Ring-closure to Phenanthridines and Acridines of Some 2-Arylaminomethylene Derivatives of Cyclohexanone and 1-Tetralone

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Ring-closure of 2-(naphthylaminomethylene)cyclohexanones affords either the derived tetrahydrobenzophenanthridine or the isomeric tetrahydrobenzacridine. Ring-closure with formic acid gave a preponderance of the phenanthridine but other reagents favoured formation of the acridine. An intermediate rearrangement of the Hofmann-Martius type may account for the formation of the acridines.

The formation of 5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine in the ring-closure of 2-anilinomethylene-1-tetralone with formic acid has been confirmed and an explanation of this observation is presented, but similar ring-closure of 2-(1-naphthylaminomethylene)-1-tetralone gave 7,8-dihydrodibenzo[*c*,*k*]phenanthridine.

THE Beyer-Combes synthesis of quinolines [1] by ring-closure of the mono-anils of β-diketones with concentrated sulphuric acid is reputedly [2] a satisfactory procedure for the preparation of 2,4-disubstituted quinolines. On the other hand early workers [3,4] who attempted, in similar fashion, to cyclise the analogous anils of β-ketoaldehydes (α-hydroxymethylene ketones) were unsuccessful and

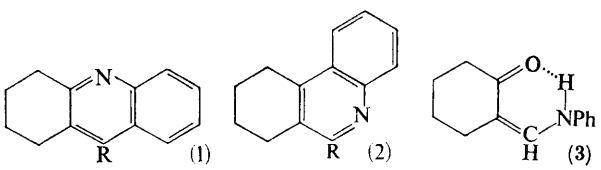
[1] C. Beyer, *Ber.*, 1887, **20**, 1767; A. Combes, *Compt. rend.*, 1887, **106**, 142; *Bull. Soc. chim. France*, 1888, **49**, 90.

[2] C. Hollins, 'The Synthesis of Nitrogen Ring Compounds,' Benn, London, 1924, p. 267; E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1927, 1832; N. H. Cromwell, *Chem. Rev.*, 1946, **38**, 83.

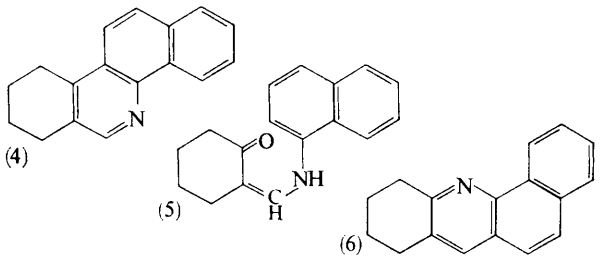
[3] L. Claisen and L. Fischer, *Ber.*, 1888, **21**, 1135.

[4] W. Borsche, *Annalen*, 1910, **377**, 78.

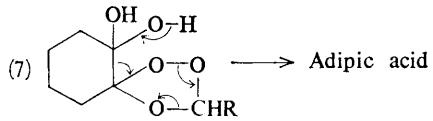
this failure was ascribed to an unfavourable *trans*-configuration of the anil.[5] Thus Borsche[4] succeeded in the ring-closure of the mono-anil of 2-acetylcyclohexanone with sulphuric acid to a difficultly separable mixture of the acridine (1; R = Me) and phenanthridine (2; R = Me) but failed with 2-anilinomethylenecyclohexanone (3); the latter, however, underwent ring-closure with phosphoric oxide or with phosphoryl chloride, but gave the tetrahydroacridine (1; R = H) and not the expected phenanthridine (2; R = H).[6] Failure has also been reported in the attempted ring-closure of 2-anilinomethylenecyclohexane-1,3-dione with phosphoric anhydride–phosphoric acid or anhydrous hydrofluoric acid,[7] although other 2-arylaminomethylenecyclohexane-1,3-diones are said to undergo ready cyclisation in polyphosphoric acid to give the expected phenanthridines.[8] Romet[9] found that cyclisation of the anil of 2-(hydroxymethylene)pentan-3-one with zinc chloride in amyl alcohol gave 2-ethyl-3-methylquinoline and little of the expected 4-ethyl-3-methylquinoline, and the anil of hydroxymethyleneacetone gave quinaldine and not the expected lepidine. The ambiguity of this synthesis of quinolines has also been emphasised by others.[10,11] Petrow[12] has shown that the anils of β-keto-aldehydes undergo ring-closure when heated with the amine hydrochloride directly, or in alcoholic solution, and with the optional addition of zinc chloride, to give quinolines with the orientation observed by Romet;[9] thus 1,2,3,4-tetrahydroacridine (1; R = H) resulted from 2-anilinomethylenecyclohexanone (3). Hollingsworth and Petrow[13] subsequently showed that the alternative, and expected, route was followed in the ring-closure of 2-arylaminomethylenecyclohexanones in hot formic acid, when tetrahydrophenanthridines were produced.



During a study[14] of some biological properties of the alkaloid sanguinarine we required the parent unsubstituted heterocycle, benzo[*c*]phenanthridine, and sought it by way of 7,8,9,10-tetrahydrobenzo[*c*]phenanthridine (4) which had already been described.[13,15] Ring-closure of 2-(1-naphthylaminomethylene)cyclohexanone (5) in hot formic acid followed by its isolation by way of the picrate was reported to give 7,8,9,10-tetrahydrobenzo[*c*]-phenanthridine (4);[13] we elected, however, to purify the crude product of this reaction by column chromatography on alumina, and found that, while the phenanthridine (4) was the major product, a substantial proportion of the isomeric 8,9,10,11-tetrahydrobenz[*c*]acridine (6) was also formed. As we had observed the occurrence of orange and yellow forms of the starting material we were concerned to establish its identity conclusively, though there can be little doubt that it was correctly represented —without specification of the *cis*- or *trans*-configuration— by the structure (5). Direct condensation of 2-hydroxymethylenecyclohexanone with 1-naphthylamine gave



predominantly the orange form but alumina column chromatography of this form gave some of the yellow form, while a condensation of 2-methoxymethylenecyclohexanone with 1-naphthylamine gave predominantly the yellow form. The two forms had the same m.p. and u.v. and i.r. spectra. The i.r. spectrum (potassium chloride disc or chloroform solution) showed two bands, at 1645 and 1570 cm.$^{-1}$, consistent with a partial structure –CO·C:C·NH– (cf., *e.g.*, 3-acetylindole,[16] $\nu_{max.}$ 1642 cm.$^{-1}$) and with observations on similar compounds.[17] Ozonolyses of the anil and of 2-methoxymethylenecyclohexanone were not informative, as both gave adipic acid in high yield, presumably by fission of the ozonide (7) in the manner indicated.[18] The p.m.r. spectra of the orange and yellow forms, obtained for us by Dr. N. Sheppard in Cambridge in 1962, were identical.

