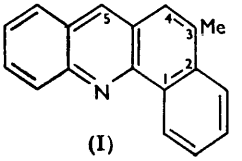
99. *Carcinogenic Nitrogen Compounds. Part XXI.* New Alkyl Homologues of Phenanthridine, Benzacridines, and Related Nuclei.*

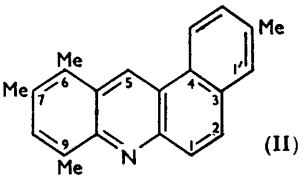
By Ng. Ph. Buu-Hoï, P. Jacquignon, and C. T. Long.

In continuation of earlier work, several new tri-, tetra-, and penta-methyl homologues of the angular benzacridines, similar derivatives of the related 3 : 4-benzophenarsazine and 3-methyl-1 : 2-benzocarbazole, and a large number of 9-alkylphenanthridines have been synthesised for testing as potential carcinogens.

Of the 155 possible trimethyl homologues of 1 : 2-benzacridine, only five have hitherto been prepared,[1] and only one of the 330 possible tetramethyl homologues has been described,[2] whilst none of the 462 possible pentamethyl derivatives is known. Now, in view of the high carcinogenic activity of 1 : 2-benzacridine derivatives, especially in compounds bearing several alkyl groups,[3] it was desirable to synthesise a number of homologues with three and more methyl substituents, for correlation of their carcinogenic potency with physical properties.[4] Especially important were compounds which would have a methyl group in the so-called *K*-region (*meso*phenanthrenic zone), because of the theories which endow this part of the molecule with a predominant rôle in carcinogenesis.[5]



(I)



(II)

A convenient intermediate for the synthesis of 3-substituted 1 : 2-benzacridines (I) is 4-methyl-1-naphthol, readily accessible from 1-naphthol.[6] Its condensation with 2 : 3-, 2 : 4-, and 3 : 4-dimethylaniline in the presence of paraformaldehyde [7] afforded, in low yields, 3 : 8 : 9-, 3 : 7 : 9-, and 3 : 7 : 8-trimethyl-1 : 2-benzacridine; 6 : 7 : 9 : 2′-tetramethyl-3 : 4-benzacridine (II) was similarly prepared from 2-naphthol and ψ-cumidine.

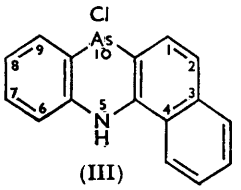
* Part XX, Buu-Hoï, Jacquignon, and Lavit, *J.*, 1956, 2593.

[1] Buu-Hoï, *J.*, 1949, 670; Senier and Austin, *J.*, 1907, **91**, 1233.
[2] Buu-Hoï, *J.*, 1946, 792.
[3] Cf. Lacassagne, Buu-Hoï, Rudali, and Lecocq, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22.
[4] Cf. Chalvet, Daudel, Pagès, Roux, Buu-Hoï, and Royer, *J. Chim. phys.*, 1954, **51**. 548.
[5] Cf. Pullman and Pullman, "Les théories électroniques de la chimie organique," Masson, Paris, 1952; Boyland, *J. Chim. phys.*, 1950, **47**, 942.
[6] Buu-Hoï and Lavit, *J.*, 1955, 2776.
[7] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.

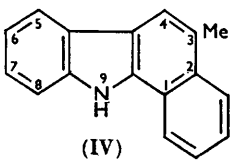
An iodine-catalysed Knoevenagel condensation of 4-methyl-1-naphthol with 2 : 3-, 2 : 4-, 2 : 5-, and 3 : 4-dimethylaniline, and with ψ-cumidine, gave the corresponding *N*-aryl-1-naphthylamines, which underwent Bernthsen cyclisations with acetic anhydride [8] to give 3 : 5 : 8 : 9-, 3 : 5 : 7 : 9-, 3 : 5 : 6 : 9-, and 3 : 5 : 7 : 8-tetramethyl- and 3 : 5 : 6 : 7 : 9-pentamethyl-1 : 2-benzacridine, in excellent yields. Of these polymethylbenzacridines, the 7 : 8-substituted ones showed comparatively high melting points (>200°), a characteristic also found with 5-ethyl-3 : 7 : 8-trimethyl-1 : 2-benzacridine (m. p. 193°), prepared from *N*-ψ-cumyl-1-naphthylamine and propionic anhydride. The m. p.s of all the picrates of 9-alkyl-1 : 2-benzacridines were remarkably low, a feature obviously connected with steric hindrance around the nitrogen atom, since it does not exist in the 3 : 4-benzacridine series.

