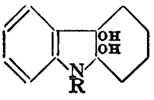
767. *Oxindoles formerly regarded as ψ-Indoxyls.*

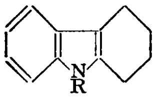
By R. F. Moore and S. G. P. Plant.

*cyclo*Pentane*spiro*oxindole, *cyclo*hexane*spiro*oxindole, and several derivatives of the latter have been synthesised from the appropriate phenylhydrazides of *cyclo*pentane- or *cyclo*hexane-carboxylic acid. Some of these products had hitherto been regarded as ψ-indoxyls. The position of the substituent in the nitration product of *cyclo*hexane*spiro*oxindole has been established, and the course of the Friedel–Crafts reaction in the 3 : 3-disubstituted oxindole group has been investigated.

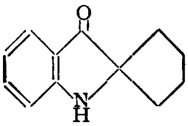
It was observed by Perkin and Plant (*J.*, 1923, **123**, 676) that 9-acylhexahydro-10 : 11-dihydroxycarbazoles (I; R = acyl), from the action of nitric acid on the corresponding acyltetrahydrocarbazoles (II; R = acyl) in acetic acid, undergo a pinacolinic change on being heated alone or in acetic anhydride to give compounds which can readily be deacylated. Of the two alternative structures for the product, $C_{12}H_{13}ON$, the ψ-indoxyl formulation (III) seemed the more probable at the time, and this was later supported by observations which are referred to below. It has more recently been shown by Plant and Robinson (*Nature*, 1950, **165**, 36) that this view is untenable and that the substance must be *cyclo*pentane*spiro*oxindole (IV). Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614) independently reached the same conclusion, and Patrick and Witkop (*ibid.*, p. 633) indirectly confirmed the oxindole formulation by showing that nitration of the material obtained by condensing 1-methyloxindole with tetramethylene dibromide gave a compound (V; R = Me) identical with the substance prepared by Perkin and Plant by nitration of the compound $C_{12}H_{13}ON$ and subsequent methylation. The position of the nitro-group is not hereby established, but it follows from the fact that the unmethylated substance (V; R = H) has also been obtained (Massey and Plant, *J.*, 1931, 2218) by applying the above sequence of reactions to 9-acetyl-6-nitrotetrahydrocarbazole (VI).



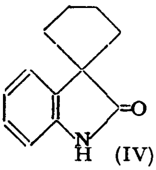
(I)



(II)

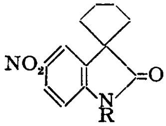


(III)

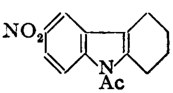


(IV)

It seemed desirable to add the confirmation of a direct synthesis of (IV), and this has now been done by using a method of preparing oxindoles developed by Brunner (*Monatsh.*, 1896, **17**, 479; 1897, **18**, 95), *viz.*, the elimination of ammonia from phenylhydrazides of the type, $C_6H_5{\cdot}NR{\cdot}NH{\cdot}CO{\cdot}CHR'R''$, by heating with quicklime. For the present purpose, the phenylhydrazide of *cyclo*pentanecarboxylic acid was prepared.



(V)



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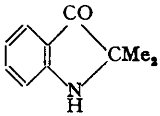
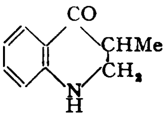


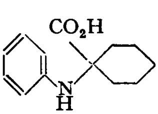
(VII)



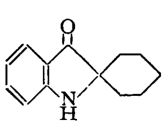
(VIII)

