Carcinogenic Nitrogen Compounds. Part LXXVIII.[1] Some Indeno-[1,7-*bc*]-, Benz[*a*]indeno[7,1-*hi*]-, and Benz[*c*]indeno[7,1-*hi*]-acridines

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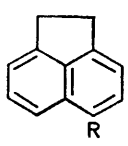
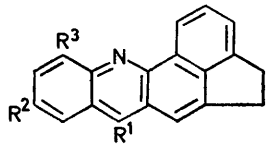
The synthesis is recorded of a number of indeno[1,7-*bc*]-, benz[*a*]indeno[7,1-*hi*]-, and benz[*c*]indeno[7,1-*hi*]-acridines by the Ullmann–Fetvadjian and Bernthsen reactions. In the course of this work, the iodine-catalysed condensation of 1-naphthol with 5-aminoacenaphthene was unexpectedly complex, leading to di-(5-acenaphthyl)-amine and 4,5,9,10-tetrahydroindeno[1,7-*bc*]indeno[7,1-*hi*]acridine, besides the normal product.

SEVERAL carcinogenic hydrocarbons, among them the highly potent cholanthrenes, possess an acenaphthene arrangement in their molecule,[2] and certain acenaphthene derivatives such as acephenalene and 5-cyclohexyl-acenaphthene are stimulators of mitosis in plants.[3] It was therefore of interest to synthesise, for biological studies, 4,5-dihydroindeno-analogues of benz[*c*]-, dibenz-[*a*,*h*]-, and dibenz[*c*,*h*]-acridines which are already known to include several carcinogens.[4] Prior to this study, only a few indenoacridines [5,6] and one di-indeno-acridine [7] were known.

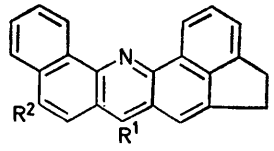
The most accessible intermediates for such syntheses were 5-amino- (I) and 5-hydroxy-acenaphthene (II),



(I); R = NH_2
(II); R = OH



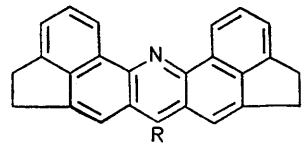
(III); $R^1 = R^2 = R^3 = H$
(IV); R^1 = Me, $R^2 = R^3 = H$
(V); $R^1 = R^3 = H$, R^2 = Me
(VI); $R^1 = H$, $R^2 = R^3$ = Me
(VII); $R^1 = R^2$ = Me, $R^3 = H$
(VIII); $R^1 = R^2 = R^3$ = Me



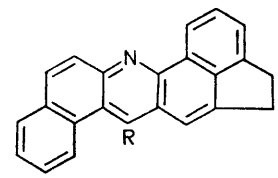
(IX); $R^1 = R^2 = H$
(X); $R^1 = H$, R^2 = Me
(XI); R^1 = Me, $R^2 = H$

the latter being readily obtained by hydrolysis of the former.[8] The three 4,5-dihydroindeno[1,7-*bc*]acridines (III), (V), and (VI), which are unsubstituted in the *meso*-position, were obtained in one step by Ullmann–Fetvadjian condensation of acenaphthen-5-ol (II) with paraformaldehyde and, respectively, aniline, *p*-toluidine, and 2,4-dimethylaniline (as long as large excesses of paraformaldehyde were not used, nuclear methylation side-reactions [9] could be avoided); compound (III) had earlier been synthesised by a multi-step procedure.[6] The *meso*-methylated compounds (IV), (VII), and (VIII) were prepared by a modified Bernthsen reaction [10] from the corresponding 5-arylaminoacenaphthenes, which were readily obtained in one step from the alcohol (II) and the appropriate aniline, a far more convenient route than the procedure of Saikachi *et al.*[6] for the preparation of similar diarylamines starting from the amine (I).

Some difficulty was encountered in the preparation of 4,5-dihydrobenz[*c*]indeno[7,1-*hi*]acridine (IX) by an Ullmann–Fetvadjian reaction of the amine (I) and 1-naphthol, because of some concomitant methylation † of naphthol, with the result that both (IX) and its 9-methyl-derivative (X) were obtained; the structure of the latter was confirmed by an independent Ullmann–Fetvadjian synthesis from the amine (I) and 4-methyl-1-naphthol. No nuclear methylation was observed in the Ullmann–Fetvadjian reaction of the amine (I) with the alcohol (II), and the preparation of 4,5,9,10-tetrahydro-indeno[1,7-*bc*]indeno[7,1-*hi*]acridine (XII) was straightforward; such was also the case in the preparation of



(XII); R = H
(XIII); R = Me



(XIV); R = H
(XV); R = Me

4,5-dihydrobenz[*a*]indeno[7,1-*hi*]acridine (XIV) from the amine (I) and 2-naphthol (which is known to be easily methylated, but only at the 1-position).