10-Chloro-5 : 10-dihydro-6 : 9-dimethyl-3 : 4-benzophenarsazine provokes benign tumours in mice on skin painting [9] and, in the hope that malignancy might be reached with more substituted compounds, the synthesis was undertaken of four trimethyl derivatives of the nucleus (III) by condensation of the appropriate diarylamines with arsenic trichloride.[10] For the same reason, 3-methyl-1 : 2-benzocarbazole (IV) was prepared by a Japp–Maitland condensation [11] of 4-methyl-1-naphthol with phenylhydrazine and its hydrochloride.

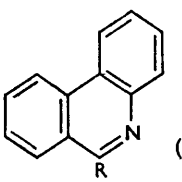
Homologues of phenanthridine have rarely been studied, and of the 9-alkyl derivatives only the two first members are known.[12] A large number of higher homologues (V) (listed in Table 1) have now been prepared by a slightly modified Morgan–Walls [13] method, from the appropriate 2-acylaminodiphenyls listed in Table 2.



(III)



(IV)



(V)

The carcinogenic activity of the benzacridines described is under investigation in this Institute (Dr. Zajdela) and will be reported later; several *meso*-substituted 1 : 2-benzacridines have proved active.

Experimental

Preparation of 2-Acylaminodiphenyls.—The following technique derived from Scarborough and Waters's method [14] was found superior to Morgan and Walls's procedure: To a water-cooled solution of 2-aminodiphenyl (1 part) in anhydrous pyridine (5 parts), the theoretical amount of acid chloride (dissolved in ether if solid) was added in small portions with stirring; after a few minutes at room temperature, the mixture was treated with dilute hydrochloric acid in excess, the amide taken up in benzene, the benzene solution washed with water, then dried (Na_2SO_4), the solvent removed, and the residue distilled *in vacuo*. The yields ranged from 80 to 98% for the pure products, which were recrystallised from light petroleum for the lower homologues, and from ethanol for the higher ones.

Cyclisation of 2-Acylaminodiphenyls.—A mixture of the amide (1 part) and phosphorous oxychloride (2 parts) was refluxed on the water-bath for 2 hr., and, after cooling, poured into cold water; after basification with sodium hydroxide, the phenanthridine was taken up in

[8] Cf. Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792.
[9] Lacassagne, Buu-Hoï, Royer, and Rudali, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451.
[10] Lewis and Hamilton, *J. Amer. Chem. Soc.*, 1921, **43**, 2219; Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1; Burton and Gibson, *J.*, 1926, 2243; Buu-Hoï *et al.*, *Compt. rend.*, 1945, **220**, 50; *Rev. sci.*, 1944, **82**, 453; 1945, **83**, 41; *J.*, 1951, 795; 1953, 3584.
[11] Japp and Maitland, *J.*, 1903, **83**, 267.
[12] Morgan and Walls, *J.*, 1931, 2447.
[13] Cf. Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792.
[14] Scarborough and Waters, *J.*, 1927, 89.

benzene, the benzene solution dried over potassium hydroxide, the solvent removed, and the residue distilled *in vacuo* (yield: 65—75%). Crystallisation of the solid bases was best effected from aqueous ethanol for the lower homologues, and from ethanol for the higher ones; their picrates were recrystallized from ethanol or benzene.

TABLE 1 (a). *9-Substituted phenanthridines.*[a]

