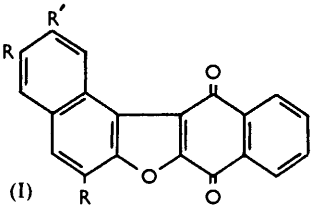
998. *Carcinogenic Nitrogen Compounds. Part XXIII.* New Polymethylated Homologues of 3 : 4-Benzacridine and 3 : 4-Benzocarbazole, and Related Compounds.*

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

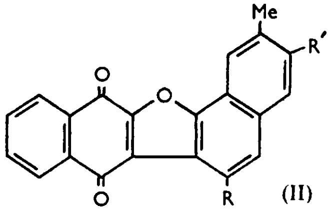
The synthesis is reported of several penta- and hexa-methyl-3 : 4-benzacridines, dimethyl-3 : 4-benzocarbazoles, and tetra- and penta-methyl homologues of 10-chloro-5 : 10-dihydro-1 : 2-benzophenarsazine, for test as carcinogens; in connexion with these syntheses, the chemistry of several mono- and di-methylnaphthols has been investigated.

Although, unlike the corresponding compounds in the 1 : 2-benzacridine series,[1] mono- and di-methyl-3 : 4-benzacridines have, with a few exceptions, been found to be non-carcinogenic, some trimethyl-3 : 4-benzacridines have shown pronounced carcinogenic activity.[2] This suggested an investigation of the influence on carcinogenicity due to a further increase in the number of methyl groups; accordingly, some of the 462 possible pentamethyl- and the 462 possible hexamethyl-3 : 4-benzacridines have been prepared.

Convenient intermediates are dimethyl-2-naphthols, some of which have now been thoroughly investigated. 3 : 6-, 3 : 7-, and 6 : 7-Dimethyl-2-naphthol were prepared from 2 : 6-, 2 : 7-, and 2 : 3-dimethylnaphthalene *via* the sulphonic acids,[3] and found to condense readily with 2 : 3-dichloro-1 : 4-naphthaquinone, giving brasanquinones[4] (I), a reaction which provides further proof of the position occupied by the hydroxy-group in these three naphthols. Further, it was confirmed that sulphonation of 2 : 6-dimethylnaphthalene at low temperature yields the 4-sulphonic acid, whereas 1 : 6-dimethylnaphthalene gave only the 4-sulphonic acid at both high and low temperature. 3 : 7- and 4 : 7-Dimethyl-1-naphthol, prepared from these sulphonic acids, reacted with 2 : 3-dichloro-1 : 4-naphthaquinone to give the brasanquinones (II), proof that the β-position adjacent to the hydroxy-group was free.



(I)



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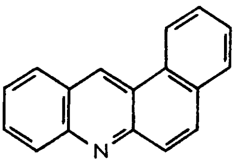

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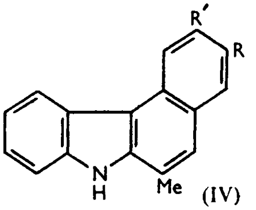

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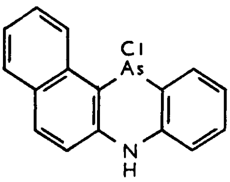

(V)

Among the pentamethyl derivatives of 3 : 4-benzacridine (III), the 1 : 6 : 7 : 9 : 3′- and 6 : 7 : 9 : 2′ : 3′-derivative were obtained by Ullmann–Fetvadjian condensation[5] of 3 : 7- and 6 : 7-dimethyl-2-naphthol with 3 : 4 : 5-trimethylaniline and paraformaldehyde. 3 : 7-Dimethyl-*N*-(3 : 4-dimethylphenyl)-2-naphthylamine, resulting from a Knoevenagel

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* Part XXII, *J.*, 1957, 3126.

[1] See Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

[2] Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22.

[3] Weissgerber and Kruber, *Ber.*, 1919, **52**, 346, 367; Coulson, *J.*, 1935, 77.

[4] Cf. Buu-Hoï, *J.*, 1952, 489; Buu-Hoï and Demerseman, *J.*, 1952, 4699.

[5] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.

condensation[6] of 3 : 7-dimethyl-2-naphthol with 3 : 4-dimethylaniline, underwent a Bernthsen reaction[7] with acetic anhydride, to give 1 : 5 : 7 : 8 : 3′-pentamethyl-3 : 4-benzacridine; the 1 : 5 : 7 : 8 : 2′- and the 5 : 7 : 8 : 2′ : 3′-pentamethyl isomers were similarly prepared from *N*-(3 : 4-dimethylphenyl)-3 : 6- and 6 : 7-dimethyl-2-naphthylamine. In the group of hexamethyl-3 : 4-benzacridines, the 1 : 5 : 6 : 7 : 9 : 2′- and the 5 : 6 : 7 : 9 : 2′ : 3′-isomer were prepared by Bernthsen reactions with 3 : 6- and 6 : 7-dimethyl-*N*-(2 : 4 : 5-trimethylphenyl)-2-naphthylamine.

