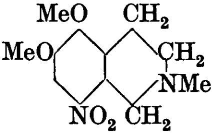
# CCCV.—5 : 6-*Dimethoxy-2-methyl-*1 : 2 : 3 : 4-*tetrahydro*iso*quinoline and some Derivatives.*

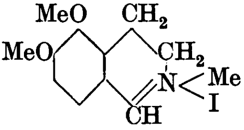
By ROBERT DOWNS HAWORTH.

THE present communication describes some experiments which were undertaken in order to discover whether the introduction of a nitro-group into a suitable position in the benzene nucleus of a 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline derivative is capable of inducing such a reactivity in the 1-methylene group as could be utilised in synthetical work connected with the *iso*quinoline alkaloids. Suitable nitro*iso*quinoline derivatives are not readily accessible, and it has been necessary to synthesise 8-*nitro*-5 : 6-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (I) in order to test the above possibility.

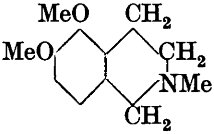
2 : 3-Dimethoxycinnamic acid, prepared by condensing 2 : 3-dimethoxybenzaldehyde with malonic acid, was converted into β-2 : 3-dimethoxyphenylpropionic acid by reduction with sodium amalgam (Perkin and Robinson, J., 1914, **105**, 2387). The *amide* of this acid was treated with sodium hypochlorite, and the resulting β-2 : 3-*dimethoxyphenylethylamine* converted into its N-*formyl* derivative, which yielded 5 : 6-*dimethoxy*-3 : 4-*dihydro*iso*quinoline* on treatment with phosphorus oxychloride. This oily base was converted to a crystalline *methiodide* (II), which was reduced by zinc dust and dilute sulphuric acid to 5 : 6-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (III), a colourless, oily base, which gave a crystalline *hydriodide* and *picrate*. When this base was nitrated in glacial acetic acid it was converted into the required base (I), which,



(I.)



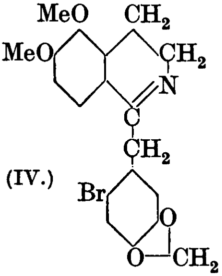
(II.)



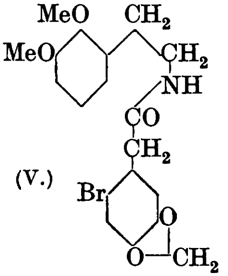
(III.)

however, did not condense with piperonal or veratraldehyde in the presence of either piperidine or methyl-alcoholic potassium hydroxide, from which it might be inferred that the effect of the nitro-group on the 1-methylene group is neutralised by the methylimino-grouping.

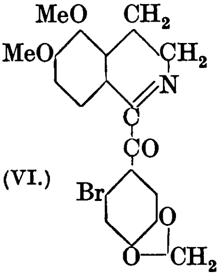
6′-*Bromo*-5 : 6-*dimethoxy*-3′ : 4′-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (IV) has been prepared from 3′ : 4′-*methylenedioxy*-6′-*bromophenylaceto*-β-2 : 3-*dimethoxyphenylethylamide* (V), and, like other bases of this type, it is oxidised by the air to 6′-*bromo*-5 : 6-*dimethoxy*-3′ : 4′-*methylenedioxy*-1-*benzoyl*-3 : 4-*dihydro*iso*quinoline* (VI) (compare Buck, Haworth, and Perkin, J., 1924, **125**, 2176).



(IV.)



(V.)



(VI.)

## EXPERIMENTAL.

β-2 : 3-Dimethoxyphenylpropionic acid was prepared as follows : 2 : 3-Dimethoxybenzaldehyde (10 g.), malonic acid (13 g.), pyridine (25 c.c.), and piperidine (0·5 c.c.) were heated for 1½ hours on the water-bath, then boiled for ¼ hour, and poured into dilute hydrochloric acid; the 2 : 3-dimethoxycinnamic acid was collected (yield, 95%), dissolved in 20% sodium hydroxide, and reduced at 80° with 4% sodium amalgam (200 g.). The mixture was filtered, acidified with hydrochloric acid, and the β-2 : 3-dimethoxyphenylpropionic acid collected and recrystallised from hot water (m. p. 68°).

β-2 : 3-*Dimethoxyphenylpropionamide*.—The foregoing acid (10 g.) was dissolved in chloroform (20 c.c.) and allowed to react for 1½ hours with thionyl chloride (6 c.c.) at the ordinary temperature. The mixture was poured into concentrated ammonia (50 c.c.) and water (50 c.c.), the chloroform removed by distillation, the residual liquid filtered from a little tar, and cooled; the resulting *amide* (9·5 g.) was crystallised from benzene in large, irregular prisms, m. p. 99—100° (Found: C, 62·8; H, 7·1. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2%), readily soluble in ether, alcohol, and hot water or benzene, but sparingly soluble in petroleum ether.

β-2 : 3-*Dimethoxyphenylethylamine*.—The amide (10 g.) was shaken with a solution of sodium hypochlorite, prepared by absorbing chlorine (from 33 g. of potassium permanganate and concentrated hydrochloric acid) in 10% sodium hydroxide (100 c.c.). When it had dissolved, the temperature was raised to 70° for 1 hour, the solution cooled, treated with sodium hydroxide (90 g.), heated to 80° for 1½ hours, cooled, thoroughly extracted with benzene, the extract dried, the benzene removed, and the residual oil (8 g.) distilled under diminished pressure. β-2 : 3-*Dimethoxyphenylethylamine* boils at 190°/70 mm. (Found: C, 66·5; H, 8·4. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%).

