69. *New Syntheses of Heterocyclic Compounds. Part XV.** 9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrenes.*

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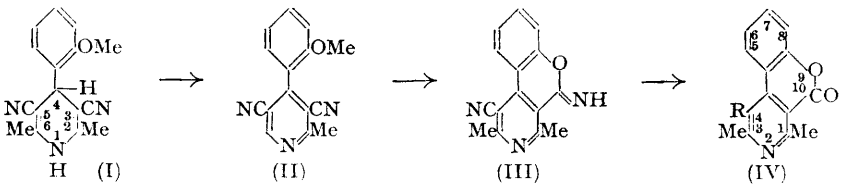
A new extension of the Hantzsch–Meyer–Mohr group of pyridine syntheses is reported whereby certain derivatives of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene may be obtained. The limitations of the method are indicated and the nitration of the parent ring system is described.

Reduced forms of the 9 : 10-dihydro-2-aza-9-oxaphenanthrene ring system,† which bear a formal resemblance to the psychogenic drugs of the cannabinol group, have formed the object of study. Work on the fully aromatic nucleus, in contrast, appears to be



confined to the observations of Kahn, Petrow, Rewald, and Sturgeon (*J.*, 1949, 2128), who obtained (IV; R = H) while attempting ring closure of 4-*o*-methoxyphenyl-2 : 6-dimethylpyridine-3-carboxylic acid to the corresponding methoxy-2-azafluorenone. We have, therefore, carried out some preparative experiments in this field, and now report a novel synthesis whereby certain derivatives of (IV) may be obtained.

Condensation of *o*-methoxybenzaldehyde with 2 mols. of β-aminocrotononitrile in glacial acetic acid (cf. Part XIII, *loc. cit.*) led to the formation of 3 : 5-dicyano-1 : 4-dihydro-4-*o*-methoxyphenyl-2 : 6-dimethylpyridine (I) in nearly quantitative yield. Oxidation of this with chromium trioxide furnished the corresponding pyridine derivative (II). The latter, on being heated with 48% hydrobromic acid, in which it is freely soluble, passed smoothly into 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene (IV; R = CN), presumably by way of the intermediate (III). By employing β-aminocinnamonitrile in the synthesis, 4-cyano-9 : 10-dihydro-10-keto-1 : 3-diphenyl-2-aza-9-oxaphenanthrene was likewise obtained in excellent overall yield. Hydrolysis to the corresponding 4-carboxylic acids, however, could not be effected, the nitriles being recovered unchanged after even 8 hours' refluxing with concentrated hydrobromic acid.

Mononitration was readily effected by heating (IV; R = CN) with fuming nitric acid on the water-bath. The product, obtained in nearly quantitative yield, was assigned the constitution of 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene (see below). In marked contrast to the un-nitrated compound (IV; R = CN), treatment with boiling hydrobromic acid led to hydrolysis of the cyano-group with formation of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene-4-carboxylic acid, characterised as its ethyl ester. The structure of this compound was rigidly confirmed by its alternative synthesis from 2-methoxy-5-nitrobenzaldehyde and β-aminocrotonitrile. Its decarboxylation, which occurred with explosive facility, furnished 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene in low yield, identical with the product obtained by direct nitration of (IV; R = H), the constitution of which is accordingly established.

The foregoing nitro-derivatives retained the characteristic property of nitrophenols in being freely soluble in alkali with production of intensely yellow salts formed, no doubt, by

* Part XIV, *J.*, 1952, 228.

† *Note on nomenclature :* In view of the structural similarity between (IV) and the diazaphenanthrenes described in Parts V, VII, and XIII of this series (Petrow, *J.*, 1946, 200, 884; Courts and Petrow, *J.*, 1952, 1), the nomenclature of (IV) is based on phenanthrene and not on pyridinocoumarin.

rupture of the 9 : 10-lactone bridge, which was reconstituted on acidification. Reduction of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene, and of its 4-cyano-derivative with reduced iron in acidulated ethanol gave the corresponding amines in good yield.

