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REACTION OF *o*-XYLYLENE WITH ACRIDINE

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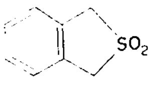
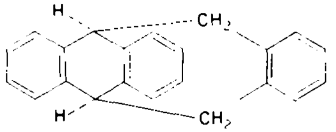
Abstract—Acridine and 1,3-dihydroisothianaphthene-2,2-dioxide in diethyl phthalate at 300° give a complex mixture, from which six new compounds (V–X) have been isolated and identified. The formation of these products is discussed.

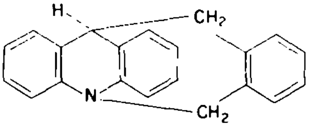
PREVIOUS work[1] on the chemistry of xylylenes, has led to an investigation on the reaction of acridine with 1,3-dihydroisothianaphthene-2,2-dioxide (I) in diethyl phthalate at 300°. This cyclic sulphone (I) decomposes into *o*-xylylene and sulphur dioxide under similar conditions.[2] As the adduct II is obtained by the thermal reaction of anthracene with sulphone,[1a,b] it was anticipated that the bridged acridan III would result from the reaction of anthracene and acridine.[3] The reaction, however, yields a complex mixture, from which instead of the desired product (III) six new compounds (V–X) were isolated by elution chromatography on an alumina column and identified mostly by independent syntheses. N.M.R. spectra[4] served as an invaluable tool in structure assignment.



I



II



III

9-(*o*-Methylbenzyl)acridine (V) was isolated in 2 per cent yield and the structure was assigned on the basis of light absorptions, which indicate the presence of an

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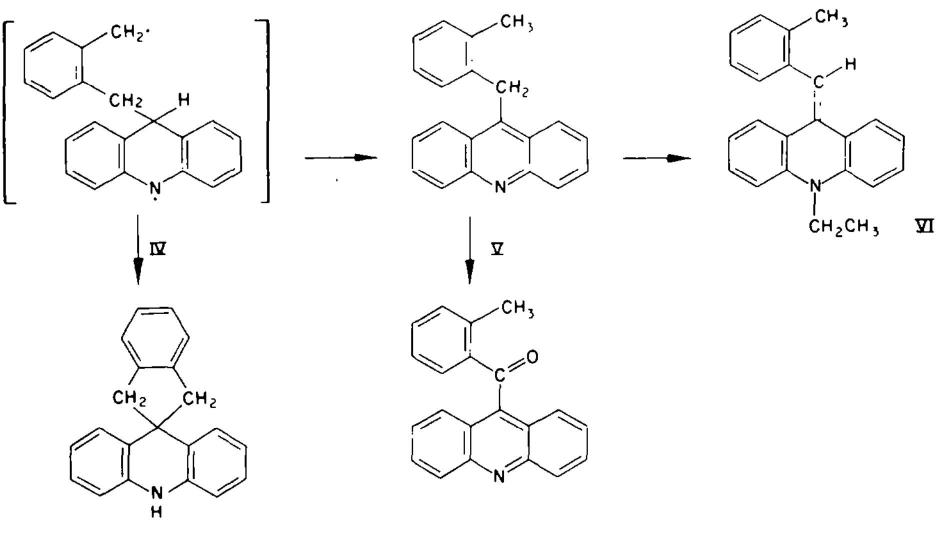
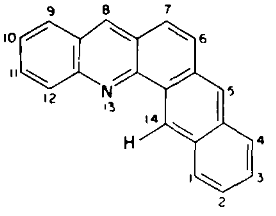
[1a] K. Sisido, Y. Udô and H. Nozaki, *J. Org. Chem.* **26**, 584 (1961); [b] K. Sisido, R. Noyori and H. Nozaki, *J. Amer. Chem. Soc.* **84**, 3562 (1962); [c] K. Sisido, N. Kusano, R. Noyori, Y. Nozaki, M. Simonsaka and H.Nozaki *J. Polymer Sci.* in press; [d] K. Sisido, R. Noyori, N. Kôzaki and H. Nozaki, *Tetrahedron* **19**, 1185 (1963).

[2] M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.* **81**, 4266 (1959).

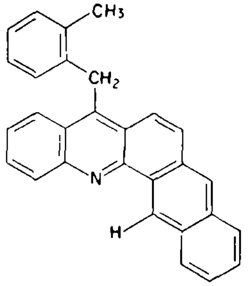
[3] For reactions of benzyl radicals, see [a] A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.* 1001 (1957); [b] W. A. Waters and D. H. Watson, *Ibid.* 253 (1957).

