74. *Derivatives of Arsacridine. Part II.*

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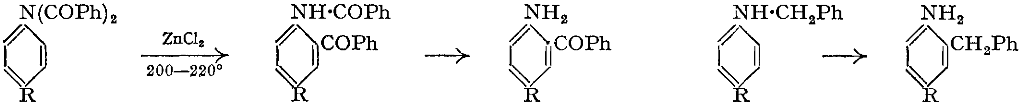
4-Substituted 2-aminodiphenylmethanes are readily obtained by the rearrangement of *p*-substituted *N*-benzylanilines under the influence of aluminium chloride in presence of excess of the parent arylamine. Two of these products have been converted into derivatives of arsacridine.

In the synthesis of derivatives of arsacridine by the method of Gump and Stoltzenberg (*J. Amer. Chem. Soc.*, 1931, **53**, 1428) the principal limitation is the availability of the substituted 2-aminodiphenylmethanes required as intermediates. One method for the preparation of such substances has been described in Part I (preceding paper), but it has the disadvantage of involving a considerable number of stages. In attempting to overcome this difficulty, we first investigated the conversion of diacylanilides of type (I) into the corresponding benzophenone derivatives (II) by the catalytic migration of a benzoyl group (Chattaway, *J.*, 1904, **85**, 589). In the two cases investigated (R = Cl and R = Me), the yields of 5-chloro-2-amino- and 2-amino-5-methyl-benzophenone were 8·8% and 12·3% respectively. The latter compound was characterised by reduction and acetylation, 2-acetamido-5-methyldiphenylmethane (see below) being obtained.

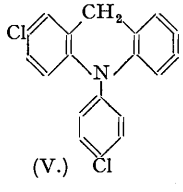


(I.) (II.) (III.) (IV.)

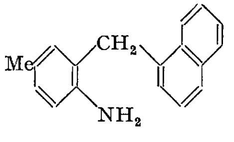
In view of these unsatisfactory yields, attention was turned to the rearrangement of *N*-benzylanilines. Hickinbottom (*J.*, **1937**, 1119) obtained a mixture of 2- and 4-aminodiphenylmethanes in moderate yield (31·9%) by heating *N*-benzylaniline with anhydrous cobalt chloride. On applying this procedure to *N*-benzyl-*p*-toluidine (III; R = Me), we obtained a 23·9% yield of 2-amino-5-methyldiphenylmethane (IV; R = Me), characterised as its *acetyl* and p-*nitrobenzylidene* derivatives. The use of aluminium chloride gave a slightly higher yield; zinc chloride was less effective. A considerable quantity of a high-boiling material was also produced in the reaction. It seemed probable that this was, at least in part, composed of 2-benzylamino-5-methyldiphenylmethane or 2 : 6-dibenzyl-*p*-toluidine, formed by attack of a free benzyl radical on a molecule of unchanged *N*-benzyl-*p*-toluidine or of the newly formed 2-amino-5-methyldiphenylmethane (Hickinbottom, *loc. cit.*, observed the formation of 2 : 4-dibenzylaniline in the reaction carried out by him). If this were so, addition of *p*-toluidine to the reaction mixture should increase the yield of the desired product. This proved to be the case; by heating a mixture of equal weights of *N*-benzyl-*p*-toluidine and *p*-toluidine with aluminium chloride, the yield of (IV; R = Me) was raised to 50%. On treating a mixture of *p*-chloroaniline and its *N*-benzyl derivative in the same manner, 5-chloro-2-aminodiphenylmethane (IV; R = Cl), characterised as its *hydrochloride*, was obtained, together with a high-melting product which from its mode of formation and its composition is almost certainly 3-*chloro*-10-p-*chlorophenyl*-5 : 10-*dihydroacridine* (V). 4-*Amino*-m-*tolyl*-α-*naphthylmethane* (VI) was similarly obtained from N-α-*naphthylmethyl*-p-*toluidine* in 68% yield. An attempt to achieve a similar rearrangement of benzoyl-*p*-toluidine, using cobalt chloride as catalyst in presence of excess *p*-toluidine, failed to give any of the desired aminobenzophenone.

