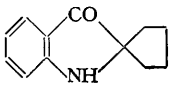
833. *Peroxides of Tetrahydrocarbazole and Related Compounds. Part III.* A Synthesis of 5 : 6-Dimethoxy*cyclo*pentane*spiro*-2-ψ-indoxyl.*

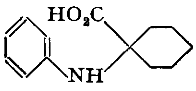
By R. J. S. Beer, T. Broadhurst, Alexander Robertson, and (in part) L. McGrath.

5 : 6-Dimethoxy*cyclo*pentane*spiro*-2-ψ-indoxyl (VI) was obtained from 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxycarbazolyl hydroperoxide by way of the corresponding hydroxycarbazolenine (VII; R = OH), and was identical with a specimen prepared by cyclisation of (V) which was synthesised from (IV), when R = H, NO_2, NH_2, and NHAc, successively.

The decomposition of 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide under a variety of conditions has been shown to give *cyclo*pentane*spiro*-2-ψ-indoxyl (I) (Part I, *J.*, 1950, 2118), the structure of which has been the subject of discussion (Plant and Robinson, *Nature*, 1950, **165**, 36; Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614). Although there are substantial reasons for believing that the indoxyl is correctly formulated, the only direct synthetical evidence is that of Plant and Robinson (*loc. cit.*) who, in a preliminary account, describe the preparation of the compound, evidently in low yield, by the alkylation of *N*-acetylindoxyl with 1-bromo-4-chloro-*n*-butane and sodamide. Earlier attempts to synthesise compounds similar to (I) by cyclisation of acids of type (II) gave products which are now recognised as *cyclo*hexane*spiro*oxindoles, type (III) (see, *e.g.*, Moore and Plant, *J.*, 1951, 3475), whilst the alkaline fusion of 1-anilino*cyclo*pentane-1-carboxylic acid gave carbazole (Plant and Facer, *J.*, 1925, **127**, 2037).



(I)



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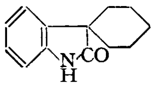

(III)

It appeared to us that application of Baeyer's synthesis of indoxyl from *o*-acetamido-ω-bromoacetophenone (*Ber.*, 1884, **17**, 963) might provide a rational route to *spiro*-ψ-indoxyls of type (I). For the synthesis of the parent *spiro*-2-ψ-indoxyl (I), the preparation of the required intermediate *o*-nitrophenyl *cyclo*pentyl ketone presents considerable difficulties, but nitration of the corresponding veratrole derivative (IV; R = H) was expected to furnish (IV; R = NO_2) required for 5 : 6-dimethoxy*cyclo*pentane*spiro*-2-ψ-indoxyl (VI), which had already been prepared in this laboratory from 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxycarbazolyl hydroperoxide (VII; R = O·OH) (*Nature*, 1949, **164**, 362). This peroxide closely resembled 1 : 2 : 3 : 4-tetrahydrocarbazolyl hydroperoxide (Part I, *loc. cit.*) and on reduction with aqueous sodium sulphite gave 11-hydroxy-6 : 7-

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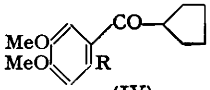
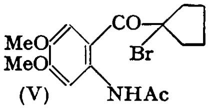
* Part II, *J.*, 1950, 3283.

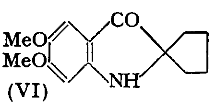
dimethoxycarbazolenine (VII; R = OH) which, with warm aqueous sodium hydroxide, rearranged to the *spiro*-2-ψ-indoxyl (VI) having the expected properties.



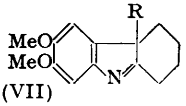
(IV)



(V)



(VI)



(VII)

Accordingly, 3 : 4-dimethoxyphenyl *cyclo*pentyl ketone was prepared from veratrole and *cyclo*pentanecarboxyl chloride by the Friedel–Crafts method and, on nitration, gave a moderate yield of a mononitro-derivative, which was shown by the ultimate success of the synthesis to be 4 : 5-dimethoxy-2-nitrophenyl *cyclo*pentyl ketone (IV; R = NO_2) and on catalytic reduction furnished 2-amino-4 : 5-dimethoxyphenyl *cyclo*pentyl ketone (IV; R = NH_2), forming the acetyl derivative (IV; R = NHAc). *N*-Bromosuccinimide did not react with this acetamido-ketone but, after some preliminary experiments, the compound was found to react satisfactorily with bromine in acetic acid to give (V). With warm aqueous sodium hydroxide this product (V) was smoothly converted into 5 : 6-dimethoxy*cyclo*pentane*spiro*-2-ψ-indoxyl, identical with the specimen previously prepared, thus confirming the structures assigned to this class of compound.