Bucherer and Grolée (*Ber.*, 1906, **39**, 986) heated the anilino*iso*butyric acid, m. p. 185°, with a mixture of sodium ethoxide and potassium hydroxide and isolated a product which they thought to be 2 : 2-dimethyl-ψ-indoxyl (VII) or 1 : 2 : 3 : 4-tetrahydro-4-keto-3-methylquinoline (VIII). Betts, Muspratt, and Plant (*J.*, 1927, 1310), using similar conditions with 1-anilino*cyclo*hexane-1-carboxylic acid (IX), obtained a substance regarded as *cyclo*hexane-*spiro*-ψ-indoxyl (X), and the close resemblance of the latter to the *spiro*-compound $C_{12}H_{13}ON$ obtained from tetrahydrocarbazole provided strong mutual support for the formulations proposed. By an extension of the synthetical method and reactions with the products, Betts and Plant (*J.*, 1928, 2070) have prepared other substances formulated as derivatives of (X). It is now evident (Plant and Robinson, *loc. cit.*) that the isomeric oxindole structure almost certainly must also be attributed to these compounds, and Mr. L. J. Goldsworthy has shown that the substance described by Bucherer and Grolée is identical with 3 : 3-dimethyloxindole (XI) obtained from *iso*butyrophenylhydrazide (see Plant, Robinson, and Tomlinson, *Nature*, 1950, **165**, 928).

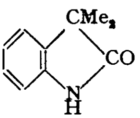
The application of Brunner's reaction to the phenylhydrazide and the *o*- and *p*-tolylhydrazides of *cyclo*hexanecarboxylic acid has now given *cyclo*hexane*spiro*oxindole (XII) and derivatives identical with the substances referred to above, and afforded synthetical confirmation of the more recent structural views.



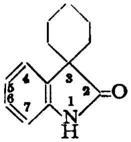
(IX)



(X)



(XI)



(XII)

Like the *cyclo*pentane analogue, the compound (XII) very readily gives a nitro-derivative (*J.*, 1927, 1310), but the position of the substituent has not hitherto been rigidly established. In an attempt to do this, *cyclo*hexane*spiro*-5-methoxyoxindole was synthesised from the *p*-methoxyphenylhydrazide of *cyclo*hexanecarboxylic acid, and the nitro-compound reduced to the amine, but the conversion of the latter into the corresponding phenol proved to be difficult. The amine was accordingly converted by a Sandmeyer reaction into a chloro-compound identical with *cyclo*hexane*spiro*-5-chloro-oxindole prepared from the appropriate *p*-chlorophenylhydrazide.

The possibility of applying the Friedel–Crafts reaction to the 3 : 3-disubstituted oxindoles has been studied. The action of acetyl chloride and aluminium chloride on 3 : 3-dimethyloxindole in carbon disulphide gave 5-acetyl-3 : 3-dimethyloxindole, the nature of which was confirmed by the preparation of a *N*-acetyl derivative and an oxime. Its constitution followed from the fact that the oxime, by a Beckmann rearrangement, gave an acetamido-compound which on hydrolysis yielded 5-amino-3 : 3-dimethyloxindole, already prepared by an unambiguous route (Brunner, *Monatsh.*, 1931, **58**, 369). The 5-acetyl compound was added to molten potassium hydroxide, and acidification of the mixture gave 3 : 3-dimethyloxindole-5-carboxylic acid.

Similar treatment of the compound (XII) gave *cyclo*hexane*spiro*-5-acetyloxindole, the structure of which was also proved by rearrangement of its oxime and hydrolysis of the product to *cyclo*hexane*spiro*-5-amino-oxindole. In fact this is a more convenient way of obtaining the amine than by reduction of the nitro-compound.

EXPERIMENTAL.