The conversion of the aminodiphenylmethanes (IV; R = Me or Cl) into arsacridine derivatives followed the lines described in Part I (preceding paper); 10-*chloro*-3-*methyl* (VII; R = Me; R′ = Cl), 3 : 10-*dichloro*- (VII; R = R′ = Cl) and 3-*chloro*-10-*cyano*-5 : 10-*dihydroarsacridine* (VII; R = Cl, R′ = CN) were thus obtained. Conversion of the amine (VI) into the corresponding arsonic acid appeared to give such low yields that the further stages in the synthesis of a 3 : 4-benzarsacridine derivative from this material were not investigated.

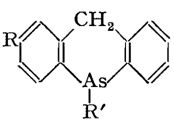
For the preparation of nitro- and amino-derivatives of arsacridine, both the rearrangement of *N*-benzyl-*p*-nitroaniline and the nitration of arsacridinic acid were found impracticable. Nitration of 2-acetamidodiphenylmethane gave, after hydrolysis of the initially formed 5-*nitro*-2-*acetamidodiphenylmethane*, a good yield of 5-*nitro*-2-*aminodiphenylmethane*, but the conversion of this substance into the corresponding acid was not investigated since it was at this stage already clear that the projected synthesis was for various reasons unlikely to be of technical interest.



(V.)



(VI.)



(VII.)

Experimental.

5-*Chloro*-2-*aminobenzophenone*.—A mixture of *p*-chloroaniline (23·8 g.), benzoyl chloride (52·5 g.; 2 mols.), and zinc chloride (1·5 g.) was kept at 220—230° for 14 hours. The mixture was cooled and hydrolysed by refluxing for 60 hours with a mixture of ethyl alcohol (100 c.c.) and concentrated hydrochloric acid (50 g.). Excess of alcohol and ethyl benzoate were removed in a rapid current of steam, the residue decanted from undistillable tarry oil, and made alkaline with sodium hydroxide solution. Superheated steam was then blown through the mixture, *p*-chloroaniline coming over first followed by 5-chloro-2-aminobenzophenone which quickly solidified in yellow flocks; after one crystallisation from chloroform–light petroleum, it had m. p. 97—98° (yield, 3·8 g., 8·8%).

2-*Amino*-5-*methylbenzophenone*.—*p*-Toluidine (22·3 g.), benzoyl chloride (58·6 g.), and zinc chloride

(1·5 g.) were treated as described above, giving 2-amino-5-methylbenzophenone (5·4 g.; 12·3%) which after one crystallisation from chloroform–light petroleum had m. p. 65—66°.

Reduction of 5-*Chloro*-2-*aminobenzophenone*.—A solution of 5-chloro-2-aminobenzophenone (2·2 g.) in boiling *iso*amyl alcohol (22 c.c.; b. p. 129—131°) was poured on sodium slices (2·2 g.) heated in an oil-bath to 80°. The reaction was allowed to proceed unchecked but an efficient reflux condenser was employed; when the reaction had moderated, amyl alcohol (5 c.c.) was added and the last traces of sodium were dissolved by heating and shaking. The reaction mixture was diluted with water (45 c.c.) and shaken vigorously, the aqueous layer separated, and amyl alcohol removed in steam. The residual amine was distilled from a bath at 160—170° with superheated steam. Distillation was fairly rapid, the amine collecting in about 1 litre of distillate; this was extracted with ether, the extract dried (sodium sulphate), and the ether removed. The residue was distilled in a vacuum, the product collecting as a pale yellow oil which could not be induced to crystallise.

