73. *Derivatives of Arsacridine. Part I.*

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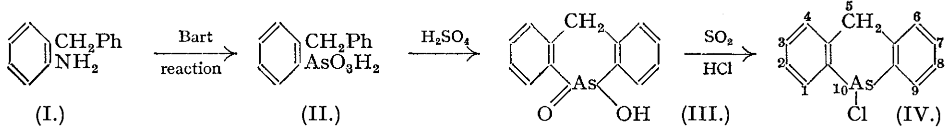
2-Aminodiphenylmethane has been prepared from phthalic anhydride in 53% yield by a four-stage process. Its conversion into 10-chloro-5 : 10-dihydroarsacridine (IV) (Gump and Stoltzenberg, *J. Amer. Chem. Soc.*, 1931, **53**, 1428) has been improved. The 2-*methyl* derivative of (IV) has been prepared in a similar manner, and (IV) has been converted into 10-*cyano*-5 : 10-*dihydroarsacridine.*

A re-examination of the physiological properties of a number of arsenical heterocyclic compounds (carried out during the war at the Chemical Defence Research Establishment, Porton) showed that 10-chloro-5 : 10-dihydroarsacridine * (IV) possessed outstanding sternutatory activity. This substance had been prepared by Gump and Stoltzenberg (*loc. cit.*) by conversion of 2-aminodiphenylmethane (I) into the arsonic acid (II), followed by cyclisation to arsacridinic acid (III) and subsequent reduction.



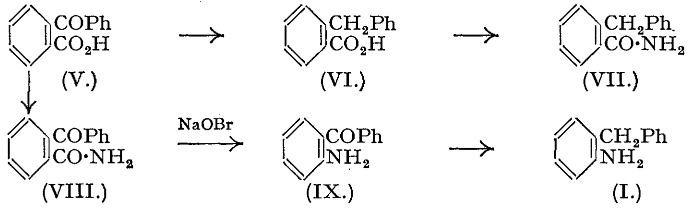
(I.) (II.) (III.) (IV.)

The amine (I) was prepared from *o*-nitrobenzyl chloride by a Friedel–Crafts reaction with benzene and subsequent reduction. The scarcity of toluene, together with the low conversion efficiencies from toluene to *o*-nitrobenzyl chloride, and *o*-nitrobenzyl chloride to the amine (I), made this method of synthesis quite unsuitable for bulk production, and alternative routes were therefore sought.

No appreciable reaction occurred when diphenylmethane was heated with arsenic trichloride alone or in the presence of mercuric chloride or stannic chloride. When aluminium chloride was used as catalyst, a vigorous reaction ensued with decomposition of some of the diphenylmethane (Scholl and Seer, *Ber.*, 1922, **55**, 338), but none of the desired product (IV) could be isolated from the reaction mixture. Attempts were made to condense diphenylchloroarsine with methylene chloride, in the presence of aluminium chloride, in a variety of solvents (carbon disulphide, tetrachloroethane, and nitrobenzene) and at various temperatures, with negative results. Freshly prepared aluminium bromide being used with carbon disulphide as solvent, a vigorous reaction set in, but the only product was a black tar, together with unchanged diphenylchloroarsine. Similarly, attempted condensation of paraformaldehyde with diphenylchloroarsine in the presence of phosphoric oxide, sulphuric acid, or phosphorus oxychloride at 200—250° afforded only unworkable black tars.

In view of the lack of success of these direct condensation methods further investigation was limited to improvement of the method of Gump and Stoltzenberg, and in particular to finding a satisfactory method for the preparation of 2-aminodiphenylmethane. Two alternative routes starting from *o*-benzoylbenzoic acid (V) were examined.

2-Aminobenzophenone (IX) has been prepared in moderate yield by Graebe and Ullmann (*Annalen*, 1896, **291**, 13) from *o*-benzoylbenzoic acid by conversion into the amide and treatment with sodium hypobromite, but its reduction to the desired 2-aminodiphenylmethane has not been described. Ullmann (*ibid.*, p. 24) reduced (V) to *o*-benzylbenzoic acid (VI) but failed to convert it into (I) by the same series of reactions.



(V.) (VI.) (VII.) (VIII.) (IX.) (I.)

