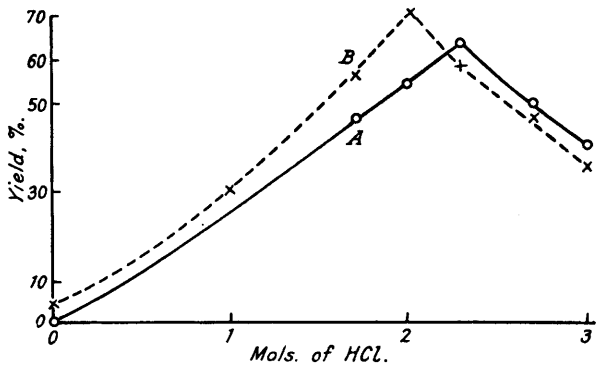
83. *Acridine Synthesis and Reactions. Part II. Synthesis of Proflavine from* m-*Phenylenediamine and its Derivatives (continued).*

By Adrien Albert.

In continuation of the investigation of the mechanism of the reaction whereby proflavine is produced in good yield from *m*-phenylenediamine, glycerol, and formic acid (this vol., p. 121) the relative importance of diphenylamine and of benzhydrol derivatives as intermediates is discussed, and it is concluded that the evidence points to the dihydrochloride of (anhydro)-2 : 4 : 2′ : 4′-tetra-aminobenzhydrol (V*b*) as the immediate precursor of proflavine.

The reaction by which proflavine is produced on heating *m*-phenylenediamine and glycerol with oxalic or formic acid was assumed (Albert, *loc. cit.*) to depend on the partial formylation of the diamine to *m*-aminoformanilide (I) and on the latter's reacting with unchanged *m*-phenylenediamine. That *m*-aminoformanilide is indeed an intermediate in this reaction is upheld by the higher yields obtained when it was condensed with *m*-phenylenediamine in comparison with the results of condensing two equivalents of the latter base with formic acid. Moreover, it was found (Figure, A) that hydrogen chloride promoted this reaction



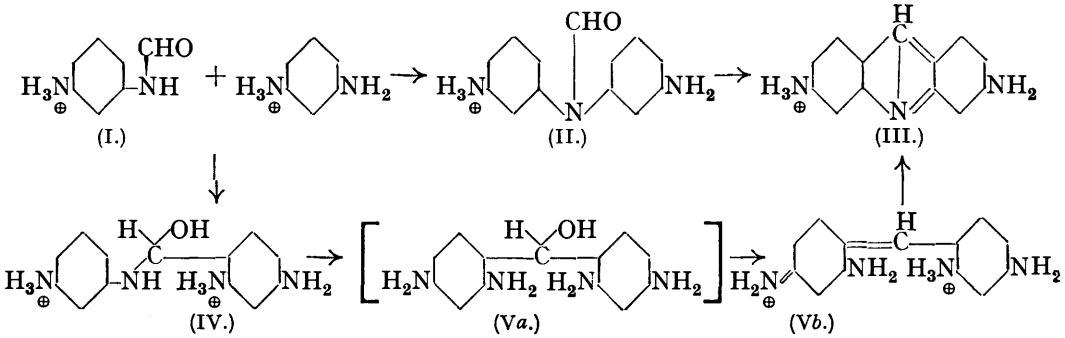
A. *Yield of proflavine from* 1 *mol. each of* m-*phenylenediamine and* m-*aminoformanilide at* 155° *with increasing amounts of hydrogen chloride.*
B. *The same with, in addition,* 2·7 *mols. of zinc chloride.*

in proportion to the quantity present up to a maximum of 2·3 mols. for one mol. each of *m*-phenylenediamine and *m*-aminoformanilide, the maximum yield (63% of proflavine) being depressed by further additions of hydrogen chloride. When zinc chloride (2·7 mols.) was also present (Figure, B), the maximum yield (70%) was obtained with 2 mols. of hydrogen chloride and these yields became 71% and 80% (without and with zinc chloride respectively) when the temperature was raised from 155° to 180°, although the products of the reaction at the higher temperature were less readily purified.

These results (see Figure) are interpreted thus : As soon as each amine has become the monohydrochloride, further additions of hydrogen chloride deprive the one remaining primary amino-group of its required para-directing properties, owing to salt formation, and the condensation cannot proceed. Further, it was observed that excess of hydrogen chloride brought about loss of the formyl compound by hydrolysis. The peak yield at or about 2HCl had also been noted in the various original condensations (Part I). The effect of zinc chloride (Figure, B) is ascribed to the liberation by hydrolysis of a little hydrogen chloride, although a small extra catalytic effect appears to be exerted at, and around, the peak yield.

