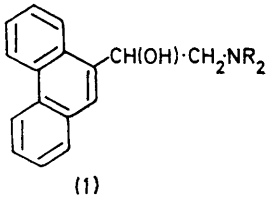
Total Synthesis of Acephenanthren-5-one [1]

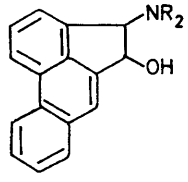
By **Robert E. Harmon,* Mohammed Mazharuddin,** and **Surendra K. Gupta,** Department of Chemistry, Western Michigan, University, Kalamazoo, Michigan 49001, U.S.A.

Acephenanthren-5-one, a key intermediate in the preparation of certain acephenanthrene amino-alcohols as potential antimalarials, has been synthesised in five stages from 1-methylphenanthrene.

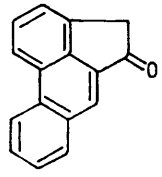
THE appearance of drug-resistant *falciparum* malaria has stimulated the search for new antimalarials. Coatney *et al.*[2] have discussed the efficacy of many simple phenanthrene-9-methanols (1) against *Plasmodium gallinaceum* in chicks. As an extension of this work we were interested in the synthesis of 4-aminoacephenanthren-5-ols (2) as potential anti-malarials. This required the total synthesis of acephenanthren-5-one (3) as the key intermediate. Our initial approach, involving



(1)



(2)

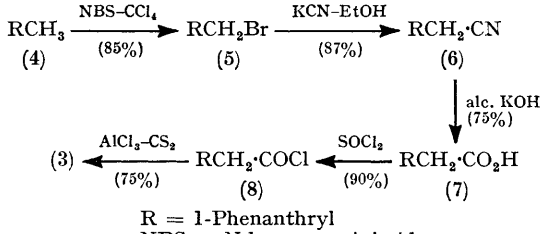


(3)

the monocondensation of substituted benzaldehydes with indan-2-one followed by photochemical ring closure, failed.[3] However, the synthesis outlined in the Scheme was successful.

A three-step low-yield synthesis of compound (5) has been described previously.[4] Hydrolysis of the cyano-compound (6) with hydrochloric or sulphuric acid (conc. acid–water; 1 : 1) was not satisfactory because it led to the formation of much tarry material from which the desired phenanthrene-1-acetic acid (7) could be isolated in only low yield; this difficulty was overcome as shown.

Treatment of compound (7) with polyphosphoric acid,[5] hydrofluoric acid,[6] thionyl chloride–tin(IV) chloride,[7] phosphorus pentachloride–tin(IV) chloride,[8] or



R = 1-Phenanthryl
NBS = *N*-bromosuccinimide

SCHEME

aluminium chloride failed to give a satisfactory yield of compound (3).

All the compounds involved in this synthesis were well characterised by spectroscopic data and elemental analysis.

EXPERIMENTAL

M.p.s were determined with a Thomas-Hoover apparatus. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis. A Beckman IR-8 spectrophotometer was used for recording the i.r. spectra. The n.m.r. spectra were obtained on a Varian A-60 spectrometer with deuteriochloroform or carbon tetrachloride as solvent and tetramethylsilane as internal standard. Mass spectral data were obtained on an Atlas CH-4 spectrometer at the Upjohn Company, Kalamazoo, Michigan. Silica gel G

[1] R. E. Harmon, M. Mazharuddin, S. K. Gupta, and H. N. Subbarao, Abstracts, 164th National Meeting of the American Chemical Society, New York, Sept. 1972,

[2] G. R. Coatney, W. C. Cooper, N. Bieddy, and J. Greenbert, 'Survey of Antimalarial Agents,' Public Health Monograph No. 9, Washington, D.C., 1953.

[3] R. E. Harmon, H. N. Subbarao, and S. K. Gupta, *J. Org. Chem.*, in the press.

[4] W. E. Bachmann, *J. Amer. Chem. Soc.*, 1935, **57**, 1381.

[5] A. J. Birch, R. Jaeger, and R. Robinson, *J. Chem. Soc.*, 1945, 582.

[6] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272

[7] T. E. Young and C. R. Hamel, *J. Org. Chem.*, 1970, **35**, 816.

[8] A. Rahman and O. L. Tomberi, *Chem. and Ind.*, 1968, 1840.

(Brinkman Instruments) was used for t.l.c., either on glass slides or 6 × 20 cm² glass plates. Spots on plates were detected by use of iodine vapour. Column chromatography was carried out on a 5 × 40 cm² glass column packed with silica gel or alumina as specified. A Hanovia photochemical reactor consisting of a u.v. lamp with a Pyrex filter contained in a quartz well was used for the photochemical cyclization of *trans-o*-methylstilbene.[9]

1-*Bromomethylphenanthrene* (5).—A solution of compound (4) (1·92 g, 0·01 mol), *N*-bromosuccinimide (1·78 g, 0·01 mol), and benzoyl peroxide (120 mg) in dry carbon tetrachloride (125 ml) was refluxed with stirring for 2 h, then cooled to room temperature. Precipitated succinimide was removed and the filtrate was evaporated under reduced pressure. Decolourization of the residue with activated charcoal and recrystallization from n-hexane afforded light brown needles (2·3 g, 85%) of 1-bromomethylphenanthrene (5), m.p. 95—96° (lit.,[4] 97°), δ ($CDCl_3$) 4·83 (2H, s, CH_2Br), 7·4—8·1 (7H, m, aromatic), and 8·4—8·7 (2H, m, 4- and 5-H).

