SYNTHETICAL EXPERIMENTS IN THE GROUP OF SYMPATHOMIMETICS

Part II. Poly- and Hetero-cyclic Ring Systems

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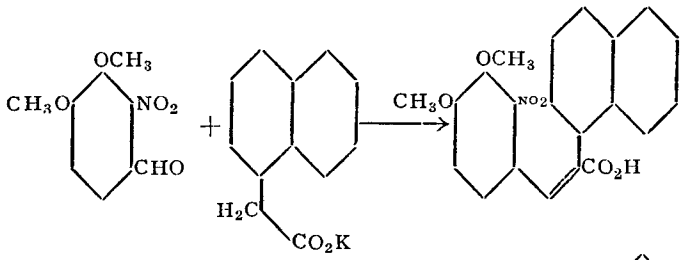
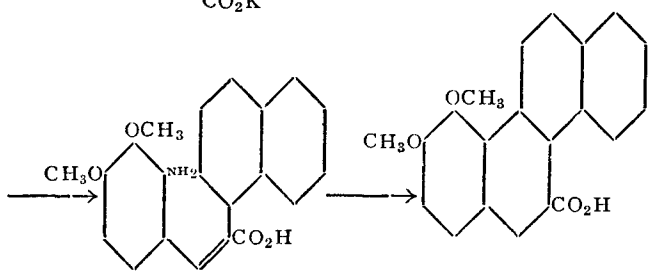
AN earlier paper described the synthesis of some naphthalene compounds,[1] possessing the requisite structure necessary for sympathomimetic activity. In accordance with the programme of the study of the relation between chemical constitution and physiological activity, the present communication is concerned with attempts to synthesise a new group of sympathomimetically active amines in which the customary benzene nucleus of such substances was replaced by the phenanthrene, chrysene, quinoline and isoquinoline rings. In addition, the synthesis of a few more naphthalene compounds of this group was attempted incidentally.

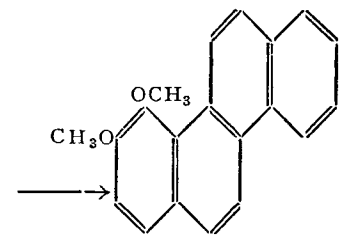
It may be well to stress the fact that the scheme so far as it relates to the new ring-systems involves two distinct steps. First, the choice has to be made of starting materials containing the ring-systems with the requisite groups in suitable positions and without the β-amino ethyl side-chain. Secondly, the methods for the introduction of the aminoethyl chain in a favourable position in these substances have to be explored.

Actually, four (Nos. I–IV) of the starting materials (I–VI) chosen had to be synthesised for the first time for purposes of the present study, as under the first category. The additional naphthalene compounds that were included in the scheme were α-naphthol and 1 : 2-dihydroxy naphthalene.

The classical method of Pschorr as modified by Bogert and co-workers[2] was adopted for the synthesis of 3 : 4-dimethoxy chrysene (I), starting from *o*-nitro-veratraldehyde[3] and α-naphthyl acetic acid.[4]

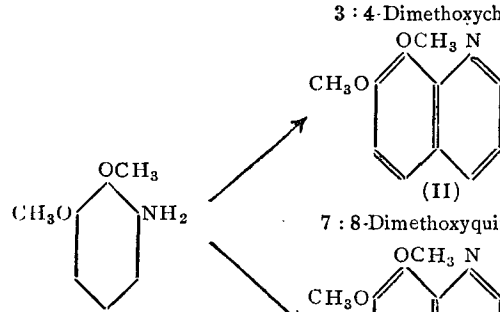






(I)

3 : 4-Dimethoxychrysene

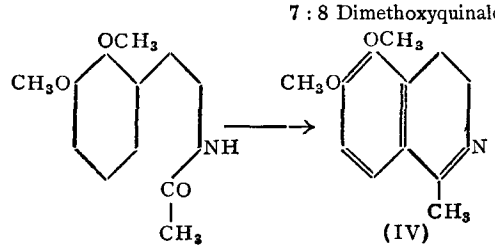


(II)

7 : 8-Dimethoxyquinoline

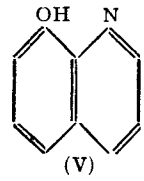
(III)

7 : 8 Dimethoxyquinaldine



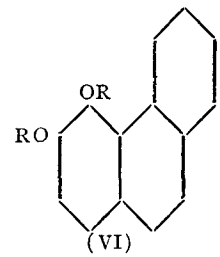
(IV)

1-Methyl-3 : 4-dihydro-
5 : 6-dimethoxy-isoquinoline



(V)

8-Hydroxyquinoline



(VI)

Morphol (R=H) ; Morphol dimethyl ether ($R=CH_3$)

The dimethoxy quinoline (II) and the dimethoxy quinaldine (III) were prepared in good yields from *o*-amino-veratrole[5] by application of the Skraup and the Doebner-Miller reactions respectively. The dimethoxy isoquinoline (IV) was obtained by cyclisation of the N-acetyl derivative of 2 : 3-dimethoxy phenylethylamine[6] by means of the usual Bischler-Napieralsky procedure.

