Carcinogenic Nitrogen Compounds. Part XVII. The Synthesis of Angular Benzacridines.*

By Ng. Ph. Buu-Hoï, René Royer, and Michel Hubert-Habart.

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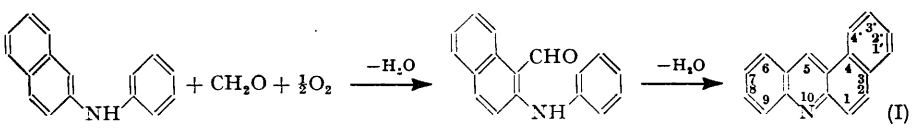
Some features of the synthesis of benzacridines by the Ullmann–Fetvadjian and the Bernthsen method have been more closely investigated, and the reaction between paraformaldehyde, *m*-toluidine, and 1- or 2-naphthol is shown to give two isomeric angular methylbenzacridines in each case. The Mayer cyclisation of diarylamine-*o*-aldehydes has been successfully extended to the synthesis of 3 : 4-benzacridine and related compounds, and a number of new homologues of 1 : 2- and 3 : 4-benzacridine have been prepared for testing as potential carcinogens.

In the Ullmann–Fetvadjian reactions between *m*-toluidine, paraformaldehyde, and 1- or 2-naphthol, the cyclisation can theoretically involve the positions *ortho* or *para* to the methyl group, which would give 6- and 8-methyl-1 : 2- or 6- and 8-methyl-3 : 4-benzacridine, respectively. The formation of two isomers would be parallel to the behaviour of *m*-substituted anilines in the various quinoline cyclisations. Hitherto, only 8-methyl-1 : 2- and -3 : 4-benzacridine had been obtained in this way, the 6-methyl isomers being prepared by pyrolysis of *N*-2′ : 3′-xylyl-1- and -2-naphthylamine with lead oxide (Buu-Hoï, *J.*, 1949, 670). The isolation of small quantities of 6-methyl-1 : 2- and -3 : 4-benzacridine in the Ullmann–Fetvadjian reaction has now been achieved by fractional crystallisation of the picrates of the crude bases obtained. The *ortho*-cyclisation was not observed in the reaction of *m*-toluidine and 6-methyl-2-naphthol with paraformaldehyde, only 8 : 2′-dimethyl-3 : 4-benzacridine (Buu-Hoï, Royer, Hubert-Habart, and Mabille, *J.*, 1953, 3584) being obtained. Nor did the Bernthsen reaction between *N*-*m*-tolyl-2-naphthylamine, acetic anhydride, and zinc chloride yield two isomers, 5 : 8-dimethyl-3 : 4-benzacridine (Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792) alone being isolated.

The mechanism of the Ullmann–Fetvadjian condensation is still unknown, but there is some evidence that it involves the intermediate formation of diarylamines rather than diarylmethanes (cf. Albert, " The Acridines," Arnold, London, 1951, p. 90); such being the case, a possibility would be a transient conversion of the diarylamine into an *ortho*-aldehyde which would subsequently undergo thermal cyclodehydration, as in the Mayer acridine synthesis (Kalischer and Mayer, *Ber.*, 1916, **49**, 1994; Mayer and Stein, *Ber.*, 1917, **50**, 1306). In the reaction of 2-naphthol with aniline and paraformaldehyde, for instance, the mechanism would be :



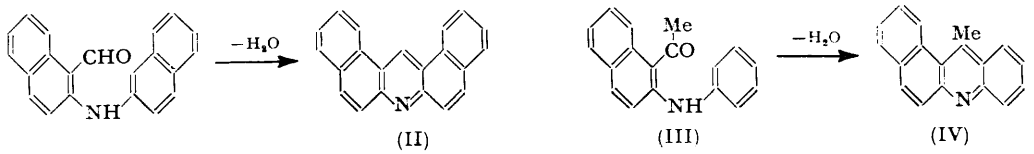
(I)

It has now been found that 2-anilino-1-formylnaphthalene undergoes cyclisation to 3 : 4-benzacridine on pyrolysis or, better, when heated with sulphuric acid in acetic acid (cf. Albert, *J.*, 1948, 1225). 3 : 4-6 : 7-Dibenzacridine (II) was similarly prepared from 1-formyldi-2-naphthylamine. These two aldehydes were obtained by treating *N*-phenyl-2-naphthylamine and di-2-naphthylamine, respectively, with *N*-methylformanilide and phosphorus oxychloride.