In the 3 : 4-benzocarbazole group, the 1 : 2′- and 1 : 3′-derivatives (IV) were obtained by a Japp–Maitland condensation[8] of 3 : 6- and 3 : 7-dimethyl-2-naphthol with phenylhydrazine and its hydrochloride. In view of the known oncogenic activity of some 10-chloro-5 : 10-dihydrobenzophenarsazines,[9] the 4 : 7 : 8 : 2′- and 7 : 8 : 2′ : 3′-tetramethyl and the 6 : 8 : 9 : 2′ : 3′-pentamethyl derivative of 10-chloro-5 : 10-dihydro-1 : 2-benzophenarsazine (V) were prepared, by a Wieland–Rheinheimer condensation[10] of arsenic trichloride with the appropriate *N*-aryl-2-naphthylamine.

The benzacridines prepared have not caused tumours to develop during 4 months' test on mice by Dr. Zajdela of this Institute.

EXPERIMENTAL

Dimethylnaphthols.—2 : 6- and 2 : 7-Dimethylnaphthalene were sulphonated at 135—140° with 98% sulphuric acid, and the sulphonic acids obtained were converted into 3 : 7- (m. p. 176·5°; lit., 173—174°) and 3 : 6-dimethyl-2-naphthol (m. p. 173°; lit., 171—172°) by alkaline fusion, according to Weissgerber and Kruber;[3] alkaline fusion of the product of sulphonation of 2 : 6-dimethylnaphthalene at room temperature yielded 3 : 7-dimethyl-1-naphthol (m. p. 104—105°; lit., 105—106°). 4 : 7-Dimethyl-1-naphthol, prepared by alkaline fusion of the sulphonation product of 1 : 6-dimethylnaphthalene, crystallised from light petroleum as colourless needles, m. p. 84° (lit., 82°), b. p. 175—176°/18 mm.

3″ : 7″-*Dimethyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (I; R = R″ = Me, R′ = H).—This *compound* was prepared by refluxing for 10 min. a solution of 3 : 7-dimethyl-2-naphthol (1 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (1·3 g.) in dry pyridine (15 c.c.); the precipitate, formed on cooling, recrystallised from pyridine as orange-yellow needles (1·2 g.), m. p. 269°, giving a turquoise colour in sulphuric acid (Found: C, 80·7; H, 4·1. $C_{22}H_{14}O_3$ requires C, 81·0; H, 4·3%). The 3″ : 6″-*dimethyl isomer* (I; R = R′ = Me, R″ = H), similarly prepared from 3 : 6-dimethyl-2-naphthol, formed orange needles, m. p. 274° (decomp. >262°), from pyridine (Found: C, 80·9; H, 4·1%). The 6″ : 7″-*dimethyl isomer* (I; R = H, R′ = R″ = Me), obtained from 6 : 7-dimethyl-2-naphthol, crystallised as orange needles, m. p. 291°, from pyridine (Found: C, 80·7; H, 4·5%).

3″ : 7″-*Dimethyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-5 : 4)*furan*-1′ : 4′-*quinone* (II; R = Me, R′ = H).—Prepared from 3 : 7-dimethyl-1-naphthol, this *quinone* formed deep yellow needles, m. p. 292°, from pyridine (Found: C, 80·9; H, 4·3%); the 4″ : 7″-*dimethyl isomer* (II; R = H, R′ = Me) formed orange-yellow, sublimable needles, m. p. 350°, from pyridine, giving a deep blue halochromy in sulphuric acid (Found: C, 80·9; H, 4·1%).