Synthesis of cyclo*Pentane*spiro*oxindole.*—Phenylhydrazine (72 g., 2 mols.) in dry ether (150 c.c.) was slowly added to *cyclo*pentanecarboxyl chloride (44 g.) in dry ether (100 c.c.) with mechanical stirring under a reflux condenser, and cooling in ice-water. After the mixture had been stirred for a further 20 minutes, the ether was removed by evaporation, the residue shaken with water, and the insoluble material crystallised from aqueous ethanol, from which the *phenylhydrazide* of *cyclo*pentanecarboxylic acid separated in colourless needles (yield, 70%), m. p. 111° (Found : C, 71·1; H, 7·8. $C_{12}H_{16}ON_2$ requires C, 70·6; H, 7·8%). A mixture of the phenylhydrazide (15 g.) and powdered quicklime (45 g.) was heated for 3 hours at 230—250°, and, when cold, it was powdered and cautiously treated with hydrochloric acid (300 c.c. of 20%), and the whole refluxed for an hour. The insoluble product was extracted with ether, the extract dried ($CaCl_2$), the solvent removed, and the residue distilled under reduced pressure. Crystallisation of the distillate from light petroleum gave nearly pure *cyclo*pentane*spiro*oxindole (6 g.), m. p. 105—110°. Further purification was effected by refluxing the product with acetic anhydride (30 c.c.) for an hour, and pouring the cold solution into an excess of water. The precipitated *cyclo*pentane*spiro*-1-acetyloxindole separated from ethanol in long, colourless prisms (6 g.), m. p. 104°, and was hydrolysed by boiling for ½ hour with aqueous-ethanolic potassium hydroxide; the resulting *cyclo*pentane*spiro*oxindole then crystallised from light petroleum in colourless plates (4·5 g.), m. p. 113°. This substance and its acetyl derivative were shown to be identical (mixed m. p.) with the substances obtained by Perkin and Plant (*loc. cit.*) by heating 9-acetyl-10 : 11-dihydroxyhexahydrocarbazole either alone or with acetic anhydride.

Synthesis of cyclo*Hexane*spiro*oxindole and Derivatives.*—By using steps similar to those described above, the phenylhydrazide of *cyclo*hexanecarboxylic acid, m. p. 164° (compare Rupe and Metz, *Ber.*, 1903, **36**, 1092), was prepared and converted into *cyclo*hexane*spiro*oxindole (yield, 35%), colourless prisms (from light petroleum), m. p. 124°, and *cyclo*hexane*spiro*-1-acetyloxindole, colourless prisms (from methanol), m. p. 105°. The last two were shown by mixed m. p. to be identical with the substances obtained by Betts, Muspratt, and Plant (*loc. cit.*) from 1-anilino*cyclo*hexane-1-carboxylic acid.

In a similar manner the o-*tolylhydrazide*, colourless needles (from aqueous ethanol), m. p. 167° (Found : C, 72·7; H, 8·7. $C_{14}H_{20}ON_2$ requires C, 72·4; H, 8·6%), and p-*tolylhydrazide*, colourless needles (from aqueous ethanol), m. p. 156° (Found : C, 72·6; H, 8·6%), of *cyclo*hexanecarboxylic acid were obtained. From them, *cyclo*hexane*spiro*-7-methyloxindole, colourless prisms (from petroleum), m. p. 197°, *cyclo*hexane*spiro*-5-methyloxindole, colourless prisms (from petroleum), m. p. 164°, and *cyclo*hexane*spiro*-1-acetyl-5-methyloxindole, colourless prisms (from methanol), m. p. 144°, were prepared and found to be identical (mixed m. p.) with the compounds obtained by Betts and Plant (*loc. cit.*) from the 1-*o*- and 1-*p*-toluidino*cyclo*hexane-1-carboxylic acids.

cyclo*Hexane*spiro-5-*methoxyoxindole.*—The interaction of *p*-methoxyphenylhydrazine and *cyclo*hexanecarboxylic acid chloride under conditions similar to those described above gave NN′-*di*cyclo-*hexanecarboxyl*-p-*methoxyphenylhydrazine*, colourless needles (from aqueous ethanol), m. p. 199° (Found : C, 70·4; H, 8·5; N, 7·2. $C_{21}H_{30}O_3N_2$ requires C, 70·4; H, 8·4; N, 7·8%), but, when the acid chloride in ether was added to the hydrazine (3 mols.), the p-*methoxyphenylhydrazide* of the acid, colourless needles (from aqueous ethanol), m. p. 164° (Found : C, 68·1; H, 8·3. $C_{14}H_{20}O_2N_2$ requires C, 67·7; H, 8·1%), was formed (yield, 65%). The latter was heated with quicklime as above, but it was not necessary to purify the product through its acetyl derivative. After the crude cyclo*hexane*spiro-5-*methoxyoxindole* had been distilled under reduced pressure, it crystallised from benzene in colourless plates (yield, 28%), m. p. 226° (Found : C, 72·7; H, 7·7. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4%).