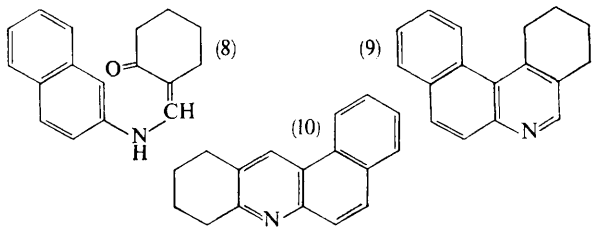


In carbon tetrachloride with tetramethylsilane as reference two bands with some fine structure at τ 8·3 and 7·6 represented the two types of methylene group and there was a complex region, τ 1·5—3·2, corresponding to the aromatic protons; a doublet at τ –2·9, probably due to a single proton, could have been due to the aldehydic proton in the alternative isomeric struc-

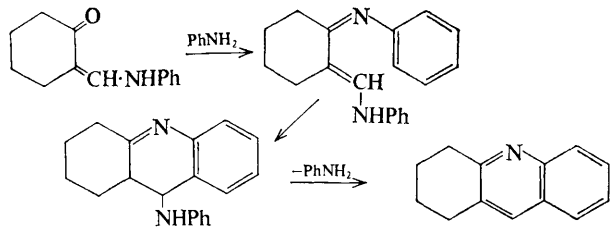
[5] E. Thielepape, *Ber.*, 1922, **55**, 127.
[6] G. E. Calf and E. Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1949, **83**, 117.
[7] N. A. J. Rogers and H. Smith, *J. Chem. Soc.*, 1955, 341.
[8] S. V. Kessar, I. Singh, and A. Kumar, *Tetrahedron Letters*, 1965, 2207.
[9] M. Romet, *Compt. rend.*, 1935, **200**, 1676.
[10] L.-M. Roch, *Ann. Chim.* (*France*), 1961, **6**, 101.
[11] F. Boyer and J. Décombe, (*a*) *Compt. rend.*, 1962, **255**, 1945; (*b*) *Bull. Soc. chim. France*, 1967, 2373.
[12] V. A. Petrow, *J. Chem. Soc.*, 1942, 693.
[13] B. L. Hollingsworth and V. Petrow, *J. Chem. Soc.*, 1948, 1537.
[14] S. A. E. Hakim, V. Mijovic, and J. Walker, *Nature*, 1961, **189**, 201.
[15] J. Kenner, W. H. Ritchie, and F. S. Statham, *J. Chem. Soc.*, 1937, 1169.
[16] D. R. Liljegren and K. T. Potts, *Proc. Chem. Soc.*, 1960, 340.
[17] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337; N. J. Leonard and J. A. Adamcik, *ibid.*, 1959, **81**, 595.
[18] Cf. D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 1956, 4150; P. S. Bailey, *Chem. Rev.*, 1958, **58**, 925.

ture but was better assigned to the NH proton resonance split by coupling with the neighbouring vinyl proton (which was itself ' lost ' as part of the aromatic complex) in structure (5), since it is in a strongly hydrogen-bonded situation, in accord with experience with related compounds.[19] Polymorphic orange and yellow forms of 2-anilinomethylene-1-tetralone have also been noted [20] and we confirm this observation.

As the cyclisation of 2-(1-naphthylaminomethylene)-cyclohexanone (5) to the phenanthridine (4) is formally an acid-catalysed ring closure and dehydration, and should owe nothing to the reducing properties of formic acid [21] as had been suggested,[13] other acidic reagents have been examined (see Table 1). Except for polyphosphoric acid no reagent other than formic acid gave any appreciable yield of the phenanthridine (4) but most of them gave good yields of the acridine (6). In similar fashion 2-(2-naphthylaminomethylene)cyclohexanone (8) gave with hot formic acid a moderate yield of 1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (9), with a little 8,9,10,11-tetrahydrobenz[*a*]acridine (10); each of three other reagents gave a rather better yield of the acridine (10) and no phenanthridine (9) (Table 2).



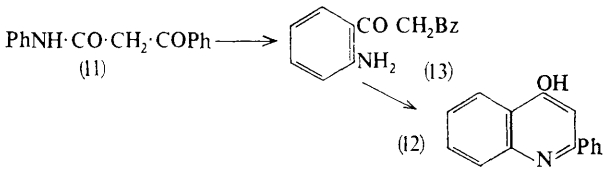
In terms of Petrow's mechanism,[13] ring-closure of the arylaminomethylene ketone in the presence of amine hydrochloride occurs through reaction of the second molecule of amine with the remaining carbonyl group in the starting material with final extrusion of the amine residue originally present after the ring-closure stage (see Scheme). This mechanism is supported by



SCHEME

our observation that ring-closure of 2-(1-naphthyl-aminomethylene)cyclohexanone (5) in the presence of 2-naphthylamine hydrochloride gave a moderate yield of 8,9,10,11-tetrahydrobenz[*a*]acridine (10), identical with the minor product of ring-closure of 2-(2-naphthyl-aminomethylene)cyclohexanone (8) in hot formic acid, and not 8,9,10,11-tetrahydrobenz[*c*]acridine (6). The matter is not so simple, however, as 2-(2-naphthyl-aminomethylene)cyclohexanone (8) gave on ring-closure in presence of aniline hydrochloride a substantial yield of the tetrahydrobenz[*a*]acridine (10), though in some-somewhat lower yield than was obtained in the presence of 2-naphthylamine hydrochloride, and we may have failed to observe the formation of some 1,2,3,4-tetra-hydroacridine as required by the Petrow mechanism.

