Experiments on the Synthesis of Lysergic Acid. Part I. Derivatives of Indole.

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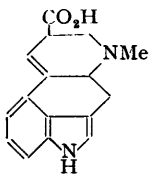
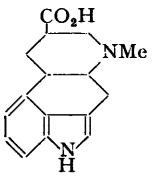
As a model for the synthesis of lysergic acid (I), the compound (VII; R = Me), prepared by condensing 2-methylindole with formyl*cyclo*hexanone, has been reduced to (VI) and cyclised in small yield to the tetracyclic system (VIII) or (IX). A projected alternative, which envisaged the cyclisation of (X) by an intramolecular Grignard reaction, failed because it was found to be impossible to prepare the essential intermediate, 4-bromoindole.

THE problem presented by the synthesis of lysergic acid (I) has attracted the attention of several investigators, and two syntheses of dihydrolysergic acid (II) have been reported, the first by Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76), and the second by Stoll and his collaborators (Stoll, Rutschmann, and Schlientz, *Helv. Chim. Acta*, 1950, **33**, 375; Stoll and Rutschmann, *ibid.*, p. 67). So far, however, no synthesis of lysergic acid has been reported. Both syntheses of dihydrolysergic acid, referred to above, produce the trimethyleneindole system peculiar to lysergic acid by the reduction of a naphthastyril. In the first, 8-amino-1 : 2 : 3 : 4-tetrahydro-1-methyl-1-azaphenanthrene-3 : 9-dicarboxylic acid lactam (III) was reduced with sodium in butanol, giving dihydrolysergic acid in small yield, while in the second the reduction of 8-amino-3-ethoxycarbonyl-4-hydroxy-1-azaphenanthrene-9-carboxylic acid lactam (IV) with the same reagent was used to give dihydronorlysergic acid, the methyl ester of which isomerised on heating to give dihydrolysergic acid.

We have been investigating possible methods of synthesising lysergic acid for some time now and, in view of the papers which have recently appeared on this subject, our results may be of interest.



(I)



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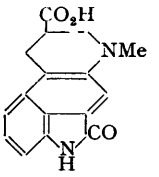

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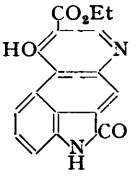
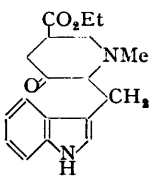


(IV)

It seems that the crucial point is the introduction of the ethylenic linkage in the 9 : 10-position, and we have thus attempted to design a synthesis in which the double bond appears naturally as an essential feature of the synthesis and does not have to be specially introduced after completion of the ergoline skeleton. We hoped that the cyclisation of 3-(5-ethoxycarbonyl-3-oxo-1-methyl-2-piperidylmethyl)indole (V) might represent such a synthesis, and the present paper records our attempts to perform a model of this scheme.



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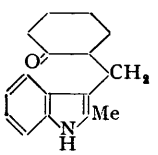

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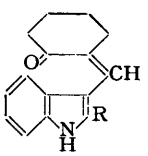
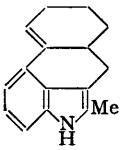


(VII)

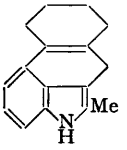
In the first instance, we decided to attempt the ring closure with 2-methyl-3-2′-oxo-*cyclo*hexylmethylindole (VI) as a model, the methyl group being introduced into the indole nucleus in order to prevent cyclisation on to that position. The preparation of this compound was achieved by a two-stage reaction which involved, first, the condensation between formyl*cyclo*hexanone and 2-methylindole, which gave 2-methyl-3-2′-oxo*cyclo*hexylidene-

methylindole (VII; R = Me), and, secondly, the reduction of this compound to (VI) over palladised charcoal, which proceeded smoothly and in good yield. 3-2′-Oxo*cyclo*hexylidenemethylindole (VII; R = H) was also prepared from indole and formyl*cyclo*hexanone, but it was found that 2-phenylindole was not reactive enough to condense except in the presence of hydrogen chloride, a blue substance, apparently of complex structure, being then obtained. Although the substance (VI) resisted the action of phosphoric oxide in boiling toluene, cyclisation was effected in small yield by hot metaphosphoric acid. The product presumably has the structure (VIII) or (IX).