1 : 6 : 7 : 9 : 3′-*Pentamethyl*-3 : 4-*benzacridine.*—To a mixture of 3 : 7-dimethyl-2-naphthol (7 g.) and 3 : 4 : 5-trimethylaniline (7 g.) at 250°, paraformaldehyde (3 g.) was added in small portions; after the vigorous evolution of water had subsided, the mixture was refluxed for 5 min. and fractionated *in vacuo*. The portion of b. p. *ca.* 303°/18 mm. was treated in benzene with picric acid, and the picrate recrystallised several times from benzene, giving orange needles, m. p. 183° (decomp. > 162°). Basification with aqueous ammonia furnished the free *acridine*, yellowish prisms (0·8 g.), m. p. 179° (from benzene) (Found: C, 88·0; H, 7·1. $C_{22}H_{21}N$ requires C, 88·3; H, 7·1%). 6 : 7 : 9 : 2′ : 3′-*Pentamethyl*-3 : 4-*benzacridine*, b. p. 289°/13 mm., similarly prepared from 6 : 7-dimethyl-2-naphthol (7 g.), formed yellowish prisms (1·2 g.), m. p. 196°, from benzene (Found: C, 88·6; H, 6·8%), and gave a *picrate*, crystallising as yellow prisms,

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[6] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346.
[7] Cf. Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 648; *Rec. Trav. chim.*, 1945, **64**, 251.
[8] Japp and Maitland, *J.*, 1903, **83**, 267.
[9] Lacassagne, Rudali, Buu-Hoï, and Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451.
[10] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1.

m. p. 263° (decomp. > 250° from *o*-dichlorobenzene (Found: N, 10·3. $C_{28}H_{24}O_7N_4$ requires N, 10·6%).

N-(3 : 4-*Dimethylphenyl*)-3 : 7-*dimethyl*-2-*naphthylamine*.—A mixture of 3 : 7-dimethyl-2-naphthol (10 g.) and 3 : 4-dimethylaniline (7 g.) was refluxed for 30 hr. with iodine (0·2 g.), taken up in benzene, washed with dilute aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The solvent was removed, and the residue fractionated *in vacuo*. The *diarylamine* (8 g.) obtained, b. p. 267—268°/16 mm., formed colourless leaflets, m. p. 136°, from ethanol (Found: C, 87·0; H, 7·9. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7%), giving a picrate, crystallising as deep violet needles, m. p. 131°, from ethanol.

10-*Chloro*-5 : 10-*dihydro*-4 : 7 : 8 : 2′-*tetramethyl*-1 : 2-*benzophenarsazine*, prepared by refluxing for 1 hr. a solution of this diarylamine (2 g.) and arsenic trichloride (1·3 g.) in *o*-dichlorobenzene (10 c.c.), crystallised from that solvent as yellow needles (2 g.), m. p. 305° (decomp. > 228°), giving a brown-red halochromy in sulphuric acid (Found: C, 62·7; H, 5·1. $C_{20}H_{19}NAsCl$ requires C, 62·6; H, 5·0%).

1 : 5 : 7 : 8 : 3′-*Pentamethyl*-3 : 4-*benzacridine*.—A mixture of the foregoing diarylamine (5 g.), acetic anhydride (3 g.), and zinc chloride (6 g.) was heated at 185° for 40 hr.; after cooling, the product was treated with hot aqueous sodium hydroxide, and the acridine taken up in benzene, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The portion boiling at 310—320°/18 mm. was converted into a picrate, crystallising as orange-yellow needles, m. p. 289° (decomp. > 226°) from *o*-dichlorobenzene; basification with aqueous ammonia furnished the *acridine* as yellowish needles (1 g.), m. p. 160° (Found: C, 88·1; H, 7·3%).

N-(3 : 4-*Dimethylphenyl*)-3 : 6-*dimethyl*-2-*naphthylamine*.—Prepared from 3 : 6-dimethyl-2-naphthol (10 g.) and 3 : 4-dimethylaniline (7 g.) in the presence of iodine (0·5 g.), this *diarylamine*, b. p. 257—258°/13 mm., formed colourless prisms (8 g.), m. p. 100°, from light petroleum (Found: C, 87·2; H, 7·9%), giving a picrate, crystallising as dark violet needles, m. p. 155° (decomp. > 145°), from ethanol.

1 : 5 : 7 : 8 : 2′-*Pentamethyl*-3 : 4-*benzacridine*, prepared from this amine (5 g.), acetic anhydride (3 g.), and zinc chloride (6 g.), formed yellowish needles (1 g.), m. p. 190°, from ethanol (Found: C, 87·9; H, 7·2%), giving a *picrate*, crystallising from chlorobenzene as orange-yellow leaflets, m. p. 279° (decomp. > 246°) (Found: N, 10·3%).

N-(3 : 4-*Dimethylphenyl*)-6 : 7-*dimethyl*-2-*naphthylamine*.—Obtained as above from 6 : 7-dimethyl-2-naphthol, this *diarylamine*, b. p. 275°/17 mm., formed colourless prisms, m. p. 140°, from ethanol (Found: C, 87·0; H, 7·7%), giving a picrate, crystallising from ethanol as violet-black needles, m. p. 134°.