The mechanism of the Bernthsen synthesis of 5-substituted acridines has been postulated as involving the intermediate formation of *ortho*-amino-ketones (Albert, *op. cit.*, p. 67), a hypothesis which would account well for the high yields observed in the syntheses of 5-substituted angular benzacridines. In the reaction between *N*-phenyl-2-naphthylamine and acetic acid in the presence of zinc chloride, 1-acetyl-2-anilinonaphthalene (III) would be the intermediate; this ketone was prepared by a Knoevenagel reaction (*J.*

* Part XVI, Buu-Hoï and Jacquignon, *J.*, 1954, 513.

pr. Chem., 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346) of aniline with 1-acetyl-2-naphthol, and found to cyclise readily to (IV). Further support for the intermediate formation of amino-ketones is the fact that, although such ketones had not been isolated as a result of normal Bernthsen reactions, they could be obtained in the reaction of organic acids and zinc chloride on certain diarylamines such as carbazole which are unable to undergo acridine cyclisations. Bizzari (*Gazzetta*, 1890, **20**, 407, 414; 1891, **21**, 159, 352; 1892,



23, 1) claimed to have obtained " carbazoacridines " in the reaction of carbazole with acetic and benzoic acid under these conditions, but it has recently been suggested (Acheson and Sansom, *J.*, 1953, 1900) that these " carbazoacridines " are impure 3-acetyl- and 3-benzoyl-carbazole, and this is now confirmed.

For biological testing as potential carcinogens, a number of new homologues of 1 : 2- and 3 : 4-benzacridine bearing one or more substituents (some with long alkyl chains) were prepared by the Ullmann–Fetvadjian and the Bernthsen method; they are listed in the Table.

Experimental (with B. Eckert)

Reaction of m-*Toluidine and* 2-*Naphthol.*—To a boiling mixture of purified *m*-toluidine (15 g.) and 2-naphthol (21 g.), paraformaldehyde (4·5 g.) was added in small portions. When evolution of water ceased, the product was refluxed for 1 min. and fractionated, giving an orange-yellow resin, b. p. 265—275°/30 mm., which was dissolved in ethanol and treated with picric acid. The crude picrate (15 g.) gave on recrystallisation from nitrobenzene two fractions: (*a*) 8-methyl-3 : 4-benzacridine picrate, orange-yellow prisms, m. p. 263—264°, which on treatment with aqueous ammonia yielded the free base (5 g.), almost colourless needles, m. p. 144°, from methanol (Buu-Hoï, *J.*, 1949, 670, gave m. p. 143° for 8-methyl-3 : 4-benzacridine and m. p. 262—263° for its picrate); (*b*) 6-methyl-3 : 4-benzacridine pictrate, m. p 278°, whose base (0·8 g.) crystallised as almost colourless needles, m. p. 130°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 129° for 6-methyl-3 : 4-benzacridine and m. p. 276—278° for the picrate).

Preparation of 6- *and* 8-*Methyl*-1 : 2-*benzacridine.*—A similar reaction performed on *m*-toluidine (20 g.), α-naphthol (28 g.), and paraformaldehyde (6 g.) afforded an oily benzacridine mixture, b. p. 260—270°/15 mm. Fractional crystallisation of the picrates from nitrobenzene gave: (*a*) 8-methyl-1 : 2-benzacridine picrate, orange-yellow needles, m. p. 241—242°, whose base formed pale yellow prisms (2 g.), m. p. 148°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 148° for the base and m. p. 239—240° for the picrate); (*b*) 6-methyl-1 : 2-benzacridine picrate, orange-yellow needles, m. p. 251°, whose base formed yellowish prisms (0·5 g.), m. p. 136°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 136° for 6-methyl-1 : 2-benzacridine, and m. p. 249—251° for the picrate).

