720. *Carcinogenic Nitrogen Compounds. Part XV.* New Polysubstituted Angular Benzacridines and Benzophenarsazines.*

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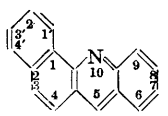
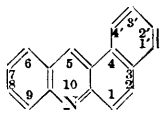
Polysubstituted angular benzacridines and benzophenarsazines bearing alkyl, fluorine, chlorine, methoxy-, and acetamido-groups, have been prepared. 2′ : 5′-Dimethyl-1 : 2-6 : 7-dibenzacridine has been synthesised from 1 : 6-dimethylnaphthalene, several derivatives of which are recorded.

In recent years, one of the most important tasks connected with research on chemical carcinogenesis has been the comparison of carcinogenic activities as determined experimentally in a given group of molecules, with the theoretical data derived from calculation of π-electron densities in these molecules by means of wave mechanics (Schmidt, *Naturwiss.*, 1941, **29**, 146; Lacassagne, Buu-Hoï, Rudali, and Lecocq, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Pullman, *ibid.*, p. 120; Buu-Hoï, Daudel, Lacassagne, Lecocq, Martin, and Rudali, *Compt. rend.*, 1947, **225**, 238; Daudel, Daudel, and Buu-Hoï, *Acta Un. int. Cancr.*, 1950, **7**, 91). The value of such a work depends on the number of compounds investigated within each series and, chemically, it necessitates the preparation of as many

(I)   (II)

derivatives as possible of a given parent hydrocarbon or heterocycle. In the relatively simple case of methyl derivatives of 1 : 2- (I) or 3 : 4-benzacridine (II), the number of theoretically possible isomers is :

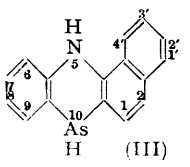
No. of Me groups	1	2	3	4	5	6	7	8	9	10	11
No. of isomers	11	55	165	330	462	462	330	165	55	11	1

Hitherto, only one tetramethyl- (Buu-Hoï, *J.*, 1946, 792), seven trimethyl- (Senier and Austin, *J.*, 1907, **91**, 1233; Buu-Hoï, *loc. cit.*), seven dimethyl- (Senier and Compton, *J.*, 1907, **91**, 1927; 1909, **95**, 1623; Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1949, 670), and five monomethyl-3 : 4-benzacridines (Ullmann and Naef, *Ber.*, 1900, **33**, 905; Buu-Hoï, *loc. cit.*) had been prepared. We now report the preparation of a further one monomethyl, three dimethyl, two trimethyl, and four tetramethyl derivatives of 3 : 4-benzacridine; these, together with some 2′-methyl-3 : 4-benzacridines bearing in addition higher alkyl or methoxy-groups, are listed in Table 1. All were synthesised from 6-methyl- and 7-methyl-2-naphthol, either by the Ullmann–Fetvadjian reaction (*Ber.*, 1903, **36**, 1029), or in the case of the *meso*-substituted compounds, by the modified Bernthsen reaction (Buu-Hoï, *J.*, 1946, 792; 1949, 670); in view of the carcinogenic activity of 2-acetamidofluorene and other polycyclic amides, 7-acetamido-2′-methyl-3 : 4-benzacridine was prepared by condensing 6-methyl-2-naphthol with the reaction product of formaldehyde on *p*-aminoacetanilide (cf. Ullmann, *Chem. Zentr.*, 1901, II, 568); the free amine was obtained by hydrolysis. The pronounced carcinogenic activity of some fluorine-containing benzacridines described in a recent paper (Buu-Hoï and Jacquignon, *J.*, 1952, 4173) induced us to prepare several new *meso*-substituted 7-fluoro-1 : 2- and -3 : 4-benzacridines, listed in Table 1. Attempts to synthesise benzacridines bearing trifluoromethyl groups failed, as extensive decomposition occurred with *o*- and *p*-trifluoromethylaniline in the Knoevenagel reaction with naphthols and iodine (Knoevenagel, *J. pr. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346), and also under the conditions of the Ullmann–Fetvadjian reaction.