Only a limited range of compounds proved capable of synthesis by this route. 2 : 4-Dimethoxybenzaldehyde behaved in the expected manner, furnishing 3 : 5-dicyano-4-(2 : 4-dimethoxyphenyl)-2 : 6-dimethylpyridine after oxidation. Short treatment of this compound with hydrobromic acid gave 4-cyano-9 : 10-dihydro-10-keto-7-methoxy-1 : 3-dimethyl-2-aza-9-oxaphenanthrene, the corresponding 7-hydroxy-compound being obtained if contact with the hydrolytic agent was prolonged beyond 30 minutes. The pyridine derivatives derived from 2 : 4-dimethoxy-5-nitro- and 2 : 5-dimethoxy-6-nitrobenzaldehyde, however, failed to yield oxazaphenanthrenes on treatment with hydrobromic acid, unidentified products being obtained. 2-Methoxy-1-naphthaldehyde did not appear to react with β-aminocrotononitrile, an unexpected result as the unsubstituted aldehyde behaves normally in the Hantzsch condensation (Kahn, Petrow, Rewald, and Sturgeon, *loc. cit.*). Attempts to prepare (IV; R = COMe) also proved unsuccessful. *o*-Methoxybenzaldehyde failed to condense with acetylacetone (cf. Part XIII; Courts and Petrow, *loc. cit.*). Somewhat better results were obtained employing 2-methoxy-5-nitrobenzaldehyde, which gave 3-(2-methoxy-5-nitrobenzylidene)pentane-2 : 4-dione in 73% yield. Reaction with β-aminocrotononitrile, followed by oxidation gave 5-acetyl-3-cyano-4-(2-methoxy-5-nitrophenyl)-2 : 6-dimethylpyridine, but ring closure of this compound to the corresponding azaoxaphenanthrene could not be accomplished.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss.

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-o-*methoxyphenyl*-2 : 6-*dimethylpyridine* (I), prepared by heating *o*-methoxybenzaldehyde (4 g.), β-aminocrotononitrile (5·25 g.), and glacial acetic acid (25 ml.) under reflux for 1 hour, formed prismatic needles, m. p. 190°, from acetic acid–light petroleum (Found: C, 72·2; H, 5·6; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·8%).

3 : 5-*Dicyano*-4-o-*methoxyphenyl*-2 : 6-*dimethylpyridine* (II), large pale yellow plates (74%) (from glacial acetic acid), m. p. 177° (Found: C, 73·0; H, 4·7; N, 15·8. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%), was obtained by oxidising the foregoing compound (5 g.) in hot glacial acetic acid (15 ml.) with chromium trioxide (1·5 g.) added dropwise in aqueous solution.

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene* (IV; R = CN) separated (82%) when the foregoing compound (9 g.) was heated with 48% hydrobromic acid (60 ml.) under reflux for 2 hours. It formed light brown needles, m. p. 281°, from glacial acetic acid (Found: C, 71·9; H, 3·9; N, 11·0. $C_{15}H_{10}O_2N_2$ requires C, 71·7; H, 4·0; N, 11·2%).

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-o-*methoxyphenyl*-2 : 6-*diphenylpyridine*, obtained in nearly quantitative yield by gently heating *o*-methoxybenzaldehyde (2·25 g.), β-aminocinnamonitrile (5 g.), and glacial acetic acid (15 ml.) under reflux for 20 minutes, formed lemon-yellow prisms (from ethanol), m. p. 242·5° (Found: C, 80·2; H, 5·0; N, 10·7. $C_{26}H_{19}ON_3$ requires C, 80·2; H, 4·9; N, 10·8%).

3 : 5-*Dicyano*-4-o-*methoxyphenyl*-2 : 6-*diphenylpyridine*, obtained (80%) by treating a hot suspension of the foregoing compound (5 g.) in glacial acetic acid (30 ml.) with chromium trioxide (1·5 g.) dissolved in a little water, separated from a large volume of glacial acetic acid in faintly yellow needles, m. p. 219—220° (Found: C, 80·7; H, 4·3; N, 11·0. $C_{26}H_{17}ON_3$ requires C, 80·6; H, 4·4; N, 10·8%).

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*diphenyl*-2-*aza*-9-*oxaphenanthrene* was obtained (40%) by heating the foregoing dinitrile (250 mg.) with 48% hydrobromic acid (100 ml.) for 3 hours under reflux, most of the solid dissolving. After cooling, the mixture was filtered through sintered glass and poured into water (150 ml.), and the precipitated solids were crystallised from glacial acetic acid, whereupon feathery needles were obtained, having m. p. 299° (Found: C, 79·9; H, 3·4; N, 7·2. $C_{25}H_{14}O_2N_2$ requires C, 80·2; H, 3·7; N, 7·5%).

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*, obtained by warming a solution of (IV; R = CN) (1 g.) in fuming nitric acid (5 ml.) for 7—8 minutes on the water-bath, followed by precipitation on to crushed ice, formed flat needles (from ethanol),

m. p. 191° (Found : C, 60·7; H, 2·8; N, 13·9. $C_{15}H_9O_4N_3$ requires C, 61·0; H, 3·0; N, 14·2%). An aqueous solution of the compound gave a transient red colour with 1 drop of ferric chloride solution.