A search for similar pairs of isomers in the Ullmann–Fetvadjian reaction of 6-methyl-2-naphthol with *m*-toluidine and paraformaldehyde, and in the Bernthsen condensation of *N*-*m*-tolyl-2-naphthylamine with acetic anhydride, was unsuccessful.

Synthesis of Benzacridines by the Mayer Reaction.—A mixture of *N*-phenyl-2-naphthylamine (3 g.), *N*-methylformanilide (3 g.), and phosphorus oxychloride (2·3 g.) was heated on the water-bath for 12 hr., the product treated with aqueous sodium acetate and steam-distilled, and the residue taken up in benzene. The crude aldehyde obtained after evaporation of the solvent was heated at 100° for 5 min. with acetic (10 c.c.) and sulphuric acid (15 c.c.). Basification afforded 3 : 4-benzacridine, which was purified through its picrate and crystallised as almost colourless needles (1·5 g.), m. p. 131°, from ethanol. A similar reaction with di-2-naphthylamine (3 g.), *N*-methylformanilide (3 g.), and phosphorus oxychloride (4 g.) gave 3 : 4-6 : 7-dibenzacridine, pale yellow needles, m. p. 216°, from ethanol–benzene.

1-*Acetyl*-2-*anilinonaphthalene.*—A mixture of 1-acetyl-2-naphthol 15 g.) and aniline (25 g.) was refluxed for 24 hr. with a trace of iodine, the product treated with dilute hydrochloric acid, and the *amino-ketone* taken up in benzene; recrystallisation gave yellow prisms (4 g.), m. p. 115° (benzene) (Found: C, 82·3; H, 6·1; N, 5·1. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8;

N, 5·3%). Cyclisation with acetic and sulphuric acid, as above, afforded 5-methyl-3 : 4-benzacridine, prisms, m. p. 144° (cf. Postovskii and Lundin, *J. Gen. Chem. U.S.S.R.*, 1940, **19**, 71), in 80% yield.

Reaction of Carbazole with Benzoic Acid and Zinc Chloride.—A mixture of carbazole (10 g.), benzoic acid (10 g.), and fused zinc chloride (20 g.) was heated at 150—155°, and treated according to Bizzari (*loc. cit.*). Distillation *in vacuo* gave recovered carbazole, and 3-benzoylcarbazole (Acheson and Sansom, *loc. cit.*) in 20% yield.

2-(3 : 4-*Dimethylanilino*)-6-*methylnaphthalene.*—A mixture of 3 : 4-dimethylaniline (7 g.) and 6-methyl-2-naphthol (8·3 g.) was heated at 220° with iodine (0·2 g.) for 15 hr., the product taken up in benzene, washed with aqueous sodium hydroxide, and dried (Na_2SO_4), the solvent evaporated, and the residue distilled *in vacuo*, affording 6 g. of a *product*, b. p. 270—272°/18 mm., needles, m. p. 112°, from light petroleum (Found : C, 87·3; H, 7·5. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3%).

