Carcinogenic Nitrogen Compounds. Part LXXIII.[1] Cyclisation of 12-(*o*-Chloroaryl)benz[*a*]acridines: a Route to New Condensed Acridines Derived from Naphtho[2,1,8-*def*]quinoline (1-Azapyrene)

By **N. P. Buu-Hoï,*** (Mrs.) **O. Périn-Roussel,** and **P. Jacquignon,** Institut de Chimie des Substances Naturelles du C.N.R.S., 91-Gif-sur-Yvette, France

12-(*o*-Chlorophenyl)benz[*a*]acridine undergoes cyclisation with sodium hydroxide in benzo[*h*]quinoline to give 10-azadibenzo[*a,l*]pyrene, a new type of condensed polycyclic acridine derived from naphtho[2,1,8-*def*]quinoline. This reaction can be extended to the synthesis of substituted derivatives of this new heterocyclic system such as benzo[*j*]phenanthra[9,10,1-*mna*]acridine.

It is known that upon replacement of a –CH= by a nitrogen atom in polycyclic aromatic hydrocarbons the biological activity [2] is often retained and sometimes even enhanced.[3] Since dibenzo[*a,l*]pyrene (I) is one of the most potent carcinogens known,[4] it was of interest to synthesize aza-derivatives of this and related hydrocarbons, for biological evaluation.

A convenient route to phenanthra[9,10,1-*mna*]acridine (IV) consisted of extending to 12-(*o*-chlorophenyl)-benz[*a*]acridine (II) the cyclisation method previously used to prepare dibenzo[*a,l*]pyrene itself,[5] *i.e.* treatment with sodium hydroxide in boiling benzo[*h*]quinoline; this readily afforded (IV) along with small amounts of two secondary reaction-products: (*a*) a compound melting at

[1] Part LXXII, N. P. Buu-Hoï, G. Saint-Ruf, D. Deschamps, P. Bigot, and H.-T. Hieu, *J. Chem. Soc.* (*C*), 1971, **2606**.

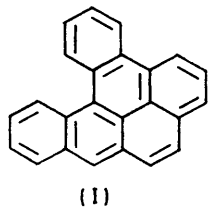
[2] See for instance, J. W. Cook, G. A. D. Haselwood, C. L. Hewett, I. Hieger, E. L. Kennaway, and W. V. Mayneord, *Amer. J. Cancer*, 1937, **29**, 219; A. Lacassagne, N. P. Buu-Hoï, R. Daudel, and F. Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315; N. P. Buu-Hoï, *Cancer Res.*, 1964, **24**, 1511.

[3] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, F. Périn, and P. Jacquignon, *Nature*, 1961, **191**, 1005.

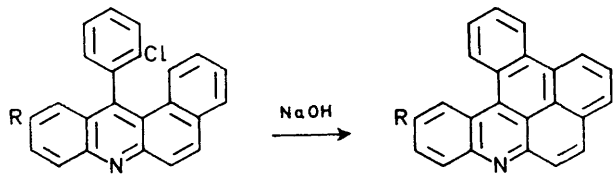
[4] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and F. A. Vingiello, *Naturwiss.*, 1968, **55**, 43.

[5] N. P. Buu-Hoï, O. Périn-Roussel, and P. Jacquignon, *Chem. Comm.*, 1968, 718; *Bull. Soc. chim. France*, 1969, 3566.

235° (M, 546) of unknown constitution, and (*b*) an *x*,*x*'-bibenzo[*h*]quinolyl engendered by the action of the alkali on the solvent *via* a reaction similar to the formation of bipyridyls and biquinolyls.[6] Since Tschitschibabin and Kursanova had obtained 2-hydroxybenzo[*h*]quinoline by alkali fusion of benzo[*h*]quinoline with



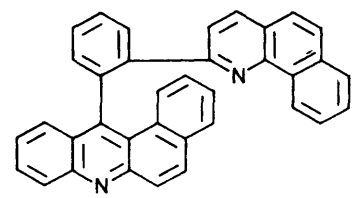
(I)



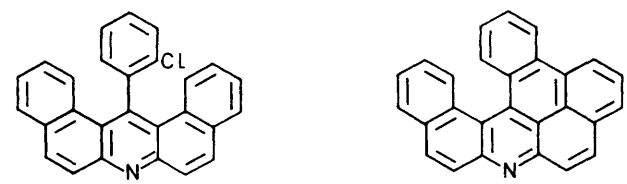
(II) R = H
(III) R = Me
(IV) R = H
(V) R = Me

potassium hydroxide,[7] it is probable that in our bibenzo[*h*]quinolyl at least one of the positions involved is position 2.