Reduction of 2-*Amino*-5-*methylbenzophenone*.—2-Amino-5-methylbenzophenone (4·8 g.) was reduced with sodium (4·8 g.) and *iso*amyl alcohol (48 c.c.) as above. The product was again a pale yellow oil (4·0 g.) which contained 62·0% of primary amine, *M* 197, hence 55·4% yield. The product gave a solid acetyl derivative, m. p. 164·5—165·5°, which was shown to be identical with 2-acetamido-5-methyldiphenylmethane (m. p. and mixed m. p.).

N-*Benzyl*-p-*toluidine*.—A mixture of *p*-toluidine (428 g.; 4 mols.), sodium hydrogen carbonate (105 g.; 1·25 mols.) and water (100 c.c.) was kept at 90—95°, and benzyl chloride (127 g.; 1 mol.) run in during 1½—2 hours with vigorous stirring. The hot mixture was filtered, the aqueous layer separated, and the oil washed with saturated salt solution. After drying (sodium sulphate), the mixture was distilled under reduced pressure, giving *p*-toluidine, b. p. 80—90°/12 mm., followed by *N*-benzyl-*p*-toluidine, b. p. 180—190°/12 mm. (148 g.; 75·1%). The latter formed a pale yellow oil which was employed in the migration experiments without further purification. The hydrochloride after one recrystallisation from alcohol–ether had m. p. 179—181° (Law, *J.*, 1912, **101**, 158, gives m. p. 181—182°).

2-*Amino*-5-*methyldiphenylmethane*.—The method described here is typical of all the benzyl rearrangements shown in the table below. The yields quoted in these experiments are based on an analytical method for primary amines supplied by Messrs. I.C.I., Ltd. (Dyestuffs Division), in which the diazotised amine is coupled with a standard solution of *p*-sulphophenylmethylpyrazolone.

A mixture of benzyl-*p*-toluidine (50 g.), *p*-toluidine (50 g.), and aluminium chloride (10 g.) was heated at 200° for 16 hours. The hot reaction mixture was poured into an excess of sodium hydroxide solution with stirring. Ether was added to assist the separation of the two layers. The mixture was filtered, and the ethereal layer separated and dried. After removal of the ether, the residue was fractionated, the two higher fractions being analysed for primary amine: Fraction I, up to 130°/12 mm., 22·6 g. of *p*-toluidine. Fraction II, 150—170°/0·1 mm., 23·0 g., 68·5% primary amine (*M*, 197). Fraction III, 165—200°/0·1 mm., 18·4 g., 48·7% primary amine (*M*, 197). Fraction IV, high-boiling residue, 21·7 g. Total yield of primary amine (*M*, 197) = 49·6%.

The *acetyl* derivative separated from alcohol as needles, m. p. 165·5° (Found: C, 80·4; H, 7·4. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2%). The p-*nitrobenzylidene* derivative separated from alcohol as yellow needles, m. p. 119° (Found: C, 76·8; H, 5·4; N, 8·5. $C_{21}H_{18}O_2N_2$ requires C, 76·4; H, 5·5; N, 8·5%).

Rearrangement of N-*benzyl*-p-*toluidine at* 200°.

(25 G. used in each experiment.)

Expt. No.	Catalyst.	Free base added.	Time (hrs.).	Yield (%).
I	$CoCl_2$, 10 g.	—	16	23·9
II	$AlCl_3$, 5 g.	—	16	25·1
III	$ZnCl_2$, 5 g.	—	16	12·8
IV	$CoCl_2$, 10 g.	*p*-Toluidine, 25 g.	17	1·5
V	$AlCl_3$, 5 g.	*p*-Toluidine, 25 g.	17	51·0
VI	$AlCl_3$, 5 g.	*p*-Toluidine, 50 g.	35	24·6