In order to carry out the second stage of the scheme, it was decided, in the first instance, to examine the applicability to the present case of an apparently direct and elegant method, developed by Hinsberg,[7] consisting in the smooth condensation of phenols and phenol ethers with amino acetal. The reaction, which was studied under a variety of conditions, was successful so far as α-naphthol was concerned, but gave rise to by-products or did not proceed at all in the case of others. α-Naphthol gave in good yields a hydrochloride, $(HO \cdot C_{10}H_6)_2 CH \cdot CH_2NH_2, HCl$. The products obtained from 1 : 2-dihydroxy naphthalene and 3 : 4-dihydroxy phenanthrene (VI, R = H) were characteristically unstable and non-crystalline and only in the case of the latter was it possible to prepare a stable picrate. The attempts with 8-hydroxy-quinoline (V) proved fruitless, the original compound being recovered unreacted. The condensation of the dimethoxy heterocyclics (II, III, IV) with aminoacetal was expected to yield products having an ethanol amine chain, $R \cdot CH(OH) \cdot CH_2 \cdot NH_2$, which could then be demethylated to give analogues of 'arterenol'. This expectation has, however, not been realised, the dimethoxy hetero-cyclics like 8-hydroxyquinoline being unreactive.

The Friedel-Craft reaction between morphol dimethyl ether (VI, R = CH_3) and hippuryl chloride gave 3 : 4-dimethoxy-N-benzoyl-ω-aminoacetophenanthrone, but, however, in poor yields. Hence the use of the material for the ultimate synthesis of 3 : 4-dihydroxy phenanthryl ethanolamine could not be contemplated.

It is hoped to make further trials to condense aminoacetal with the various compounds described above changing, necessarily, the experimental

conditions. It is also proposed to investigate other methods for the introduction of the β-aminoethyl side-chain in these ring-systems. These studies will form the subject of a further communication.

Experimental

Synthesis of 3 : 4-*dimethoxychrysene* (I):

α-*Naphthyl*-2-*nitro*-3 : 4-*dimethoxycinnamic acid.*—A mixture of potassium α-naphthyl acetate (44. g.), 2-nitroveratraldehyde (39·5 g.) and freshly distilled acetic anhydride (275 c.c.) was heated in an oil-bath at 105–10° for 24 hours, cooled and the excess of acetic anhydride cautiously decomposed with water. The resulting acrylic acid was purified through an ammoniacal solution and crystallised from alcohol as yellow needles, m.p. 238–39° (decomp.); yield 56 g. (Found: C, 66·31; H, 4·39. $C_{21}H_{17}O_6N$ requires C, 66·49; H, 4·49 per cent.)

α-*Naphthyl*-2-*amino*-3 : 4-*dimethoxy-cinnamic acid.*—A mixture of ferrous sulphate hexahydrate (303 g.), liquor ammonia (70 c.c.) and water (1 litre) was boiled and treated with a mixture of the nitro-acid (55 g.) and concentrated ammonia. Ammonia (550 c.c.) was then added in the course of the next half hour, followed by more (150 c.c.) during a further 45 minutes. The reaction mixture was filtered hot, and the residue washed thrice with hot dilute ammonia. The amino-acid was liberated by addition of acetic acid and crystallised from alcohol as almost colourless, prismatic needles, m.p. 201° (decomp.); yield 35 g. (Found: C, 71·72; H, 5·10. $C_{21}H_{19}O_4N$ requires C, 72·21; H, 5·45 per cent.)

3 : 4-*Dimethoxy-chrysene*-11-*carboxylic acid.*—The crude amino-acid (32 g.) suspended in *iso*amyl ether (200 c.c.) was treated with concentrated sulphuric acid (4·9 c.c.) followed by freshly prepared *iso*amyl nitrite (12·2 c.c.), and the mixture shaken for 3 hours when it almost solidified. It was then added to a solution of sodium hypophosphite (70 g.) in water (70 c.c.) containing a little active copper at 40–50°, heated upto 80° and kept at 80–90° with stirring for 1 hour, poured into excess of ammonia (2 liters), filtered and the aqueous solution acidified with hydrochloric acid. The crude acid (20 g.) was recrystallised from acetone, benzene-petroleum ether and finally alcohol as colourless needles, m.p. 200–02° (decomp.). (Found: C, 71·55; H, 5·05. $C_{21}H_{16}O_4H_2O$ requires C, 71·99; H, 5·15 per cent.)