To obtain light on the subsequent course of this reaction, it was interrupted at various temperatures and the melt was cooled, diluted with water, and neutralised with ammonia. The most informative results were obtained by interrupting the reaction at 140° after it had been proceeding for 10 minutes; a white, water-insoluble, basic material was then

obtained, which was separated into a substance insoluble in alcohol, a substance soluble in cold alcohol, and a substance crystallising from hot alcohol on cooling. The last fraction (1% yield) consisted of white needles, m. p. 137°, identified as 3 : 3′-*diamino*-N-*formyldiphenylamine* (II), which was synthesised for comparison from 3 : 3′-*dinitro*-N-*formyldiphenylamine*. Bernthsen's synthesis of acridine, although in poor yield, from *N*-formyldiphenylamine (*Annalen*, 1884, **224**, 6) lent colour to the assumption that the above diaminoformyldiphenylamine (II) might be the precursor of proflavine (III). However, it seems unlikely that any considerable amount of a diphenylamine could form at so low a temperature as 155°; moreover, no 3 : 3′-diaminodiphenylamine was obtained on heating *m*-phenylenediamine with hydrogen chloride at 155°, and only a trace of *N*-formyldiphenylamine from aniline and formanilide under similar conditions. Finally, when 3 : 3′-diamino-*N*-formyldiphenylamine was warmed in glycerol with either ethereal or aqueous hydrogen chloride, no more than a 30% yield of proflavine could be obtained together with large amounts of an unidentified resinous material not encountered in the normal reaction. It is therefore unlikely that the reaction being studied proceeds mainly *via* diaminoformyldiphenylamine.



The alcohol-soluble substance obtained (14% yield) in the interrupted reaction was white and was readily hydrolysed in moist air, or on boiling with N-hydrochloric acid, to *m*-phenylenediamine (identified as its *picrate*) and a resin. On warming with hydrogen chloride in glycerol, it gave a 75% yield of proflavine, of which it is therefore considered a true precursor. It was also obtained by heating *m*-phenylenediamine and formic acid in slowly distilling toluene. The analytical figures correspond to N-2′ : 4′-*diamino-α-hydroxybenzyl*-m-*phenylenediamine* (IV). Dimroth's synthesis of *N*-2′ : 4′ : α-trihydroxybenzylaniline from formanilide and resorcinol (*Ber.*, 1902, **35**, 984) provides an analogy.

The alcohol-insoluble material isolated in the interrupted reaction was identified as *bis*-2 : 4 : 2′ : 4′-*tetra-aminobenzhydryl ether* (6% yield). Higher yields of this substance (70%) were obtained in the absence of glycerol, if the hydrogen chloride was replaced by boric acid. Hydrochloric acid (HCl : NH_2 = 1 : 4) in 50% aqueous acetone hydrolysed the ether to 2 : 4 : 2′ : 4′-*tetra-aminobenzhydrol* (V*a*), but hydrochloric acid (HCl : NH_2 = 1 : 2) in glycerol at 155° gave a 40% yield of proflavine, the remainder of the product consisting of tetra-aminotetrahydrobisacridyl ether (Part I). The latter was the sole product when the ether was boiled with dilute acid. It would appear that the ether is not an intermediate in the synthesis of proflavine, but is produced during isolation from the highly unstable salts (V*b*) of tetra-aminobenzhydrol. Moreover, the diaminohydroxybenzylphenylenediamine (IV) changed to the ether when dried in a vacuum or when boiled in dilute alcoholic solution.

Although tetra-aminobenzhydrol (V*a*) or salts of its anhydro-form (V*b*) could not be isolated from the reaction mixture, its formation as an intermediate is to be inferred as a necessary step between the compounds (IV) and (III). It was synthesised by reduction of tetra-aminobenzophenone and found to be a white, highly reactive substance. When it was neutralised with acetic acid or with one equivalent of hydrogen chloride, the intensely crimson monoacid salt of the anhydro-form, similar in structure to the highly coloured monoacid salts of triphenylmethane dyes, was formed. This colour change was reversible.