We then attempted to synthesise the substance (X; R = H), a suitably protected derivative of which, it was expected, would cyclise under Grignard conditions. Unfortunately, we have been unable to prepare 4-bromoindole, the required intermediate for the production of (X).



(VIII)



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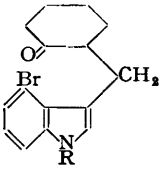


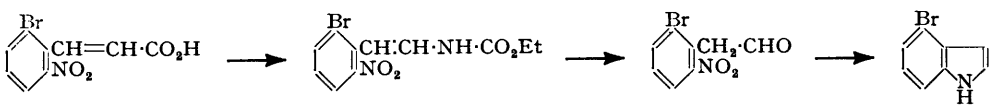
(X)

Uhle (*J. Amer. Chem. Soc.*, 1949, **71**, 761) has prepared 4-chloroindole from 2-chloro-6-nitrotoluene by the Reissert synthesis but, although we were able to obtain 4-bromoindole-2-carboxylic acid by an analogous process, we could not decarboxylate this acid. Similar difficulty in decarboxylating indole acids has been reported by other workers and, indeed, the conditions employed by Uhle for the decarboxylation of 4-chloroindole-2-carboxylic acid, which consisted in refluxing in quinoline with half a molecular proportion of cuprous chloride for 8 hours, seem rather drastic and suggest that this decarboxylation, too, may have proved difficult.

2-Bromo-6-nitrotoluene was readily prepared by brominating *o*-nitrotoluene, following Gluud's method (*Ber.*, 1915, **48**, 433), and fractionally distilling the mixture of isomers obtained. The amounts of 2-bromo-6-nitro- and 4-bromo-2-nitro-toluene obtained were approximately 40% and 50% respectively, the remainder consisting of an unresolved mixture of isomers. This result is in fair agreement with the work of Mehta and Ayyar (*J. Univ. Bombay*, 1942, **10**, 99) who analysed the mixture by oxidation to the bromonitrobenzoic acids, which they separated by fractional crystallisation. They concluded that 40% of the product was 2-bromo-6-nitrotoluene.

The condensation between 2-bromo-6-nitrotoluene and ethyl oxalate in the presence of sodium ethoxide gave 2-bromo-6-nitrophenylpyruvic acid, which was characterised as its semicarbazone. Reduction of 2-bromo-6-nitrophenylpyruvic acid with sodium dithionite (hydrosulphite) or ferrous sulphate and ammonia gave 4-bromoindole-2-carboxylic acid in excellent yield, but this acid could not be decarboxylated under any discoverable conditions. The acid was recovered substantially unchanged after being heated with water at 260° for 3 hours. Refluxing it with quinoline, alone or in the presence of cuprous bromide, cupric oxide, or copper powder, or refluxing it in resorcinol, gave no indoles detectable with Ehrlich's reagent.

6-Bromoindole-2-carboxylic acid was also made from the 4-bromo-2-nitrotoluene



obtained as a by-product in the bromination, and decarboxylation experiments were performed on this less valuable material. These were also not attended with success.

The fusion of 2-bromo-6-formamidotoluene with potassium *tert.*-butoxide, and of the acetyl derivative with sodamide, yielded only negligible amounts of indoles. It is, perhaps, not surprising that the bromine atom should be attacked under these drastic conditions.

An attempt was also made to prepare 4-bromoindole from 2-bromocinnamic acid by the method shown, but the nitration of methyl 2-bromocinnamate gave, not the required methyl 2-bromo-6-nitrocinnamate, but methyl 2-bromo-5-nitrocinnamate. This orientation was established by permanganate oxidation, 2-bromo-5-nitrobenzoic acid being obtained.