12-(*o*-Chloroaryl)benz[*a*]acridines being readily available by Bernthsen reaction of the appropriate *o*-chlorobenzoic acid and *N*-aryl-β-naphthylamine, this synthesis can be applied to the preparation of numerous homologues and analogues of phenanthra[9,10,1-*mna*]acridine. More condensed aza-hydrocarbons can also be prepared in this way: 14-(*o*-chlorophenyl)dibenz[*a*,*j*]acridine (VII) (obtained from ββ-dinaphthylamine and *o*-chlorobenzoic



(VI)



(VII) (VIII)

acid) was readily cyclised to benzo[*j*]phenanthra[9,10,1-*mna*]acridine (VIII); here, no by-product was isolated. The outstanding stability of the heterocyclic system (VIII) is manifest in its behaviour under electron impact, almost no fragmentation being observed under our experimental conditions (70 eV, $t = 280°$), and the doubly charged molecular ion being remarkably prominent (38% of base peak, which is the singly charged molecular ion). The same was true of phenanthra-[9,10,1-*mna*]acridine (IV) for which, at $t = 170°$, practically only two peaks were observed, the molecular peak $m/e = 303$, and the peak at $m/e = 151{\cdot}5$ (40%)

N.m.r. data [a]

Compound (IV)		Compound (V)		Compound (VIII)	
Signal	Proton	Signal	Proton	Signal	Proton
8·83—9·09 (m,2H)	1-H, 14-H	8·88—9·12 (m,1H)	1-H	8·86 (dd,1H)	5-H ($J_{5,6}$ 7·5, $J_{5,7}$ 2)
8·58—8·83 (m,2H)	4-H, 5-H	8·58—8·91 (m,3H)	4-H, 5-H, 14-H		
8·33—8·59 (m,1H)	11-H	8·75 (bs,1H)	14-H	8·43—8·77 (c,3H)	1-H, 4-H, 16-H
8·08 (s,2H)	8-H, 9-H	8·38 (d,1H)	11-H (J 8·5)	8·28 (d,1H)	11-H ($J_{11,12}$ 9)
7·33—8·16 (c,6H)	Remaining protons	8·08 (s,2H)	8-H, 9-H	8·21 (s,2H)	8-H, 9-H
		7·5—8·16 (c,5H)	Remaining aromatic protons	8·06 (d,1H)	12-H ($J_{11,12}$ 9)
				7·0—8·43 (c,11H)	Remaining protons
		2·65 (s,3H)	Me group		

[a] In p.p.m., J in Hz; bs = broad singlet, c = complex.

Thus, the 13-methyl-homologue (V) of (IV) was conveniently obtained from *o*-chlorobenzoic acid and *N*-*p*-tolyl-β-naphthylamine, *via* 12-(*o*-chlorophenyl)-10-methylbenz[*a*]acridine (III); an interesting minor by-product here was a substance arising from the replacement of the chlorine atom in (III) by a benzo[*h*]-quinolyl group [in view of the tendency of quinoline derivatives to undergo such substitutions at position 2 (ref. 8), the probable structure of this substance is (VI)].

corresponding to the doubly charged molecular ion. The n.m.r. spectra of the aza-hydrocarbons (IV), (V), and (VIII) (taken with a Varian A-60 spectrometer in $CDCl_3$, with Me_4Si as internal reference) confirmed their structure; the signals observed are listed in the Table.

Tests on carcinogenicity will be reported at a later date.

EXPERIMENTAL

12-(o-*Chlorophenyl*)*benz*[a]*acridine* (II).—A mixture of 2-anilinonaphthalene (14·7 g), *o*-chlorobenzoic acid (15 g), and anhydrous zinc chloride (15 g) was heated at 200—220° for 24 h; the cooled product was then triturated with 25% aqueous sodium hydroxide in the presence of toluene. The

[6] H. Weidel, *Monatsh.*, 1887, **8**, 120.
[7] A. Tschitschibabin and Kursanova, *J. Russ. Phys. Chem. Soc.*, 1930, **62**, 1211 (*Chem. Abs.*, 1931, **25**, 2727).
[8] B. Oddo, *Gazzetta*, 1907, **37**[*I*], 574.

toluene solution was washed with water and dried (Na_2SO_4), the solvent was distilled off, and the residue was fractionated *in vacuo*. The portion boiling at 310—315°/18 mmHg was dissolved in benzene and converted into the *picrate of* (II) as bright yellow prisms from chlorobenzene, m.p. inst., 237—238°, m.p. on gradual heating, 219—220° (Found: N, 10·2. $C_{29}H_{17}ClN_4O_7$ requires N, 9·9%). Basification with aqueous ammonia afforded the *acridine* (II) (7 g), as colourless prisms, m.p. 166°, from ethanol; the ethanol solution showed an intense violet-blue fluorescence (Found: C, 81·0; H, 4·0; Cl, 10·6; N, 4·0. $C_{23}H_{14}ClN$ requires C, 81·2; H, 4·2; Cl, 10·4; N, 4·1%).

Cyclisation of Compound (II).—A mixture of the acridine (II) (2 g), benzo[*h*]quinoline (14 g), and sodium hydroxide (10 g) was heated at 350° for 4 h; the mixture was cooled and diluted with water and chloroform; the chloroform solution was separated, and the solvent and then the benzo[*h*]quinoline were distilled off. The residue from this distillation was taken up in chloroform and fractionated by chromatography on a silica column. Elution with benzene + 2% ethanol gave, along with some of the starting material (0·2 g) the following compounds. (a) *x*,*x*′-Bibenzo[*h*]quinolyl, colourless, sublimable needles (15 mg), m.p. 286° (from benzene–ethanol), giving an orange halochromism in sulphuric acid (Found: C, 87·4; H, 4·4; N, 7·9%; M^+, 356. $C_{26}H_{17}N_2$ requires C, 87·6; H, 4·5; N, 7·9%; *M*, 356).