A somewhat analogous production of an anomalous product has been reported in the ring-closure of benzoyl-acetanilide (11) with polyphosphoric acid, when about 20% of 4-hydroxy-2-phenylquinoline (12) was produced; this was interpreted in terms of a Fries-like rearrangement of the benzoylacetanilide (11) to 2-amino-ω-benz-oylacetophenone (13) prior to ring-closure.[22]



The arylaminomethylene ketones [*e.g.* (5)] with which we are dealing must be extremely weakly basic substances in view of the fact that the arylamine carries as *N*-substituent a vinylogous acyl group. Protonation in the acid-catalysed ring-closure may occur either at the carbonyl group (14) or at the nitrogen atom (15). In the case of the former (14) ring-closure would give the phenanthridine (4) and in the case of the latter (15) a re-arrangement of the Hofmann-Martius type (16), followed by ring-closure, would afford the acridine (6). The mecha-nism of the presumed rearrangement [(15) ⟶ (16)] is a matter for speculation, but it could occur by attack by a nucleophile (HX:; solvent or acidic reagent) at the electrophilic exocyclic carbon atom, followed by dismutation, recombination, and finally extrusion of the nucleophile prior to ring-closure of the intermediate (16) or as part of a concerted process leading to the acridine (6) without formal intervention of the intermediate (16).* An intermolecular rearrangement of this type would also account for the fact that displacement of one aromatic amine by another may, or may not, take place. This hypothesis offers no reason why, with the same substrate, the results with formic acid and poly-phosphoric acid should be different from those obtained with the other acidic reagents (Table 1) unless one in-vokes the further hypothesis that formylation or phosphorylation on oxygen in the intermediate proton-ated species (14) favours the route to the phenanthridine.† Ordinarily rearrangements of the Hofmann-Martius type

* The authors are indebted to a referee for a comment on a point of detail.

† One may note the pertinent comment by Boyer and Décombe: [11b] ' Si les transpositions observées dans les réactions de cyclisation des anilinométhylènecétones sont difficiles à expliquer, elles sont par contre très faciles à mettre en évid-ence. . . .'

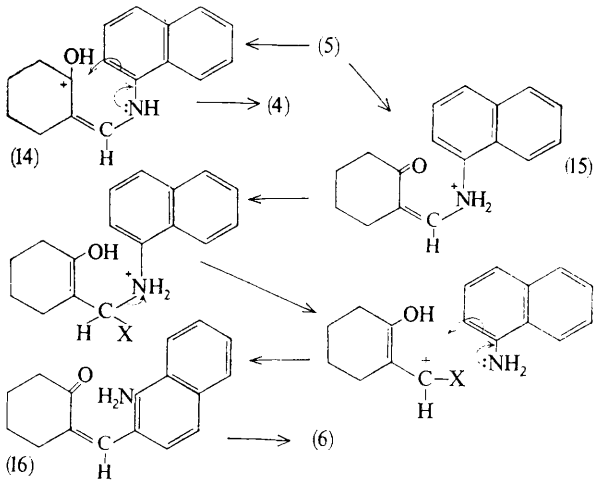
[19] Cf. G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, 1961, **83**, 2099, 3914; 1962, **84**, 2691.

[20] B. Mills and K. Schofield, *J. Chem. Soc.*, 1956, 4213.

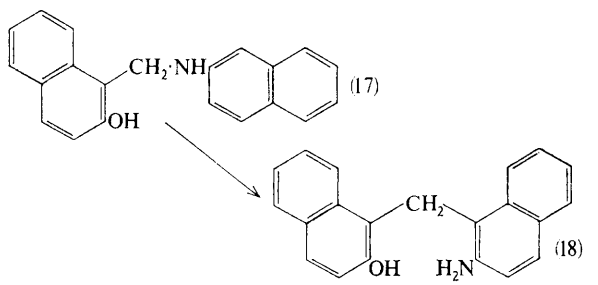
[21] Cf. N. B. Chapman and H. Taylor, *J. Chem. Soc.*, 1961, 1908.

[22] B. Staskun and S. S. Israelstam, *J. Org. Chem.*, 1961, **26**, 3191.

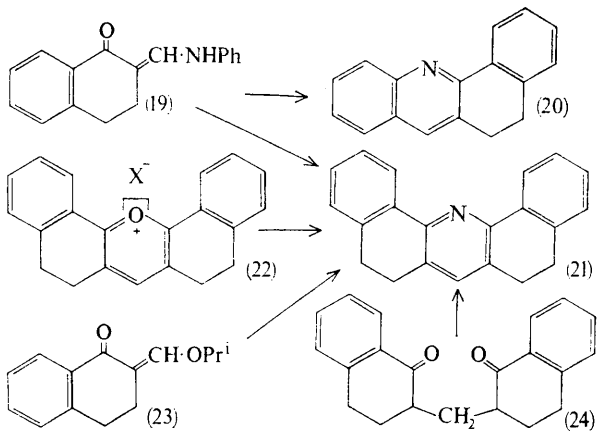
have taken place at higher temperatures than those used here but high temperatures are not essential in suitable cases.[23] As a rule Hofmann-Martius rearrangements involve *p*-migration if that position is available, though



o-migration is also observed and is implicit in the present circumstances. Extremely ready *o*-migration has been observed in the conversion of 1-(2-naphthylaminomethyl)-2-naphthol (17) into 2-amino-2′-hydroxy-1,1′-dinaphthylmethane (18), which takes place in nearly quantitative yield in boiling benzene,[24] and the latter compound (18) changed readily at its m.p. into 7,14-dihydrodibenz[*a*,*j*]acridine and dibenz[*a*,*j*]acridine;[25] in this case a Mannich-base type of decomposition (β-elimination) followed by recombination may be implicated.[24,25]