† 4-Methyl-1-naphthol could be isolated in such reactions; see ref. 9.

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[2] G. Barry, J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger, and E. L. Kennaway, *Proc. Roy. Soc.*, 1935, **117** [*B*], 318, 333.

[3] R. Garrigues, N. P. Buu-Hoï, and P. Cagniant, *Compt. rend.*, 1952, **234**, 553.

[4] *Cf.* A. Lacassagne, N. P. Buu-Hoï, R. Daudel, and F. Zajdela, *Adv. Cancer Res.*, 1956, **4**, 316.

[5] N. P. Buu-Hoï and P. Cagniant, *Rev. sci.*, 1943, **81**, 503.

[6] H. Saikachi, O. Tsuge, and M. Tashiro, *J. Pharm. Soc. Japan*, 1960, 584; W. H. Edwards and V. Petrow, *J. Chem. Soc.*, 1954, 2853.

[7] *Cf.* ref. 5; also G. T. Morgan and H. A. Harrison, *J. Soc. Chem. Ind. Trans.*, 1930, **49**, 413 T, who, in attempts to prepare '5,5'-diamino-3,3'-di(acenaphthyl)methane,' isolated a compound, m.p. 300°, to which they assigned the structure (XII).

[8] I.G. Farbenindustrie, G.P. 517,264/1931.

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

[10] N. P. Buu-Hoï and J. Lecocq, *Rec. trav. chim.*, 1945, **64**, 250; *Compt. rend.*, 1944, **218**, 792.

The synthesis of 5-(1-naphthylamino)acenaphthene, needed for proceeding to the *meso*-methylated compound (XI) by the Bernthsen reaction, proved more complicated than expected considering the generally simple Knoevenagel iodine-catalysed condensations of naphthols with primary arylamines.[11] When the amine (I) was condensed with 1-naphthol under those conditions, only a poor yield of 5-(1-naphthylamino)acenaphthene was recorded, with considerable amounts of the symmetrical di-(1-naphthyl)amine and di-(5-acenaphthyl)amine [the latter is a product of the condensation between 2 mol. of the amine (I), with elimination of ammonia, and the presence of the former is an indication of the transient formation of 1-naphthylamine] and some of the symmetrical acridine (XII) being formed. A similar unusual formation of an acridine during a Knoevenagel reaction was recently observed with 5-aminobenzo[*b*]-selenophen,[12] which, like 5-aminoacenaphthene, possesses a two-carbon unit; in the present case, the carbon unit needed for closure of the acridine ring must come from some degradation of the ethano-bridge of the amine (I). The desired 5-(1-naphthylamino)acenaphthene could, however, be obtained free from by-products by heating the amine (I) with 1-naphthol in the presence of calcium chloride. A similar complication arose in the preparation of the 5-(2-naphthylamino)acenaphthene required for the Bernthsen synthesis of the acridine (XV).

The n.m.r. data of the acenaphthenes are consistent with the formulations here and are listed in Supplementary Publication No. SUP 20352 (3 pp., 1 microfiche *). Biological examination preliminary to long-term carcinogenicity tests [13] shows them to be inducers of the microsomal enzymatic system zoxazolamine hydroxylase in young rats, but less so than the corresponding acridines without ethano-bridges.[14] The results are in Supplementary Publication No. 20352 (3 pp., 1 microfiche *) and show that the benz[*a*]indeno[7,1-*hi*]-acridine structure is again [14] the most favourable.

EXPERIMENTAL

4,5-Dihydro-9-methylindeno[1,7-bc]*acridine* (V).—To a mixture of acenaphthen-5-ol (4 g; m.p. 129°, b.p. 218° at 55 mmHg) and *p*-toluidine (2·7 g) heated at 190—200°, paraformaldehyde (1·2 g) was added in small portions during 30 min, and the product then fractionated *in vacuo*. The portion boiling at 230—330° and 12 mmHg was crystallised from cyclohexane to give the *methylacridine* (V) as pale yellow prisms (1 g), m.p. 167° [Found: C, 89·1; H, 5·6; N, 5·1%; *M* (by mass spectrometry), 269. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6; N, 5·2%; *M*, 269]; *picrate*, orange prisms, m.p. 253° (decomp. >230°) (from ethanol) (Found: N, 10·9. $C_{26}H_{18}N_4O_7$ requires N, 11·2%). *4,5-Dihydro-9,11-dimethylindeno*[1,7-bc]*acridine* (VI), similarly prepared from 2,4-xylidine (5·5 g) and the alcohol (II) (6 g), formed pale yellow needles (1·5 g), m.p. 174° (from ethanol) (Found: C, 89·1; H, 6·0; N, 4·8%; *M*, 283. $C_{21}H_{17}N$ requires C, 89·0; H, 6·1; N, 4·9%; *M*, 283); *picrate*, orange prisms, m.p. 208° (from ethanol) (Found: N, 11·0. $C_{27}H_{20}N_4O_7$ requires N, 10·9%).