The mild tumour-provoking activity of certain 10-chloro-5 : 10-dihydrobenzophenarsazines (Lacassagne, Rudali, Buu-Hoï, and Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451) prompted

* Part XIV, Buu-Hoï and Xuong, *J.*, 1953, 386.

the preparation of a series of new polysubstituted derivatives of 5 : 10-dihydro-1 : 2- (III) and -3 : 4-benzophenarsazines (IV) by known methods (cf. Buu-Hoï and Royer, *J.*, 1951, 795). In the dibenzacridine group, 3 : 2′-dimethyl-1 : 2-6 : 7-dibenzacridine (V) was prepared by an Ullmann–Fetvadjian reaction on β-naphthol and 4 : 7-dimethyl-1-naphthylamine;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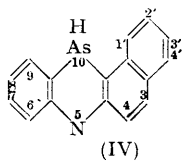
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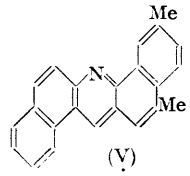
(V)

the last compound was obtained from 4-acetyl-1 : 6-dimethylnaphthalene (cf. Feist, *J. pr. Chem.*, 1934, **139**, 261; Buu-Hoï and Cagniant, *Rev. sci.*, 1943, **81**, 173) by Beckmann rearrangement of its oxime; 4-ethyl- and 4-*iso*butyl-1 : 6-dimethylnaphthalene were also prepared.

The substances described here are under biological test in this Institute by Professor Lacassagne and Dr. Zajdela, and the results will be reported elsewhere.

Experimental

4 : 7-*Dimethyl*-1-*naphthylamine*.—4-Acetyl-1 : 6-dimethylnaphthalene (70 g.), prepared in the usual way from 1 : 6-dimethylnaphthalene (100 g.), acetyl chloride (55 g.), and aluminium chloride (100 g.) in carbon disulphide, was characterised by a Pfitzinger reaction with isatin, to give 2-(4 : 7-*dimethyl*-1-*naphthyl*)*cinchoninic acid*, which formed pale yellow needles, m. p. *ca.* 254—256° (decomp. from 238°), from acetic acid (Found: C, 80·3; H, 5·2. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·1%). The oxime of the ketone (40 g.) was rearranged in ether with phosphorus pentachloride at 0°, and the crude amide obtained hydrolysed with concentrated hydrochloric acid. 4 : 7-*Dimethyl*-1-*naphthylamine* (16 g.) obtained on basification was a pale yellow oil, b. p. 184—185°/15 mm. (Found: C, 84·0; H, 7·5. $C_{12}H_{13}N$ requires C, 84·2; H, 7·6%); its *benzoyl* derivative formed silky, sublimable needles, m. p. 225—226°, from methanol (Found: C, 82·6; H, 6·3. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2%), and its *toluene*-p-*sulphonyl* derivative formed needles, m. p. 218°, from ethanol (Found: C, 70·1; H, 6·0. $C_{19}H_{19}O_2NS$ requires C, 70·2; H, 5·8%).

3 : 2′-*Dimethyl*-1 : 2-6 : 7-*dibenzacridine* (V).—To a boiling mixture of the foregoing amine (4 g.) and β-naphthol (4 g.), heated at 250°, paraformaldehyde (0·8 g.) was added in small portions, and the product fractionated *in vacuo*; the portion of b. p. >300°/20 mm. was converted into a picrate (orange-yellow needles, from nitrobenzene) which gave on treatment with aqueous ammonia the free *base*, crystallising as pale yellow prisms, m. p. 175°, from ethanol (Found: C, 89·6; H, 5·4. $C_{23}H_{17}N$ requires C, 89·9; H, 5·5%).

4-*Ethyl*-1 : 6-*dimethylnaphthalene*.—4-Acetyl-1 : 6-dimethylnaphthalene (10 g.), reduced by 48 hours' refluxing with amalgamated zinc (50 g.), hydrochloric acid (250 c.c.) and toluene (10 c.c.), gave the *hydrocarbon* as a colourless oil (5 g.), b. p. 275—277°, $n_D^{19\cdot5}$ 1·5980 (Found: C, 91·1; H, 8·7. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%).

4-iso*Butyl*-1 : 6-*dimethylnaphthalene*, a colourless oil, b. p. 290°, n_D^{21} 1·5725 (Found: C, 90·3; H, 9·5. $C_{16}H_{20}$ requires C, 90·6; H, 9·4%), was similarly obtained from 4-iso*butyryl*-1 : 6-*dimethylnaphthalene* (12 g.), b. p. 195—198°/16 mm., n_D^{20} 1·5915, prepared from 1 : 6-dimethylnaphthalene (17 g.), *iso*butyryl chloride (15 g.), and aluminium chloride (15 g.) in carbon disulphide (Found: C, 85·2; H, 8·1. $C_{16}H_{18}O$ requires C, 85·0; H, 8·0%).