[4] All NMR spectra in this paper were taken on a Varian A60 spectrometer with tetramethylsilane as an internal reference and are given in the order of peak position in ppm from the reference signal, area in parentheses, splitting pattern and assignment.





IX



X

acridine chromophore.[5] According to the established method[6] of acridine synthesis, an authentic sample of V prepared from diphenylamine and *o*-tolylacetic acid, proved identical on mixed m.p. determination and comparison of I.R. spectra. The formation of V can be explained as proceeding through the initial addition of *o*-xylylene to acridine and the following migration of hydrogen under aromatization.

10-Ethyl-9-(*o*-methylbenzal)-9,10-dihydroacridine (VI) was isolated in 5 per cent yield. The N.M.R. spectrum[4,7] indicates the presence of an ethyl group in this product. The structure assigned to VI supported by the spectroscopic data was confirmed by independent synthesis from V and diethyl sulphate by a method based on the work

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[5] λ_{max}^{EtOH} in mμ (log ε): 245sh. (4·77), 252 (5·16), 343 (3·84), 352sh. (3·89), 360 (4·03), 370sh. (3·84) and 386 (3·63).

[6a] A. Bernthsen, *Liebig's Ann.* **224**, 1 (1884). For synthesis of 9-benzylacridine, see [b] H. Decker and T. Hock, *Ber. Dtsch. Chem. Ges.* **37**, 1564 (1904); [c] Ng. Ph. Buu-Hoï and J. Lecocq, *Rec. Trav. Chim.* **64**, 250 (1945).

[7] N.M.R. absorptions of VI in carbon tetrachloride: 6·95 (12), multiplet, aromatic hydrogens; 6·50 (1), singlet, olefinic hydrogen; 3·99 (2), quartet, methylene protons of ethyl group; 2·21 (3), singlet, methyl protons of the *o*-methylbenzyl group; 1·37 (3), triplet, methyl protons of ethyl group (J_{HH} 7 cps). λ_{max}^{EtOH} in mμ (log ε): 232 (4·75), 294 (4·11) and 386 (4·05).

of Decker and Hock.[6b] The ethyl group probably originates from the solvent, diethyl phthalate, the nitrogen atom of V being attacked by an ethyl cation, followed by the loss of proton from the methylene group to afford the compound VI. The exact nature of the transformation of the solvent ethyl group into ethyl cation is still obscure.

The ketone 9-(*o*-methylbenzoyl)acridine (VIII) was isolated in 7 per cent yield. The spectroscopic data[4,8] supports the assigned structure, and an authentic sample prepared by oxidation of V with selenium dioxide proved to be identical.

The U.V. spectrum of VIII, which is characteristic of the acridine system, indicates that the acridine ring may not be coplanar with the *o*-methylbenzoyl group.

The spiro compound VII was obtained in 3 per cent yield and the U.V., I.R. and N.M.R. spectra all give strong evidence in favour of the structure VII.[4,9] The formation may involve initial migration of hydrogen from the 9-position to nitrogen of the acridine ring with formation of the supposed intermediate (IV) which cyclizes to VII.

Naphth[2,3-c]acridine (IX) was obtained in 7 per cent yield and the U.V. and N.M.R. spectra support this structure.[4,10] The compound is identical with an authentic sample prepared by zinc dust distillation of naphth[2,3-c]acridan-5,8,14-trione.[11]

Finally, 8-(*o*-methylbenzyl)naphth[2,3-c]acridine (X) was isolated in 4 per cent yield; the U.V. absorptions are similar to those of IX with a blue shift of about 3–4 mμ for each peak. Analyses and N.M.R. spectrum[4,12] support the structure given. The position of *o*-methylbenzyl group is assumed from the reaction of acridine itself. Although in extremely low yield, this compound was synthesized from N-phenyl-1-aminoanthracene and *o*-tolylacetic acid in the manner similar to the preparation of V. Both products proved identical on mixed m.p. determination and comparison of I.R. and U.V. spectra. N-Phenyl-1-aminoanthracene required in this synthesis was prepared from 1-aminoanthraquinone and bromobenzene as described in the Experimental.

The formation of IX probably proceeds by addition of *o*-xylylene to the 3,4-positions of acridine, followed by dehydrogenation of the adduct under aromatization.