Experimental

2-Methyl-3-2'-oxocyclohexylidenemethylindole.—A solution of 2-methylindole (9·5 g.) and 2-formylcyclohexanone (20 g.) in ethanol (50 c.c.) was refluxed for 2 hr. and concentrated under reduced pressure. The viscous residual oil, when taken up in ether and set aside overnight, deposited *2-methyl-3-2'-oxocyclohexylidenemethylindole* (10 g., 57%) in yellow prisms which, after recrystallisation from ethanol, had m. p. 126° (Found: C, 79·6; H, 7·1; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). The *dinitrophenylhydrazone* formed orange needles, m. p. 234° (from ethanol) (Found: C, 63·2; H, 4·8. $C_{22}H_{21}O_4N_5$ requires C, 63·0; H, 5·0%).

2-Methyl-3-2'-oxocyclohexylmethylindole.—The above substance (0·67 g.), dissolved in ethanol (50 c.c.), was hydrogenated at room temperature and pressure over palladised charcoal for 1 hr. (absorption 58 c.c.; calc. 63 c.c.). After filtration, the colourless solution was evaporated to dryness *in vacuo*. *2-Methyl-3-2'-oxocyclohexylmethylindole* was obtained as a colourless oil, which slowly reddened in air. For analysis it was regenerated from the recrystallised picrate, by decomposition with ammonia and extraction with ether (Found: C, 79·4; H, 7·9. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9%). The *picrate* formed very dark red needles, m. p. 135°, from benzene (Found: C, 56·2; H, 4·5. $C_{16}H_{19}ON,C_6H_3O_7N_3$ requires C, 56·2; H, 4·7%). The semicarbazone crystallised from ethanol in colourless plates, m. p. 199—200° (decomp.).

3-2'-Oxocyclohexylidenemethylindole.—A solution of indole (2 g.) and 2-formylcyclohexanone (4 g.) in ethanol (20 c.c.) was refluxed for 2 hr. The solvent having been evaporated under reduced pressure, addition of ether gave a yellow crystalline precipitate. After being kept overnight the solid was collected and recrystallised from ethanol; *3-2'-oxocyclohexylidenemethylindole* was obtained as yellow needles, m. p. 232° (Found: C, 79·75; H, 6·65. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7%).

Condensation between 2-Phenylindole and 2-Formylcyclohexanone.—A solution of 2-formylcyclohexanone (2 g.) in a little ethanol was added to a solution of 2-phenylindole (1 g.) in ethanol saturated with hydrogen chloride. The deep red liquid was poured into water after 10 min. An intensely blue solid substance was precipitated, which crystallised from ethanol in microscopic crystals, m. p. *ca.* 200° (Found: C, 80·5; H, 6·15; N, 4·3%).

Experiments on the Cyclisation of 2-Methyl-3-2'-oxocyclohexylmethylindole.—(*a*) Phosphoric oxide (4 g.) and syrupy phosphoric acid (3 c.c.) were mixed in a small flask. The temperature rose to 150°. When the temperature had fallen to 130°, 2-methyl-3-2'-oxocyclohexylmethylindole (1 g.) was added, and the mixture stirred in an oil-bath kept at 130° for 2 min. The use of a higher temperature or longer period of heating led to extensive decomposition, and the production of a purple solid. After cooling, water was added, the insoluble residue collected, washed with water, and dissolved in methanol (20 c.c.). The solution was brought to pH 6 by the addition of acetic acid and ammonia, Girard's reagent " P " (2 g.) was added, and the solution was boiled under reflux for 20 min. After dilution with water (200 c.c.) the mixture was adjusted to pH 6·5 with sodium carbonate, and the non-ketonic fraction was extracted with ether. After evaporation of the ether, the residue was converted into its picrate from which, after repeated crystallisation from ethanol, the *picrate* of 4 : 6 : 6*a* : 7 : 8 : 9- (VIII) or 4 : 6 : 7 : 8 : 9 : 10-hexahydro-5-methyldibenz[*cd*, *f*]*iso*indole (IX) (cf. Ring Index No. 2457) was obtained as dark red needles, m. p. 144° (Found: C, 58·8; H, 4·45. $C_{16}H_{17}N,C_6H_3O_7N_3$ requires C, 58·4; H, 4·4%).

