# Carcinogenic Nitrogen Compounds. Part LXXXIII.[1] New Condensed Acridines Derived from Benz[*c*]indeno[1,3-*mn*]-, Benz[*c*]indeno[1,3-*kl*]-, and Phenanthro[9,10,1-*mna*]-acridines

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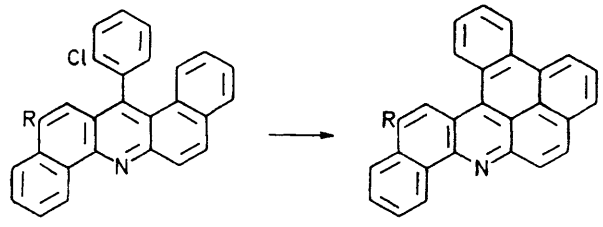
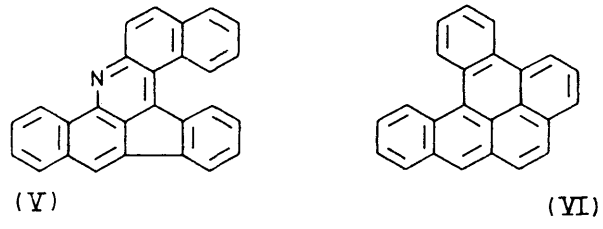
7-*o*-Chlorophenyl-5-methylbenz[*c*]acridine underwent cyclisation with sodium hydroxide in benzo[*h*]quinoline to give a mixture of 14-methylbenz[*c*]indeno[1,3-*kl*]- and 9-methylbenz[*c*]indeno[1,3-*mn*]-acridine, and a similar reaction with 7-*o*-chlorophenyl-5,9-dimethyldibenz[*c,h*]acridine gave 5,11-dimethyldibenz[*c,h*]indeno-[1,3-*kl*]acridine. In both cases, by-products were isolated. 2-Methylphenanthro[9,10,1-*mna*]acridine was obtained from 12-(2-chloro-5-methylphenyl)benz[*a*]acridine, but the 6-methyl isomer did not cyclise. Some methyl-substituted 14-*o*-chlorophenyldibenz[*a,h*]- and -dibenz[*a,j*]-acridines furnished the corresponding 1-azapyrenes.

RECENTLY, we reported the preparation of compounds containing the cyclopent[*kl*]acridine skeleton by treatment of 7-*o*-chlorophenylbenz[*c*]- and 7-*o*-chlorophenyldibenz[*c,h*]-acridines with sodium hydroxide in boiling benzo[*h*]quinoline, but found that the cyclisation of 14-*o*-chlorophenyldibenz[*a,h*]acridine (I) furnished only

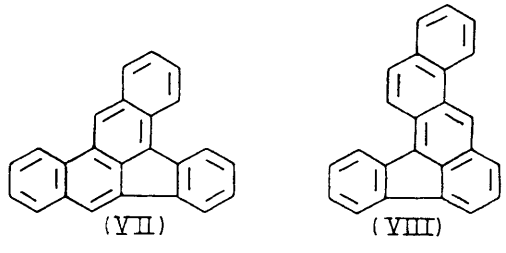


(I) R = H
(II) R = Me

(VII) R = H
(IV) R = Me

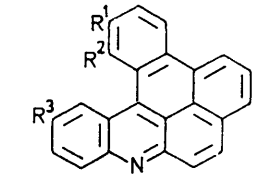


(V) (VI)

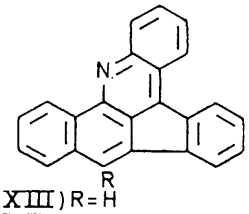


(VII) (VIII)

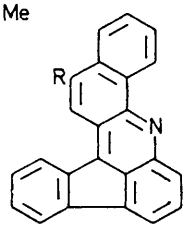
benzo[*h*]phenanthro[9,10,1-*mna*]acridine (III) and not the isomeric dibenz[*a,h*]indeno[1,3-*kl*]acridine (V).[2] To determine the scope of this cyclisation, we have now synthesised a series of compounds containing the cyclopent[*kl*]acridine nucleus and bearing one or more methyl substituents. Furthermore, in view of the carcinogenic activity [3-5] of hydrocarbons (VI),[6] (VII), and (VIII), and the fact that current biological tests indicate that some of their nitrogen analogues [(IX), (X), (XIII), and (XV)] are less sarcomagenic, this study might throw light on the influence of methyl substitution on carcinogenicity in this series.