Further addition of hydrochloric acid produced (at p_H 2) a pale yellow diacid salt. Aqueous solutions of the monoacid salt quickly decolorised on standing, giving the above-described ether, whereas the diacid salt, when boiled for ½ hour with hydrochloric acid, gave a nearly quantitative yield of pure proflavine. The reason for the increased yield in the original reaction (see Figure) in the presence of *two* molecules of hydrochloric acid, as against *one*, is now seen, and the evidence points to the dihydrochloride (V*b*) of tetra-aminobenzhydrol as being the immediate precursor of proflavine. The ready formation of 2 : 4 : 2′ : 4′-tetrahydroxybenzhydrol by treating resorcinol and formic acid with hydrogen chloride (Cross and Bevan, J., 1911, **99**, 1455) lends additional support to this theory.

Finally it must be recorded that 2 : 6- or 4 : 6-diaminoacridine could not be isolated from the products of reaction of substance (I), (II), (IV) or (V). Similarly, 3-*amino*-N-*formyldiphenylamine*, from 3-*nitro*-N-*formyldiphenylamine*, gave a 20% yield of 2- but no 4-aminoacridine on heating with hydrogen chloride in glycerol.

Experimental.

Condensation of m-*Aminoformanilide with* m-*Phenylenediamine.*—*m*-Aminoformanilide (1·9 g.; 1 mol.), *m*-phenylenediamine (1·5 g.; 1 mol.), and hydrogen chloride (0·5 g.; 1 mol.) in the form of a 31% aqueous or 7% ethereal solution were mixed with glycerol (10 g.) in which zinc chloride (when used) (5 g.; 2·7 mols.) had been dissolved. The whole was warmed in an open vessel to 155° during ½ hour and kept at 155° for 45 minutes. The melt was cooled and treated with sodium hydroxide solution, and the proflavine recrystallised as the sulphate from 2N-sulphuric acid, basified, and, where necessary, recrystallised from 55 parts of alcohol. The other intermediates were cyclised similarly.

Diphenylamine Compounds (With Miss Dorothy K. Large).—3-Nitrodiphenylamine (6 g.), zinc chloride (5 g.), and formic acid (40 ml.; 90%) were refluxed for 2 hours, the mixture poured into water, and the 3-*nitro*-N-*formyldiphenylamine* recrystallised from 3 parts of alcohol until colourless (yield, 50%). It had m. p. 77°, decomposed above 100°, and was readily soluble in benzene and acetone and very sparingly soluble in light petroleum (Found: N, 11·4. $C_{13}H_{10}O_3N_2$ requires N, 11·55%). 3 : 3′-*Dinitro*-N-*formyldiphenylamine*, similarly prepared from 3 : 3′-dinitrodiphenylamine (Albert and Linnell, J., 1936, 89) and recrystallised from acetone and then from alcohol, gave light buff crystals (65% yield), m. p. 145—146° (corr.), very soluble in alcohol, only slightly soluble in ether and benzene (Found: N, 14·4. $C_{13}H_9O_5N_3$ requires N, 14·6%). These formyl compounds, unlike their parent diphenylamines, are soluble in formic acid without temperature gradient.

3 : 3′-Dinitro-*N*-formyldiphenylamine (15 g.), formic acid (3 ml.), and water (60 ml.) were stirred in a basin on the water-bath while reduced iron (30 g.) was added during ½ hour. The mixture was heated for 20 minutes longer, treated with calcium carbonate (3 g.), and the liquid filtered. The residue contained the 3 : 3′-*diamino*-N-*formyldiphenylamine* (II). This was extracted with acetone (two portions of 50 ml.), the solvent evaporated, and the amine extracted with N-hydrochloric acid and precipitated with sodium acetate (yield, 85%). It formed white needles, sparingly soluble in benzene; m. p. 138·5° (corr.), not raised by recrystallisation from water or alcohol (Found: C, 68·2; H, 5·65; N, 18·3. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7; N, 18·5%). The hydrochloride and the sulphate were very soluble in water. The amine gave no colour with equal parts of 5N-sulphuric acid and 3% hydrogen peroxide in the presence of a trace of ferrous sulphate, but after 1 minute's boiling with 5N-sulphuric acid repetition of the test gave the deep red colour characteristic of 3 : 3′-diaminodiphenylamine. 3-Nitro-*N*-formyldiphenylamine, similarly treated, gave white crystals of 3-*amino*-N-*formyldiphenylamine*, m. p. 131—132° (corr., decomp.) after recrystallisation from *cyclo*hexane and alcohol (Found: C, 73·3; H, 5·8; N, 13·1. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%). These amines were also satisfactorily prepared by reduction with hydrogen and Raney-nickel at atmospheric pressure by the method of Albert and Ritchie (*Proc. Roy. Soc. N.S.W.*, 1940, **74**, 77).