In view of the ready accessibility of *o*-benzoylbenzoic acid and the good yield (80%) of the reduced acid (VI) obtained by zinc dust and ammonia reduction (Barnett, Cook, and Nixon,

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* The numbering of the arsacridine ring follows the acridine numbering customary in the *Journal.*—Editor.

J., 1927, 504) the possibilities of the latter route were first investigated. However, the findings of Ullmann were confirmed, the amide (VII) on treatment with sodium hypobromite giving only a small amount of an amine which was not 2-aminodiphenylmethane. It is probable that the main reaction is substitution of the methylene group by bromine, a reaction which cannot occur with *o*-benzoylbenzamide.

Attention was therefore turned to the alternative route involving the reduction of 2-aminobenzophenone (IX). Of the various methods tried only sodium and ethyl or amyl alcohol was effective; amalgamated zinc and hydrochloric acid under various conditions gave a brown resin; zinc dust and glacial acetic acid reduced only as far as 2-aminobenzhydrol; iron filings and acetic acid were without effect. Attempts to effect the reduction electrolytically and catalytically (Raney nickel) were without success, although high-pressure hydrogenation with a copper chromite catalyst afforded 33% conversion. The reduction by the sodium and alcohol method was sufficiently effective, however, to make this route attractive provided that Graebe and Ullmann's conversion of the acid (V) into the amine (IX) could be improved.

Attempts to convert the acid (V) or its methyl ester directly into the amide by the action of ammonia were unsuccessful, but the number of operations required to carry out this conversion by the published method (Graebe and Ullmann, *loc. cit.*) through the acid chloride has been reduced and the yield increased to 80%. The original Hofmann degradation of the amide (VIII) to the amine (IX) was considerably improved by the addition of bromine to the alkaline solution of (VIII) in place of using preformed sodium hypobromite, and even better results were obtained by using sodium hypochlorite. The overall yield of 2-aminodiphenylmethane (I) from phthalic anhydride was thus raised to 53%.

The Bart reaction for the conversion of (I) into the arsonic acid (II) was re-investigated; by using a " simultaneous addition " technique under conditions of controlled pH (Booker, Murray, Spring, Stanley, and Todd, forthcoming publications) the yield was raised to 50%. Even better results were obtained by using a modification of the Doak procedure. Under the original conditions of the Doak method (*J. Amer. Chem. Soc.*, 1940, **62**, 167) 2-aminodiphenylmethane gave poor and variable yields of arsonic acid; among other products a considerable amount of fluorene was always obtained. Consistent yields of 70—75% were obtained, however, when the method was modified by increasing the amount of arsenic trichloride to 100% excess, lowering the temperature of diazotisation and increasing the quantity of cuprous bromide from a catalytic amount to slightly more than one molar equivalent.

The final stages of the synthesis, involving the cyclisation of (II) to arsacridinic acid (III), followed by reduction to (IV), presented no difficulty and gave an 85% yield of crude product. By an analogous series of reactions, 2-*p*-toluoylbenzoic acid was converted into 2-amino-4′-methylbenzophenone (Kippenberg, *Ber.*, 1897, **30**, 1133), which was reduced to 2-*amino*-4′-*methyldiphenylmethane*, from which 10-*chloro*-2-*methyl*-5 : 10-*dihydroarsacridine* was obtained. Interaction of (IV) with potassium cyanide yielded 10-*cyano*-5 : 10-*dihydroarsacridine* which proved to be an even more powerful sensory irritant than the chloro-compound.

EXPERIMENTAL.

o-*Benzoylbenzamide*.—*o*-Benzoylbenzoic acid monohydrate (108 g.) was dehydrated by heating in a basin on the water-bath for 1½ hours, with frequent stirring and crushing. The dehydrated acid (100 g.) was dissolved in dry chloroform (200 c.c.) and after the addition of thionyl chloride (40 c.c.) was warmed gently under reflux on the water-bath until reaction was complete. The solvent and excess of thionyl chloride were distilled off, the last traces being removed by distillation with dry benzene (20 c.c.) in a vacuum, this treatment being repeated once.