Ullmann–Fetvadjian Reaction of the Amine (I) *with 1-Naphthol*.—The product of the condensation of paraformaldehyde (2·2 g) with 1-naphthol (9 g) and the amide (I) (performed as before) was fractionated *in vacuo* to afford a portion, b.p. 280—360° at 0·4 mmHg, which, after several fractional crystallisations from ethanol–benzene (3 : 1), gave: (a) *4,5-dihydrobenz*[c]*indeno*[7,1-hi]*acridine* (IX), pale yellow needles (1·1 g), m.p. 215° (Found: C, 90·6; H, 5·1; N, 4·8%; *M*, 305. $C_{23}H_{15}N$ requires C, 90·5; H, 5·0; N, 4·6%; *M*, 305); *picrate*, orange prisms, m.p. 197° (from benzene) (Found: C, 65·0; H, 3·7; N, 10·3. $C_{29}H_{18}N_4O_7$ requires C, 65·2; H, 3·4; N, 10·5%); (b) *4,5-dihydro-9-methylbenz*[c]*indeno*[7,1-hi]*acridine* (X), yellow prisms (1·9 g), m.p. 265° (Found: C, 90·2; H, 5·6; N, 4·3%; *M*, 319. $C_{24}H_{17}N$ requires C, 90·3; H, 5·4; N, 4·4%; *M*, 319); *picrate*, orange prisms, m.p. 238—239° (from benzene) (Found: C, 65·8; H, 3·9; N, 10·5. $C_{30}H_{20}N_4O_7$ requires C, 65·7; H, 3·7; N, 10·2%). The same acridine (X) (0·1 g) was prepared directly from the amine (I) (3·5 g), 4-methyl-1-naphthol [15] (2 g), and paraformaldehyde (1 g).

4,5,9,10-Tetrahydroindeno[1,7-bc]*indeno*[7,1-hi]*acridine* (XII).—The crude product of condensation of the amine (I) (3·4 g) and the alcohol (II) (3·5 g) with paraformaldehyde (1·2 g) did not withstand distillation *in vacuo* and so was purified by column chromatography on silica, giving the acridine (XII) as yellow prisms (0·8 g), m.p. 314° (from benzene) (Found: C, 90·4; H, 5·1; N, 4·0. Calc. for $C_{25}H_{17}N$: C, 90·6; H, 5·2; N, 4·2%); *picrate*, orange prisms, m.p. 286° (from xylene) (Found: N, 9·9. $C_{31}H_{20}N_4O_7$ requires N, 10·0%).

Knoevenagel Reactions of Acenaphthen-5-ol (II).—A mixture of (II) (17 g) and 2,4-xylidine (18 g) was heated under reflux for 6 h with iodine (0·1 g), and the product was then fractionated *in vacuo*. *5-(2,4-Dimethylphenylamino)-acenaphthene* (15 g) was a viscous yellow oil, b.p. 310° at 12 mmHg (Found: C, 87·9; H, 6·9; N, 5·0. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0; N, 5·1%). This compound (14 g) could be prepared by heating the amine (I) (17 g) and 2,4-xylidine (18 g) at 240° for 16 h with *p*-sulphanilic acid (0·15 g).[16] The already known [17] 5-phenylaminoacenaphthene and 5-*p*-tolylaminoacenaphthene could also be prepared from (I) similarly.

5-(1-Naphthylamino)acenaphthene.—(a) A mixture of the amine (I) (20 g) and 1-naphthol (20 g) was heated with iodine (0·5 g) at 220° for 28 h; the product was then taken up in chloroform, the insoluble portion was filtered off, the filtrate was washed with aqueous sodium hydroxide and dried (Na_2SO_4), the solvent was distilled, and the residue was fractionated *in vacuo*. The portion of b.p. 315° at 12 mmHg was *5-(1-naphthylamino)acenaphthene*, a viscous oil (3 g) which did not solidify (Found: C, 89·2; H, 5·8; N, 4·8%; *M*, 295. $C_{22}H_{17}N$ requires C, 89·5; H, 5·8; N,

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. will be supplied as full page copies).

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[12] N. P. Buu-Hoï, M. Dufour, P. Jacquignon, M. Renson, G. Maréchal, and A. Ruwet, *J. Chem. Soc.* (*C*), 1971, 2308.

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[15] N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 1955, 2776.

[16] *Cf.* S. W. Tinsley, S. Charleston, and J. T. Fitzpatrick, U.S.P. 2,938,058/1960.

[17] G. Benz, *Ber.*, 1883, **16**, 8.