Substituent	B. p./mm.	M. p. or n_D	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
n-Propyl	228°/22	$n_D^{25\cdot5}$ 1·6409	$C_{16}H_{15}N$	86·7	7·1	86·8	6·8
*iso*Propyl	232°/34	57°	$C_{16}H_{15}N$	86·5	7·0	86·8	6·8
*iso*Butyl	232°/27	n_D^{21} 1·6372	$C_{17}H_{17}N$	87·0	7·2	86·8	7·3
n-Pentyl	263°/39	$n_D^{22\cdot5}$ 1·6182	$C_{18}H_{19}N$	86·8	7·5	86·7	7·7
n-Heptyl	272°/28	51°	$C_{20}H_{23}N$	86·3	8·6	86·6	8·4
n-Undecyl	—	56	$C_{24}H_{31}N$	86·0	9·4	86·4	9·4
n-Tridecyl	—	64	$C_{26}H_{35}N$	86·0	9·8	86·4	9·8
n-Tetradecyl	286°/18	65	$C_{27}H_{37}N$	86·2	9·8	86·3	9·9
n-Pentadecyl	295°/24	67	$C_{28}H_{39}N$	86·0	10·3	86·3	10·1
n-Heptadecyl	310°/34	70	$C_{30}H_{43}N$	86·3	10·1	86·3	10·4
*cyclo*Hexyl	264°/22	82	$C_{19}H_{19}N$	87·2	7·5	87·3	7·3

[a] In view of the hygroscopic properties of the free bases and their tendency to give solvated crystals, the analyses were performed on distilled samples.

(b) *Picrates of 9-substituted phenanthridines.*

Substituent	M. p.	Formula	Found (%) N	Reqd. (%) N	Substituent	M. p.	Formula	Found (%) N	Reqd. (%) N
n-Propyl	204°	$C_{22}H_{18}O_7N_4$	12·4	12·4	*n*-Tridecyl	135°	$C_{32}H_{38}O_7N_4$	9·5	9·5
*iso*Propyl	229	$C_{22}H_{18}O_7N_4$	12·6	12·4	*n*-Tetradecyl	123	$C_{33}H_{40}O_7N_4$	9·0	9·3
*iso*Butyl	194	$C_{23}H_{20}O_7N_4$	12·0	12·1	*n*-Pentadecyl	115	$C_{34}H_{42}O_7N_4$	9·2	9·1
n-Pentyl	167	$C_{24}H_{22}O_7N_4$	11·4	11·7	*n*-Heptadecyl	111	$C_{36}H_{46}O_7N_4$	9·0	8·7
n-Undecyl	149	$C_{30}H_{34}O_7N_4$	10·3	10·0	*cyclo*Hexyl	227	$C_{25}H_{22}O_7N_4$	11·1	11·4

TABLE 2. *2-Acylaminodiphenyls.*

Acyl group	B. p./mm.	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
n-Butyryl	228°/22	87°	$C_{16}H_{17}ON$	80·5	7·4	80·3	7·2
*iso*Butyryl	225°/25	128	$C_{16}H_{17}ON$	80·0	7·2	80·3	7·2
*iso*Valeryl	241°/40	101	$C_{17}H_{19}ON$	80·5	7·5	80·6	7·6
n-Hexanoyl	267°/42	73	$C_{18}H_{21}ON$	81·0	8·0	80·9	7·9
n-Octanoyl	260°/20	72	$C_{20}H_{25}ON$	81·0	8·8	81·3	8·5
Lauroyl	293°/19	66	$C_{24}H_{33}ON$	82·0	9·2	82·0	9·5
Myristinoyl	308°/22	68	$C_{26}H_{37}ON$	82·2	10·0	82·3	9·8
n-Pentadecanoyl	—	71	$C_{27}H_{39}ON$	82·1	10·3	82·4	10·0
Palmitoyl	—	75	$C_{28}H_{41}ON$	82·2	10·2	82·5	10·1
Stearoyl	—	79	$C_{30}H_{45}ON$	83·0	10·2	82·7	10·4
Hexahydrobenzoyl	278°/35	135	$C_{19}H_{21}ON$	81·4	7·4	81·7	7·6

3 : 8 : 9-*Trimethyl*-1 : 2-*benzacridine*.—To a boiling mixture of 4-methyl-1-naphthol (5 g.) and 2 : 3-dimethylaniline (10 g.), paraformaldehyde (1 g.) was added in small portions; when evolution of steam had ceased, the mixture was refluxed for 10 min., then fractionated *in vacuo*. The portion boiling at 320—328°/54 mm. was dissolved in hot ethanol and treated with ethanolic picric acid. The picrate, which formed deep yellow prisms, m. p. 189°, from xylene, was decomposed with aqueous ammonia, giving the *acridine*, which crystallised as yellowish needles (1·5 g.), m. p. 157—158°, from ethanol–benzene (Found: C, 88·5; H, 6·5. $C_{20}H_{17}N$ requires C, 88·5; H, 6·3%). 3 : 7 : 9-*Trimethyl*-1 : 2-*benzacridine*, b. p. 300—305°/22 mm., similarly prepared from 2 : 4-dimethylaniline, formed pale yellow leaflets, m. p. 169°, from benzene (Found: C, 88·8; H, 6·3%). 3 : 7 : 8-*Trimethyl*-1 : 2-*benzacridine*, b. p. 278—280°/14 mm., formed yellowish needles, m. p. 208°, from benzene (Found: C, 88·6; H, 6·5%); its *picrate* crystallised as orange-yellow prisms, m. p. 291° (decomp. > 235°), from xylene (Found: N, 10·9. $C_{26}H_{20}O_7N_4$ requires N, 11·2%).

