372. *Experiments on the Synthesis of* iso*Quinoline Derivatives. Part II.*

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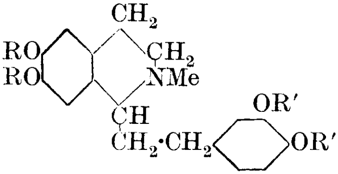
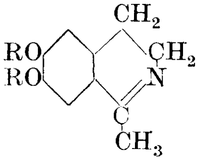
Attempts to prepare homologues of papaverine, containing a substituted 1-β-phenylethyl group (I) in place of the substituted 1-benzyl group, on the lines of the Bischler–Napieralski method were successful, but an alternative method, dependent on the condensation of (II) with aldehydes, failed because only *o*-nitrobenzaldehyde would react with this substance.

The acid amides derived from phthalic and camphoric anhydrides with β-piperonylethylamine and β-veratrylethylamine respectively gave the substances (III) and (IV).

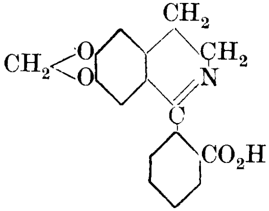
(I.)

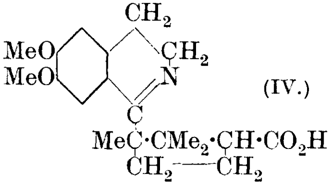




(II.)

(III.)





(IV.)

EXPERIMENTAL.

A mixture of 1-methylnorhydrastinine (II; $2RO = CH_2O_2$) (Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 299) (0·5 g.), *o*-nitrobenzaldehyde (0·4 g.), and a trace of NaOEt in abs. EtOH (10 c.c.), warmed for 5 mins. and kept for 2 hrs. at room temp., deposited yellow cryst. 1-*o*-*nitrostyrylnorhydrastinine* (0·75 g.), m. p. 132° after recrystn. from EtOH (Found : N, 8·6. $C_{18}H_{14}O_4N_2$ requires N, 8·7%).

1-Methylhydrastininium iodide (0·5 g.) (m. p. 257° after crystn. from C_6H_6), prepared from (II) and MeI, was reduced by hot H_2O (25 c.c.), Al–Hg, and a few drops of conc. HCl to 1-methyldihydrohydrastinine (0·2 g.); *picrate*, m. p. 192—193° (Found : N, 12·8. $C_{18}H_{18}O_9N_4$ requires N, 12·9%); hydrochloride, pale yellow needles, m. p. 221°.

The amide (m. p. 146°. Found : N, 4·0; calc., 4·0%) prepared from *β*-3 : 4-dimethoxyphenylpropionyl chloride and *β*-piperonylethylamine was dissolved (2 g.) in toluene (80 c.c.) and heated with $POCl_3$ (1·3 g.) at 110° for 1 hr. From the product, hot dil. HCl aq. (1 : 1) extracted 1-*β*-3′ : 4′-*dimethoxyphenylethylnorhydrastinine* (1 g.), m. p. 90° after crystn. from dil. EtOH (Found : N, 4·4. $C_{20}H_{21}O_4N$ requires N, 4·1%). This compound (1·5 g.) and MeI (2·5 g.) in warm dry C_6H_6 (10 c.c.) gave a cryst. *methiodide* (1·7 g.), m. p. 196° (Found : N, 2·6. $C_{21}H_{24}O_4NI$ requires N, 2·9%). The methiodide (0·4 g.), reduced with H_2O and Al–Hg as described above, furnished 1-*β*-3′ : 4′-*dimethoxyphenylethyldihydrohydrastinine* (0·25 g.) (I; $2RO = CH_2O_2$, $R' = Me$), m. p. 101° after crystn. from C_6H_6–ligroin (Found : N, 4·2. $C_{21}H_{25}O_4N$ requires N, 3·9%).

β-Piperonylpropiono-β-3′ : 4′-dimethoxyphenylethylamide (m. p. 149° after crystn. from dil. EtOH. Found : N, 4·1. $C_{20}H_{23}O_5N$ requires N, 3·9%) was treated (3·0 g.) in $CHCl_3$ (30 c.c.) with PCl_5 (4 g.), the solvent removed in vac. after 12 hrs., and the residue extracted with hot dil. HCl aq. (1 : 1);

from the extract, the hydrochloride of the dihydro*iso*quinoline crystallised in bright yellow needles, m. p. 187—188°. 6 : 7-*Dimethoxy*-1-*β*-*piperonylethyl*-3 : 4-*dihydro*iso*quinoline* (1·2 g.) had m. p. 75·5° after crystn. from xylene–ligroin; it gave a deep greenish-yellow fluorescence in C_6H_6 (Found : N, 4·4. $C_{20}H_{21}O_4N$ requires N, 4·1%). The *methiodide*, m. p. 175° after crystn. from EtOAc–MeOH (Found : N, 3·0. $C_{21}H_{24}O_4NI$ requires N, 2·9%), reduced (0·8 g.) with Al–Hg, gave the *tetrahydro*iso*quinoline* (0·5 g.), m. p. 101° (Found : N, 4·15. $C_{21}H_{25}O_4N$ requires N, 3·9%), which formed a *picrate*, m. p. 137° (Found : N, 9·6. $C_{27}H_{28}O_{11}N_4$ requires N, 9·6%). A trace of the base gave in conc. H_2SO_4 a permanganate-violet colour which became yellow on addition of H_2O, then persistent deep yellow on addition of a drop of HNO_3.