3 : 4-*Dimethoxychrysene* (I).—The above crude acid (5 g.) was refluxed with quinoline (30 c.c.) and a little copper powder for 1½ hours and worked up in the usual way for a neutral substance. The dimethoxy chrysene was obtained as a pale, viscous oil, b.p. 210–20°/ 1–2 mm.; yield 3·2 g. (Found: C, 82·74; H, 5·38. $C_{20}H_{16}O_2$ requires C, 83·83; H, 5·56 per cent.)

The *picrate* crystallised from alcohol as yellow needles, m.p. 153–55° (decomp.). (Found: C, 58·19; H, 4·17. $C_{26}H_{19}O_9N_3H_2O$ requires C, 58·33; H, 3·92 per cent.)

7 : 8-*Dimethoxyquinoline* (*II*).—Glycerine (36·7 g.), nitrobenzene (6·7 g.) concentrated sulphuric acid (26·7 g.) and *o*-amino-veratrole (12 g.) were heated together on the water-bath for 1 hour, transferred to a metal-bath at 100° and the temperature gradually raised to 135°, when a violent reaction set in. The flask was removed and after violence had subsided was heated at 130–35° for 3 hours. The mixture was poured into water, extracted thrice with ether, the aqueous layer cooled, basified with excess of dilute sodium hydroxide and extracted thoroughly with ether. The extract was washed, dried over anhydrous sodium carbonate and the solvent distilled off. The residual oil was heated with acetic anhydride (10 c.c.) and a little sodium acetate on the water-bath for 2 hours, poured into water and extracted with ether. The aqueous solution was cooled, basified with excess of sodium hydroxide and repeatedly extracted with ether. The ether extract was washed, dried and distilled. The dimethoxyquinoline was a faintly yellow oil b.p. 148–50°/3 – 4 mm.; yield 8·5 g. (Found: C, 69·20; H, 5·52. $C_{11}H_{11}O_2N$ requires C, 69·84; H, 5·82 per cent.)

The *picrate* crystallised from alcohol in yellow needles, m.p. 182–84° after softening at 180°. (Found: N, 13·39. $C_{17}H_{14}O_9N_4$ requires N, 13·40 per cent.)

The *methiodide* crystallised from chloroform-benzene in yellow needles, m.p. 182° (decomp.) Found: I, 37·86. $C_{12}H_{14}O_2NI$ requires I, 38·37 per cent.)

7 : 8-*Dimethoxyquinaldine* (*III*).—A mixture of *o*-amino-veratrole (15·3 g.), concentrated hydrochloric acid (35 c.c.) and zinc chloride (6 g.) was cooled, treated with freshly distilled paraldehyde (20 g.) and heated on the boiling water-bath for 1½ hours, transferred to a metal-bath at 100°, and the temperature gradually raised to 130° and refluxed at 130–35° for 4 hours, cooled and poured into water and worked up in the same way as for the quinoline derivative (II). The quinaldine was obtained as a thick yellow oil, b.p. 147–48°/2–3 mm.; yield 7·5 g. (Found: C, 71·23; H, 6·12. $C_{12}H_{13}O_2N$ requires C, 70·94; H, 6·40 per cent.)

The *picrate* separated from alcohol in yellow needles, m.p. 155–56° (decomp.). (Found: N, 11·88. $C_{18}H_{16}O_9N_4$ requires N, 12·96 per cent.)

The *methiodide* crystallised from chloroform containing a trace of methanol in yellow needles, m.p. 176–77° (decomp.). (Found: I, 35·99. $C_{13}H_{16}O_2NI$ requires I, 36·81 per cent.)

1-*Methyl*-3 : 4-*dihydro*-5 : 6-*dimethoxy isoquinoline* (*IV*) *and Its Derivatives*:

β-(2 : 3-*Dimethoxy*)-*phenylethyl acetamide*, prepared in the usual way, separated from benzene-petroleum ether in long, colourless needles, m.p. 64–66°. (Found: N, 6·24. $C_{12}H_{17}O_3N$ requires N, 6·28 per cent.)

The *dihydroisoquinoline* (*IV*).—A mixture of the above amide (crude m.p. 61–3°; 11·4 g.) in dry toluene (75 c.c.) and phosphorus oxychloride (30 c.c.) was gently refluxed on the sand-bath for 2 hours with the exclusion of moisture, cooled and poured on to crushed ice. The aqueous solution was extracted with ether, cooled, basified with excess of ammonia and repeatedly extracted with ether. The extract was washed, dried over anhydrous sodium carbonate and distilled. The *iso*quinoline was a faintly yellowish oil, b.p. 141–43°/3 mm.; yield 8·5 g. (Found: C, 70·11; H, 7·14. $C_{12}H_{15}O_2N$ requires C, 70·25; H, 7·32 per cent.)