(IX) $R^1 = R^2 = R^3 = H$
(X) $R^1 = R^2 = H, R^3 = Me$
(XI) $R^1 = Me, R^2 = R^3 = H$
(XII) $R^1 = R^3 = H, R^2 = Me$



(XIII) R = H
(XIV) R = Me



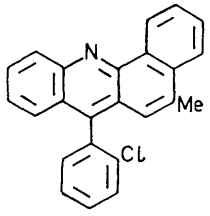
(XV) R = H
(XVI) R = Me

Cyclisation of 7-*o*-chlorophenyl-5-methylbenz[*c*]acridine (XVII) (prepared by Bernthsen reaction [7] of *o*-chlorobenzoic acid and 4-methyl-*N*-phenyl-1-naphthylamine) furnished the two isomeric dibenzacridines, (XIV) and (XVI), along with small amounts of a bi-(benzo[*h*]quinolyl). Identification of the two expected products was based on comparison of their u.v. spectra with those of the known [2] non-substituted analogues (XIII) and (XV), respectively.

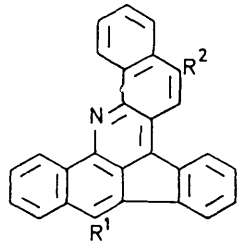
Condensation of 4-methyl-1-naphthol with 4-methyl-1-naphthylamine led easily to compound (XXIV), and

[1] Part LXXXII, P. Bigot, G. Saint-Ruf, and N. P. Buu-Hoï, *J.C.S. Perkin I*, 1972, 2573.
[2] N. P. Buu-Hoï, O. Périn-Roussel, P. Jacquignon, and A. Cheutin, *J.C.S. Perkin I*, 1972, 1263.
[3] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and F. A. Vingiello, *Naturwiss.*, 1968, **55**, 43.
[4] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and D. Lavit-Lamy, *Compt. rend.*, 1963, **256**, 2728.
[5] M. Shear, *Amer. J. Cancer*, 1936, **28**, 334.
[6] N. P. Buu-Hoï, O. Périn-Roussel, and P. Jacquignon, *Chem. Comm.*, 1968, 718; *Bull. Soc. chim. France*, 1969, 3566.
[7] A. Bernthsen, *Ber.*, 1883, **16**, 767.

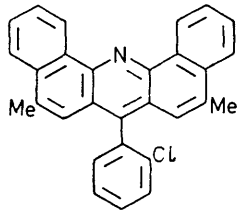
Bernthsen reaction of this furnished the dibenzacridine (XIX), which was cyclised with sodium hydroxide in benzo[*h*]quinoline to 5,11-dimethyldibenz[*c*,*h*]indeno-[1,3-*kl*]acridine (XVIII). However, the same procedure was unsuccessful for compounds (XX) and (XXI), because the required starting material, *N*-1-naphthyl-4-methyl-1-naphthylamine (XXII), could not be separated from di-1-naphthylamine (XXIII).



(XVII)

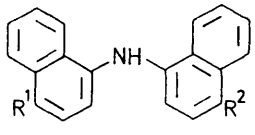


(XVIII) $R^1 = R^2 = Me$
(XX) $R^1 = H$, $R^2 = Me$
(XXI) $R^1 = Me$, $R^2 = H$

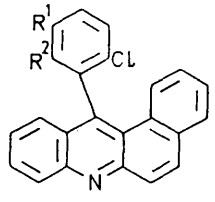


(XIX)

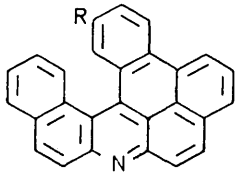
Previously,[8] we described the preparation of some compounds containing the naphtho[2,1,8-*def*]quinoline (1-azapyrene) nucleus, by cyclisation of several benz[*a*]- and dibenz[*a*,*j*]-acridines, and we now extend this method



