Experiments on the Synthesis of Lysergic Acid. Part II. Derivatives of 1-Azaphenanthrene.*

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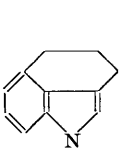
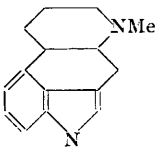
3 : 4-Trimethyleneindole (I) has been prepared by cyclising *N*-formyl-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine. A number of substituted and reduced 1-azaphenanthrenes have been prepared as intermediates for the synthesis of the ergoline ring system.

THIS paper is largely concerned with an investigation of derivatives of 1-azaphenanthrene which are related to lysergic acid and from which the ergoline system might be obtained by finally fabricating the pyrrole ring.

Initial experiments established that 3 : 4-trimethyleneindole (1 : 3 : 4 : 5-tetrahydrobenz[*cd*]indole) (I) could be prepared in 5% yield by fusing *N*-formyl-5 : 6 : 7 : 8-tetrahydro-1-naphthylamine with potassium *tert.*-butoxide. An extension of this mode of synthesis to 6-methylergoline (II) would require 8-formamido-1-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-azaphenanthrene (III) as an intermediate. This we attempted to prepare



(I)



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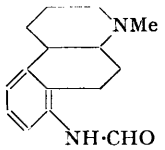


(III)

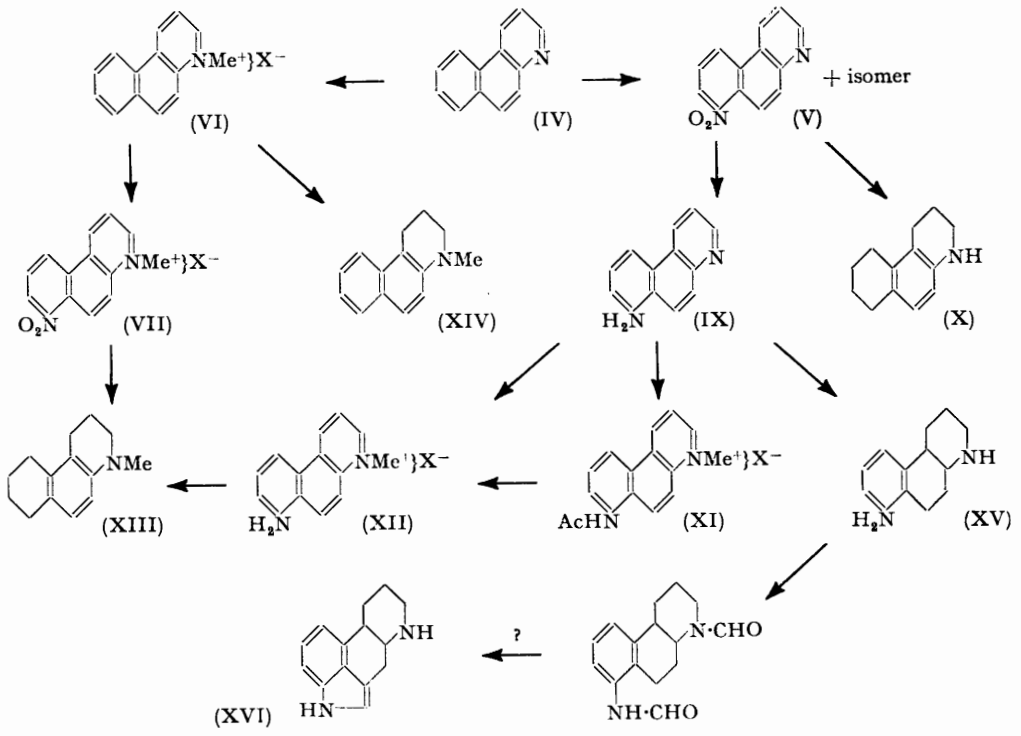
from 1-azaphenanthrene (IV), nitration of which had been shown by Armit and Robinson (*J.*, 1925, 1614) to yield the 8-nitro-derivatives (V). In our hands, the preparation of 8-nitro-1-azaphenanthrene according to the directions of Claus and Besseler (*J. pr. Chem.*, 1898, **57**, 63) and Hepner, (*Monatsh.*, 1906, **27**, 1053) gave only small yields, but under modified conditions an almost quantitative yield of mononitro-derivatives was obtained. From these, we have isolated in addition to the known 8-nitro-compound, a new isomer which has been characterised by reduction to the corresponding amine but not orientated.