N-2′ : 4′-*Diamino*-α-*hydroxybenzyl*-m-*phenylenediamine* (IV) (With W. Kennard).—*m*-Phenylenediamine (6 g.; 2 mols.), formic acid (1 g.; 1 mol.), boric acid (0·1 g.), and toluene (30 ml.) were heated so that the toluene slowly distilled (5 hours) through a 16-inch column, the whole being mechanically shaken. The lower layer, after cooling, was rapidly recrystallised from aqueous alcohol. Yield, 30% of white crystals, m. p. approx. 120° (decomp.), soluble in acetone, insoluble in benzene (Found: C, 64·2; H, 6·8; N, 22·6. $C_{13}H_{16}ON_4$ requires C, 63·9; H, 6·6; N, 22·95%).

m-*Phenylenediamine picrate*, m. p. 184° (corr.), was prepared in water and recrystallised from

7 parts of boiling water and from 17 parts of boiling alcohol [Found : picric acid, by titration against methylene-blue (Bolliger, *Analyst*, 1939, **64**, 416), 80·5. $C_6H_8N_2,2C_6H_3O_7N_3$ requires picric acid, 80·9%].

2 : 4 : 2′ : 4′-*Tetra-aminobenzhydrol* (V*a*).—2 : 4 : 2′ : 4′-Tetra-aminobenzophenone (2·4 g.) (Gulland and Robinson, J., 1925, **127**, 1499) was dissolved in 2N-hydrochloric acid (10 ml.) and precipitated by 2N-sodium hydroxide (10 ml.) (in later experiments it was simply dissolved in morpholine, 6 ml.), and 70 ml. of water added during 5 hours with shaking. A colloidal solution of 2 : 4 : 2′ : 4′-*tetra-aminobenzhydrol* (V*a*) was produced, which, on the addition of ammonium chloride or acetic acid, began to deposit the base at p_H 9·5. By bringing the p_H to 8 and repeatedly filtering the crimson solution, a 75% yield of the free base was obtained as a white powder, decomposing at about 200° with evolution of steam and remelting at about 290°. It was moderately readily soluble in glycol and glycerol (red solutions) and in pyridine, slightly soluble in acetone and alcohol, and very sparingly soluble in ether (Found : C, 63·8; H, 6·6; N, 23·2. $C_{13}H_{16}ON_4$ requires C, 63·9; H, 6·6; N, 23·0%). Dr. Sydney D. Rubbo (University of Melbourne) reports that this substance has no antiseptic properties.

Bis-2 : 4 : 2′ : 4′-*tetra-aminobenzhydryl Ether.*—*m*-Phenylenediamine (0·75 g.), *m*-aminoformanilide (0·95 g.), and boric acid (0·1 g.) were heated at 155° for 45 minutes, and the product extracted with alcohol. The insoluble portion (70% yield) consisted of *bis*-2 : 4 : 2′ : 4′-*tetra-aminobenzhydryl ether*, m. p. approx. 295° (decomp.) (sealed tube in a bath initially at 265°). It was moderately readily soluble in boiling (and sparingly soluble in cold) pyridine and glycol (separation from tetra-aminobenzhydrol), but very sparingly soluble in boiling water, alcohol, butanol, acetone, benzene, chloroform, morpholine, cellosolve, and anisole (Found : C, 66·7; H, 6·35; N, 23·7. $C_{26}H_{30}ON_8$ requires C, 66·4; H, 6·4; N, 23·8%). It was stable in boiling alkali, dissolved in dilute acids with a pale yellow colour, and on diazotisation gave a brown precipitate and solution that coupled with β-naphthol (scarlet). Boiling dilute acetic acid initiated hydrolysis to tetra-aminobenzhydrol (crimson solution), but before this was completed cyclisation to tetra-aminotetrahydrobisacridyl ether (Part I) set in.

The author wishes to thank Professor J. C. Earl and Mr. N. G. Hills for helpful suggestions. The assistance of a Commonwealth Research Fellowship is gratefully acknowledged.

THE UNIVERSITY OF SYDNEY. [*Received, April 26th;* 1941.]