The following diarylamines were similarly prepared : N-(p-n-*heptylphenyl*)-2-*naphthylamine* (from 2-naphthol and *p*-*n*-heptylaniline), b. p. 250—260°/19 mm., colourless prisms, m. p. 59°, from light petroleum (Found : C, 87·0; H, 8·6. $C_{23}H_{27}N$ requires C, 87·1; H, 8·5%); N-(p-n-*butylphenyl*)-2-*naphthylamine* (from 2-naphthol and *p*-*n*-butylaniline), colourless needles, m. p. 48°, from light petroleum (Found : C, 87·6; H, 7·6. $C_{20}H_{21}N$ requires C, 87·3; H, 7·6%); N-p-n-*propylphenyl*-2-*naphthylamine* (from 2-naphthol and *p*-*n*-propylaniline), a viscous yellow oil, b. p. 250—260°/15 mm. (Found : C, 87·3; H, 7·2. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3%); 2-(2-*ethyl*-4 : 5-*dimethylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 2-ethyl-4 : 5-dimethylaniline; Eckert, Buu-Hoï, and Royer, *Compt. rend.*, 1951, **233**, 1461), a viscous yellow oil, b. p. 270°/12 mm. (Found : C, 87·0; H, 8·0. $C_{21}H_{23}N$ requires C, 87·2; H, 8·0%); 2-(4-*ethyl*-2 : 5-*dimethylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 4-ethyl-2 : 5-dimethylaniline; Eckert, Buu-Hoï, and Royer, *loc. cit.*), b. p. 278—280°/18 mm. (Found : C, 87·3; H, 8·2%); 2-(3-*methyl*-4-n-*octylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 3-methyl-4-*n*-octylaniline), b. p. 278—280°/10 mm. (Found : C, 86·6; H, 9·3. $C_{26}H_{33}N$ requires C, 86·9; H, 9·2%); 2-(4-*ethyl*-3-*methylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 4-ethyl-3-methylaniline; Buu-Hoï, Eckert, and Royer, *ibid.*, p. 627), b. p. 278—280°/20 mm. (Found : C, 87·5; H, 7·5. $C_{20}H_{21}N$ requires C, 87·3; H, 7·6%); N-(p-n-*butylphenyl*)-1-*naphthylamine* (from 1-naphthol and *p*-*n*-butylaniline), b. p. 272—274°/20 mm. (Found : C, 87·5; H, 7·9%).

Synthesis of New Benzacridines.—The benzacridines not substituted at position 5 were prepared by the Ullmann–Fetvadjian reaction, and the 5-substituted ones by the modified Bernthsen reaction (cf. Buu-Hoï, *J.*, 1946, 792). All were purified by distillation *in vacuo*, and recrystallised from ethanol.

	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
New 3 : 4-*benzacridines.*						
7-*n*-Propyl-	79°	$C_{20}H_{17}N$	88·5	6·1	88·6	6·3
5-Methyl-7-*n*-propyl-[a]	70	$C_{21}H_{19}N$	88·1	6·9	88·4	6·7
5 : 7 : 8 : 2′-Tetramethyl-	175	$C_{21}H_{19}N$	88·3	6·7	88·4	6·7
7-*n*-Butyl-[b]	91	$C_{21}H_{19}N$	88·5	6·8	88·4	6·7
7-*n*-Heptyl-	80	$C_{24}H_{25}N$	87·9	7·5	88·1	7·6
7-*n*-Butyl-2′-methyl-[c]	87	$C_{22}H_{21}N$	88·1	7·1	88·3	7·0
7-*n*-Butyl-5-methyl-	77	$C_{22}H_{21}N$	88·2	7·3	88·3	7·0
9-Ethyl-5 : 6 : 7 : 2′-tetramethyl-[d]	82	$C_{23}H_{23}N$	88·4	7·5	88·2	7·3
7-Ethyl-5 : 6 : 9 : 2′-tetramethyl-	165	$C_{23}H_{23}N$	88·1	7·5	88·2	7·3
7-Ethyl-5 : 8 : 2′-trimethyl-	167	$C_{22}H_{21}N$	88·5	7·1	88·3	7·0
5 : 8 : 2′-Trimethyl-7-*n*-octyl-[e]	106	$C_{28}H_{33}N$	87·4	8·8	87·7	8·6
7-*n*-Heptyl-5-methyl-	125	$C_{25}H_{27}N$	88·1	7·8	88·0	7·9
New 1 : 2-*benzacridines.*						
7-*n*-Heptyl-	60	$C_{24}H_{25}N$	88·0	7·6	88·1	7·6
7-*n*-Butyl-5-methyl-	104	$C_{22}H_{21}N$	88·0	7·1	88·3	7·0
7-*n*-Butyl-[f]	70	$C_{21}H_{19}N$	88·1	6·9	88·4	6·7

Picrates, m. p. (*a*) 216°, (*b*) 235° (*c*) 244°, (*d*) 220°, (*e*) 215°, (*f*) 214°.

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Department of Organic Chemistry,
The Radium Institute, University of Paris. [*Received, December 3rd*, 1954.]