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[8] N.M.R. absorptions of VIII in carbon tetrachloride and deuteriochloroform mixture: 8·25 (2), multiplet, aromatic hydrogens; ca. 7·4 (10), multiplet, aromatic hydrogens; 2·90 (3), singlet, methyl protons of the *o*-methylbenzoyl group. λ_{max}^{EtOH} in mμ (log ϵ): 252 (5·09), 296 (3·50), 327sh. (3·52), 344sh. (3·82), 361 (4·03) and 382sh. (3·69). $\nu_{C=O}^{Nujol}$ 1660 cm^{-1}.

[9] N.M.R. absorptions of VII in carbon tetrachloride: ca. 7·1 (1), broad line, hydrogen attached to nitrogen or impurity; ca. 6·8 (12), multiplet, aromatic hydrogens; 5·96 (1), singlet, hydrogen attached to nitrogen or impurity; 3·55 (4), methylene protons of indan system. λ_{max}^{EtOH} in mμ (log ϵ): 271sh. (4·12), 276sh. (4·23), 290 (4·30) and 340sh. (3·65). These light absorptions are characteristic of acridan system. ν_{NH}^{Nujol} 3360 cm^{-1}.

[10] N.M.R. absorptions of IX in deuteriochloroform: 9·90 (1), singlet, aromatic hydrogen probably attached to 14-position; 8·30 (2), multiplet, aromatic hydrogens; ca. 7·5 (10), multiplet, aromatic hydrogens. λ_{max}^{EtOH} in mμ (log ϵ): 223 (4·79), 243 (4·79), 256 (4·71), 266sh. (4·37), 275sh. (4·33), 290sh. (4·46), 301 (4·68), 313 (4·78), 321sh. (4·66), 327sh. (4·60), 343 (4·31), 353 (4·13), 380 (3·47), 402 (3·79) and 424 (3·80).

[11] F. Ullmann and P. Ochsner, *Liebig's Ann.* **381**, 1 (1911).

[12] N.M.R. absorptions in deuteriochloroform: 10·01 (1), singlet, aromatic hydrogen (probably attached to 14-position of naphthacridine system); 8·28 (2), multiplet, aromatic hydrogens; ca. 7·6 (?), multiplet, aromatic hydrogens; 4.73 (2), singlet, methylene protons of *o*-methylbenzyl group; 2·63 (3), singlet, methyl protons of *o*-methylbenzyl group. λ_{max}^{EtOH} in mμ (log ϵ): 225 (4·78), 246 (4·81), 257 (4·68), 268sh. (4·21), 282sh. (4·20), 293sh. (4·41), 304 (4·65), 317 (4·79), 323sh. (4·67), 331sh. (4·49), 343 (4·31), 360 (4·27), 384 (3·46), 405 (3·78) and 428 (3·81).

The formation of X may either be by attack of *o*-xylylene on IX or the addition of *o*-xylylene to V followed by dehydrogenation.

Remarkably low field shift (9·90 or 10·01 p.p.m.) of an aromatic proton was observed in the N.M.R. spectra of IX and X. Each of the signals was assigned to hydrogen attached to the 14-position of the naphthacridine system. A similar, but not so drastic a paramagnetic shift has been recorded.[13]

The nature of the oxidizing agents participating in the formation of VIII, IX and X is not certain.

EXPERIMENTAL[14]

Reaction of 1,3-*dihydroisothianaphthene*-2,2-*dioxide* (I) *with acridine.* A solution of 3·0 g (18 mmoles) of 1,3-dihydroisothianaphthene-2,2-dioxide (I)[2] and 3·3 g (18 mmoles) of acridine in 50 ml of diethyl phthalate was heated at about 290° for 1·5 hr in an atmosphere of nitrogen. The reaction mixture was hydrolysed by stirring at 90° with 170 ml 15% sodium hydroxide solution for 24 hr. Extraction of the hydrolysate with benzene and concentration of the extract afforded a black tarry material (5·2 g). The residue was dissolved in a minimum volume of benzene and the solution chromatographed on an alumina column. Elution with benzene gave the following products: an oily material (1·0 g) which was not further investigated; VI (0·28 g, 5% based on I) which crystallized from n-hexane in yellow fine needles, m.p. 115–117°; X (0·14 g, 4%) which crystallized from benzene in yellow granules, m.p. 238–240° (dec), and showed violet fluorescence in benzene or ethanol solution; IX (0·35 g, 7%) which crystallized from benzene in yellow leaflets, m.p. 223–224°, and showed violet flouresence in benzene or ethanol solution; V (0·10 g, 2%) which crystallized from a mixture of benzene and n-hexane in yellow leaflets, m.p. 167–169°; acridine (0·85 g); VII (0·15 g, 3%) which crystallized from a mixture of benzene and n-hexane in colourless needles, m.p. 194–195°; and VIII (0·37 g, 7%) which crystallized from benzene in yellowish prisms, m.p. 200–201°.