Without further purification the acid chloride was dissolved in dry benzene (200 c.c.) and slowly treated with ammonia solution (*d* 0·880; 100 c.c.) with cooling. Considerable heat was developed and the whole set to a pasty mass. The crude amide was filtered off and washed with water. It was subsequently found that the purity of the amide greatly influenced the yield in the next stage, specimens of amide with an m. p. below 161—162° giving consistently poor yields of amine. The chief trouble appeared to be due to the retention of ammonium chloride and probably ammonium benzoylbenzoate by the crude amide. Purification could be carried out by recrystallising the crude product (m. p. 150—153°) from dilute alcohol (which raised the m. p. to 155—160°) and then from a large volume of toluene which gave a product of m. p. 161°.

To overcome this troublesome crystallisation another method of purification was sought and it was found that the crude amide (from 100 g. of dehydrated acid) was readily purified by washing twice more, preferably by grinding in a mortar, with hot water. By this treatment the m. p. was raised directly to 160—161°, one crystallisation from 40% alcohol raising it to 162—163° (yield, 75—80 g.; 75—80%).

2-*Aminobenzophenone*.—(a) Pure *o*-benzoylbenzamide (45 g.; m. p. 161°) was added to a solution of sodium hydroxide (20 g.; 2¼ mols.) in water (150 c.c.); the amide dissolved completely and rapidly. The solution was cooled in ice and a slight excess (*ca.* 5%) of sodium hypochlorite solution (97 c.c. of a solution containing 0·075 g. of chlorine per c.c. as sodium hypochlorite) added slowly with shaking or stirring; little heat was developed. The clear solution was warmed on a water-bath to about 80°, whereupon the amine began to separate as fine yellow droplets. The mixture was heated for a further ½ hour at 100° and cooled, and the amine which readily crystallised was collected; yield 33—36 g. (85—92%), m. p. 95—102°. Recrystallised from alcohol, it had m. p. 107° (Geigy and Königs, *Ber.*, 1885, **18**, 2403, give m. p. 105—106°; Carré, *Compt. rend.*, 1909, **148**, 493, gives 110—111°).

(b) The pure amide (45 g.; m. p. 161°) was dissolved in sodium hydroxide solution (300 c.c.; 15%) and cooled to 0° in ice; bromine (10·2 c.c.) was then added dropwise with stirring. The mixture was then heated as under (a), and the amine collected on cooling; this was usually slightly less pure (m. p. 90—100°) than that obtained as described under (a); yield 80—85%.

Reduction of 2-*Aminobenzophenone*.—(a) *Reduction with sodium and alcohol.* The pure amino-ketone (10 g.) was dissolved in absolute alcohol (100 c.c.), and the hot solution rapidly added to small pieces of sodium (10 g.; 100% excess) in a flask fitted with an efficient reflux condenser. The reaction was allowed to proceed unchecked; when it moderated a further amount of hot alcohol (20 c.c.) was added, and the last of the sodium dissolved by external heating and shaking. The reaction mixture was then diluted with water (250 c.c.), the alcohol removed in a vacuum, and the amine distilled with steam. Distillation was slow, but the product was reasonably pure, and the amine, which came over as a colourless oil, crystallised on cooling. Ether extraction of the aqueous part of the distillate yielded a further amount of amine; total yield, 8·4 g. (90%), m. p. 44°. The pure amine, crystallised from light petroleum, had m. p. 52° (Carré, *Compt. rend.*, 1909, **148**, 102, gives m. p. 52°). The acetyl derivative crystallised from dilute alcohol; m. p. 130° (Fischer and Schutte, *Ber.*, 1893, **26**, 3086, give m. p. 135°). The benzoyl derivative, from dilute alcohol, had m. p. 116° (Fischer and Schmidt, *Ber.*, 1894, **27**, 2786, give m. p. 116°).

(b) *Reduction with sodium and amyl alcohol.* The amino-ketone (10 g.) was dissolved in hot *iso*amyl alcohol (b. p. 129—131°; 100 c.c.), and the boiling solution added all at once to small pieces of sodium (10 g.). The reaction was much slower than when using ethyl alcohol; towards the end of the reaction a further 20 c.c. of amyl alcohol were added, and the last traces of sodium dissolved by heating and shaking. Water (200 c.c.) was then added and after thorough shaking the aqueous layer was removed and the amyl alcohol distilled with steam. The residual crude amine was dissolved in benzene (40 c.c.), and the solution shaken with concentrated hydrochloric acid until the hydrochloride crystallised; this was filtered off, washed with benzene, and dried. On treatment with dilute ammonia it gave the amine as a colourless solid, m. p. 49—50° (yield, 80%). An alternative method of isolation involving distillation of the crude amine with superheated steam followed by distillation at reduced pressure gave a higher yield (92%), but the product was not as pure and did not crystallise readily.