(XXII) $R^1 = Me$, $R^2 = H$
(XXIII) $R^1 = R^2 = H$
(XXIV) $R^1 = R^2 = Me$

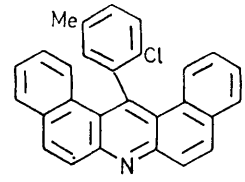


(XXV) $R^1 = Me$, $R^2 = H$
(XXVI) $R^1 = H$, $R^2 = Me$



(XXVII) R = H
(XXVIII) R = Me

to give new methyl homologues of (IX), (III), and (XXVII). For example, compound (XI) was obtained by reaction of 2-chloro-5-methylbenzoic acid and *N*-phenyl-2-naphthylamine *via* 12-(2-chloro-5-methylphenyl)benz[*a*]acridine (XXV), but attempts to synthesise 1-methylphenanthro[9,10,1-*mna*]acridine (XII) were unsuccessful as the acridine (XXVI) resisted cyclisation, probably on account of steric hindrance. The dibenzacridine (II) also readily underwent cyclisation and afforded 15-methylbenz[*h*]phenanthra[9,10,1-*mna*]acridine (IV) and some identifiable by-products. Lastly, compound (XXVIII) was easily obtained *via* cyclisation of 14-(2-chloro-5-methylphenyl)dibenz[*a*,*j*]acridine (XXIX).



(XXIX)

All the compounds derived from the benz[*c*]indeno-[1,3-*mn*]-, benz[*c*]indeno[1,3-*kl*]-, and phenanthro[9,10,1-*mna*]-acridine nuclei were stable to electron impact; very little fragmentation (loss of $CH_3^{\bullet}$) occurred, and doubly charged molecular ions were very prominent (*ca.* 35—40% of the base peak).

Results of carcinogenicity tests will be reported later.

## EXPERIMENTAL

Mass spectra were determined with an A.E.I. MS9 apparatus at 70 eV. U.v. spectra were taken for solutions in cyclohexane with a Leres S 66 instrument. M.p.s were taken on a Maquenne block. The purity of the secondary amines and intermediary acridines was checked by g.l.c. on a Girdel 75 instrument.

*Preparation of* o-*Chlorophenylbenzacridines by the Bernthsen Reaction* (Table).—*General procedure.* A mixture of the secondary amine (0·05 mol; prepared according to Knoevenagel [9]), an *o*-chlorobenzoic acid (0·06 mol), and anhydrous zinc chloride (0·055 mol) was heated at 200—220° for 24 h and, on cooling, treated with aqueous 20% sodium hydroxide in the presence of toluene. The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated, and the residue was distilled *in vacuo*. Yields were 35—40%.

*Cyclisation of* o-*Chlorophenylbenzacridines.*—*General procedure.* A mixture of the acridine (3 g), sodium hydroxide (15 g), and benzo[*h*]quinoline (15 g) was heated in a Kjeldahl matrass at 360° for 4 h. After cooling, the product was diluted with water and extracted with chloroform, and was purified by chromatography on a silica column [eluant cyclohexane, then benzene–cyclohexane (1 : 1)].

(a) *Cyclisation of compound* (XVII). Elution with cyclohexane, then with benzene, gave: (i) x,x′-bi(benzo[*h*]-quinolyl), as sublimable needles (0·08 g), m.p. 286° (from benzene–ethanol) (Found: N, 7·7%; $M^+$, 356. Calc. for $C_{26}H_{16}N_2$: N, 7·9%; *M*, 356); (ii) some unchanged acridine (XVII) (0·1 g); (iii) 14-*methylbenz*[c]*indeno*[1,3-kl]*acridine* (XVI), purified *via* its *picrate* [orange-red prisms, m.p. 240—242° (from ethanol–benzene) (Found: N, 9·8. $C_{30}H_{18}N_4O_7$ requires N, 10·2%)]. The free base (XVI) crystallised as bright yellow needles (0·02 g), m.p. 256—257° (from benzene), and gave bright orange-red solutions in sulphuric