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine*, obtained in nearly quantitative yield by heating 2-methoxy-5-nitrobenzaldehyde (4·5 g.), β-aminocrotononitrile (4 g.), and glacial acetic acid (20 ml.) under reflux for 15 minutes, formed needles, m. p. 226—229°, from absolute ethanol (Found : C, 62·0; H, 4·4; N, 18·1. $C_{16}H_{14}O_3N_4$ requires C, 61·9; H, 4·5; N, 18·1%).

3 : 5-*Dicyano*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine* formed pale yellow needles (90%), m. p. 222·5—223°, from ethanol (Found : C, 62·4; H, 4·0; N, 18·4. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%).

9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*-4-*carboxylic Acid*.—(i) The foregoing compound (4 g.) was heated under reflux with 48% hydrobromic acid (40 ml.) for 8 hours, the solution was poured on ice, and the precipitated solids were crystallised from 100 vols. of glacial acetic acid. The *acid* (25%) formed small dark yellow crystals, m. p. 264° (vigorous decomp.) (Found : C, 56·8; H, 3·4; N, 8·6. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2; N, 8·9%).

(ii) When 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene (200 mg.) was heated with 48% hydrobromic acid (3 ml.) under reflux for 2 hours, and the solution poured on crushed ice, 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene-4-carboxylic acid was obtained, m. p. 264°, alone or on admixture with a sample prepared by method (i).

The acid (1 g.), suspended in absolute ethanol (200 ml.), was treated with a stream of dry hydrogen chloride (*ca.* 8 g.), the material passing into solution. After 8 hours' heating under reflux the bulk of the solvent was removed by distillation, and water (50 ml.) added. After addition of dilute aqueous ammonia until faintly acid, the mixture was set aside overnight; then the precipitated solids were collected and crystallised from benzene. The *ethyl* ester formed pale yellow plates (68%), m. p. 159—160° (Found : N, 8·0. $C_{17}H_{14}O_6N_2$ requires N, 8·2%).

9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*.—(i) 9 : 10-Dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene (IV; R = H) was prepared by the following improved procedure (cf. Kahn *et al.*, *loc. cit.*) : 4-*o*-Methoxyphenyl-2 : 6-dimethylpyridine-3-carboxylic acid hydrogen sulphate (10 g.) was cautiously treated with thionyl chloride (50 ml.). When the initial reaction had subsided the mixture was heated under reflux for 10 minutes. After removal of excess of thionyl chloride under reduced pressure, dilute aqueous ammonia was added until the mixture was just alkaline to litmus, and the precipitated solids were collected and crystallised from benzene, giving (IV; R = H), m. p. 203° (Found : N, 6·3. Calc. for $C_{14}H_{11}O_2N$: N, 6·2%) alone or on admixture with an authentic specimen.

The foregoing compound (250 mg.), dissolved in fuming nitric acid (5 ml.), was heated on the water-bath for 2 hours. The mixture was then poured into water (10 ml.). The precipitated solids, on crystallisation from alcohol, gave 9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene* (73%), small needles, m. p. 241° (Found : C, 62·1; H, 3·7; N, 10·4. $C_{14}H_{10}O_4N_2$ requires C, 62·2; H, 3·7; N, 10·4%).

(ii) When the 6-nitro-derivative of (IV; R = CO_2H) (see above) was cautiously heated above its m. p., 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene was obtained, having m. p. 241° alone or on admixture with a sample prepared by method (i).

6-*Amino*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene*, obtained in nearly quantitative yield by heating the foregoing nitro-compound (30 mg.) in ethanol (20 ml.) containing 1 drop of concentrated hydrochloric acid with reduced iron (100 mg.) under reflux for 20 minutes and then concentrating the filtrate until crystallisation commenced, formed feathery yellow needles (from ethanol), m. p. 281·5° (decomp.) (Found : C, 69·9; H, 5·0; N, 11·6. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%).

The *acetyl* derivative formed needles (84%) (from chloroform), m. p. 286·5—287° (Found : C, 67·6; H, 5·0. $C_{16}H_{14}O_3N_2$ requires C, 68·0; H, 5·0%).

6-*Amino*-4-*cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene*, prepared by reduction of the corresponding nitro-compound (500 mg.) in ethanol (50 ml.) containing 2 drops of concentrated hydrochloric acid with reduced iron (1·5 g.) under reflux for 40 minutes, separated from the filtrate on cooling in lemon-yellow needles (62%), m. p. >310° (Found : C, 67·4; H, 4·2; N, 15·5. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·8%). The compound diazotises and couples with alkaline β-naphthol in the usual manner.