4·7%; *M*, 295). The higher-boiling portion was *di-(5-acenaphthyl)amine*, crystallising as prisms (3 g), m.p. 138° (from ethanol) (Found: C, 89·9; H, 6·0; N, 4·1%; *M*, 319. $C_{24}H_{19}N$ requires C, 89·7; H, 6·0; N, 4·4%; *M*, 319). The chloroform-insoluble fraction (0·7 g) was identical with the acridine (XII). When this Knoevenagel reaction was conducted under less drastic conditions (180° for 22 h), considerable amounts of di-(1-naphthyl)amine (*ca.* 2 parts) along with the expected amine (1 part) were obtained.

(b) The title amine (6·5 g) was best obtained by heating a mixture of the amine (I) (10 g) and the alcohol (II) (10 g) with anhydrous calcium chloride (30 g) at 250° for 17 h.

5-(2-Naphthylamino)acenaphthene.—This amine (7·5 g), prepared from (I) (20 g), 2-naphthol (15·5 g), and iodine (0·1 g) at 200° for 16 h, crystallised as prisms, m.p. 142—143° (from hexane) (Found: C, 89·7; H, 5·7; N, 4·6%). Di-(5-acenaphthyl)amine was obtained similarly in 30% yield from an equimolar mixture of (I) and (II) and iodine (18 h at 180°).

Bernthsen Syntheses.—A mixture of 5-phenylaminoacenaphthene (11 g), acetic anhydride (7·2 g), and anhydrous zinc chloride (7·5 g) was heated at 160° for 24 h, and the cooled product was triturated with 20% aqueous sodium hydroxide in the presence of chloroform; the organic layer was washed with water and dried, the solvent was removed, and the residue was purified by chromatography on silica. Elution with benzene afforded 4,5-dihydro-7-methylindeno[1,7-*bc*]acridine (IV), pale yellow needles, (1·3 g), m.p. 180° (from benzene) (lit.,[6] 178°); *picrate*, orange needles, m.p. 252° (from ethanol) (Found: C, 62·8; H, 3·8; N, 11·2. $C_{26}H_{18}N_4O_7$ requires C, 62·6; H, 3·7; N, 11·2%). Elution with ethanol furnished *5-(N-acetylphenylamino)-acenaphthene*, prisms, m.p. 164° (from ethanol) (Found: C, 83·5; H, 5·9; N, 4·9; O, 5·5. $C_{20}H_{17}NO$ requires C, 83·6; H, 6·0; N, 3·8; O, 5·6%). *4,5-Dihydro-7,9-dimethylindeno-[1,7-bc]acridine* (VII), similarly prepare, formed pale yellow prisms, m.p. 192° (from ethanol) (Found: C, 88·7; H, 6·1; N, 4·7. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0; N, 4·9%); *picrate*, m.p. 251° (Found: C, 63·4; H, 3·8; N, 10·6. $C_{27}H_{20}N_4O_7$ requires C, 63·3; H, 3·9; N, 10·9%). *4,5-Dihydro-7,9,11-trimethylindeno[1,7-bc]acridine* (VIII) formed pale yellow prisms, m.p. 190° (from ethanol) (Found: C, 88·8; H, 6·4; N, 4·6. $C_{22}H_{19}N$ requires C, 88·9; H, 6·4; N, 4·7% *picrate*, m.p. 202° (from benzene) (Found: N, 10·5. $C_{28}H_{22}N_4O_7$ requires N, 10·6%). *4,5-Dihydro-7-methylbenz[c]-indeno[7,1-hi]acridine* (XI), pale yellow leaflets, had m.p. 251° (from ethanol) (Found: C, 90·3; H, 5·4; N, 4·1. $C_{24}H_{17}N$ requires C, 90·3; H, 5·4; N, 4·4%); *picrate*, ochre-yellow needles, m.p. 168° (from benzene) (Found: N, 10·2. $C_{30}H_{20}N_4O_7$ requires N, 10·2%). *4,5-Dihydro-7-methylbenz[a]indeno[7,1-hi]acridine* (XV), pale yellow needles, had m.p. 187° (from ethanol) (Found: C, 90·1; H, 5·4; N, 4·2%); *picrate*, orange leaflets, m.p. (*inst.*) 252° (Found: N, 10·4%). *4,5,9,10-Tetrahydro-7-methylindeno-[1,7-bc]indeno[7,1-hi]acridine* (XIII), yellow leaflets, had m.p. 331° (from benzene) (Found: C, 90·6; H, 5·7; N, 4·0. $C_{26}H_{19}N$ requires C, 90·4; H, 5·5; N, 4·1%); *picrate*, orange prisms, m.p. 196° (from benzene) (Found: N, 9·6. $C_{32}H_{22}N_4O_7$ requires N, 9·7%).

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