[8] N. P. Buu-Hoï, O. Périn-Roussel, and P. Jacquignon, *J.C.S. Perkin I*, 1972, 234.
[9] E. Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17.

acid (Found: C, 90·9; H, 4·7; N, 4·4%; $M^+$, 317. $C_{24}H_{15}N$ requires C, 90·8; H, 4·7; N, 4·4%; $M$, 317); $\lambda_{max.}$ (cyclohexane) 226 (log ε 4·79), 241 (4·43), 252 (4·52), 270 (4·43), 295 (4·65), 302 (4·70), 335 (3·36), 350 (3·60), 370 (3·96), 392 (4·16), 397 (4·15), 404 (4·20), 415 (4·06), 430 (4·20), and 440 nm (3·76); and (iv) 9-*methylbenz*[c]*indeno*[1,3-mn]*acridine* (XIV), purified *via* its *picrate* [bright red prisms, m.p. 234—235° (Found: N, 10·3%)]. Basification afforded the acridine (XIV) (0·09 g) as yellow prisms, m.p. 175—176° (from benzene), which gave orange-red solutions in sulphuric acid (Found: C, 90·2; H, 4·7; N, 4·4%; $M^+$, 317); $\lambda_{max.}$ 219 (log ε 4·55), 228 (4·46), 239 (4·56), 242 (4·55), 258 (4·65), 270 (4·42), 278 (4·50), 287 (4·42), 295 (4·50), 300 (4·43), 308 (4·45), 326 (3·70), 330 (3·70), 336 (3·50), 390 (4·18), 402 (4·14), 415 (4·18), and 440 nm (3·10).

(b) *Cyclisation of compound* (XIX). Chromatography [silica; cyclohexane–benzene (4 : 1) as eluant] furnished: (i) 5,9-dimethyldibenz[*c*,*h*]acridine (0·5 g), *m/e* 307, m.p. and mixed m.p. with an authentic sample [11] 285° (from benzene); and (ii) 5,11-*dimethyldibenz*[c,h]*indeno*[1,3-kl]*acridine* (XVIII), bright yellow needles (0·03 g), m.p. 299° (resolidifies at 284°) (from benzene), giving bright red solutions in sulphuric acid (Found: C, 91·2; H, 5·3; N, 3·4%; $M^+$, 381. $C_{29}H_{19}N$ requires C, 91·3; H, 5·0; N, 3·6%; $M$, 381); picrate, orange-red prisms, m.p. 218° (decomp. >190°).

(c) *Cyclisation of compound* (XXV). Chromatography gave: (i) x,x'-bi(benzo[*h*]quinolyl) (0·02 g); (ii) unchanged acridine (XXV) (0·05 g); and (iii) 2-*methylphenanthro*[9,10,1-mna]*acridine* (XI), golden needles (0·1 g), m.p. 111—112° (from petroleum) (Found: C, 90·4; H, 5·1; N, 4·3%; $M^+$, 317. $C_{24}H_{15}N$ requires C, 90·8; H, 4·8; N, 4·4%; $M$, 317); *picrate*, orange prisms, m.p. 276° (decomp. >255°) (from nitrobenzene) (Found: N, 10·3. $C_{30}H_{18}N_4O_7$ requires N, 10·2%).

(d) *Cyclisation of Compound* (XXIX). This cyclisation gave 2-*methylbenzo*[j]*phenanthro*[9,10,1-mna]*acridine* (XXVIII) as yellow needles, m.p. 226—227° (resolidifies at ~120°) (from benzene), giving orange solutions in sulphuric acid (Found: C, 91·4; H, 4·9; N, 4·0. $C_{28}H_{17}N$ requires C, 91·5; H, 4·6; N, 3·8%); *picrate*, orange prisms, m.p. 230—231° (from chlorobenzene) (Found: N, 9·2. $C_{34}H_{20}N_4O_7$ requires N, 9·4%).