Boyer and Décombe [11] have shown that ring-closure of 2-anilinomethylene-1-tetralone (19) when heated with aniline and zinc chloride gave 5,6-dihydrobenz[*c*]acridine (20) with implicit transposition. On the other hand, Mills and Schofield [20] made the remarkable observation, which we have amply confirmed, that ring-closure of 2-anilinomethylene-1-tetralone (19) with hot formic acid, followed by treatment with ammonia, leads in low yield to the formation of 5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (21). They offered no explanation of this result, but it seems probable that an intermediate formed in the formic acid ring-closure of the anil (19) is, in fact, 5,6,8,9-tetrahydrodibenzo[*c*,*h*]xanthylium formate (22; X = HCO_2), and the nitrogen atom in the product (21) comes from the ammonia used in the work up. The latter point was proved by dividing a formic acid reaction mixture from the anilinomethylenetetralone (19) into two equal parts, working one up with ammonia to give the tetrahydrodibenzacridine (21) in



moderate yield, and working up the other with sodium hydroxide to give only a trace of the tetrahydrodibenzacridine (21) (presumably arising from adventitious ammonia), detected by extremely sensitive chromatographic methods. The formation of the tetrahydrodibenzoxanthylium salt (22; X = HCO_2) in the formic acid reaction mixture formally requires reversion of one molecule of the anil (19) to 1-tetralone with loss of the entire side-chain and condensation of the resulting 1-tetralone with a further molecule of the anil (19) to give aniline and the 1,5-diketone, 2,2′-methylidynebis-1-tetralone, which exists in the acid solution as the xanthylium salt (22). It was therefore obvious that other simple derivatives of 2-hydroxymethylene-1-tetralone should likewise afford the tetrahydrodibenzacridine (21) when treated with hot formic acid and then ammonia, and 2-isopropoxymethylene-1-tetralone (23) gave a modest yield of the tetrahydrodibenzacridine (21) under such circumstances; 1-tetralone itself, when treated with hot formic acid and then ammonia, gave traces of the tetrahydrodibenzacridine (21), detectable chromatographically.

The structure (21) of the tetrahydrodibenzacridine, previously characterised by Mills and Schofield [20] by dehydrogenation to the parent dibenz[*c*,*h*]acridine, was further confirmed by two unequivocal syntheses. Thus it (21) was obtained directly by reaction of 2,2′-methylenebis-1-tetralone (24) with ammonium acetate in acetic acid;[26] the starting material (24) and product (21)

[23] Cf. J. Thesing, H. Mayer, and S. Klüssendorf, *Chem. Ber.*, 1954, **87**, 901; J. Thesing and H. Mayer, *ibid.*, p. 1084; K. Bodendorf and H. Raaf, *Annalen*, 1955, **592**, 26. These authors report Hofmann-Martius rearrangements at room temperature in glacial acetic acid or in N-hydrochloric acid.

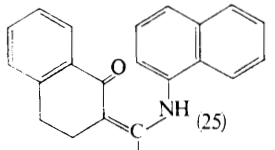
[24] R. S. Corley and E. R. Blout, *J. Amer. Chem. Soc.*, 1947, **69**, 761.

[25] R. S. Corley and E. R. Blout, *J. Amer. Chem. Soc.*, 1947, **69**, 755; E. R. Blout and R. S. Corley, *ibid.*, p. 763.

[26] J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. chim. France*, 1957, 447; these authors erroneously described this product as the dibenzo-octahydroacridine although they gave the correct molecular formula.

in this reaction are in different states of oxidation and the fate of the two hydrogen atoms lost is not known. Secondly, condensation of 2-hydroxymethylene-1-tetralone with 1-tetralone in acetic acid in the presence of perchloric acid [27] gave 5,6,8,9-tetrahydrodibenzo[*c*,*h*]-xanthylium perchlorate (22; X = ClO_4), which changed when treated with ammonia into the tetrahydrodibenzacridine (21) in high yield; after this work had been completed this same route to the tetrahydrodibenzacridine (21) was described briefly by Dorofeenko *et al.*[28]

In contrast with the behaviour shown by 2-anilinomethylene-1-tetralone (19), ring-closure of 2-(1-naphthylaminomethylene)-1-tetralone (25) with hot formic acid * gave in modest yield 7,8-dihydrodibenzo[*c*,*k*]phenanthridine (26). This difference in behaviour in hot formic acid between 2-anilinomethylene- (19) and 2-(1-naphthylaminomethylene)-1-tetralone (25) may be due to a steric effect of the bulky naphthalene nucleus, retarding any tendency towards the formation of the tetrahydrodibenzoxanthylium salt (22; X = HCO_2). The dihydrodibenzophenanthridine structure (26) was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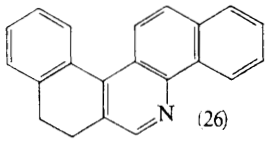
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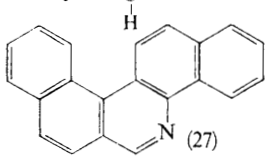
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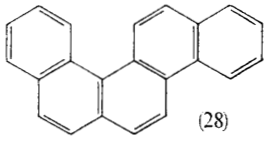
(28)

assigned on the basis of the analytical data, the mode of synthesis, and the fact that dehydrogenation gave a new compound, $C_{21}H_{13}N$, distinct from dibenzo[*c*,*h*]-acridine, which must therefore have been dibenzo[*c*,*k*]-phenanthridine (27). The dibenzo[*c*,*k*]phenanthridine structure (27) was further supported by the u.v. absorption spectrum, which closely resembled that of its carbocyclic analogue, dibenzo[*c*,*k*]phenanthrene (benzo[*c*]chrysene) (28) [29] with increased intensity of the long wavelength bands in line with previous general experience of comparing the spectra of fused polynuclear aza-heterocycles with their carbocyclic analogues.[30]

EXPERIMENTAL

Formic acid refers to B.D.H. 98—100% material. Light petroleum refers to the fraction b.p. 60—80°. Column chromatography was performed with Spence type H alumina, Brockmann activity I/II, with benzene as eluant. T.l.c. was effected with Merck silica gel G, with, in practically all cases, chloroform as solvent; chromatograms were viewed in filtered u.v. light (365 nm.). U.v. absorption spectra were observed for solutions in 95% ethanol. Fluorescence spectra were obtained with an Aminco-Bowman spectrophotofluorimeter for solutions (*a*) in 95% ethanol or (*b*) in 95% ethanol diluted with an equal volume of 0·1N-sulphuric acid; activation (act.) and emission (em.) wavelength maxima are uncorrected instrumental readings; the italicised activation wavelengths denote those used in determining fluorescence spectra and *vice versa*.

2-(1-*Naphthylaminomethylene*)*cyclohexanone* (5).— (*a*) Condensation of equimolecular proportions of 2-hydroxymethylenecyclohexanone and 1-naphthylamine in ethanol at room temperature afforded 2-(1-naphthylaminomethylene)cyclohexanone (5) (87%) as orange crystals, m.p. 119—120° (from ethanol) (lit.,[12] 118—119°), $\lambda_{max.}$ 245infl, 283, and 379 nm. (log ε 4·10, 3·43, and 4·33) (Found: C, 81·0; H, 6·7; N, 5·7. Calc. for $C_{17}H_{17}NO$: C, 81·25; H, 6·8; N, 5·6%).