cyclo*Hexane*spiro-5-*amino-oxindole.*—After a mixture of *cyclo*hexane*spiro*-5-nitro-oxindole (3 g.; Betts, Muspratt, and Plant, *loc. cit.*), granulated tin (6 g.), and concentrated hydrochloric acid (18 c.c.) had been boiled under reflux until all the nitro-compound had dissolved and for a further ½ hour, the solution was cooled, filtered, and evaporated to dryness. The residue was dissolved in warm 0·1N-hydrochloric acid, the tin precipitated with hydrogen sulphide, and the filtered solution concentrated and made just alkaline with ammonia. The precipitated cyclo*hexane*spiro-5-*amino-oxindole* was dried, washed with a little hot light petroleum, and crystallised from aqueous ethanol, from which it separated in pale yellow prisms (58%), m. p. 175° (Found : C, 72·7; H, 7·1. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4%).

cyclo*Hexane*spiro-5-*chloro-oxindole.*—(*a*) The above amine (8·6 g.) in hydrochloric acid (100 c.c. of 20%) was diazotised at 5° with sodium nitrite (2·8 g.) in water (20 c.c.), and the solution gradually added with shaking to a cold solution of cuprous chloride prepared by dissolving copper carbonate

(5 g.) in concentrated hydrochloric acid (50 c.c.) and boiling the whole for 10 minutes with excess of copper turnings. After several hours, the mixture was heated on the steam-bath, and the cyclo*hexane*spiro-5-*chloro-oxindole* which separated was obtained from aqueous ethanol in yellow needles (yield, 52%), m. p. 188° (Found : C, 66·0; H, 5·9. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 5·9%). When this substance (0·5 g.) was refluxed for an hour with acetic anhydride (5 c.c.) and the mixture shaken with water, cyclo*hexane*spiro-1-*acetyl-5-chloro-oxindole*, pale yellow needles (from ethanol), m. p. 154°, separated (Found : C, 65·3; H 5·9. $C_{15}H_{16}O_2NCl$ requires C, 64·9; H, 5·8%).

(*b*) Prepared from the appropriate hydrazine by the usual process (above), the p-*chlorophenylhydrazide* of *cyclo*hexanecarboxylic acid separated from ethanol in colourless needles (yield, 73%), m. p. 176° (Found : C, 61·3; H, 6·6. $C_{13}H_{17}ON_2Cl$ requires C, 61·8; H, 6·7%). It was converted into the corresponding oxindole by a procedure similar to that used for *cyclo*pentane*spiro*oxindole, but the crude product, after distillation under reduced pressure, could not be made to crystallise. The syrup was accordingly refluxed for an hour with acetic anhydride, the mixture shaken with an excess of aqueous sodium carbonate, the oil extracted with ether, and the extract evaporated. The residue solidified when rubbed with ethanol, and *cyclo*hexane*spiro*-1-acetyl-5-chloro-oxindole separated from that solvent in pale yellow needles, m. p. 154°. On hydrolysis with aqueous ethanolic potassium hydroxide, it gave *cyclo*hexane*spiro*-5-chloro-oxindole, which crystallised from aqueous ethanol in yellow needles (yield, 25%), m. p. 188°. The latter and its acetyl derivative proved to be identical (mixed m. p.) with the substances described above under (*a*).