Nitration of 1-azaphenanthrene methosulphate (VI; X = $MeSO_4$) proceeded in good

* Part I, preceding paper.

yield, the major product being 8-nitro-1-azaphenanthrene methosulphate (VII; X = $MeSO_4$) which was isolated as the derived picrate and identified as the chloride. The method is not so convenient as that described above. Reduction of 8-nitro-1-azaphenanthrene to the 8-amino-compound (IX) with stannous chloride as described by Claus and Besseler (*loc. cit.*) is very satisfactory and, in our view, considerably more convenient than the method of Armit and Robinson (*loc. cit.*) who used sodium sulphide in boiling aniline. Catalytic hydrogenation of the nitro-compound over Raney nickel gave an octahydro-azaphenanthrene, identified through its *N*-nitroso-derivative as the 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-isomer (X), which had been previously prepared by Bamberger and Müller (*Ber.*, 1891, **24**, 2660) by reducing 1-azaphenanthrene with sodium and amyl alcohol. The loss of the nitro-group presumably depends on the intermediate formation of 8-amino-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-azaphenanthrene, which as a benzylamine undergoes hydrogenolysis. The direct conversion of the amine (IX) into its methiodide (XII; X = I) as described by Claus and Besseler (*loc. cit.*) was found to give poor yields and a large amount of tar was formed. However, if the primary amino-group was first protected by acetylation, the acetyl methiodide (XI) was readily obtained and hydrolysis then gave the required methochloride (XII; X = Cl).

Hydrogenation of the methochloride over Raney nickel in the presence of diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108) did not lead to the required product, but proceeded with the elimination of the primary amino-group to give an octahydro-*N*-methylazaphenanthrene which, from analogy with the formation of (X) from (V), is believed to be 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-methyl-1-azaphenanthrene (XIII). This substance



was also obtained by the catalytic hydrogenation of 8-nitro-1-azaphenanthrene methochloride (VII; X = Cl). An alternative route to the required intermediate (III) appeared to lie in the nitration of 1-methyl-1 : 2 : 3 : 4-tetrahydro-1-azaphenanthrene (XIV) (Barltrop and Taylor, *loc. cit.*), but only tars were obtained from the reaction.

Success was ultimately attained by reducing 8-amino-1-azaphenanthrene with sodium and amyl alcohol. This gave 8-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-1-azaphen-

anthrene (XV), the structure of which follows from the fact that it could be diazotised and coupled with β-naphthol to give a deep red dye. The diformyl derivative of this compound was fused with potassium *tert.*-butoxide and a product obtained which gave the characteristic Keller test for the ergot alkaloids when treated with Ehrlich's reagent. The colour reaction was presumably due to the presence of a small amount of ergoline (XVI) or of its *N*-formyl derivative, but the amount obtained was too small to permit its isolation.

Experimental

3 : 4-*Trimethyleneindole* (1 : 3 : 4 : 5-*Tetrahydrobenz*[cd]*indole*).—5 : 6 : 7 : 8-Tetrahydro-1-naphthylamine (20 g.) was heated on the steam-bath overnight with anhydrous formic acid (20 c.c.) and distilled. The *formyl* derivative (20·2 g.) was collected at 245°/44 mm. A specimen, recrystallised from benzene, formed colourless crystals, m. p. 98° (Found : C, 75·5; H, 7·6. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·4%). Potassium (6·6 g.) was dissolved in *tert.*-butanol (140 c.c.), and the *N*-formyltetrahydronaphthylamine (20 g.) was added. The solvent was evaporated in nitrogen, and the residue heated at 240° during 1 hr. and finally to 300° with a slow stream of nitrogen continually passing. When cold, water was added and, the soluble products were isolated with chloroform, then dissolved in low-boiling petroleum and adsorbed on an alumina column. The chromatogram was developed with benzene containing 5% of chloroform. The first fraction of eluate yielded, on evaporation, a pale brown oil which soon crystallised. Sublimation of this material in a high vacuum yielded 3 : 4-trimethyleneindole (1 g.) as colourless plates, m. p. 53°. Recrystallisation from petroleum raised the m. p. to 56° (Found : C, 84·0; H, 7·1. Calc. for $C_{11}H_{11}N$: C, 84·1; H, 7·0%). Jacobs and Craig (*J. Biol. Chem.*, 1934, **106**, 393) give m. p. 56°. The picrate, prepared in ethanol, had m. p. 165° (Jacobs and Craig, *loc. cit.*, give m. p. 165°). The substance gave a colour reaction with Erlich's reagent very similar to that given by skatole.

