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BENZYLISOQUINOLINE STUDIES. PART II

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The purpose of the present investigation was to develop a synthesis for pharmacologically interesting 4-benzylisoquinolines, if possible through the amino-alcohols of the type prepared in Part I (1).

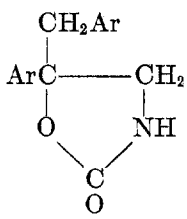
The first starting material investigated was β,γ-di-(3,4-dimethoxyphenyl)-β-hydroxypropylamine (II), which was easily available from 5′-(3,4-dimethoxyphenyl)-5′-(3,4-dimethoxybenzyl)-2′-oxazolidone (I) (1). The hydrochloride of II, upon treatment with boiling formic acid (2), did not give the expected N-formyl-derivative, but lost water and yielded the hydrochloride of β,γ-di-(3,4-dimethoxyphenyl)allylamine (III), which could be hydrogenated to β,γ-di-(3,4-dimethoxyphenyl)propylamine (IV). III was also obtained when II was heated with potassium hydrogen sulfate, but the yield was low, a neutral substance being the main product of the reaction. Treated with methylal and hydrochloric acid (3), II was not converted into an isoquinoline derivative; only a tar resulted.

A more satisfactory route to IV (over-all yield 75%) was found in the catalytic reduction of α-(3′,4′-dimethoxyphenyl)-3,4-dimethoxycinnamonitrile (V) (4, 5) which was obtained from veratraldehyde (VI) and homoveratryl cyanide (VII) (6) in the presence of catalytic amounts of sodamide in alcohol (7). Treatment of the N-acetyl compound (VIII) with phosphorus oxychloride in boiling xylene gave easily 4-(3′,4′-dimethoxybenzyl)-1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX), which was dehydrogenated with palladium-charcoal to 4-(3′,4′-dimethoxybenzyl)-1-methyl-6,7-dimethoxyisoquinoline (X).

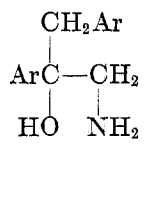
Compounds I, IV, VIII, IX, and X and the N-methyl derivative of I were devoid of analgesic action (Table I). Thanks are due to Dr. Hentrich of J.R. Geigy A.G. (Basle, Switzerland) for his courtesy in carrying out the pharmacological examination.

CHART I

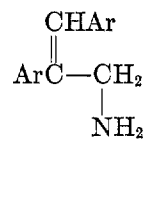
Ar = 3, 4-Dimethoxyphenyl



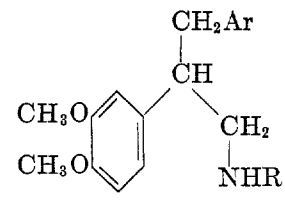
I



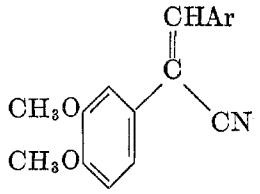
II



III



IV R = H
VIII R = $COCH_3$



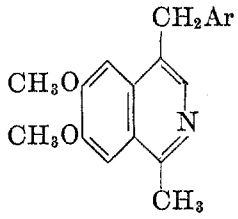
V

ArCHO

VI

$ArCH_2CN$

VII



X

IX 3, 4-dihydro

EXPERIMENTAL

β,γ-Di-(3,4-dimethoxyphenyl)-β-hydroxypropylamine (II). When 13 g. of 5'-(3,4-dimethoxyphenyl)-5'-(3,4-dimethoxybenzyl)-2-oxazolidone (I) (1) was introduced in portions into 30 cc. of concentrated hydrochloric acid, vigorous effervescence occurred. The clear solution was heated on the water-bath for 30 minutes. (Prolonged heating results in partial conversion into the hydrochloride of III). The solution was chilled, neutralized with potassium carbonate, and the base isolated by addition of an excess of sodium hydroxide solution and extraction with ether and benzene. Evaporation of the solvent left a viscous oil (8 g.) which solidifed upon standing. Recrystallized from anhydrous alcohol, the substance had m.p. 112°.