6 : 7 : 9 : 2′-*Tetramethyl*-3 : 4-*benzacridine* (II).—This *compound*, prepared from 6-methyl-2-naphthol [15] (5 g.), ψ-cumidine (9 g.), and paraformaldehyde (1 g.), formed yellowish needles,

[15] Dziewoński, Schoeńowna, and Waldmann, *Ber.*, 1925, **58**, 1912.

m. p. 168°, from ethanol–benzene (Found: C, 88·7; H, 6·5. $C_{21}H_{19}N$ requires C, 88·4; H, 6·7%); the *picrate* formed bright yellow needles, m. p. 263—264° (decomp.), from xylene (Found: N, 11·2. $C_{27}H_{22}O_7N_4$ requires N, 10·9%).

N-(2 : 3-*Dimethylphenyl*)-4-*methyl*-1-*naphthylamine*.—A mixture of 4-methyl-1-naphthol (15 g.), 2 : 3-dimethylaniline (18 g.), and iodine (0·05 g.) was refluxed for 22 hr., and the product taken up in benzene, washed with dilute aqueous sodium hydroxide, then with water, and dried (Na_2SO_4); the residue from evaporation of the solvent gave on distillation *in vacuo* a *product*, b. p. 256—258°/17 mm., crystallising as colourless needles, (45%), m. p. 72—73°, from ethanol (Found: C, 87·0; H, 7·0. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3%).

N-(2 : 4-*Dimethylphenyl*)-4-*methyl*-1-*naphthylamine*, b. p. 242—244°/12 mm., similarly prepared in 45% yield with 2 : 4-dimethylaniline, formed colourless prisms, m. p. 65°, from ethanol (Found: C, 87·1; H, 7·0%), and gave a picrate as brown-violet needles, m. p. 126°, from ethanol. N-(2 : 5-*Dimethylphenyl*)-4-*methyl*-1-*naphthylamine* (yield 52%) was a pale yellow, viscous oil, b. p. 244—245°/14 mm., n_D^{26} 1·6564 (Found: C, 87·3; H, 7·5%). N-(3 : 4-*Dimethylphenyl*)-4-*methyl*-1-*naphthylamine* (yield 70%), b. p. 256—257°/12 mm., formed colourless leaflets, m. p. 66—67°, from ethanol (Found: C, 87·0; H, 7·2%). N-*ψ*-*Cumyl*-4-*methyl*-1-*naphthylamine* (yield 70%), was a viscous yellow oil, b. p. 248—249°/13 mm., darkening rapidly in air (Found: C, 87·0; H, 8·0. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7%).

3 : 5 : 6 : 7 : 9-*Pentamethyl*-1 : 2-*benzacridine*.—A mixture of the foregoing amine (9 g.), acetic anhydride (10 g.), and freshly fused powdered zinc chloride (9 g.) was refluxed for 40 hr., and the cooled mixture treated with hot benzene and 20% aqueous sodium hydroxide in great excess. The benzene solution was then dried (KOH), the solvent removed, and the residue distilled *in vacuo*. The portion boiling at 290—295°/13 mm. was converted into a picrate which crystallised as golden-yellow prisms, m. p. 219—220° (decomp. > 209°), from ethanol; treatment with aqueous ammonia yielded the *base* (45%), forming yellowish needles, m. p. 155°, from ethanol (Found: C, 88·0; H, 7·4. $C_{22}H_{21}N$ requires C, 88·3; H, 7·1%).