N-*Benzyl*-p-*chloroaniline*.—A mixture of *p*-chloroaniline (245·7 g.; 1·9 mols.), sodium hydrogen carbonate (105 g.; 1·25 mols.), and water (150 c.c.) was kept at 90—95°, and benzyl chloride (127 g.; 1 mol.) run in during 1 hour with vigorous stirring which was continued for a further 3 hours. The hot mixture was filtered, the aqueous layer separated, and the oil washed with saturated salt solution. Ether was added, and the ethereal solution dried (Na_2SO_4). The ether was removed, and the mixture distilled under reduced pressure, giving *p*-chloroaniline (126 g.), b. p. 120—135°/12 mm., followed by N-*benzyl*-p-*chloroaniline*, b. p. 207°/12 mm. (193 g.; 89%), m. p. 44°; after crystallisation from aqueous alcohol it had m. p. 45° (Found: C, 72·1; H, 5·8. $C_{13}H_{12}NCl$ requires C, 71·7; H, 5·5%).

5-*Chloro*-2-*aminodiphenylmethane*.—A mixture of benzyl-*p*-chloroaniline (185 g.), *p*-chloroaniline (126·1 g.), and aluminium chloride (38 g.) was heated at 200° for 15 hours. The reaction mixture was allowed to cool and while still fluid was poured into excess of sodium hydroxide solution with stirring. Ether was added, and the ethereal layer separated and dried (Na_2SO_4). The ether was removed, and the residue fractionated: Fraction I, up to 140°/12 mm., *p*-chloroaniline (83·5 g.). Fraction II, 145—190°/0·1 mm., brown liquid (104·1 g.). Fraction III, b. p. 190—225/0·1 mm., yellow crystalline solid (31 g.). There was a considerable tarry distillation residue (45 g.). Fraction II consisted essentially of 5-chloro-2-aminodiphenylmethane, which on redistillation through a fractionating column was obtained as a slightly brownish liquid, b. p. 140—145°/0·1 mm. (69 g.; 37%). It readily gave a *hydrochloride*, separating from dilute hydrochloric acid in colourless needles, m. p. 183—184° (Found: C, 61·2; H, 5·5; N, 5·8. $C_{13}H_{13}NCl_2$ requires C, 61·4; H, 5·2; N, 5·5%). Fraction III recrystallised once from alcohol and then several times from ethyl acetate formed yellow needles, m. p. 258—260° (Found: C, 70·7; H, 3·7; N, 4·5; Cl, 21·3. $C_{19}H_{13}NCl_2$ requires C, 70·0; H, 3·9; N, 4·3; Cl, 21·8%). This material is probably a *dihydroacridine* derivative of structure (V).

N-*a-Naphthylmethyl*-p-*toluidine*.—A 2-litre, three-necked flask was fitted with stirrer, condenser, and dropping-funnel. In the flask were placed *p*-toluidine (214 g.; 2 mols.), sodium hydrogen carbonate (126 g.; 1·5 mols.), and water (300 c.c.), and the whole heated on a steam-bath. 1-Chloromethylnaphthalene (160 g.; 0·9 mol.), dissolved in the minimum amount of benzene, was run in during 1 hour with vigorous stirring. The reaction was completed by heating on the steam-bath for a further 3 hours with stirring. After the mixture had been allowed to cool, ether was added, and the organic layer separated, dried (Na_2SO_4), and distilled. After a first fraction of unchanged *p*-toluidine (118·4 g.), N-*a-naphthylmethyl*-p-*toluidine* (200 g.; 89·5%) distilled at 185—200°/10^{-4} mm. It had m. p. 64—65° (Found: C, 86·6; H, 7·2. $C_{18}H_{17}N$ requires C, 87·4; H, 6·9%). The compound oxidised slowly on standing in air.

4-*Amino*-m-*tolyl-a-naphthylmethane*.—*N*-a-Naphthylmethyl-*p*-toluidine (200 g.; 0·8 mol.), *p*-toluidine (160 g.; 1·5 mols.), and aluminium chloride (40 g.) were heated at 200° for 8 hours with stirring. The product was made alkaline with sodium hydroxide whilst hot, cooled, and ether-extracted. The combined extracts were dried (Na_2SO_4) and distilled, yielding 4-*amino*-m-*tolyl-a-naphthylmethane* (135 g.; 67·5%), b. p. 190°/10^{-3} mm. Recrystallised from alcohol it formed colourless needles, m. p. 88° (Found: C, 87·6; H, 6·4. $C_{18}H_{17}N$ requires C, 87·4; H, 6·9%). The *acetyl* derivative separated from aqueous alcohol as colourless needles, m. p. 147·5° (Found: C, 83·0; H, 6·4. $C_{20}H_{19}ON$ requires C, 83·0; H, 6·6%).