The *hydrochloride* crystallised from alcohol-ether in colourless needles, m.p. 202-03° (decomp.). (Found: Cl, 14·6. $C_{12}H_{16}O_2NCl$ requires Cl, 14·16 per cent.)

The *picrate* separated from alcohol-acetic acid in yellow needles, m.p. 214° (decomp.) after slight sintering at 210°. (Found: N, 12·67. $C_{18}H_{18}O_9N_4$ requires N, 12·90 per cent.)

The *methiodide* crystallised from chloroform-benzene in colourless, silky needles, m.p. 106–07° (decomp.). (Found: I, 36·48. $C_{13}H_{18}O_2NI$ requires I, 36·60 per cent.)

1-*Methyl*-5 : 6-*dimethoxy*-1 : 2 : 3 : 4-*tetrahydroisoquinoline*.—The dihydro base (1 g.) in sulphuric acid (40 c.c. of 1 : 3) was heated with zinc dust (5 g.) on the boiling water-bath for 4 hours. The solution was cooled, basified with a large excess of ammonia and extracted with ether. The extract after washing, drying and distilling gave the tetrahydro-*iso*quinoline as a pale yellow oil; yield 1 g.

The *hydrochloride* separated from alcohol-ether in colourless needles, m.p. 213–14° (decomp.). (Found: Cl, 14·13. $C_{12}H_{18}O_2NCl$ requires Cl, 14·05 per cent.)

The *picrate* separated from alcohol in yellow, prismatic needles, m.p. 196–98° (decomp.), after sintering at 194°. (Found: N, 12·82. $C_{18}H_{20}O_9N_4$ requires N, 12·84 per cent.)

β, *β*-*Bis* (4-*hydroxy-naphthyl*)-*ethylamine hydrochloride*.—A mixture of *α*-naphthol (2·1 g.), aminoacetal (1 g.) and glacial acetic acid (8 c.c.) was treated with concentrated hydrochloric acid (15 c.c.), allowed to stand at room temperature for 3 days and treated with hydrochloric acid till complete separation of the hydrochloride. The separated crystals were filtered,

washed with a little acetic acid followed by alcohol-ether and recrystallised from alcohol-ether as white, feathery needles, m.p. 237–38° (decomp.); yield 1·4 g. (Found: Cl, 9·20. $C_{22}H_{20}O_2NCl$ requires Cl, 9·47 per cent.)

β-(3 : 4-Dihydroxy-) phenanthryl-β-hydroxy-ethylamine.—A mixture of morphol (1·8 g.), aminoacetal (1·3 g.), acetic acid (12 c.c.) and concentrated hydrochloric acid (23 c.c.) was allowed to stand at room temperature for 3 days, poured into excess of water and filtered from considerable amount of tarry matter. The aqueous solution, after freeing from non-basic impurities by extraction with ether, was evaporated under reduced pressure. An aqueous solution of the residue on treatment with Hager's reagent gave the *picrate* as a greenish yellow powder, after washing repeatedly with alcohol and acetic acid, decomposing at 195–97°. (Found: N, 10·74. $C_{22}H_{18}O_{10}N_4$ requires N, 11·24 per cent.)

3 : 4-Dimethoxy-N-benzoyl-ω-aminoacetophenanthrone.—3 : 4-Dimethoxy-phenanthrene (VI, R = CH_3; 6 g.) in carbon bisulphide (50 c.c.) was condensed with hippuryl chloride (7 g.) in the presence of anhydrous aluminium chloride (7 g.) and worked up in the usual way. The reaction product was obtained as a thick oil which solidified in contact with alcohol-acetic acid. The ketone crystallised from acetic acid as almost colourless plates, m.p. 268–69° (decomp.). (Found: C, 74·82; H, 5·18. $C_{25}H_{21}O_4N$ requires, C, 75·18; H, 5·51 per cent.)

Summary

With a view to study the relation between chemical constitution and physiological activity, attempts have been made chiefly to synthesise a group of sympathomimetically active amines derived from phenanthrene, chrysene quinoline and *iso*quinoline ring-systems.

3 : 4-Dimethoxy chrysene, 7 : 8-dimethoxy-quinoline, 7 : 8-dimethoxy quinaldine and 1-methyl-3 : 4-dihydro-5 : 6-dimethoxy-*iso*quinoline, which were required as intermediates, have been synthesised.

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