(b) An orange-yellow compound which was converted into *phenanthra*[9,10,1-mna]*acridine picrate*, orange microprisms, m.p. 253° (decomp. >235°) (from nitrobenzene) (Found: N, 10·7. $C_{29}H_{16}N_4O_7$ requires N, 10·5%); basification afforded phenanthra[9,10,1-*mna*]acridine (IV) as pale yellow needles (0·3 g), m.p. 139—140° (from aqueous ethanol), giving an orange halochromism in sulphuric acid and a blue fluorescence in ethanol solutions (Found: C, 90·8; H, 4·3; N, 4·7%; M^+, 303. $C_{23}H_{13}N$ requires C, 91·1; H, 4·3; N, 4·6%; *M*, 303).

(c) An unidentified compound, colourless prisms (20 mg), m.p. 235°, from ethanol, giving a greenish yellow halochromism in sulphuric acid (Found: C, 87·4; H, 4·7; N, 5·5%; M^+, 546).

12-(o-*Chlorophenyl*)-10-*methylbenz*[a]*acridine* (III).—This compound was prepared as for (II), from *N*-*p*-tolyl-β-naphthylamine (b.p. 245—250°/20 mmHg) and formed shiny colourless *needles* (yield, 50%), m.p. 184° (from ethanol); b.p. 315—320°/20 mmHg (Found: C, 81·3; H, 4·5; N, 4·0. $C_{24}H_{16}ClN$ requires C, 81·5; H, 4·6; N, 4·0%); *picrate*, lemon yellow prisms, m.p. 253° (decomp. >220°) (from chlorobenzene) (Found: N, 10·0. $C_{30}H_{19}ClN_4O_7$ requires N, 9·6%).

Cyclisation of Compound (III).—This cyclisation was effected at 350—355° during 4 h (at 320° no cyclisation occurred) with the foregoing acridine (5 g), sodium hydroxide (20 g), and benzo[*h*]quinoline (30 g). Chromatographic fractionation (on silica; elution with benzene + 20% ethyl acetate) of the product furnished, along with the recovered acridine (III) (1·8 g) the following compounds. (a) 12-[2-(2(?)-*Benzo*[h]*quinolyl*)*phenyl*]-10-*methylbenz*[a]*acridine* (VI), pale yellow microprisms (0·1 g), m.p. 250—251° (from isopropyl alcohol) (Found: C, 88·9; H, 4·9; N, 5·5%; M^+, 496. $C_{37}H_{24}N_2$ requires C, 88·7; H, 4·8; N, 5·6%; *M*, 496).

(b) 13-*Methylphenanthra*[9,10,1-mna]*acridine* (V), pale yellow needles (0·5 g), m.p. 126°, from methanol (Found: C, 91·0; H, 4·9; N, 4·5. $C_{24}H_{15}N$ requires C, 90·8; H, 4·8; N, 4·4%); *picrate*, bright orange needles, m.p. 245° (decomp. >235°) (from nitrobenzene) (Found: N, 10·1. $C_{30}H_{18}N_4O_7$ requires N, 10·3%).

14-(o-*Chlorophenyl*)*dibenz*[a,j]*acridine* (VII).—This compound was prepared from ββ-dinaphthylamine (20 g), *o*-chlorobenzoic acid (15 g), and zinc chloride (15 g); it was purified by chromatography (silica; elution with benzene + 2% ethanol), and formed colourless *needles* (5 g), m.p. 238—239° (from benzene) (Found: C, 83·0; H, 4·3; N, 3·4. $C_{27}H_{16}ClN$ requires C, 83·2; H, 4·2; N, 3·6%); *picrate*, orange prisms, m.p. 240° (decomp. >215°) (from chlorobenzene) (Found: N, 8·8. $C_{33}H_{19}ClN_4O_7$ requires N, 9·1%).

Benzo[j]*phenanthra*[9,10,1-mna]*acridine* (VIII).—This compound was prepared from the foregoing acridine (3 g), sodium hydroxide (15 g), and benzo[*h*]quinoline (18 g), at 360° during 4 h; it was purified by chromatography as above and formed yellow needles (0·4 g), m.p. 247—248° (from benzene), giving an orange halochromism in sulphuric acid (Found: C, 91·4; H, 4·3; N, 3·9%; M^+, 353. $C_{27}H_{15}N$ requires C, 91·7; H, 4·3; N, 4·0%; *M*, 353°); *picrate*, orange needles, m.p. 284—285°, from chlorobenzene (Found: N, 9·6. $C_{33}H_{18}N_4O_7$ requires N, 9·6%).

The mass spectra were determined with an MS-9 spectrometer in the Mass Spectrometry Dept. (Director, Dr. B. Das) of this Institute.

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