(*b*) The ketone (9·3 g.), dissolved in dry toluene (50 c.c.), was refluxed with phosphoric oxide (2 g.) for 1 hr., and the solution was filtered and washed with water. The toluene layer was evaporated and the residue treated with the Girard reagent. No non-ketonic fraction could be isolated.

2-Bromo-6-nitrotoluene.—Crude bromonitrotoluene (1 kg.) obtained as described by Gluud (*loc. cit.*) was fractionated at 15 mm. through a 1-m. column packed with Fenske helices. Three arbitrary fractions (approx. 400, 200, and 400 g.) were collected, of which the first and last largely crystallised. The crystals were collected and the mother-liquors added to the middle fraction, which was again separated into three fractions. The crystals obtained from the two low-boiling fractions were mixed and recrystallized from light petroleum; pure 2-bromo-6-

nitrotoluene (*ca.* 400 g.), m. p. 42°, was obtained (lit., m. p. 42°). From the two higher-boiling fractions there was obtained after recrystallisation 4-bromo-2-nitrotoluene (*ca.* 500 g.), m. p. 47° (lit., m. p. 47°). The mother-liquors were added to the next batch for fractionation. This method of working required practically no attention, and was found to be much more convenient than attempting to cut the fractions accurately.

2-Bromo-6-nitrophenylpyruvic Acid.—A solution of sodium ethoxide, prepared from sodium (23 g.) and ethanol (500 c.c.), was treated with ethyl oxalate (143 g.) and 2-bromo-6-nitrotoluene (216 g.), and the mixture refluxed on the water bath for 45 min. and cooled. Water (500 c.c.) was added and all volatile material was removed by steam-distillation. The residual solution was cooled again, washed with ether, and acidified with hydrochloric acid. A red oil separated which was isolated with ether. *2-Bromo-6-nitrophenylpyruvic acid* was obtained as a red oil (119 g., 41%) which crystallised during 3 months. After recrystallisation from benzene it formed colourless crystals, m. p. 117° (Found : C, 37·8; H, 2·3; Br, 26·7. $C_9H_6O_5NBr$ requires C, 37·5; H, 2·1; Br, 27·8%). From the steam-distillate 2-bromo-6-nitrotoluene (115 g., 53%) was recovered. The *semicarbazone* of 2-bromo-6-nitrophenylpyruvic acid formed colourless crystals, m. p. 216°, from ethanol (Found : C, 35·0; H, 2·45. $C_{10}H_9O_5N_4Br$ requires C, 34·8; H, 2·6%).

4-Bromo-2-nitrophenylpyruvic Acid.—This was prepared by a method analogous to that employed for its isomer. *4-Bromo-2-nitrophenylpyruvic* acid (40%) formed colourless needles, m. p. 144°, from benzene (Found : C, 37·75; H, 2·0; N, 4·75. $C_9H_6O_5NBr$ requires C, 37·5; H, 2·1; N, 4·9%). The recovery of 4-bromo-2-nitrotoluene amounted to 51%.

4-Bromoindole-2-carboxylic Acid.—(*a*) 2-Bromo-6-nitrophenylpyruvic acid (28 g.) was reduced with a boiling solution of ferrous sulphate heptahydrate (150 g.) and ammonia (60 c.c.; *d* 0·880) in water (600 c.c.) for 5 min., and filtered hot. The precipitate, on repeated extraction with boiling dilute ammonia and acidification, gave *4-bromoindole-2-carboxylic acid* (18 g., 75%), fluffy needles, m. p. 266° (from ethanol) (Found : C, 45·0; H, 2·7; N, 6·4. $C_9H_6O_2NBr$ requires C, 45·0; H, 2·5; N, 5·8%).

(*b*) 2-Bromo-6-nitrophenylpyruvic acid (28 g.) was dissolved in 10% sodium hydroxide solution (45 c.c.), and water (100 c.c.) added. The deep red solution thus obtained was cooled in ice and stirred mechanically while sodium dithionite (53 g.) was added during 1 hr. The solution was acidified with hydrochloric acid, heated on a steam-bath for 2 hr. to expel sulphur dioxide, and then cooled. The acid (22 g., 90%) was collected and crystallised from aqueous ethanol.