N-(2 : 4-*Dimethylphenyl*)-7-*methyl*-2-*naphthylamine*.—A mixture of 7-methyl-1-naphthol (10 g.; Shreve and Lux, *Ind. Eng. Chem.*, 1943, **35**, 306), 2 : 4-dimethylaniline (8·5 g.), and iodine (0·5 g.) was refluxed for 20 hr. and the product taken up in benzene, washed with aqueous alkali, and fractionated; the *diarylamine* (13 g.), b. p. 246—249°/16 mm., formed colourless prisms, m. p. 56°, from methanol (Found: N, 5·4. $C_{19}H_{19}N$ requires N, 5·4%); N-(3 : 5-*dimethylphenyl*)-7-*methyl*-2-*naphthylamine*, similarly prepared from 3 : 5-dimethylaniline, formed needles, m. p. 112°, from ethanol (Found: N, 5·2%). N-(2 : 4-*Dimethylphenyl*)-6-*methyl*-2-*naphthylamine* (15 g.), prepared from 6-methyl-2-naphthol (10 g.; cf. Dziewoński, Schoeńowna, and Waldmann, *Ber.*, 1925, **58**, 1213), 2 : 4-dimethylaniline (8·5 g.), and iodine (0·5 g.), formed

colourless prisms, m. p. 75°, from ethanol (Found : N, 5·2%); N-(2 : 3-*dimethylphenyl*)-6-*methyl*-2-*naphthylamine* formed colourless prisms, m. p. 103°, from ethanol (Found : N, 5·3%); N-(5-*ethyl*-2-*methylphenyl*)-6-*methyl*-2-*naphthylamine* (16 g.) was a thick yellow oil, b. p. 248—250°/15 mm. (Found : N, 4·9. $C_{20}H_{21}N$ requires N, 5·1%).

TABLE 1.

(a) *Substituted* 1 : 2-*benzacridines.*

Substituent	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
5-Ethyl-7-fluoro-	118°	$C_{19}H_{14}NF$	82·6	5·0	82·9	5·1
7-Fluoro-5-propyl	93	$C_{20}H_{16}NF$	83·1	5·5	83·0	5·3
7-Fluoro-5-pentyl- [a]	105	$C_{23}H_{20}NF$	83·1	6·5	83·3	6·3
5-Benzyl-7-fluoro- [b]	145	$C_{24}H_{16}NF$	85·2	4·8	85·5	4·7