Ozonolysis of this material (216 mg.) in ethyl acetate (50 c.c.) at 0° for 2 hr. gave a colourless solution in 1 hr. The mixture was kept overnight with water (40 c.c.) and the material recovered from the organic layer was twice crystallised from ethyl acetate–light petroleum, to give adipic acid (100 mg.), identified by its i.r. spectrum.

(*b*) (i) 2-Methoxymethylenecyclohexanone was prepared from 2-hydroxymethylenecyclohexanone by the method of Royals and Brannock [31] (50%), b.p. 85°/2 mm., n_D^{23} 1·5060 (lit.,[31] b.p. 85°/3·2 mm., n_D^{25} 1·5025) (Found: C, 68·0; H, 8·6. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·6%); although the analytical figure for carbon was not particularly good, g.l.c. showed the substance to be essentially pure with traces of two other components. It became discoloured fairly quickly and was redistilled immediately before use.

(ii) Ozonolysis in the manner described above gave adipic acid (84%), identified by m.p., mixed m.p., and i.r. spectrum.

(iii) 1-Naphthylamine (13·7 g.) in ethanol (75 c.c.) was added to an ethanolic solution (25 c.c.) of 2-methoxymethylenecyclohexanone (13·7 g.) and the yellow solution was boiled under reflux for 1 hr. and cooled. The product (19·2 g., 80%) crystallised from ethanol in yellow crystals (16·4 g.), m.p. and mixed m.p. with the orange form [see (*a*)] 116—118°; the respective i.r. and u.v. spectra of the two forms were indistinguishable (Found: C, 81·2; H, 6·8; N, 5·5; MeO, 0·0%).

Ring-closure of 2-(1-*Naphthylaminomethylene*)*cyclohexanone* (5) *in Formic Acid*.—The red solution of the substance (5) (15·5 g.) in formic acid (120 c.c.) was heated under reflux for 20 hr. and then evaporated under reduced pressure to about one quarter of its bulk. The residue was poured with stirring into 15% aqueous ammonia (270 c.c.), and the mixture was extracted with benzene. The deep red extract was washed with water and dried (Na_2SO_4). T.l.c. showed the presence of two compounds which exhibited a blue fluorescence in filtered u.v. light. Chromatography on alumina gave in succession 8,9,10,11-tetrahydrobenz[*c*]-acridine (6) (2·44 g., 17%), as prisms, m.p. 95—96·5° (from light petroleum) (lit.,[12] 96·5—97·5°), $\lambda_{max.}$ 238infl, 242, 271, 287infl, 320, 334·5, and 349·5 nm. (log ε 4·62, 4·63, 4·45, 4·10, 3·46, 3·73, and 3·80); fluorescence: (*a*) act. *280*, 320infl, 333, *350*; em. *355*, 370; (*b*) 240infl, *282*, 328, 355, *370*; em. *420* nm. (Found: C, 87·4; H, 6·6; N, 6·1.

* Mills and Schofield [20] reported that this reaction merely gave a small yield of 1-formamidonaphthalene.

[27] Cf. W. Schroth and G. Fischer, *Z. Chem.*, 1963, **3**, 147; G. N. Dorofeenko and G. I. Shungijetu, *Zhur. obshchei Khim.*, 1965, **35**, 589.

[28] G. N. Dorofeenko, J. A. Shdanow, G. I. Shungijetu, and S. W. Kriwun, *Tetrahedron*, 1966, **22**, 1821.

[29] E. Clar and D. G. Stewart, *J. Amer. Chem. Soc.*, 1952, **74**, 6235.

[30] Cf. H. H. Jaffé and M. Orchin, ' Theory and Applications of Ultraviolet Spectroscopy,' Wiley, New York, 1964, p. 371.

[31] E. E. Royals and K. C. Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050.

Calc. for $C_{17}H_{15}N$: C, 87·6; H, 6·4; N, 6·2%), and 7,8,9,10-tetrahydrobenzo[*c*]phenanthridine (4) (4·1 g., 28%) as prisms from light petroleum, m.p. 120—121° (lit.,[13] 118—119°), $\lambda_{max.}$ 245·5, 262, 270·5, 301·5, 317, 324, 331·5, 339, and 347 nm. (log ε 4·64, 4·41, 4·43, 3·87, 3·23, 3·00, 3·43, 3·00, and 3·54); fluorescence: (*a*) act. *280*, 298, *330*, 345; em. 345, *361*, 377infl, (*b*) act. *280*, 310, 350infl, *360*, em. *407* nm. (Found: C, 87·4; H, 6·5; N, 6·4%).

The stabilities of the tetrahydrobenzophenanthridine (4) and tetrahydrobenzacridine (6) under the conditions of reaction were checked by submitting both to formic acid under reflux for 20 hr. Both were recovered in 95% yield, unchanged in m.p., and shown by t.l.c. to be uncontaminated. The former (4) was similarly recovered after treatment with phosphoric acid at 140° for 7 hr.

Ring-closure of 2-(1-*Naphthylaminomethylene*)*cyclohexanone* (5) *with Various Reagents* (*Table* 1).—In each of the experiments summarised in Table 1 the reaction mixture was made alkaline with an excess of aqueous ammonia and then extracted three or four times with benzene. The extracts were dried, examined by t.l.c., and chromatographed on alumina. The percentage yields (Table 1) refer to weights isolated from the appropriate eluted fractions, and the products were crystallised from petroleum to give material of the correct m.p. in every case.

