

filtered off, digested for 5 minutes with hot aqueous ammonia, cooled, and filtered. The cake, which contained 6% of carbon, was recrystallised from alcohol giving *4-nitro-3'-dimethylaminodiphenylamine* as large dark brown plates, m. p. 139°, in 70% yield (Found: C, 65·2; H, 5·9; N, 16·2. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·8; N, 16·3%).

This compound (10 g.) was reduced in alcohol (25 ml.) with Raney nickel and hydrogen and gave *4-amino-3'-dimethylaminodiphenylamine* as a colourless highly viscous liquid, b. p. 251°/5 mm., in 85% yield (Found: C, 74·6; H, 7·3; N, 18·2. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%). It absorbs oxygen in the cold and becomes brown.

Diphenylamine-2-aldehyde.—Ethyl diphenylamine-2-carboxylate (20 g.) was refluxed with hydrazine hydrate (6·25 g.) for 10 hours, cooled, shaken out twice with water (10 ml.), then diluted with ether. The solution was dried (Na_2SO_4) and quickly filtered before crystallisation took place. The product was recrystallised from 5 parts of alcohol giving white crystals of *diphenylamine-2-carboxyhydrazide* (12 g.), m. p. 121°, moderately soluble in water (with gradient) and poorly soluble in ether, benzene, or light petroleum (Found: C, 68·1; H, 5·8; N, 18·3. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·8; N, 18·5%). It was readily soluble in dilute hydrochloric acid, the solution giving a white precipitate of the azide with sodium nitrite. When the hydrazide was treated with potassium ferricyanide and ammonia, by the general method of Kalb and Gross (*Ber.*, 1926, **59**, 727), no aldehyde was isolated.

This hydrazide (3·15 g.), dissolved in dry pyridine (6 ml.), was treated with *p*-toluenesulphonyl chloride (2·66 g.; 1 mol.) during 5 minutes, the temperature being kept below 60°. The solution was kept at about 20° for 2 hours and then poured into a mixture of ice and dilute hydrochloric acid. The solid was recrystallised from a little alcohol giving white crystals of *diphenylamine-2-carboxy-(β-p-toluenesulphon)hydrazide*, m. p. 186—187°, in 90% yield. It was very soluble in acetone but sparingly soluble in benzene, ether, or boiling water (Found: N, 11·0. $C_{20}H_{19}O_3N_3S$ requires N, 11·0%).

This toluenesulphonyl derivative was degraded by the general method of McFadyen and Stevens (*J.*, 1936, 584) by maintaining 2·6 g. (dissolved in ethylene glycol, 13 ml.) in a bath kept at 160° whilst freshly dehydrated sodium carbonate (1·7 g.; 5 equivs.) was added as fast as foaming allowed. The reaction was allowed to continue for only 75 seconds more, and the product was then cooled, diluted with water (50 ml.), and filtered. The cake was recrystallised from as little methanol as possible giving *diphenylamine-2-aldehyde*, as odourless yellow crystals, m. p. 72·5°, in 80% yield. It was very soluble in *cyclo*hexane, benzene, and alcohol, less soluble in light petroleum, only slightly soluble in water (but with a good gradient), and volatile in steam without decomposition. The solutions were not fluorescent (Found: C, 78·5; H, 5·6; N, 7·2. $C_{13}H_{11}ON$ requires C, 79·1; H, 5·6; N, 7·1%). Like 2-aminobenzaldehyde it has little effect on Schiff's reagent or hot ammoniacal silver nitrate. The pure yellow solution in cold glacial acetic acid is turned red by a trace of sulphuric acid. This indicates that the molecule is accepting a proton on the carbonyl group. The red colour fades as ring closure to acridine occurs, and in 90 minutes at room temperature the solution is yellow again.

3-Nitrodiphenylamine-6-carboxyhydrazide.—Methyl 3-nitrodiphenylamine-6-carboxylate (3·3 g.) and hydrazine hydrate (1·5 g.) did not react under mild conditions and so were heated under reflux for 6 hours in a bath at 130°. The product was stirred with ether (7 ml.) and the crystals filtered off. After recrystallisation from alcohol (16 pts.), red crystals of *3-nitrodiphenylamine-6-carboxyhydrazide*, m. p. 162—163°, were obtained in 40% yield. It is very soluble in benzene and pyridine with gradients (Found: C, 57·0; H, 4·5; N, 20·45. $C_{13}H_{12}O_3N_4$ requires C, 57·3; H, 4·45; N, 20·6%). Hydrochloric acid, of over 0·5N, dissolves it to form an orange solution.

The mother liquors of the nitro-compound yielded white crystals of *5-aminodiphenylamine-2-carboxyhydrazide*, m. p. 189° (50% yield on the original ester), on concentration, partial reduction by hydrazine having occurred during the condensation. This substance can be crystallised from 25 parts of boiling alcohol, and is moderately soluble in benzene, sparingly soluble in ether, and boiling water (Found: C, 63·8; H, 5·8; N, 22·9. $C_{13}H_{14}ON_4$ requires C, 64·4; H, 5·8; N, 23·1%). The solution in dilute hydrochloric acid can be diazotised (orange) and then coupled with β-naphthol (scarlet).

5-Nitrodiphenylamine-2-carboxyhydrazide (2 g.) was dissolved in dry pyridine (15 ml.) and acylated with *p*-toluenesulphonyl chloride as before, giving orange crystals of *5-nitrodiphenylamine-2-carboxy-(β-p-toluenesulphon)hydrazide* which, after being dried at 120° and recrystallised from alcohol, melted at approx. 247° (decomp.) and were insoluble in benzene and ether (Found: N, 13·2. $C_{20}H_{18}O_5N_4S$ requires N, 13·15%).

5-Nitrodiphenylamine-2-carboxyanilide.—This was prepared by the action, in turn, of thionyl chloride and aniline on the free acid in an unsuccessful endeavour to synthesise 3-aminodiphenylamine-6-aldehyde by the general method of Sonn and Muller (*Ber.*, 1919, **52**, 1927), using phosphorus pentachloride followed by stannous chloride. *5-Nitrodiphenylamine-2-carboxyanilide* formed orange crystals from 10 parts of alcohol or 25 parts of benzene, m. p. 153—154° (Found: N, 12·6. $C_{19}H_{15}O_3N_3$ requires N, 12·6%).

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