Nitration of 1-*Azaphenanthrene.*—After a systematic investigation, the following procedure was found to give the best results. Finely powdered 1-azaphenanthrene (89·5 g.) was added with stirring to fuming nitric acid (360 c.c.) cooled in ice, and kept overnight in a refrigerator. The mixture was poured into water preheated to 90°, cautiously neutralised with ammonia, and allowed to cool. The product (100—110 g.) was collected, dried, and extracted with benzene (2 × 200 c.c.). The undissolved residue, crystallised from ethanol, gave 8-nitro-1-azaphenanthrene (85 g.), m. p. 165°. Claus and Besseler (*loc. cit.*) give m. p. 165°. Occasionally, crystals of m. p. 173° were obtained instead. These appear to be a polymorphic form since, on reduction, both forms give the same amine. This m. p. is also recorded, without comment, by Hepner.

The benzene extract was purified by filtering through a 1 cm. layer of alumina and concentrated. A product of m. p. *ca.* 100° separated. It was purified by chromatography in benzene on alumina. The first fraction of eluate deposited stout yellow prisms of x-*nitro*-1-*azaphenanthrene*, m. p. 145° (Found : C, 69·6; H, 3·8. $C_{13}H_8O_2N_2$ requires C, 69·65; H, 3·6%).

Nitration of 1-*Azaphenanthrene Methosulphate.*—1-Azaphenanthrene (9 g.) and methyl sulphate (6 g.) were heated together on the steam-bath for 10 min. After crystallisation from methanol, 1-*azaphenanthrene methosulphate* formed needles, m. p. 177° (Found : C, 59·2; H, 4·8. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9%). The material so obtained was dissolved in concentrated sulphuric acid (10 c.c.) and cooled in ice. A mixture of fuming nitric acid (2 c.c.) and sulphuric acid (5 c.c.) was added with stirring during 10 min., the temperature being kept at 0°. After 30 min. the mixture was poured on ice (400 g.), allowed to attain room temperature, then treated with an aqueous solution of picric acid (15 g.). The precipitate was collected, and washed with ethanol to remove excess of picric acid, giving crude 8-*nitro*-1-*azaphenanthrene methopicrate* (17 g., 93%). A specimen, crystallised from ethanol, formed yellow needles, m. p. 253° (Found : C, 51·1; H, 2·5. $C_{20}H_{14}O_9N_5$ requires C, 51·3; H, 3·0%). The picrate (10 g.), suspended in concentrated hydrochloric acid (100 c.c.), was washed with benzene until all picric acid had been extracted. The aqueous layer was evaporated and the methochloride crystallised several times from ethanol. It formed fawn-coloured prisms, m. p. 216° (Found : C, 61·1; H, 3·9. Calc. for $C_{14}H_{11}O_2N_2Cl$: C, 61·3; H, 4·0%). Claus and Besseler (*loc. cit.*) give m. p. 218°.

Reduction of 8-*Nitro*-1-*azaphenanthrene.*—(*a*) By following the directions of Claus and Besseler, 8-amino-1-azaphenanthrene was obtained in 73% yield (m. p. 158°).

(*b*) 8-Nitro-1-azaphenanthrene (17·5 g.), dissolved in ethanol (100 c.c.), was hydrogenated over Raney nickel at 90° for 2 hr. The solution, which had a strong odour of ammonia, was filtered

and evaporated and the residual oil, dissolved in benzene–light petroleum, was chromatographed on alumina. The only pure substance isolatable was 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-azaphenanthreme, the *N*-nitroso-derivative of which had m. p. 106°, alone and when mixed with an authentic specimen (Bamberger and Müller, *Ber.*, 1891, **24**, 2660).

x-*Amino*-1-*azaphenanthrene*.—Reduction of *x*-nitro-1-azaphenanthrene with stannous chloride in concentrated hydrochloric acid at 100° gave x-*amino*-1-*azaphenanthrene* as yellow needles, m. p. 175° (Found : C, 80·5; H, 5·0. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·15%). This compound does not form a brilliant scarlet monoacid cation similar to that which is so characteristic of its isomer.