TABLE 1

Ring-closure of 2-(1-naphthylaminomethylene)cyclohexanone (5)

Reagent	Compound (5) (g.)	Temp.	Time (hr.)	Yield (%) Phenanthridine (4)	Yield (%) Acridine (6)
Formic acid (120 c.c.)	15·5	Reflux	20	28	17
Formic acid (30 c.c.) in absence of air [a]	4·3	100°	22	22	18
Formic acid (120 c.c.) and acetic anhydride (50 c.c.)	14·3	Reflux	18	26	16
Acetic acid (120 c.c.)...	15·5	Reflux	22		14
Lactic acid (40 c.c.) ...	11·5	130	7·5		61
Monochloroacetic acid (19·1 g.)	10	145	7·5	<6	62
Oxalic acid (7·4 g.) [b] ...	17·2	110	6·5		39
Phosphoric acid (35 c.c.)	10·6	135	7	<6	47
Phosphoryl chloride (40 c.c.) [c]	10·2	130	4	Small	Small
Polyphosphoric acid (54 g.) [d]	7·2	140	5	28	3
1-Naphthylamine hydrochloride (6·1 g.) and fused zinc chloride (4·5 g.), in ethanol (150 c.c.)	8·5	Reflux	8		61

[a] In sealed tube under nitrogen. [b] Components fused at 120° and mixture then stirred at 110°. [c] T.l.c. indicated a range of fluorescing products amongst which were small amounts of the acridine (6) and smaller amounts of the phenanthridine (4). [d] Acid prepared 3 days previously by mixing equal weights of phosphoric acid and phosphoric oxide, solid sprinkled on hot acid (½ hr.) and stirred in.

Reaction between 2-(1-*Naphthylaminomethylene*)*cyclohexanone* (5) *and* 2-*Naphthylamine Hydrochloride*. 8,9,10,11-*Tetrahydrobenz*[a]*acridine* (10).—The compound (5) (7·4 g.) and 2-naphthylamine hydrochloride (5·3 g.) were dissolved in hot ethanol (90 c.c.) and the red mixture was boiled under reflux for 7 hr. The crystals (2·83 g.) which separated from the cooled mixture were collected, washed with ethanol and ether, and then stirred with 2N-aqueous ammonia and chloroform. The solid (2·52 g.) recovered from the organic phase gave prisms (1·4 g.), m.p. and mixed m.p. with authentic material (10) 112—113° (from light petroleum).

Ring-closure of 2-(2-*Naphthylaminomethylene*)*cyclohexanone* (8) *in Formic Acid*.—(i) 2-(2-Naphthylaminomethylene)cyclohexanone (8), obtained (80%) from 2-hydroxymethylenecyclohexanone and 2-naphthylamine, gave light yellow needles, m.p. 178—179° (from benzene–light petroleum) (lit.,[12] 181—182°), $\lambda_{max.}$ 235, 282, 293, and 371 nm. (log ε 4·62, 3·97, 4·03, and 4·56) (Found: C, 80·9; H, 6·6; N, 5·6%).

(ii) A solution of the compound (8) (15·8 g.) in formic acid (140 c.c.) was heated under reflux for 22 hr., and then evaporated under reduced pressure to about half its bulk. The residue was poured into an excess of 20% aqueous ammonia and extracted with benzene. The washed and dried extract was chromatographed on alumina to give in succession 8,9,10,11-tetrahydrobenz[*a*]acridine (10) (1·74 g.) as prisms, m.p. 113—114° (from light petroleum), and 1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (9) (5·7 g.) as needles, m.p. 100—101° (from light petroleum) (lit.,[13] 100—101°), $\lambda_{max.}$ 203infl, 217infl, 222, 239infl, 250, 267infl, 270infl, 286infl, 297, 320, 334, and 349 nm. (log ε 4·09, 4·34, 4·36, 4·50, 4·60, 4·33, 4·31, 4·00, 3·96, 3·18, 3·47, and 3·54); fluorescence: (*a*) act. *272*, 292, 320infl, 330, *347*; em. *352*, 367; (*b*) act. 245, *278*, 307, *361*; em. *408* nm. (Found: C, 87·3; H, 6·5; N, 6·1. Calc. for $C_{17}H_{15}N$: C, 87·5; H, 6·5; N, 6·0%).

Ring-closure of 2-(2-*Naphthylaminomethylene*)*cyclohexanone* (8) *with Various Reagents* (*Table* 2).—(a) *With lactic acid*. Compound (8) (11·4 g.) was heated with lactic acid (40 c.c.) at 130° for 7 hr. The cooled red syrup was poured into an excess of aqueous ammonia (10%; 280 c.c.) and the product was extracted with benzene. The dried extracts were concentrated and chromatographed on alumina to give 8,9,10,11-tetrahydrobenz[*a*]acridine (10) (6·4 g.), m.p. 113—115° (from light petroleum).

(b) *With* 2-*naphthylamine hydrochloride*. A solution of the compound (8) (7·4 g.) and 2-naphthylamine hydrochloride (5·3 g.) in absolute ethanol (90 c.c.) was heated under reflux for 6 hr. The 8,9,10,11-tetrahydrobenz-[*a*]acridine (10) *hydrochloride* (5·7 g.) which separated was collected from the cooled solution (Found for a sample crystallised from ethanol containing a little methanol: C, 75·3; H, 5·95; N, 5·4; Cl, 13·3. $C_{17}H_{15}N$,HCl requires C, 75·7; H, 6·0; N, 5·2; Cl, 13·1%). This and mother-liquor material were distributed between aqueous ammonia and chloroform. The dried organic phase was evaporated to give an oil (5·6 g.) which slowly crystallised (m.p. *ca.* 110°). Chromatography on alumina then gave 8,9,10,11-tetrahydrobenz[*a*]acridine (10), m.p. 114—115° (lit.,[12] 115—116°), $\lambda_{max.}$ 237, 277, 320, 328infl, 335, 343, and 350 nm. (log ε 4·63, 4·35, 3·48, 3·35, 3·81, 3·42, and 3·92); fluorescence: (*a*) act. *282*, 320infl, 332, *348*; em. *352*, 365; (*b*) act. 240, *282*, 305infl, *365*; em. *415* nm. (Found: C, 87·1; H, 6·6; N, 6·1%).

(c) *With aniline hydrochloride*. A solution of the compound (8) (7·4 g.) and aniline hydrochloride (3·8 g.) in absolute ethanol (90 c.c.) was heated under reflux for 7 hr. and cooled. 8,9,10,11-Tetrahydrobenz[*a*]acridine (10) hydrochloride (4·0 g.) was collected and converted into the free base, m.p. 113—114°, as in (*b*).

As a further check on the identities of the products (4), (6), (9), and (10) they were dehydrogenated to the parent aza-heterocycles.

Benzo[c]*phenanthridine*.—The tetrahydro-compound (4) (0·89 g.) was intimately ground with selenium powder (0·89 g.) and the mixture was heated at about 300° for 5½ hr. Extraction with ethanol gave an orange solid (0·80 g.)