3 : 5 : 8 : 9-*Tetramethyl*-1 : 2-*benzacridine*, b. p. 330—335°/28 mm., yellowish needles, m. p. 170°, from benzene (Found: C, 88·0; H, 6·4%), gave a picrate forming deep yellow prisms, m. p. 162°, from xylene. Similar low-melting picrates had already been reported,[16] and have recently been observed with sterically hindered 1 : 2-benzanthracenes.[17] 3 : 5 : 7 : 9-*Tetramethyl*-1 : 2-*benzacridine* formed (from ethanol–benzene) yellowish needles, melting at 175°, resolidifying, and melting again at 183° (Found: C, 88·3; H, 6·4%), and gave a yellow picrate, m. p. 164° (decomp. > 160°), from ethanol. 3 : 5 : 6 : 9-*Tetramethyl*-1 : 2-*benzacridine*, yellow needles, m. p. 188°, from ethanol–benzene (Found: C, 88·0; H, 6·6%), gave a picrate crystallising as deep yellow needles, m. p. 184° (decomp. > 170°), from benzene. 3 : 5 : 7 : 8-*Tetramethyl*-1 : 2-*benzacridine* (yield 50%), pale yellow leaflets, m. p. 206°, from ethanol–benzene (Found: C, 88·1; H, 6·7%), gave a *picrate* which formed deep yellow leaflets, m. p. 281° (decomp. > 250°), from xylene (Found: N, 10·6%). Its homologue, 5-*ethyl*-3 : 7 : 8-*trimethyl*-1 : 2-*benzacridine*, prepared in 50% yield from *N*-(3 : 4-dimethylphenyl)-4-methyl-1-naphthylamine (9 g.), propionic anhydride (9 g.), and zinc chloride (9 g.), formed pale yellow needles, m. p. 193°, from ethanol (Found: C, 88·2; H, 7·0. $C_{23}H_{21}N$ requires C, 88·3; H, 7·1%) giving a *picrate*, deep yellow leaflets, m. p. 243—244° (decomp. > 198°) (Found: N, 10·3. $C_{28}H_{24}O_7N_4$ requires N, 10·6%).

3-*Methyl*-1 : 2-*benzocarbazole* (IV).—A mixture of 4-methyl-1-naphthol (4 g.), phenylhydrazine (8 g.), and anhydrous phenylhydrazine hydrochloride (4 g.) was refluxed for 1 hr., and dilute hydrochloric acid added after cooling; the product was taken up in benzene, and the benzene solution washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The residue after evaporation of the solvent was distilled *in vacuo*, and the *base* crystallised from ethanol to give colourless prisms, m. p. 169° (Found: C, 88·5; H, 5·5. $C_{17}H_{13}N$ requires C, 88·3; H, 5·7%).

10-*Chloro*-5 : 10-*dihydro*-2 : 6 : 7-*trimethyl*-3 : 4-*benzophenarsazine*.—A solution of *N*-(2 : 3-dimethylphenyl)-4-methyl-1-naphthylamine (1 g.) and arsenic trichloride (1 g.) in anhydrous *o*-dichlorobenzene (5 g.) was gently refluxed for 1 hr.; the precipitate obtained on cooling formed orange-yellow prisms (1 g.), m. p. 229° (decomp. > 200°), from benzene (Found: C, 61·4; H, 4·6. $C_{19}H_{17}NClAs$ requires C, 61·7; H, 4·6%), giving a blood-red halochromy in sulphuric acid.

[16] Cf. Senier and Austin, *J.*, 1907, **91**, 1240.
[17] Orchin, *J. Org. Chem.*, 1951, **16**, 1165.

10-*Chloro*-5 : 10-*dihydro*-2 : 6 : 8-*trimethyl*-3 : 4-*benzophenarsazine* formed yellow prisms, m. p. 261° (decomp. > 230°), from benzene (Found : C, 61·5; H, 4·3%), giving a red halochromy in sulphuric acid; the 2 : 6 : 9-*trimethyl-isomer* formed greenish-yellow needles, m. p. 250° (decomp. > 208°), from benzene, giving a brown-red halochromy (Found : C, 61·3; H, 4·4%); the 2 : 7 : 8-*trimethyl-isomer*, orange-yellow needles, m. p. 284° (decomp. > 224°), from xylene (Found : C, 61·5; H, 4·3%), gave a vermilion halochromy.

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