5-Acetyl-3 : 3-dimethyloxindole.—A mixture of 3 : 3-dimethyloxindole (3·2 g.; Brunner, *Monatsh.*, 1897, **18**, 95), aluminium chloride (10 g.), acetyl chloride (5 g.), and carbon disulphide (50 c.c.) was refluxed for 2½ hours, the solvent removed, and the residue added to ice–dilute hydrochloric acid. When the product was crystallised from aqueous ethanol, *5-acetyl-3 : 3-dimethyloxindole* was obtained in colourless prisms (yield, 72%), m. p. 196° (Found : C, 71·0; H, 6·5. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). After it had been refluxed for an hour with five times its weight of acetic anhydride, and the solution shaken with an excess of water, *1 : 5-diacetyl-3 : 3-dimethyloxindole*, colourless plates (from ethanol), m. p. 136°, was precipitated (Found : C, 68·4; H, 6·1. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). It was hydrolysed to the former substance by boiling aqueous-ethanolic potassium hydroxide.

Oxime of 5-Acetyl-3 : 3-dimethyloxindole.—After 5-acetyl-3 : 3-dimethyloxindole (2 g.) and a mixture of hydroxylamine hydrochloride (4 g.) with crystallised sodium acetate (8 g.) in water (30 c.c.) had been refluxed for 2 hours with sufficient ethanol to effect solution, the addition of water precipitated the *oxime*, colourless prisms (yield, 95%; from benzene), m. p. 196° (Found : C, 65·6; H, 6·2. $C_{12}H_{14}O_2N_2$ requires C, 66·1; H, 6·4%). When a solution of the oxime (1 g.) in concentrated sulphuric acid (10 c.c.) was heated on the steam-bath for an hour, cooled, poured on ice, and made alkaline with ammonia, 5-acetamido-3 : 3-dimethyloxindole, colourless plates (yield, 95%; from water), m. p. 261°, was obtained (Found : C, 66·2; H, 6·6. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·1; H, 6·4%). After the latter had been refluxed for 2 hours with an excess of sulphuric acid (40%), and the cold solution neutalised with ammonia (cooling), 5-amino-3 : 3-dimethyloxindole, colourless prisms (from benzene), m. p. 184°, was precipitated. It proved to be identical (mixed m. p.) with a specimen of the base prepared by reduction of 3 : 3-dimethyl-5-nitro-oxindole as described by Brunner (*loc. cit.*).

3 : 3-Dimethyloxindole-5-carboxylic Acid.—5-Acetyl-3 : 3-dimethyloxindole (2 g.) was gradually added to potassium hydroxide (20 g.) which had been melted by heating with water (2 c.c.). The whole was heated with stirring for a further ½ hour, and, when cold, it was dissolved in water, and the solution boiled with charcoal. After filtration, addition of hydrochloric acid precipitated *3 : 3-dimethyloxindole-5-carboxylic acid*, colourless needles (yield, 40%; from aqueous ethanol), m. p. 297° (Found : C, 64·2; H, 5·2. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%).

cyclo*Hexane*spiro-*5-acetyloxindole.*—Prepared from *cyclo*hexane*spiro*oxindole in a manner similar to that described above for 5-acetyl-3 : 3-dimethyloxindole, cyclo*hexane*spiro-*5-acetyloxindole* crystallised from aqueous ethanol in colourless plates (yield, 66%), m. p. 192° (Found : C, 74·4; H, 6·9. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0%). Its *oxime* separated from aqueous ethanol in colourless plates (yield, 95%), m. p. 212° (Found : C, 69·9; H, 7·0. $C_{15}H_{18}O_2N_2$ requires C, 69·8; H, 7·0%). When this was heated with concentrated sulphuric acid as described above for the related oxime, cyclo*hexane*spiro-*5-acetamido-oxindole*, colourless needles (yield, 95%; from aqueous ethanol), m. p. 298°, was obtained (Found : C, 70·2; H, 7·1. $C_{15}H_{18}O_2N_2$ requires C, 69·8; H, 7·0%). The substance was hydrolysed by refluxing it with 40% sulphuric acid and, when the product obtained by precipitation with ammonia was crystallised from aqueous ethanol, *cyclo*hexane*spiro*-5-amino-oxindole was obtained in pale yellow prisms, m. p. 175°, identical (mixed m. p.) with the compound described above.

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