The following compounds were prepared by the methods described above. *β-Piperonylpropiono-β-piperonylethylamide*, m. p. 135° (Found : N, 4·4. $C_{19}H_{19}O_5N$ requires N, 4·1%). 1-*β*-*Piperonylethylnorhydrastinine* (yield, 33% and 73% by the PCl_5 and the $POCl_3$ method respectively), m. p. 105° (Found : N, 4·4. $C_{19}H_{17}O_4N$ requires N, 4·3%); *methiodide*, m. p. 229° (Found : N, 3·05. $C_{19}H_{17}O_4N,MeI$ requires N, 3·0%). 1-*β*-Piperonylethyldihydrohydrastinine, an oil; *picrate*, m. p. 102° (Found : N, 10·0. $C_{20}H_{21}O_4N,C_6H_3O_7N_3$ requires N, 9·9%). *β*-3 : 4-Dimethoxyphenylpropiono-*β*-3′ : 4′-dimethoxyphenylethylamide gave 6 : 7 : 3′ : 4′-*tetramethoxy*-1-*β*-*phenylethyl*-3 : 4-*dihydro*iso*quinoline*, m. p. 94° (Found : N, 4·1. $C_{21}H_{25}O_4N$ requires N, 3·95%); *picrate*, m. p. 129° (Found : N, 9·4. $C_{21}H_{25}O_4N,C_6H_3O_7N_3$ requires N, 9·6%); *methiodide* (Found : N, 2·9. $C_{21}H_{25}O_4N,MeI$ requires N, 2·8%). 6 : 7 : 3′ : 4′-Tetramethoxy-1-*β*-phenylethyl-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, an oil; *picrate*, m. p. 166° (Found : N, 9·3. $C_{22}H_{29}O_4N,C_6H_3O_7N_3$ requires N, 9·3%).

β-Piperonylethylamine (3 g.) and phthalic anhydride (2·7 g.) were heated together with a little NaOAc at 150—160° for 3 hrs., and the cooled mass was extracted with 5% NaOH aq. The insol. *phthalo-β-piperonylethylimide* (2 g.) had m. p. 140° after crystn. from EtOH (Found : N, 4·7. $C_{17}H_{13}O_4N$ requires N, 4·7%). The alkaline filtrate on acidification furnished *β-piperonylethylphthalamic acid*, m. p. 143° after crystn. from dil. EtOH (Found : N, 4·5. $C_{17}H_{15}O_5N$ requires N, 4·5%).

The aminic acid (0·6 g.), dissolved in dry $CHCl_3$ (30 c.c.), was heated with PCl_5 (0·8 g.) on the water-bath for 6 hrs., left for 4 days at room temp., and again refluxed for ½ hr. after addition of more $CHCl_3$ (20 c.c.). The solvent was removed, and the residue extracted with hot dil. HCl aq., dissolved in EtOH, treated with alkali, and acidified with AcOH; 6 : 7-*methylenedioxy*-1-*phenyl*-3 : 4-*dihydro*iso*quinoline*-2′-*carboxylic acid* (III) (0·1 g.), m. p. 175°, was obtained (Found : C, 69·0; H, 4·8; N, 4·9. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%).

The aminic acid (3·0 g.) prepared from camphoric anhydride and *β*-3 : 4-dimethoxyphenylethylamine in toluene (30 c.c.) was converted into the iso*quinoline* (IV) in 40% yield by $POCl_3$ (10 g.) at 110°. The reaction mixture was extracted with cold dil. HCl aq. (prolonged contact), and the extract was made alkaline with NH_3 aq. and then faintly acid with AcOH and extracted with much C_6H_6. The substance crystallised from C_6H_6–ligroin in silky needles, m. p. 65° (evolution of CO_2 at 85°), and showed a bluish-green fluorescence in EtOAc (Found : C, 66·2; H, 7·9; N, 4·3. $C_{20}H_{27}O_4N$ requires C, 66·3; H, 7·8; N, 4·1%).

Veratrylidene-β-piperonylethylamine (m. p. 78°. Found: N, 4·6; calc., 4·5%), prepared from veratraldehyde and the amine, was converted into the methiodide, m. p. 259° (cryst. from hot amyl alcohol), which (0·5 g.) in aq. EtOH was shaken with excess of Ag_2O (neutral); from the resulting solution, an oily base was isolated which formed a picrate, m. p. 179°, not identical with the picrate of 1-3′ : 4′-dimethoxyphenyldihydrohydrastinine.

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[*Received, August* 15*th*, 1932.]