(b) *Substituted* 3 : 4-*benzacridines.*

2′-Methyl-	133°	$C_{18}H_{13}N$	88·8	5·5	88·9	5·3
9 : 2′-Dimethyl-	202	$C_{19}H_{15}N$	88·4	5·6	88·7	5·8
8 : 2′-Dimethyl-	170	$C_{19}H_{15}N$	88·5	5·8	88·7	5·8
7 : 2′-Dimethyl-	227	$C_{19}H_{15}N$	88·5	6·0	88·7	5·8
8 : 9 : 2′-Trimethyl-	190	$C_{20}H_{17}N$	88·3	6·3	88·6	6·3
7 : 9 : 2′-Trimethyl-	187	$C_{20}H_{17}N$	88·5	6·2	88·6	6·3
5 : 7 : 9 : 3′-Tetramethyl-	156	$C_{21}H_{19}N$	88·4	6·8	88·4	6·7
5 : 6 : 8 : 3′-Tetramethyl- [c]	—	$C_{21}H_{19}N$	88·3	6·7	88·4	6·7
5 : 7 : 9 : 2′-Tetramethyl-	168	$C_{21}H_{19}N$	88·2	6·6	88·4	6·7
5 : 8 : 9 : 2′-Tetramethyl-	147	$C_{21}H_{19}N$	88·2	6·9	88·4	6·7
5-Ethyl-8 : 2′-dimethyl-	184	$C_{21}H_{19}N$	88·0	6·8	88·4	6·7
8 : 2′-Dimethyl-5-propyl-	160	$C_{22}H_{21}N$	88·3	7·1	88·3	7·0
5-Ethyl-9 : 2′-dimethyl-	147	$C_{21}H_{19}N$	88·1	6·6	88·4	6·7
8-Chloro-5 : 9 : 2′-trimethyl-	140	$C_{20}H_{16}NCl$	78·8	5·1	78·6	5·2
6-Ethyl-5 : 9 : 2′-trimethyl-	146	$C_{22}H_{21}N$	88·1	7·2	88·3	7·0
5-Ethyl-7-fluoro-	169	$C_{19}H_{14}NF$	82·6	5·2	82·9	5·1
7-Fluoro-5-propyl-	140	$C_{20}H_{16}NF$	82·9	5·5	83·0	5·3
7-Fluoro-5-pentyl	119	$C_{22}H_{20}NF$	83·3	6·5	83·3	6·3
7-Fluoro-5-phenyl-	169	$C_{23}H_{14}NF$	85·5	4·5	85·4	4·3
7-Fluoro-5 : 2′-dimethyl-	158	$C_{19}H_{14}NF$	82·8	5·2	82·9	5·1
9-Methoxy-2′-methyl-	156	$C_{19}H_{15}ON$	83·6	5·3	83·5	5·5
7-Methoxy-2′-methyl-	220	$C_{19}H_{15}ON$	83·3	5·5	83·5	5·5
6 : 9-Dimethoxy-2′-methyl-	186	$C_{20}H_{17}O_2N$	79·3	5·4	79·2	5·6
7-Hydroxy-2′-methyl- [d]	>360	$C_{18}H_{13}ON$	83·4	5·1	83·4	5·0

(c) *Picrates of substituted* 3 : 4-*benzacridines.*

			N	N
2′-Methyl-	252°	$C_{24}H_{16}O_7N_4$	11·6	11·9
9 : 2′-Dimethyl-	256	$C_{25}H_{18}O_7N_4$	11·1	11·5
8 : 2′-Dimethyl-	280	$C_{25}H_{18}O_7N_4$	11·2	11·5
8 : 9 : 2′-Trimethyl-	262	$C_{26}H_{20}O_7N_4$	11·0	11·2
7 : 9 : 2′-Trimethyl-	309	$C_{26}H_{20}O_7N_4$	11·2	11·2
5 : 7 : 9 : 3′-Tetramethyl-	260	$C_{27}H_{22}O_7N_4$	11·0	10·9
5 : 6 : 8 : 3′-Tetramethyl-	250	$C_{27}H_{22}O_7N_4$	10·8	10·9
5 : 8 : 9 : 2′-Tetramethyl-	232	$C_{27}H_{22}O_7N_4$	10·8	10·9
5 : 7 : 9 : 2′-Tetramethyl-	238	$C_{27}H_{22}O_7N_4$	10·6	10·9
5-Ethyl-8 : 2′-dimethyl	260	$C_{27}H_{22}O_7N_4$	11·0	10·9
5-Ethyl-9 : 2′-dimethyl-	236	$C_{27}H_{22}O_7N_4$	11·1	10·9
5-Ethyl-7-fluoro-	225	$C_{25}H_{17}O_7N_4F$	10·8	11·1
7-Fluoro-5-*n*-propyl-	220	$C_{26}H_{19}O_7N_4F$	10·6	10·8
7-Fluoro-5-pentyl-	215	$C_{28}H_{23}O_7N_4F$	10·0	10·3
7-Fluoro-5 : 2′-dimethyl-	242	$C_{25}H_{17}O_7N_4F$	11·2	11·1
8-Chloro-5 : 9 : 2′-trimethyl-	228	$C_{26}H_{19}O_7N_4Cl$	10·3	10·5
6 : 9-Dimethoxy-2′-methyl-	243	$C_{26}H_{20}O_9N_4$	10·2	10·5

[a] Yellow picrate, m. p. 212°. [b] Yellow picrate, m. p. 229°. [c] The base did not crystallise, and was purified by vacuum-distillation. [d] Prepared from the corresponding methyl ether by 10 minutes' treatment with boiling pyridine hydrochloride, and decomposition with aqueous ammonia of the orange hydrochloride thus obtained; the product was recrystallised from xylene.