5-*Methyldiphenylmethane*-2-*arsonic Acid*.—A suspension of 2-amino-5-methyldiphenylmethane hydrochloride (23·4 g.; 0·1 mol.) in dilute hydrochloric acid (21 c.c., *d* 1·18; 180 c.c. water) was cooled to − 5° and diazotised with a solution of sodium nitrite (6·9 g.) in water (15 c.c.) added during 2 hours. The mixture was filtered, and the filtrate diluted with water (total volume 250 c.c.). A second solution of arsenious oxide (19·8 g.), sodium hydroxide (12 g.), and sodium carbonate (15 g.) in water (total volume 250 c.c.) was prepared. The two solutions (cooled to 0°) were run simultaneously into a mixture of crushed ice (75 g.) and ammoniacal copper sulphate solution (13 c.c.; 10%) during 1 hour, the mixture being stirred and the temperature kept below 5° throughout. The rate of addition of the two solutions was so controlled that the arsenite solution was 10 c.c. in advance of the diazonium solution.

When the addition was complete, stirring was continued until the mixture failed to give a coloration with an alkaline solution of H-acid (approx. 15 minutes). After the addition of "filtercel" (10 g.), the mixture was filtered, and the filtrate carefully neutralised to litmus by the addition of dilute hydrochloric acid. The small precipitate was removed, and the filtrate acidified to Congo-red by addition of concentrated hydrochloric acid. 5-*Methyldiphenylmethane*-2-*arsonic acid* (11·1 g.; 51%) was collected, washed with water, and dried. After crystallisation from glacial acetic acid, it had m. p. 178—179° (Found: C, 55·1; H, 5·2. $C_{14}H_{15}O_3As$ requires C, 54·9; H, 4·9%).

3-*Methylarsacridinic Acid*.—A solution of 5-methyldiphenylmethane-2-arsonic acid (10·6 g.) in concentrated sulphuric acid (40 c.c.) was kept at 100° for 5 minutes. The mixture was poured into water (600 c.c.), and the precipitated crude arsinic acid purified by solution in hot aqueous sodium carbonate (charcoal/filtercel) and careful acidification of the filtrate with dilute hydrochloric acid. A repetition of this process yielded the arsinic acid as a solid, m. p. 184° (decomp.).

10-*Chloro*-3-*methyl*-5 : 10-*dihydroarsacridine*.—A suspension of 3-methylarsacridinic acid (4·0 g.) in a mixture of hydrochloric acid (50 c.c., *d* 1·18) and chloroform (50 c.c.) was treated with a rapid stream of sulphur dioxide for 5 minutes. A crystal of potassium iodide was added, and the boiling solution again treated with sulphur dioxide for 2 hours. After cooling, the chloroform layer was dried, the solvent removed, and the residue distilled under reduced pressure. The distillate crystallised from benzene–light petroleum, giving 10-*chloro*-3-*methyl*-5 : 10-*dihydroarsacridine*, m. p. 87° (Found: C, 57·2; H, 4·2; $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·1%).