3 : 5-*Dicyano*-**1** : 4-*dihydro*-**4**-(2 : 4-*dimethoxyphenyl*)-**2** : 6-*dimethylpyridine* formed needles (80%), m. p. 210—211°, from absolute ethanol (Found : C, 69·4; H, 5·8; N, 14·0. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·8; N, 14·2%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxyphenyl*)-**2** : 6-*dimethylpyridine* was obtained in nearly quantitative yield as lustrous flat yellow needles, m. p. 134·5°, from absolute ethanol (Found : C, 69·8; H, 5·2; N, 14·3. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%).

4-*Cyano*-**9** : 10-*dihydro*-**7**-*methoxy*-**1** : 3-*dimethyl*-**2**-*aza*-**9**-*oxaphenanthrene*, obtained by heating the foregoing compound (3·5 g.) with 48% hydrobromic acid for 30 minutes, formed small needles, m. p. 236°, from absolute ethanol (Found : C, 68·1; H, 4·3; N, 10·2; OMe, 12·7. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0; OMe, 11·1%).

Hydrolysis for a further 4 hours furnished 4-*cyano*-**9** : 10-*dihydro*-**7**-*hydroxy*-**1** : 3-*dimethyl*-**2**-*aza*-**9**-*oxaphenanthrene hemihydrate*, buff spear-shaped needles, m. p. 271—273° (decomp.), from ethanol containing a few drops of ammonia (Found : C, 65·9; H, 4·1; N, 10·0. $C_{15}H_{10}O_3N_2,\frac{1}{2}H_2O$ requires C, 65·5; H, 4·0; N, 10·2%).

The *acetyl* derivative formed light brown needles (from aqueous acetic acid), m. p. 201° (Found : C, 66·1; H, 4·0; N, 9·0. $C_{17}H_{12}O_4N_2$ requires C, 66·2; H, 3·9; N, 9·1%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxy*-5-*nitrophenyl*)-**1** : 4-*dihydro*-**2** : 6-*dimethylpyridine* formed faintly yellow tetragonal prisms (80%) from absolute ethanol and had m. p. 192—193° (dried at 120° for 24 hours) (Found : C, 60·4; H, 4·8; N, 16·5. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxy*-5-*nitrophenyl*)-**2** : 6-*dimethylpyridine* formed faintly yellow prismatic needles (90%), m. p. 229°, from ethanol (Found : C, 60·9; H, 4·3; N, 16·6. $C_{17}H_{14}O_4N_4$ requires C, 60·4; H, 4·1; N, 16·6%).

3 : 5-*Dicyano*-4-(2 : 5-*dimethoxy*-6-*nitrophenyl*)-**1** : 4-*dihydro*-**2** : 6-*dimethylpyridine* formed small lemon-yellow needles (62%) (from ethanol), m. p. 268—273° (decomp.) (Found : C, 60·0; H, 4·7; N, 16·6. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

3 : 5-*Dicyano*-4-(2 : 5-*dimethoxy*-6-*nitrophenyl*)-**2** : 6-*dimethylpyridine* was obtained in flat, pale yellow needles (90%), m. p. 229—229·5°, from ethanol (Found : C, 60·4; H, 4·0; N, 16·3. $C_{17}H_{14}O_4N_4$ requires C, 60·4; H, 4·1; N, 16·6%).

3-(2-*Methoxy*-5-*nitrobenzylidene*)*pentane*-**2** : 4-*dione*, prepared by dissolving finely powdered 2-methoxy-5-nitrobenzaldehyde (3 g.) in acetylacetone, adding 5 drops of piperidine, and leaving the mixture for 4 hours in a vacuum-desiccator, formed large flat needles (73%), m. p. 122—122·5°, from ethanol (Found : C, 59·5; H, 5·0; N, 5·3. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 4·9; N, 5·3%).

5-*Acetyl*-3-*cyano*-**1** : 4-*dihydro*-**4**-(2-*methoxy*-5-*nitrophenyl*)-**2** : 6-*dimethylpyridine*, prepared by fusing the foregoing compound (1·1 g.) with β-aminocrotononitrile (300 mg.), separated from absolute ethanol in yellow needles (71%), m. p. 211—211·5° (Found : C, 62·4; H, 5·3; N, 12·6. $C_{17}H_{17}O_4N_3$ requires C, 62·4; H, 5·2; N, 12·8%).

5-*Acetyl*-3-*cyano*-4-(2-*methoxy*-5-*nitrophenyl*)-**2** : 6-*dimethylpyridine* formed small needles (88%), m. p. 166°, from ethanol (Found : C, 62·4; H, 4·7; N, 13·1. $C_{17}H_{15}O_4N_3$ requires C, 62·8; H, 4·6; N, 12·9%).

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[*Received, October 15th*, 1951.]