1-*Cyanomethylphenanthrene* (6).—Compound (5) (1·35 g, 0·005 mol), potassium cyanide (400 mg, 0·006 mol), and 95% ethanol (40 ml) were refluxed with stirring for 5 h. The mixture was cooled to room temperature and filtered, and the solid was washed with warm (40°) ethanol. The filtrate was evaporated to dryness under reduced pressure and the residue extracted with chloroform (75 ml). The extract was washed with water (3 × 30 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Recrystallization of the residue from benzene–petroleum (b.p. 30—60°) gave light brown needles (0·9 g, 87%) of 1-*cyanomethylphenanthrene* (6), m.p. 130—131°; $\nu_{max.}$ ($CHCl_3$) 2240 cm^{-1} (C≡N); δ ($CDCl_3$) 3·9 (2H, s, CH_2·CN), 7·4—7·9 (7H, m, aromatic), and 8·4—8·7 (2H, m, 4- and 5-H) (Found: C, 87·95; H, 5·25; N, 6·3. $C_{16}H_{11}N$ requires C, 88·15; H, 5·1; N, 6·45%).

Phenanthrene-1-*acetic Acid* (7).—A solution of the nitrile (6) (1·085 g, 0·005 mol) in ethanolic 25% potassium hydroxide (50 ml) was refluxed with stirring for 4 h, cooled to room temperature, and poured over crushed ice (*ca.* 50 g). The turbid solution was acidified with 1 : 1 water–conc. hydrochloric acid and the precipitate was filtered off and dried. Recrystallization from petroleum (b.p. 30—60°) gave crystals (0·87 g, 75%) of *phenanthrene*-1-*acetic acid* (7), m.p. 190—191°; $\nu_{max.}$ (Nujol) 1680 cm^{-1} (C=O); δ ($CDCl_3$) 4·0 (2H, s, CH_2·CO_2H), 7·4—8·0 (7H, m, aromatic), 8·5—8·8 (2H, m, 4- and 5-H), and 9·0 (1H, m, CO_2H) (Found: C, 81·35; H, 5·25. $C_{16}H_{12}O_2$ requires C, 81·35; H, 5·1%).

Phenanthrene-1-*acetyl Chloride* (8).—Thionyl chloride (5·0 g, 0·45 mol) was added dropwise with stirring during 10 min to a solution containing compound (7) (2·3 g, 0·01 mol), pyridine (5 ml), and anhydrous ether (80 ml), at 0—15°. The solution was stirred at room temperature for 2 h and then refluxed for 1 h, filtered, and evaporated to dryness under reduced pressure. Thionyl chloride and/or hydrogen chloride were removed by repeated azeotropic distillation with benzene. The residue, upon trituration with 1 : 1 ether–petroleum, gave *phenanthrene*-1-*acetyl chloride* (8) as a light yellow solid (2·3 g, 90%), m.p. 81—82°, $\nu_{max.}$ (Nujol) 1780 cm^{-1} (C=O), δ ($CDCl_3$) 4·52 (2H, s, CH_2·COCl), 7·4—8·0 (7H, m, aromatic), and 8·5—8·8 (2H, m, 4- and 5-H).

Acephenanthren-5-*one* (3).—A solution of the acid chloride (8) (1·27 g, 0·005 mol) in carbon disulphide (25 ml) was added dropwise to a stirred and cooled (0°) suspension of anhydrous aluminium chloride (0·67 g, 0·005 mol) in carbon disulphide (30 ml). During the addition (15 min) the colour of the mixture changed from light yellow to dark brown. The mixture was allowed to warm to room temperature, stirred for 2·5 h, then poured with stirring over crushed ice containing 5% hydrochloric acid. The organic layer was separated and the aqueous layer extracted with carbon disulphide (30 ml). The combined organic portion was washed with water (2 × 40 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure giving a yellow-orange solid which showed one major spot and some minor spots on t.l.c. A solution of this solid in dichloromethane was purified by column chromatography over neutral alumina. Benzene eluted a yellow crystalline solid. Recrystallization from petroleum (b.p. 30—60°) gave *acephenanthren*-5-*one* (3) as needles, m.p. 150—151°, $\nu_{max.}$ (Nujol) 1720—1725 cm^{-1} (C=O), δ ($CDCl_3$) 4·52 (2H, s, CH_2·CO), 7·2—8·1 (7H, m, ArH, aromatic), 8·25—8·7 (2H, m, 4- and 5-H), *m/e* 218 (Found: C, 88·15; H, 4·45. $C_{16}H_{10}O$ required C, 88·05; H, 4·6%).

This work was supported by the U.S. Army Medical Research and Development Command.

[2/2031 *Received*, 30*th August*, 1972]

[9] C. S. Wood and F. B. Mallory, *J. Org. Chem.*, 1964, **29**, 3373.