6-Bromoindole-2-carboxylic Acid.—This was prepared by the same methods as was its isomer. The *acid* formed colourless needles, m. p. 223°, from aqueous ethanol (Found : C, 44·8; H, 2·6; N, 6·3%).

2-Bromo-6-formamidotoluene.—2-Bromo-6-nitrotoluene (21·6 g.), suspended in ethanol (50 c.c.), was hydrogenated over Raney nickel at room temperature and an initial pressure of 3 atm. As the reduction proceeded the nitro-compound passed into solution. After complete reduction the solution was filtered from catalyst and evaporated. 2-Amino-6-bromotoluene (17 g., 92%) distilled as a colourless oil at 130°/16 mm. The amine (9·3 g.) in anhydrous formic acid (20 c.c.) was kept on the steam-bath overnight. In the morning, the solution was diluted with water, and the product collected, and crystallised from benzene. *2-Bromo-6-formamidotoluene* (10 g., 93%) formed leaflets, m. p. 116° (Found : C, 44·6; H, 4·0; Br, 36·5. C_8H_8ONBr requires C, 44·9; H, 3·7; Br, 37·4%).

4-Bromo-2-formamidotoluene, prepared similarly, separated from benzene in colourless needles, m. p. 137° (Found : C, 45·0; H, 4·0; Br, 36·6%).

Attempted Preparation of 4-Bromoindole.—Potassium (2·9 g.) was dissolved in *tert.*-butanol (100 c.c.), and 2-bromo-6-formamidotoluene (16 g.) was added. The butanol was distilled in a current of nitrogen, and the residue heated to 270° for 0·5 hr. and allowed to cool under nitrogen. The residue was treated with water and extracted with ether. The ethereal extract gave no colour with Ehrlich's reagent. Repetition of the experiment at various temperatures gave no more favourable results.

Attempted Preparation of 4-Bromo-2-methylindole.—2-Acetamido-6-bromotoluene (34 g.) was finely powdered and mixed with sodamide (14 g.) similarly powdered. The mixture was covered with dry ether, ammonia being at once evolved. The mixture was warmed gently under a current of dry nitrogen, until the evolution of ammonia ceased, and then heated in a metal-bath at 240° for 15 min. The mixture was cooled, and treated with aqueous ethanol (50 c.c. of 50%). After being warmed on the steam-bath for a short time, the solution was diluted with water and extracted with ether. The ethereal extract was washed with dilute acid and then with sodium

hydrogen carbonate solution, dried, and evaporated. A small amount of oil remained which gave a fairly strong Ehrlich test but did not suffice for purification.

Methyl 2-Bromo-5-nitrocinnamate.—Methyl 2-bromocinnamate (11·4 g.) was dissolved at 0° in concentrated sulphuric acid. A solution of nitric acid (3·5 c.c.; *d* 1·48) in sulphuric acid (10 c.c.) was added during 0·5 hr. with mechanical stirring and cooling. The mixture was then poured on cracked ice, and the precipitate collected, washed with much water, and dried. The solid (13·7 g.) thus obtained was boiled with successive small amounts of methanol, in which it was rather insoluble, to remove more soluble impurities. After three washings in this way, the residue had m. p. 166°. After crystallization from a large volume of methanol, *methyl 2-bromo-5-nitrocinnamate* formed very pale yellow needles (9·5 g., 70%), m. p. 169° (Found: C, 42·1; H, 2·8. $C_{10}H_8O_4NBr$ requires C, 42·0; H, 2·8%).

2-Bromo-5-nitrobenzoic Acid.—Methyl 2-bromo-5-nitrocinnamate (6 g.), suspended in 50% sulphuric acid (50 c.c.), was treated with a saturated solution of potassium permanganate (7 g.). The solution was boiled for a few minutes, and then filtered hot. On cooling, 2-bromo-5-nitrobenzoic acid (2·4 g.) separated in long, colourless needles. After recrystallisation from aqueous ethanol, it had m. p. 178° alone and when mixed with an authentic specimen.

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