The *hydrochloride* is very soluble in water or alcohol, and separates as an oil on the addition of ether to the alcoholic solution. The *picrate*, prepared in alcoholic solution, crystallised from alcohol in yellow plates, m. p. 174—176° (Found: C, 47·1; H, 4·5. $C_{16}H_{18}O_9N_4$ requires C, 46·8; H, 4·4%).

5 : 6-*Dimethoxy*-3 : 4-*dihydro*iso*quinoline Methiodide* (II).—The above amine (10 g.) and anhydrous formic acid (7 g.) were heated at 180—200° for 3 hours. The resulting N-*formyl* derivative was dissolved in toluene (50 c.c.), phosphorus oxychloride (30 c.c.) added, and the mixture boiled for 1 hour; it was then diluted with petroleum ether (b. p. 40—60°), the solvent decanted from the brown gum, the latter dissolved in a little alcohol, poured into dilute hydrochloric acid, and non-basic impurities were extracted with benzene. The acid layer was made alkaline with sodium hydroxide, extracted with benzene, the extract dried over potassium carbonate, and the benzene removed, leaving 5 : 6-*dimethoxy*-3 : 4-*dihydro*iso*quinoline* (5 g.) as an oil which did not crystallise, but which dissolved completely in dilute hydrochloric acid to a pale yellow solution. The oil was boiled under reflux with methyl iodide, excess of the latter was removed by distillation, and the solid *methiodide* dissolved in methyl alcohol and precipitated by ether; pale yellow needles, m. p. 174—175° (Found: C, 43·3; H, 4·9. $C_{12}H_{16}O_2NI$ requires C, 43·2; H, 4·8%). This methiodide is very soluble in water and in methyl and ethyl alcohols, the yellow solutions possessing a green fluorescence.

5 : 6-*Dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (III).—The methiodide (II) (2 g.) was dissolved in dilute sulphuric acid, heated with excess of zinc dust on the water-bath until the solution became colourless, and filtered; the filtrate was made alkaline with ammonia, the oily base extracted with chloroform, the extract dried over potassium carbonate, and the solvent removed, whereby the *base* (III) was obtained as an oil which did not solidify on long standing. The *hydrochloride* was very soluble in water or alcohol. The *hydriodide* was obtained by adding potassium iodide to a solution of the base in dilute hydrochloric acid and recrystallising the

precipitated solid from ethyl alcohol; colourless nodules, m. p. 201° (decomp.) (Found : C, 43·2; H, 5·5. $C_{12}H_{18}O_2NI$ requires C, 43·0; H, 5·4%). The *picrate* separates from alcohol in yellow needles, m. p. 164° (decomp.).

8-*Nitro*-5 : 6-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (I).—A solution of the tetrahydro-base (1 g.) in glacial acetic acid (25 c.c.) was treated with concentrated nitric acid (2 c.c.) in acetic acid (5 c.c.) containing urea, the temperature being maintained below 20° for 4 hours. The nitration mixture was diluted with water, made alkaline with ammonia, the buff-coloured nitro-compound collected, and crystallised from aqueous methyl alcohol; almost colourless prisms, m. p. 104—105° (Found: C, 57·1; H, 6·4. $C_{12}H_{16}O_4N_2$ requires C, 57·2; H, 6·3%). The 8-*nitro*-5 : 6-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* is readily soluble in the usual organic solvents, and gradually turns green on exposure to light. It was reduced with zinc dust and hydrochloric acid and filtered; the addition of ferric chloride then produced a blue coloration. Numerous unsuccessful attempts were made to condense this base with piperonal or veratraldehyde under a variety of conditions, piperidine and alcoholic potassium hydroxide being used as catalysts.

6′-*Bromo*-3′ : 4′-*methylenedioxyphenylaceto*-β-2 : 3-*dimethoxyphenylethylamide* (V) was obtained by heating molecular proportions of β-2 : 3-dimethoxyphenylethylamine and 6-bromohomopiperonylic acid at 180° for 1½ hours. The *amide* crystallised from ethyl alcohol in colourless needles, m. p. 131° (Found: C, 53·9; H, 4·8. $C_{19}H_{20}O_5BrN$ requires C, 54·0; H, 4·7%).

6′-*Bromo*-5 : 6-*dimethoxy*-3′ : 4′-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (IV) was prepared by boiling the amide (V) (5 g.) for 1½ hours with phosphorus oxychloride (15 c.c.) and toluene (25 c.c.), adding petroleum ether, and decanting the solvents from the gum. The latter was dissolved in dilute sulphuric acid, filtered from tarry material, and made alkaline with sodium hydroxide; the oily base which separated rapidly hardened, and was collected, washed with water, and crystallised from ethyl alcohol; rhombic plates, m. p. 134—135° (Found: C, 55·9; H, 4·6. $C_{19}H_{18}O_4NBr$ requires C, 56·4; H, 4·5%). Alcoholic solutions of this base were slowly oxidised on exposure to the air to 6′-*bromo*-5 : 6-*dimethoxy*-3′ : 4′-*methylenedioxy*-1-*benzoyl*-3-4-*dihydro*iso*quinoline* (VI), which crystallises from alcohol in colourless warts, m. p. 168° (Found: C, 54·7; H, 4·1. $C_{19}H_{16}O_5NBr$ requires C, 54·5; H, 3·8%), and gives an intense green coloration on being warmed with acetic anhydride.

THE UNIVERSITY OF DURHAM, ARMSTRONG COLLEGE,
NEWCASTLE-ON-TYNE.

[*Received, August* 9*th*, 1927.]