When the quantity of sodium was reduced to 60% instead of 100% excess, the experiment remaining the same in all other respects, the same quantity and quality of amine were obtained.

(c) *High-pressure hydrogenation of* 2-*aminobenzophenone.* The amino-ketone (200 g.) was hydrogenated at high pressure and at a temperature of 250°, a copper chromite catalyst being employed. About 20 l. (theory, 44 l.) of hydrogen were absorbed in 6 hours and the catalyst was converted into the completely inactive form. The product was taken up in ethanol, filtered from the catalyst, and the ethanol removed by distillation under reduced pressure. The crude product (178 g.) was distilled under reduced pressure and a pale yellow oil (134 g.) was collected at 130—160°/0·2 mm. It consisted of a mixture of *o*-aminodiphenylmethane and *o*-aminobenzophenone, which could not be separated satisfactorily by distillation. By fractional crystallisation of the bases and their hydrochlorides, 2-aminodiphenylmethane hydrochloride (72 g.; 33%) was isolated in a pure condition.

Diphenylmethane-2-*arsonic Acid*.—(a) *Bart method.* A series of experiments was made in order to determine the relation between the pH of the reaction mixture and yield of product in the coupling of diazotised 2-aminodiphenylmethane and sodium arsenite. It was found that the optimum pH was *ca.* 9·5, but even under the best conditions the yield of arsonic acid could not be increased above 50%, probably because of the instability of the diazo-compound and its tendency to pass into fluorene. The following details refer to the method adopted for large scale preparations:

2-Aminodiphenylmethane hydrochloride (22 g.; 0·1 mol.) was suspended in dilute hydrochloric acid (21 c.c. of 36° Tw. + 180 c.c. of water), cooled to − 5° with stirring, and diazotised with a solution of sodium nitrite (6·9 g.) in water (15 c.c.). The resulting solution was diluted to 250 c.c. with ice-water. Arsenious oxide (19·8 g.; 0·2 equiv.) was dissolved in a solution of sodium hydroxide (12 g.; 0·3 mol.) and sodium carbonate (15·9 g.; 0·3 equiv.) in water (180 c.c.), and the solution diluted to 250 c.c. The two solutions were run simultaneously into a mixture of ice (*ca.* 75 g.) and ammoniacal copper sulphate solution (13 c.c. of 10%) with stirring during 1 hour, the temperature of the mixture being kept below 5°. After the addition was complete stirring was continued for a further 20 minutes, the mixture then no longer giving a colour with an alkaline solution of H-acid. "Filtercel" (*ca.* 10 g.) was added, and the mixture filtered. The filtrate was made neutral to litmus by the careful addition of dilute hydrochloric acid with vigorous stirring. After standing overnight the small amount of precipitate was removed by filtration and the filtrate was made acid to Congo-red by the addition of hydrochloric acid. The product rapidly crystallised. It was collected, washed, and dried at 60° (14 g.; 48%), giving colourless crystals, m. p. 155—156° with previous sintering (lit. 161—162°). By salting out the mother-liquors a further 0·35 g. was obtained.

The purity of the product (average 95—99%) was estimated by titration. Electrometric titration showed that a good end-point could be obtained by titrating only the first ionisable hydrogen, the exact end-point being at pH 6·6 and the pH changing from 7·3 to 6·3 by addition of 0·2 c.c. in a titre of 17 c.c. of N-sodium hydroxide.

Titration method. Approximately 0·6 g. of acid was weighed out accurately, dissolved in 25 c.c. of N-sodium hydroxide, and titrated against N/5-hydrochloric acid, 5 drops of bromocresol-purple (B.D.H.) being added. The solution became colourless at the end point; addition of a further drop of acid produced a distinct yellow colour.