*o*-Chlorophenylbenzacridines [a]

| Compound | B.p. (° C) (mmHg) | M.p. (° C) | Formula | Analysis Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 7-(*o*-Chlorophenyl)-5-methylbenz[*c*]acridine (XVII) | 320—325 (18) | 190 | $C_{24}H_{16}ClN$ | 81·6 | 4·8 | 4·2 | 81·5 | 4·5 | 3·9 |
| Picrate | | 215 (decomp. > 195) | $C_{30}H_{19}ClN_4O_7$ | | | 9·6 | | | 9·6 |
| 7-(*o*-Chlorophenyl)-5,9-dimethyldibenz[*c*,*h*]acridine (XIX) [b] | 330—340 (15) | 320 (subl. > 285) | $C_{29}H_{20}ClN$ | 83·6 | 4·9 | 3·3 | 83·3 | 4·8 | 3·3 |
| 12-(2-Chloro-5-methylphenyl)benz[*a*]acridine (XXV) [c] | 315—320 (20) | 144 | $C_{24}H_{16}ClN$ | 80·9 | 4·6 | 4·2 | 81·5 | 4·5 | 3·9 |
| Picrate | | 233 (decomp. > 206) | $C_{30}H_{19}ClN_4O_7$ | | | 9·6 | | | 9·6 |
| 14-(2-Chloro-5-methylphenyl)dibenz[*a*,*j*]acridine (XXIX) [d] | 340—345 (15) | 254 | $C_{28}H_{18}ClN$ | 82·9 | 4·5 | 3·5 | 83·2 | 4·5 | 3·4 |
| Picrate | | 266 (decomp. > 235) | $C_{34}H_{21}ClN_4O_7$ | | | 9·0 | | | 8·8 |
| 14-(*o*-Chlorophenyl)-12-methyldibenz[*a*,*h*]acridine (II) [e] | 320—330 (15) | 176 | $C_{28}H_{18}ClN$ | 83·6 | 4·5 | 3·4 | 83·2 | 4·5 | 3·4 |
| Picrate | | 228 (decomp. > 205) | $C_{34}H_{21}ClN_4O_7$ | | | 9·2 | | | 8·8 |

[a] Recrystallised as pale yellow needles (from benzene); picrates crystallised as orange prisms. [b] Obtained from 4,4'-dimethyl-di-1-naphthylamine[(XXIV); prepared by condensation of 4-hydroxy-1-methylnaphthalene and 4-amino-1-methylnaphthalene [10]]. [c] From 2-chloro-5-methylbenzoic acid; crystallised from methanol. [d] From 2-chloro-5-methylbenzoic acid; purified by chromatography (silica) to separate dibenz[*a*,*j*]acridine also formed. [e] Crystallised from ethanol; the secondary amine was obtained by condensation of 2-naphthol and 4-methyl-1-naphthylamine, and had b.p. 295—300° at 17 mmHg, m.p. 125—126°.

(e) *Cyclisation of compound* (II). Chromatography afforded: (i) x,x'-bi(benzo[*h*]quinolyl) (0·05 g); (ii) 12-*methyl*-14-*phenyldibenz*[a,h]*acridine* (0·08 g), m.p. 224—225° (from cyclohexane) (Found: C, 90·2; H, 5·0; N, 4·4%; $M^+$, 369. $C_{28}H_{19}N$ requires C, 90·9; H, 5·1; N, 3·8%; $M$, 369); (iii) the starting acridine (II) (0·01 g); and (iv) 15-*methylbenzo*[h]*phenanthro*[9,10,1-mna]*acridine* (IV), pale yellow needles (0·2 g), m.p. 210—211° (from benzene), giving orange-red solutions in sulphuric acid (Found: C, 91·7; H, 4·7; N, 3·6. $C_{28}H_{17}N$ requires C, 91·5; H, 4·6; N, 3·8%); *picrate*, orange prisms, m.p. 252° (decomp. >240°) (from benzene) (Found: N, 9·5. $C_{34}H_{20}N_4O_7$ requires N, 9·4%).

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[10] J. M. Bonnier and J. Rinaudo, *Bull. Soc. chim. France*, 1971, 2100.

[11] J. André, P. Jacquignon, N. P. Buu-Hoï, and F. Périn, *J. Heterocyclic Chem.*, 1971, **8**, 529.