Condensation of Fluorinated Anilines with Naphthols.—*p*-Fluoroaniline (20 g.), 6-methyl-2-naphthol (23 g.), and iodine (0·3 g.) were refluxed for 5 hr.; the product, treated in the usual way, gave N-p-*fluorophenyl*-6-*methyl*-2-*naphthylamine* (22 g.), b. p. 200—204°/0·8 mm., forming colourless leaflets, m. p. 131°, from ethanol (Found : C, 81·5; H, 5·5. $C_{17}H_{14}NF$ requires C,

81·3; H, 5·6%); N-p-*fluorophenyl*-7-*methyl*-2-*naphthylamine*, b. p. 189—190°/0·5 mm., forme d colourless prisms, m. p. 127° (Found: C, 81·3; H, 5·6%).

7-*Acetamido*-2′-*methyl*-3 : 4-*benzacridine*.—A mixture of 6-methyl-2-naphthol (3 g.) with the condensation product (2·5 g.) of *p*-aminoacetanilide with formaldehyde was heated at 175—180° for 2 hr., and the product extracted with aqueous sodium hydroxide; the residue, washed with water and dried, formed grey crystals (3 g.), m. p. >350°, from xylene (Found: C, 79·9; H, 5·1. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3%); 7-*amino*-2′-*methyl*-3 : 4-*benzacridine*, obtained by hydrolysis of the foregoing *amide* with hydrochloric acid in ethanol and basification, formed grey prisms, m. p. 244° (Found: C, 83·6; H, 5·4. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4%).

Benzacridine Syntheses (*see Table* 1).—(a) *By the modified Bernthsen method*. A mixture of equal weights of the appropriate diarylamine, acetic or propionic anhydride (or a higher acid), and freshly fused zinc chloride was heated at 170—180° for 24 hours; a large excess of 20% aqueous sodium hydroxide was added, and the product taken up in benzene and distilled *in vacuo*; purification was effected *via* the picrate, giving 25—50% yields of the benzacridine.

(b) *By the paraformaldehyde method*. To a boiling mixture of equal weights of the naphthol and the primary amine, paraformaldehyde (in slight excess) was added in small portions, and the product boiled for a few minutes before fractionation; the resulting benzacridine, purified *via* the picrate, was obtained in 15—40% yield.

TABLE 2.

(a) *Substituted* 5 : 10-*dihydro*-1 : 2-*benzophenarsazines*.

Substituent	M. p.	Decomp. begins at	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
10-Chloro-8-fluoro-	297°	270°	$C_{16}H_{10}NClFAs$	55·2	3·0	55·6	2·9
8-Fluoro-10-methyl-.....	120	—	$C_{17}H_{13}NFAs$	62·5	4·0	62·8	4·0
10-Chloro-8-fluoro-3′-methyl-...	285	270	$C_{17}H_{12}NClFAs$	56·5	3·2	56·8	3·3
10-Chloro-8-fluoro-2′-methyl-...	250	212	$C_{17}H_{12}NClFAs$	56·5	3·1	56·8	3·3
10-Chloro-6 : 8 : 2′-trimethyl-...	246	233	$C_{19}H_{17}NClAs$	61·5	4·5	61·7	4·6
10-Chloro-6 : 8 : 3′-trimethyl-...	276	260	$C_{19}H_{17}NClAs$	61·4	4·6	61·7	4·6

(b) *Substituted* 5 : 10-*dihydro*-3 : 4-*benzophenarsazines*.

10-Chloro-8-fluoro-	237	220	$C_{16}H_{10}NClFAs$	55·5	3·0	55·6	2·9
8-Fluoro-10-methyl-.....	107	—	$C_{17}H_{13}NFAs$	62·5	3·9	62·8	4·0

Phenarsazine Syntheses (*see Table* 2).—(a) 10-*Chloro*-5 : 10-*dihydrobenzophenarsazines*. A solution of the appropriate diarylamine and of the calculated amount of arsenic trichloride in the minimum quantity of *o*-dichlorobenzene, was refluxed for 6—8 hr.; the precipitate obtained on cooling was recrystallised from *o*-dichlorobenzene or xylene.

(b) 10-*Alkyl*-5 : 10-*dihydrobenzophenarsazines*. The appropriate 10-chloro-compound was added to an ethereal solution of alkylmagnesium halide, and the mixture refluxed for 10 min.; the ethereal layer obtained on treatment with aqueous ammonium chloride was dried and concentrated, to give the phenarsazine, which was recrystallised from ethanol or benzene.

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