Elemental analyses of these compounds are given below:

V (Found: C, 88·73; H 6·16. $C_{21}H_{17}N$ requires: C, 89·01; H, 6·05%), VI (Found: C, 88·80; H, 6·71. $C_{23}H_{21}N$ requires: C, 88·70; H, 6.80%), VII (Found: C, 88·98; H, 6·27. $C_{21}H_{17}N$ requires: C, 89·01; H, 6·05%), VIII (Found: C, 85·26; H, 5·44. $C_{21}H_{15}NO$ requires: C, 84·82; H, 5·09%), IX (Found: C, 90·23; H, 4·70. $C_{21}H_{13}N$ requires: C, 90·29; H, 4·69%) and X (Found: C, 90·81; H, 5·77. $C_{29}H_{21}N$ requires: C, 90·83; H, 5·52%.)

9-(o-*Methylbenzyl*)*acridine* (V). A mixture of 13·5 g (80 mmoles) of diphenylamine, 11·5 g (77 mmoles) *o*-tolylacetic acid[15] and 29 g zinc chloride was heated for 20 hr at 180–200°. The resulting black solid was extracted with ethanol and the solution diluted with aqueous ammonia. The solid precipitated was taken up with benzene and the benzene solution washed, dried and concentrated. Chromatographic purification on an alumina column, followed by recrystallizations from benzene, gave 3·0 g (13%) of yellow leaflets, m.p. and mixed m.p. 167–169° (Found: C, 89·04; H, 6·23. Calc. for $C_{21}H_{17}N$: C, 89·01; H, 6·05%).

10-*Ethyl*-9-(o-*methylbenzal*)-9,10-*dihydroacridine* (VI). A mixture of 0·64 g (2·3 mmoles) 9-(*o*-methylbenzyl)acridine (V) and 1·5 g (9·7 mmoles) diethyl sulphate was heated at 115–125° for 1·5 hr. The reaction mixture was dissolved in water and treated with 0·38 g (2·3 mmoles) potassium iodide. The precipitated solid was collected, dissolved in ethanol and treated with aqueous sodium hydroxide. The resulting yellow solid was extracted with ether and the solution was dried ($MgSO_4$) and concentrated. Chromatography of the residue on an alumina column, followed by 3 recrystallizations from n-hexane, afforded 0·31 g (43%) yellow crystals, m.p. and mixed m.p. 115–117° (Found: C, 88·90; H, 7·07. Calc. for $C_{23}H_{21}N$: C, 88·70; H, 6·80%).

9-(o-*Methylbenzoyl*)*acridine* (VIII). A solution of 0·15 g (0·53 mmole) 9-(*o*-methylbenzyl)acridine (V) in 2 ml xylene was refluxed with 75 mg selenium dioxide for 12 hr. After evaporating the xylene *in vacuo*, the residue was purified through an alumina column. Two recrystallizations from benzene afforded 0·11 g (70%) of a yellowish solid, m.p. and mixed m.p. 200–201°. The analytical

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[13] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog* Spectrum No. 348. Varian Associates, California (1962).

[14] All temps were uncorrected. Analyses were carried out by Miss Kenko Ogawa.

[15] P. L. Julian, W. J. Kappel, A. Magnani and E. W. Meyer, *J. Amer. Chem. Soc.* **70**, 180 (1948).

sample was dried at 150° (3 mm) for 15 hr. (Found: C, 84·80; H, 5·17. Calc. for $C_{21}H_{15}NO$: C, 84·82; H, 5·09%).

Naphth[2,3-*c*]*acridine* (IX). A mixture of 0·5 g (1·5 mmoles) naphth[2,3-c]acridan-5,8,14-trione[11] and 25 g zinc dust was distilled at 500–570° under ordinary pressure in a hydrogen atmosphere. After 2 recrystallizations from benzene, the yellow distillate afforded 85 mg (20%), of yellow crystals m.p. and mixed m.p. 223–224° (Found: C, 90·31; H, 4·89. Calc. for $C_{21}H_{13}N$: C, 90·29; H, 4·69%).