5-*Chlorodiphenylmethane*-2-*arsonic Acid*.—5-Chloro-2-aminodiphenylmethane hydrochloride (25·4 g., 0·1 mol.) was diazotised as for the 5-methyl compound (see above), being filtered and diluted after 20 mins. A second solution of arsenious oxide (19·8 g.; 0·2 equiv.) and sodium carbonate (15·9 g.; 0·3 equiv.) in water (total volume 250 c.c.) was prepared, and the procedure was continued as before, but at ¼ hour intervals 5 g. quantities of calcium carbonate were added to the batch to improve the condition of the tar formed in the reaction. When the addition was complete, the product was worked up as above. 5-*Chlorodiphenylmethane*-2-*arsonic acid* (7·05 g.; 21·8%) was collected, washed with water and dried. After crystallisation from aqueous "cellosolve" it had m. p. 189° (Found: C, 48·4; H, 4·0. $C_{13}H_{12}O_3ClAs$ requires C, 47·8; H, 3·7%).

3-*Chloroarsacridinic Acid*.—A solution of 5-chlorodiphenylmethane-2-arsonic acid (5 g.) in concentrated sulphuric acid (17·9 c.c.) was kept at 100° for 5 minutes. The mixture was poured into water (200 c.c.) with stirring. The product soon crystallised and was collected, washed, and dried at 60° for 16 hours. The 3-*chloroarsacridinic acid* (4·2 g.; 88·5%) after crystallisation from aqueous acetic acid formed colourless needles, m. p. 210—212° (decomp.) (Found: C, 50·9; H, 3·6. $C_{13}H_{10}O_2ClAs$ requires C, 50·6; H, 3·2%).

3 : 10-*Dichloro*-5 : 10-*dihydroarsacridine*.—A suspension of 3-chloroarsacridinic acid (3·9 g.) in a mixture of hydrochloric acid (45 c.c., *d* 1·18) and chloroform (45 c.c.) was treated as above. After removal of the chloroform, the product crystallised on trituration with ether; after recrystallisation from benzene–light petroleum 3 : 10-*dichloro*-5 : 10-*dihydroarsacridine* (3·87 g.; 98·2%) was obtained as colourless needles, m. p. 116° (Found: C, 49·9; H, 2·9. $C_{13}H_9Cl_2As$ requires C, 50·2; H, 2·9%).

3-*Chloro*-10-*cyano*-5 : 10-*dihydroarsacridine*.—2 : 5-Dichloro-5 : 10-dihydroarsacridine (2·12 g.) was added to potassium cyanide (0·445 g.) dissolved in absolute methanol (7 c.c.). The mixture was refluxed for 20 minutes, filtered hot, and allowed to cool. The filtrate deposited colourless crystals of 3-*chloro*-10-*cyano*-5 : 10-*dihydroarsacridine* (1·105 g.; 49%). Recrystallised from anhydrous methanol, the product had m. p. 113—114° (Found: C, 55·7; H, 3·2; N, 4·4. $C_{14}H_9NClAs$ requires C, 55·7; H, 3·0; N, 4·7%). The compound appeared to hydrolyse rather readily when heated with aqueous solvents.

5-*Nitro*-2-*acetamidodiphenylmethane*.—2-Acetamidodiphenylmethane (40 g.) in glacial acetic acid

(30 c.c.) and concentrated sulphuric acid (80 c.c.) was cooled to − 5°, and nitric acid (8 c.c., *d* 1·5) in glacial acetic acid (25 c.c.) was added dropwise with stirring. The temperature was kept below − 5° throughout. After a further 2 hours' stirring, the reaction mixture was poured on ice, diluted with water, and left overnight. On crystallisation from acetone the *product* separated as colourless needles, m. p. 200° (yield, 41 g.; 86%) (Found: C, 66·7; H, 5·0; N, 10·7. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2; N, 10·4%).

5-*Nitro*-2-*aminodiphenylmethane*.—5-Nitro-2-acetamidodiphenylmethane (27·0 g.) was refluxed with concentrated hydrochloric acid (250 c.c.) and glacial acetic acid (50 c.c.) for 6 hours, and the mixture poured into excess of aqueous sodium hydroxide solution; the *product* was filtered off, washed, and recrystallised several times from alcohol, forming yellow prisms, m. p. 104—105° (yield, 16·0 g.; 70%) (Found: C, 68·8; H, 5·5; N, 12·1. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

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