EXPERIMENTAL

3 : 4-*Dimethoxyphenyl* cyclo*Pentyl Ketone* (IV; R = H).—Powdered aluminium chloride (4·0 g.) was added to a solution of veratrole (5·7 g.) and *cyclo*pentanecarboxyl chloride (Haworth and Perkin, *J.*, 1894, **65**, 99) (5·7 g.) in carbon disulphide (20 ml.), and 2 hours later the deep red mixture was added to crushed ice (50 g.) and concentrated hydrochloric acid (20 ml.). On isolation with ether (washing successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water) the resulting 3 : 4-*dimethoxyphenyl* cyclo*pentyl ketone* was purified by distillation and obtained as a colourless mobile oil (6·2 g.) which slowly solidified to a mass of needles, b. p. 122—124°/0·05 mm., m. p. 39—40° (Found : C, 71·8; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone*, which formed slowly in boiling alcohol, separated in minute shining plates, m. p. 162°, on recrystallisation from alcohol (Found : C, 58·4; H, 5·4; N, 13·2. $C_{20}H_{22}O_6N_4$ requires C, 58·0; H, 5·4; N, 13·5%). Under the usual conditions the ketone did not form an oxime or a semicarbazone.

4 : 5-*Dimethoxy-2-nitrophenyl* cyclo*Pentyl Ketone* (IV; R = NO_2).—A solution of the foregoing ketone (2·5 g.) in acetic acid (2 ml.) was added during 10 minutes to a well-stirred mixture of concentrated nitric acid (6·5 ml.) and concentrated sulphuric acid (2·8 ml.) at –5°. When the mixture was poured into ice-water (75 ml.) 10 minutes later, a red resin separated which slowly solidified and then, on crystallisation from methanol, gave 4 : 5-*dimethoxy-2-nitrophenyl* cyclo*pentyl ketone* (1·6 g.) in clusters of colourless rods, m. p. 97—98° (Found : C, 60·6; H, 5·9; N, 5·2. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%). This compound did not react with the usual carbonyl reagents.

2-*Acetamido*-4 : 5-*dimethoxyphenyl* cyclo*Pentyl Ketone* (IV; R = NHAc).—Reduction of the nitro-ketone (IV; R = NO_2) (2·0 g.), dissolved in methanol (100 ml.), with hydrogen at atmospheric pressure and a palladium–charcoal catalyst was complete in 2 hours and, on evaporation of the filtered solution, gave the amino-ketone as a pale green crystalline mass which was directly converted into the *acetyl* derivative with acetic anhydride (4 ml.) on the steam-bath for 1 hour. This compound separated from light petroleum (b. p. 60—80°) in colourless prisms (1·5 g.), m. p. 112°, which did not react with carbonyl reagents (Found : C, 66·1; H, 7·2; N, 5·0. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2; N, 4·8%).

2-*Acetamido*-4 : 5-*dimethoxyphenyl* 1-*Bromo*cyclo*pentyl Ketone* (V).—On the addition of bromine (0·3 g.) in acetic acid (0·5 ml.) to a solution of 2-acetamido-4 : 5-dimethoxyphenyl *cyclo*pentyl ketone (0·5 g.) in the same solvent (3 ml.) at 50°, hydrogen bromide was evolved and the *bromo-ketone* (V) separated in minute yellow prisms (0·6 g.). Recrystallised from aqueous alcohol, the ketone formed short golden-yellow rods, m. p. 146° (decomp.) (Found : C, 52·1; H, 5·4; N, 3·7. $C_{16}H_{20}O_4NBr$ requires C, 52·0; H, 5·4; N, 3·8%).

5 : 6-*Dimethoxy*-2-cyclo*pentane*spiro-ψ-*indoxyl*.—(*a*) On being heated on the steam-bath for 2 hours with 2N-aqueous sodium hydroxide (2 ml.) the foregoing bromo-ketone (V) (0·1 g.) gave 5 : 6-*dimethoxy*cyclo*pentane*spiro-2-ψ-*indoxyl*, which formed pale green prisms (55 mg.), m. p. 164—165°, from light petroleum (b. p. 60—80°) (Found : C, 68·4; H, 7·0; N, 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%).

(*b*) When a solution of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxycarbazole (Hughes and Lions, *J. Proc. Roy. Soc., N.S. Wales*, 1938, **71**, 428) (1·5 g.) in light petroleum (b. p. 60—80°) (700 ml.) was kept overnight, the hydroperoxide separated in colourless prisms (1·3 g.), m. p. *ca.* 113° (decomp.), and on recrystallisation from ethyl acetate–light petroleum had m. p. *ca.* 122° (decomp.) [cf. *Nature*, 1949, **164**, 362, where m. p. 118° (decomp.) is recorded]. A mixture of the hydroperoxide (0·8 g.), 30% aqueous sodium sulphite (20 ml.), and ether (120 ml.) was agitated for 4 hours, and the product, 11-hydroxy-6 : 7-dimethoxycarbazolenine (0·30 g.), m. p. 158°, isolated with ether. When this crude compound (0·25 g.) was heated on the steam-bath with a solution of potassium hydroxide (0·5 g.) in ethanol (3 ml.) and water (2 ml.) for 30 minutes, and the alcohol subsequently removed by distillation, 5 : 6-dimethoxy-2-*cyclo*pentane*spiro*-ψ-indoxyl (0·21 g.) separated and, on crystallisation from benzene–light petroleum, formed green elongated prisms, m. p. 165°, undepressed by admixture with the sample obtained by route (*a*) (Found : C, 68·1; H, 6·7; N, 5·7%).

The two samples had identical absorption spectra in alcohol (Light absorption : Max. at 252, 277, and 390 mμ; log ε = 4·35, 4·09, and 3·78).

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