10-*Chloro*-5 : 10-*dihydro*-7 : 8 : 2′ : 3′-*tetramethyl*-1 : 2-*benzophenarsazine*, prepared from this diarylamine, crystallised as orange-yellow, sublimable needles, m. p. 308°, from chlorobenzene, giving a brown-red halochromy in sulphuric acid (Found: C, 62·4; H, 5·3%). 5 : 7 : 8 : 2′ : 3′-*Pentamethyl*-3 : 4-*benzacridine*, b. p. 306—310°/20 mm., prepared from the same diarylamine, formed yellowish prisms, m. p. 176°, from *cyclo*hexane (Found: C, 88·0; H, 6·7%).

3 : 6-*Dimethyl*-N-(2 : 4 : 5-*trimethylphenyl*)-2-*naphthylamine*.—This *diarylamine* (8 g.), prepared by refluxing for 20 hr. a mixture of 3 : 4 : 5-trimethylaniline (8 g.), 3 : 6-dimethyl-2-naphthol (10 g.), and iodine (0·5 g.), was a pale yellow, viscous oil, b. p. 256—257°/12 mm. (Found: C, 87·5; H, 8·0. $C_{21}H_{23}N$ requires C, 87·2; H, 8·2%), giving a picrate, crystallising as violet-black needles, m. p. 106°, from benzene.

1 : 5 : 6 : 7 : 9 : 2′-*Hexamethyl*-3 : 4-*benzacridine*, b. p. 300°/12 mm., prepared from this diarylamine (5 g.), acetic anhydride (3 g.), and zinc chloride (7 g.), formed pale yellow prisms, m. p. 136°, from acetone (Found: C, 88·5; H, 7·7. $C_{23}H_{23}N$ requires C, 88·2; H, 7·4%), giving a picrate, crystallising from ethanol–benzene as orange prisms, m. p. 167°.

6 : 7-*Dimethyl*-N-(2 : 4 : 5-*trimethylphenyl*)-2-*naphthylamine*.—This *diarylamine* was a pale yellow, viscous oil, b. p. 278—280°/20 mm. (Found: C, 87·0; H, 8·1%), giving a violet-black picrate, m. p. 153—154°, unstable in ethanol.

10-*Chloro*-5 : 10-*dihydro*-6 : 8 : 9 : 2′ : 3′-*pentamethyl*-1 : 2-*benzophenarsazine* (1 g.), prepared from the foregoing diarylamine (2 g.), crystallised as yellow needles, m. p. 265° (decomp. > 240°), from *o*-dichlorobenzene, giving a brown-red halochromy in sulphuric acid (Found: C, 63·0; H, 5·0. $C_{21}H_{21}NAsCl$ requires C, 63·4; H, 5·3%).

5 : 6 : 7 : 9 : 2′ : 3′-*Hexamethyl*-3 : 4-*benzacridine*, b. p. 320—325°/18 mm., prepared from the foregoing diarylamine (5 g.), formed pale yellow needles (0·8 g.), m. p. 198°, from benzene (Found: C, 87·9; H, 7·0%); the corresponding *picrate* crystallised as yellow needles, m. p.

267° (decomp. > 256°), from *o*-dichlorobenzene (Found: N, 9·9. $C_{29}H_{26}O_7N_4$ requires N, 10·3%).

1 : 2′-*Dimethyl*-3 : 4-*benzocarbazole* (IV; R = Me, R′ = H).—A mixture of 3 : 6-dimethyl-2-naphthol (4 g.), phenylhydrazine (4 g.), and phenylhydrazine hydrochloride (4 g.) was refluxed for 90 min., then cooled. 5% Aqueous acetic acid was added, and the product taken up in benzene, washed with water, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The portion boiling at 280—285°/12 mm. was recrystallised twice from light petroleum, forming colourless leaflets (1 g.), m. p. 182° (Found: C, 87·8; H, 6·3. $C_{18}H_{15}N$ requires C, 88·1; H, 6·2%), giving a picrate, crystallising as violet-brown needles, m. p. 208° (decomp. > 190°), from ethanol.

1 : 3′-*Dimethyl*-3 : 4-*benzocarbazole* (IV; R = H, R′ = Me), similarly prepared from 3 : 7-dimethyl-2-naphthol, formed colourless leaflets (0·6 g.), m. p. 149°, from light petroleum (Found: C, 87·9; H, 6·3%), giving a picrate, violet-brown needles, m. p. 210° (decomp. > 160°), from ethanol.

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