8-*Acetamido*-1-*azaphenanthrene Methiodide*.—8-Amino-1-azaphenanthrene (15 g.) was boiled for a short time with acetic acid (50 c.c.) and acetic anhydride (15 c.c.). The solution, after being poured into water and made alkaline with ammonia, deposited 8-*acetamido*-1-*azaphenanthrene*, which crystallised from aqueous ethanol in colourless needles, m. p. 227° (Found : C, 70·7; H, 5·7. $C_{15}H_{12}ON_2,H_2O$ requires C, 70·9; H, 5·5%). The acetyl derivative (6 g.) was heated for 1 hr. at 100° with methyl iodide (6 c.c.). Crystallisation of the product from aqueous ethanol gave 8-*acetamido*-1-*azaphenanthrene methiodide* (9·2 g.) as fine orange needles, m. p. 282° (Found : C, 49·8; H, 4·3. $C_{16}H_{15}ON_2I,\frac{1}{2}H_2O$ requires C, 49·6; H, 4·4%).

8-*Amino*-1-*azaphenanthrene Methochloride*.—The above methiodide (5 g.) was hydrolysed by boiling it for 10 min. with concentrated hydrochloric acid (20 c.c.). Basification with ammonia gave the methochloride, which crystallised from ethanol in red needles, m. p. 256°. Claus and Besseler (*loc. cit.*) give m. p. 256°.

Reduction of 8-*Amino*-1-*azaphenanthrene Methochloride*.—The above methochloride (5 g.), dissolved in ethanol (100 c.c.) and diethylamine (10 c.c.), was hydrogenated over Raney nickel for 3½ hr. at 120° and an initial pressure of hydrogen of 100 atm. The solution, after filtration from catalyst, was evaporated to dryness and the residue taken up in dilute hydrochloric acid and washed with ether. Basification gave an oil, which was isolated with ether and converted into its picrate. Crystallisation from ethanol gave 1-*methyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-1-*azaphenanthrene picrate* as needles, m. p. 173° (Found : C, 55·9; H, 5·1; N, 12·7. $C_{14}H_{19}N,C_6H_3O_7N_3$ requires C, 55·8; H, 5·1; N, 13·0%). Neither 8-amino-1-azaphenanthrene methiodide nor its acetyl derivative could be reduced at room temperature over Adams catalyst.

Reduction of 8-*Nitro*-1-*azaphenanthrene Methochloride*.—8-Nitro-1-azaphenanthrene methochloride (5 g.), suspended in ethanol (90 c.c.) and piperidine (10 c.c.), was hydrogenated over Raney nickel for 3 hr. at 120° with an initial pressure of hydrogen of 100 atm. Distillation, after filtration from catalyst, gave 1-*methyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-1-*azaphenanthrene* (1·6 g.), b. p. 200°/7 mm. (Found : C, 83·8; H, 9·4. $C_{14}H_{13}N$ requires C, 83·6; H, 9·45%). The picrate formed needles, m. p. 173°, alone and when mixed with a specimen prepared as described above.

8-*Amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1-*azaphenanthrene*.—8-Amino-1-azaphenanthrene (5·7 g.), dissolved in boiling amyl alcohol (200 c.c.), was poured on to sodium (10 g.) in a flask fitted with a reflux condenser, and then boiled until all the sodium had dissolved. Water (200 c.c.) was added to the cool solution, and the organic layer was separated, washed with water, and acidified with hydrochloric acid. The amyl alcohol was distilled in steam, and the residual aqueous solution basified. 8-*Amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-1-*azaphenanthrene* was isolated with ether and was obtained, after distillation, as a pale yellow oil (4·5 g.) (Found : C, 77·4; H, 9·0. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9%). The base gave a hydrochloride crystallising from ethanol–ether in needles, m. p. *ca.* 220° (decomp.) depending on the rate of heating. The hydrochloride, diazotised and coupled with β-naphthol, gave a deep red solution.

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