TABLE 2

Ring-closure of 2-(2-naphthylaminomethylene)cyclohexanone (8)

Reagent	Yield (%) Phenanthridine (9)	Acridine (10)
Formic acid	39	12
Lactic acid		60
2-Naphthylamine hydrochloride		82
Aniline hydrochloride		50

but crystallisation from ethanol failed to remove the colour (yield 0·5 g.; m.p. 130—131°). Sublimation at 160°(bath)/0·2 mm. gave benzo[*c*]phenanthridine as crystals, m.p. 133—134° (lit.,[15] 135°, lit.,[32] 135·5°), $\lambda_{max.}$ 238infl, 254, 262·5, 308infl (broad), 342·5, and 360 nm. (log ε 4·62, 4·80, 4·90, 3·95, 3·71, and 3·78).

Benz[c]*acridine*.—The tetrahydro-compound (6) (1·0 g.) was similarly dehydrogenated with selenium (1·0 g.). The crude product, extracted with ethanol, was chromatographed on alumina. Benz[*c*]acridine gave fibrous needles (440 mg.), m.p. 109—110° (from ethanol) (lit.,[33] 108°); the u.v. absorption spectrum agreed closely with that previously recorded [34] (Found: C, 89·1; H, 4·8; N, 6·0. Calc. for $C_{17}H_{11}N$: C, 89·2; H, 4·8; N, 6·1%).

Benzo[a]*phenanthridine*.—The tetrahydro-compound (9) (0·6 g.) was dehydrogenated with selenium (1·35 g.) at 290° for 5 hr., and the crude extracted product was chromatographed on alumina. Crystallisation from light petroleum, or from methanol containing a little water, gave benzo[*a*]-phenanthridine, m.p. 107—108° (lit.,[20] 105—106°, lit.,[35] 106°, lit.,[36] 110°); the u.v. absorption spectrum agreed closely with that previously recorded.[20]

Benz[a]*acridine*.—The tetrahydro-compound (10) (1·25 g.) was heated at 330° for 4½ hr. with selenium (1·35 g.), and the crude product was chromatographed on alumina. Benz[*a*]acridine gave needles, m.p. 130—131° (from light petroleum) (lit.,[33,37] 131°); the u.v. absorption spectrum agreed closely with that previously recorded.[34a,38]

5,6,8,9-*Tetrahydrodibenz*[c,h]*acridine* (21).—(a) *From* 2-*anilinomethylene*-1-*tetralone* (19). A solution of 2-anilinomethylene-1-tetralone (19) [20] (5·63 g.) in formic acid (50 c.c.) was heated under reflux for 18 hr., cooled, and poured into 16% aqueous ammonia (200 c.c.). The mixture was extracted thrice with benzene and the crude product was chromatographed on alumina to give 5,6,8,9-tetrahydrodibenz[*c,h*]acridine (520 mg.) as needles or plates from light petroleum or from ethanol, m.p. 160—161° (Found: C, 88·8; H, 6·1; N, 4·7. Calc. for $C_{21}H_{17}N$: C, 89·0; H, 6·0; N, 4·95%).

In a similar experiment 2-anilinomethylene-1-tetralone (19) (29·8 g.) was heated under reflux with formic acid (250 c.c.) for 15 hr., and then the cooled reaction mixture was shaken and divided into two equal parts, (A) and (B). Part (A) was poured into an excess of aqueous ammonia and extracted with benzene. The other half (B) was poured into an excess of aqueous sodium hydroxide (30%) and similarly extracted. The extracts were dried and concentrated; t.l.c. with benzene–light petroleum (1 : 1) indicated the presence of tetrahydrodibenzacridine (21) in the product from (A) and its probable absence from that from (B). Chromatography on alumina with columns side by side and identical conditions led to the isolation of tetrahydrodibenzacridine (21) (2·1 g.), plates (1·1 g.), m.p. and mixed m.p. 159·5—161° (from light petroleum), from the product isolated from (A), and the detection by t.l.c. on the appropriate fractions of traces in that from (B).

(b) *From* 2-*isopropoxymethylene*-1-*tetralone* (23). A mixture of 2-hydroxymethylene-1-tetralone (10·9 g.), propan-2-ol (4·2 g.), and toluene-*p*-sulphonic acid (1·0 g.) in benzene (110 c.c.) was heated under reflux with a conventional Dean and Stark separator. The theoretical volume of water was collected in about 3 hr. The benzene solution was cooled and washed with ice-cold water, N-sodium hydroxide, and water, then dried and evaporated to give the crude enol ether (13·0 g., 96%). A solution of this enol ether (12·0 g.) in formic acid (90 c.c.) was heated under reflux for 17 hr. and then poured into an excess of aqueous ammonia (17%). The product was recovered with benzene and chromatographed on alumina to give the tetrahydrodibenzacridine (21) (2·87 g.) as plates (1·90 g.), m.p. and mixed m.p. 159—161° (from light petroleum).

A similar experiment in which 1-tetralone itself was treated directly with formic acid and then ammonia and the product chromatographed on alumina and subjected to t.l.c. indicated the formation of traces of the tetrahydrodibenzacridine (21), insufficient for practicable isolation.

(c) *From* 2,2′-*methylenebis*-1-*tetralone* (24). (i) The substance described by Kenner *et al.*[15] as 2-methylene-1-tetralone was 2,2′-methylenebis-1-tetralone (24) [39] and was obtained in improved yield by reducing the proportion of formaldehyde used in the condensation with 1-tetralone as follows. Addition of 40% aqueous sodium hydroxide (0·25 c.c.) to a solution of 1-tetralone (30 g.) and 33·5% (w/w) aqueous formaldehyde (9·0 g.) in ethanol (65 c.c.) and water (35 c.c.) produced a slight rise in temperature. Further additions of alkali (3 × 0·25 c.c.) were required at intervals to maintain the alkaline reaction to phenolphthalein. After 2½ hr., when the temperature had risen by about 10°, the mixture was heated rapidly and boiled under reflux for 2—3 min.; an oil then separated. The product was recovered with ether as an oil. A nucleus (m.p. 104—106°) was obtained by stirring a portion under ethanol and nucleation of the main bulk and stirring under a little ethanol gave a cream-coloured sticky solid (20·2 g.). Crystallisation from ethanol, or from ethyl acetate, gave 2,2′-methylenebis-1-tetralone (24) as plates (10·6 g.), m.p. (ultimately) 121—122° (lit.,[15] 106—107°, lit.,[39,40] 107° (Found: C, 82·5; H, 6·6. Calc. for $C_{21}H_{20}O_2$: C, 82·3; H, 6·7%). The initial product is probably a mixture of *meso* and racemic forms (cf. ref. 39); more crystals could be obtained by re-working the mother-liquors.