N-*Phenyl*-1-*aminoanthracene*. A solution of 3·0 g (13 mmoles) 1-aminoanthraquinone, 3·0 g (19 mmoles) bromobenzene, 0·5 g copper powder and 6·0 g anhydrous sodium carbonate in 30 ml nitrobenzene was heated at about 220° for 6 hr. After removal of nitrobenzene by steam distillation, the residue was filtered and the solid extracted with ethanol in a Soxhlet apparatus. Evaporation of the solvent afforded 4·3 g crude N-phenyl-1-amino-anthraquinone, m.p. 138–142° (lit.[16] 147·5°). This product was reduced without further purification. A mixture of 4·3 g, 7·5 g zinc dust and 150 ml of 5% sodium hydroxide solution was refluxed for 6 hr. The mixture was filtered while hot and the solid washed with hot water, dried *in vacuo* and extracted with acetone in a Soxhlet apparatus. After concentrating the acetone extract, the residue was chromatographed on a silica gel column. N-Phenyl-1-aminoanthracene (1·5 g, 42% based on 1-aminoanthraquinone) was obtained in yellow crystals after recrystallization from a mixture of benzene and pet ether (b.p. 30–50°) and showed green fluorescence in ethanol solution, m.p. 157–158°, ν_{NH}^{Nujol} 3360 cm^{-1}. λ_{max}^{EtOH} in mμ (log ε): 247 (4·89), 255 sh. (4·67), 352sh. (3·41), 360sh. (3·49), 369 (3·64) and 409 (3·82) (Found: C, 88·88; H, 5·62. $C_{20}H_{15}N$ requires: C, 89·18; H, 5·61%). Another product, N,N-*diphenyl*-1-*aminoanthracene*, was isolated from the reduction mixture as yellowish green leaflets (0·3 g, 6·5%), m.p. 225–226·5°, after 3 recrystallizations from benzene–pet ether (b.p. 30–50°). λ_{max}^{EtOH} in mμ (log ε): 221 (4·45), 250sh. (4·89), 257 (4·98), 290 (4·30), 348 (3·54), 368 (3·63) and 402 (3·73) (Found: 90·58; H, 5·72. $C_{26}H_{19}N$ requires: C, 90·40; H, 5·54%).

8-(o-*Methylbenzyl*)*naphth*[2,3-c]*acridine* (X). A mixture of 1·5 g (5·6 mmoles) N-phenyl-1-aminoanthracene, 1·1 g (7·3 moles) *o*-tolylacetic acid[15] and 2 g zinc chloride was heated at 180–200° for about 20 hr. The reaction mixture was extracted with acetone and the acetone solution poured into aqueous ammonia. Extraction with benzene followed by chromatographic purification on an alumina column and then on a silica gel column gave a trace (ca. 10 mg) of X, which was recrystallized from benzene and formed yellow crystals, m.p. and mixed m.p. 238–240° (dec). Spectroscopic properties were identical with those of the sample obtained in the acridine–sulphone reaction. Besides the compound X, about 30 mg of naphth[2,3-c]-acridine (IX) was also obtained and was identified by U.V. and I.R. spectra.

9-(o-*Methylbenzyl*)-9,10-*dihydroacridine*. This compound was prepared for comparison with the spiro acridan VII.

To a warm solution of 0·26 g (6·5 mmoles) sodium hydroxide and 0·5 g (2·9 mmoles) sodium dithionite, $Na_2S_2O_4$, in 4 ml of water at 70° boiling ethanol was added until a solid began to separate. To this mixture a solution of 0·05 g (0·18 mmole) 9-(*o*-methylbenzyl)acridine (V) in 0·5 ml of boiling ethanol was added with swirling and then the mixture was refluxed for 3 hr. After cooling, the reaction mixture was diluted with water and filtered. Recrystallization of the solid from ethanol gave 0·04 g (79%) of colourless needles, m.p. 156–157°, ν_{NH}^{Nujol} 3360 cm^{-1}. λ_{max}^{EtOH} in mμ (log ε): 285 (4·25) and 315sh. (3·70) (Found: C, 88·13; H, 6·92. $C_{21}H_{19}N$ requires: C, 88·38; 6·71%).

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[16] F. Ullman and O. Fodor, *Liebig's Ann.* **380**, 317 (1911).