(b) *Doak method.* 2-Aminodiphenylmethane (18·3 g.) was dissolved in absolute alcohol (250 c.c.), cooled to − 10°, and to the solution were then added, in order, concentrated sulphuric acid (8 c.c.), arsenic trichloride (17 c.c.), and powdered anhydrous calcium chloride (10 g.). The solution was diazotised at − 10° to − 15° with a solution of sodium nitrite (7·2 g.) in water (9 c.c.). The solution was stirred for ½ hour longer at − 10°, urea (1 g.) added to remove any excess of nitrous acid, and then freshly prepared dry cuprous bromide (15 g.) was added gradually, the reaction temperature being kept below − 10°. After being stirred for one hour at − 10° the reaction mixture was allowed to warm slowly to room temperature. Alcohol was removed by steam distillation, the residue diluted with water and cooled, and the crude arsonic acid filtered off and washed. It was purified by dissolving in warm sodium carbonate solution, filtering through charcoal, and acidifying with hydrochloric acid (yield, 21·8 g.; 74%).

Arsacridinic Acid (III).—Following the procedure of Gump and Stoltzenberg (*loc. cit.*) a 95% yield of crude product was obtained.

10-*Chloro*-5 : 10-*dihydroarsacridine* (IV).—Crude arsacridinic acid (12·5 g.) was reduced according to the directions of Gump and Stoltzenberg. The crude product (11·3 g.; 90%) solidified as soon as it was removed from the steam-bath. It was dissolved in hot benzene (50 c.c.) and treated with a little charcoal. The filtered solution was concentrated to small bulk and allowed to crystallise. The product (8·9 g.; 71%) was pale yellow and had m. p. 110—111° (lit. 114—115°).

2-*Amino*-4′-*methyldiphenylmethane*.—2-Amino-4′-methylbenzophenone (Kippenberg, *loc. cit.*) was reduced with sodium and amyl alcohol as described above, giving 2-*amino*-4′-*methyldiphenylmethane* (yield, 65%), which had m. p. 66° after recrystallisation from alcohol or light petroleum (Found: C, 85·3; H, 7·5. $C_{14}H_{15}N$ requires C, 85·4; H, 7·6%). The acetyl derivative, prepared in the usual manner and crystallised from alcohol, had m. p. 171°.

10-*Chloro*-2-*methyl*-5 : 10-*dihydroarsacridine*.—The above amine was converted into 4′-methyldiphenylmethane-2-arsonic acid in 25% yield by the Bart reaction, conditions similar to those employed for the parent substance being used. The crude arsonic acid (2·95 g.) was dissolved in concentrated sulphuric acid (12 c.c.), and the solution heated at 95° for 5 minutes. On pouring into cold water a gum was precipitated; this was dissolved in 10% aqueous sodium carbonate, heated with charcoal, and filtered. Dilute hydrochloric acid was added to the filtrate with stirring until a slight turbidity appeared; charcoal was added, and the mixture filtered. Acidification of the filtrate gave a precipitate (1·4 g.) which crystallised on standing. It was suspended in concentrated hydrochloric acid (14 c.c.), chloroform (14 c.c.) was added, together with a trace of potassium iodide, and reduction with sulphur dioxide was carried out in the usual manner. The chloroform layer on evaporation yielded a brownish oil (1·4 g.) which did not crystallise. It was distilled at 125—140° (bath temp.)/3×10^{-3} mm.; the resulting pale yellow distillate crystallised on standing and then had m. p. 55—60°. Recrystallisation from light petroleum (b. p. 40—60°) yielded 10-*chloro*-2-*methyl*-5 : 10-*dihydroarsacridine* as pale yellow prisms, m. p. 65·5—66·5° (Found: C, 57·5; H, 4·2. $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·1%).

10-*Cyano*-5 : 10-*dihydroarsacridine*.—Pure potassium cyanide (0·65 g.) was heated under reflux with anhydrous methanol (10 c.c.) until a clear solution was obtained. 10-Chloro-5 : 10-dihydroarsacridine (2·67 g.) was added, and the mixture refluxed for 20 minutes. The chloro-compound rapidly dissolved and a precipitate of potassium chloride was formed. The hot solution was filtered and allowed to cool, whereupon colourless crystals (1·5 g.; 56%) separated. After recrystallisation from anhydrous methanol the *cyanide* had m. p. 114—115°, giving a cloudy liquid. Mixed with the chloride (m. p. 110—111°) the m. p. was depressed to 103—106° (Found: C, 63·1; H, 3·5; N, 4·9. $C_{14}H_{10}NAs$ requires C, 62·9; H, 3·7; N, 5·2%).

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