[32] C. Graebe, *Annalen*, 1904, **335**, 122.
[33] F. Ullmann and A. La Torre, *Ber.*, 1904, **37**, 2922.
[34] (*a*) W. A. Waters and D. H. Watson, *J. Chem. Soc.*, 1959, 2082; (*b*) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, 1958, **23**, 789. The latter authors do not record a flat double maximum at *ca.* 335 nm.
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[38] DMS–UV Atlas of Organic Compounds, Butterworths–Verlag Chemie, 1967, H8/33.
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[40] J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. chim. France*, 1956, 1635.

(ii) 2,2′-Methylenebis-1-tetralone (0·5 g.) reacted with ammonium acetate in 85% acetic acid as described by Colonge *et al.*;[26] the resulting tetrahydrodibenzacridine (21) gave plates (240 mg.), m.p. 161—162° (from ethanol) (lit.,[26] 161°).

(d) *From 5,6,8,9-tetrahydrodibenzo*[c,h]*xanthylium perchlorate* (22; X = ClO_4). (i) A mixture of 2-hydroxymethylene-1-tetralone (3·5 g.) and 1-tetralone (2·9 g.) in glacial acetic acid (20 c.c.) was heated with 70% perchloric acid (1·7 c.c.) for 1½ hr. and cooled. The crystalline product (2·3 g.) was collected and washed with a little acetic acid. The tetrahydrodibenzoxanthylium perchlorate (22; X = ClO_4) gave yellow needles with a bronze reflex and showing a strong orange fluorescence in filtered u.v. light, m.p. 260—264° (from glacial acetic acid) (lit.,[28] 236°) (Found: C, 65·2; H, 4·4. Calc. for $C_{21}H_{17}ClO_5$: C, 65·5; H, 4·4%).

(ii) The perchlorate from (i) (100 mg.) was partly suspended and partly dissolved in t-butyl alcohol (3 c.c.) with warming and treated with conc. aqueous ammonia (2 c.c.). The solid rapidly dissolved to give a cherry-red solution. Crystals separated after about 15 min. at room temperature, and the resulting tetrahydrodibenzacridine (21) was recovered with ether in nearly quantitative yield; m.p. 161—162° (lit.,[28] 162°).

The u.v. absorption spectra of the products obtained in (a)—(d) were identical, and agreed closely with that previously recorded;[20] fluorescence: (*a*) act. 254, 290, *338*; em. *362* nm.

Dehydrogenation of the tetrahydrodibenzacridine (112 mg.) with selenium (206 mg.) at 300° for 6 hr., and alumina column chromatography of the product gave dibenz[*c,h*]acridine (86 mg.) as yellow needles (43 mg.), m.p. 189—191° (from acetone) (lit.,[20] 189°, lit.,[41] 185·5°); the u.v. absorption spectrum agreed closely with that previously recorded [20] apart from log ε_{394} 4·17 (lit.,[20] log ε_{391} 3·73); fluorescence: (*a*) act. *300*, 325, 340, 353, 372; em. *395*, 413 nm.

2-(1-*Napthylaminomethylene*)-1-*tetralone* (25).— 1-Naphthylamine (4·1 g.) in ethanol (20 c.c.) was added to freshly distilled 2-hydroxymethylene-1-tetralone (5·0 g.) in ethanol (10 c.c.). The solution became warm and commenced to deposit an oil which soon crystallised. The mixture was set aside overnight and the resulting 2-(1-naphthylaminomethylene)-1-tetralone (25) was collected and gave orange-yellow rosettes (7·4 g., 86%), m.p. 120—122·5° (from ethanol) (lit.,[20] 122—124°) (Found: C, 84·0; H, 5·8; N, 5·0. Calc. for $C_{21}H_{17}NO$: C, 84·2; H, 5·7; N, 4·7%).

7,8-*Dihydrodibenzo*[c,k]*phenanthridine* (26).—A solution of 2-(1-naphthylaminomethylene)-1-tetralone (2·12 g.) in formic acid (25 c.c.) was heated under reflux for 18 hr. The cooled deep red solution was poured into an excess of aqueous ammonia (16%; 100 c.c.) and the product was recovered with benzene. T.l.c. showed the presence of starting material and a single colourless compound which exhibited a light blue fluorescence in filtered u.v. light. Chromatography on alumina gave 7,8-*dihydrodibenzo*[c,k]-*phenanthridine* (26) (740 mg.), which gave needles (350 mg.), m.p. 138—140° (from ethanol), $\lambda_{max.}$ 237infl, 262, 278, 317, 325, 343infl, and 361 nm. (log ε 4·37, 4·52, 4·47, 4·16, 4·16, 4·00, and 3·72); fluorescence: (*a*) 280, *322*, 360; em. *385* nm. (Found: C, 89·2; H, 5·3; N, 5·1. $C_{21}H_{15}N$ requires C, 89·65; H, 5·3; N, 5·0%).

Dibenzo[c,k]*phenanthridine* (27).—The dihydro-compound (26) (125 mg.) was heated with selenium powder (290 mg.) at 310° for 5 hr. The cooled mass was extracted thrice with benzene and the crude product was chromatographed on alumina. Crystallisation from ethanol gave *dibenzo*-[c,k]*phenanthridine* as plates (100 mg.), m.p. 122·5—123°, $\lambda_{max.}$ 230, 268infl, 275, 290—295infl, 299, 320, 335infl, 350, 369, and 388 nm. (log ε 4·50, 4·58, 4·66, 4·64, 4·66, 4·39, 3·74, 3·42, 3·65, and 3·77); fluorescence: (*a*) act. *300*, 317, 370; em. *390*, 410, 430infl nm. (Found: C, 90·1; H, 4·5; N, 5·1. $C_{21}H_{13}N$ requires C, 90·3; H, 4·7; N, 5·0%).

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