TABLE I

TESTS FOR ANALGESIC ACTION (MICE)

COMPOUND	DOSE (MG./KG.)	MODE OF APPLICATION	RESULT
I	100	*per os*	Negative
N-Methyl-I (1)	100	*per os*	Negative
IV (HCl)	50	Intraperitoneally	Negative
VIII	100	*per os*	Negative
IX	10	Intraperitoneally	Negative
	25	Intraperitoneally	Toxic
X	25	Intraperitoneally	Sedative
	50	Intraperitoneally	Toxic

Anal. Calc'd for $C_{19}H_{25}NO_5$: C, 65.8; H, 7.2; N, 4.0.

Found: C, 66.2; H, 7.5; N, 4.1.

Hydrochloride, m.p. 220°.

β,γ-Di-(3,4-dimethoxyphenyl)allylamine (III). (a) II (1.2 g.) was heated for 10 minutes with an equal quantity of potassium hydrogen sulfate at 150° under 10 mm. The melt was taken up with benzene and water and the aqueous layer was made alkaline and extracted with benzene. After evaporation of the solvent, the residue (0.2 g.) was recrystallized from a mixture of benzene and petroleum ether; m.p. 103°.

Anal. Calc'd for $C_{19}H_{23}NO_4$: N, 4.3. Found: N, 4.6.

Hydrochloride, m.p. 260–262°.

When hydrogenated in methanol at 100° and 500 p.s.i., in the presence of Raney nickel, β,γ-di-(3,4-dimethoxyphenyl)propylamine (IV) was formed.

(b) The hydrochloride of II (4 g.) and formic acid (40 cc.) were refluxed for 5 hours. The liquid was evaporated to dryness *in vacuo* and the residue triturated with 50 cc. of boiling benzene. The crystals so obtained melted at 260–262° and were identified (mixture m.p.) as the hydrochloride of III.

α-(3′,4′-Dimethoxyphenyl)-3,4-dimethoxycinnamonitrile (V). To 23 g. of homoveratronitrile (VII) (6) in 100 cc. of ethanol, there was added 23 g. of veratraldehyde (VI) and 0.3 g. of sodamide, and the mixture was refluxed for 5 minutes, during which time V crystallized almost completely. After cooling, the product (37 g.) was filtered and washed with ethanol. Recrystallized from benzene, it had m.p. 155° (4).

β,γ-Di-(3,4-dimethoxyphenyl)propylamine (IV). A solution of 23 g. of (V) in 200 cc. of methanol and 75 cc. of 20% methanolic ammonia was hydrogenated, in the presence of Raney nickel, at 100° and 500 p.s.i. After 4 hours, 90% of the calculated amount of hydrogen had been absorbed. The solution was filtered and evaporated *in vacuo*, the oily remainder dissolved in 100 cc. of 5% hydrochloric acid, and the solution extracted with benzene. The aqueous layer was made alkaline and the base extracted with benzene. After evaporation of the solvent, the residue was distilled *in vacuo*: b.p. 225–227°/0.4 mm.; yield, 19.5 g. The base was recrystallized from a little benzene and had m.p. 88–89°. The *hydrochloride* crystallized from ethanol upon addition of a little water, m.p. 223°.

Anal. Calc'd for $C_{19}H_{26}ClNO_4$: C, 62.1; H, 7.1; N, 3.8.
Found: C, 62.2; H, 7.1; N, 3.9.

N-Acetyl-β,γ-di-(3,4-dimethoxyphenyl)propylamine (VIII). To 6.6 g. of the base (IV) in 30 cc. of chloroform and 1.6 cc. of pyridine, was added, with vigorous stirring, 1.6 g. of acetyl chloride and 15 cc. of chloroform at 8–10°. Stirring was continued for one-half hour and the mixture left overnight. The filtered solution was washed once with water and twice with 5% acetic acid, dried, and evaporated. The residue (7.3 g.) was distilled *in vacuo*: b.p. 255°/0.3 mm. Recrystallization from ethyl acetate gave crystals, m.p. 110–112°.

Anal. Calc'd for $C_{21}H_{27}NO_5$: C, 67.5; H, 7.2; N, 3.8.
Found: C, 67.9; H, 7.5; N, 4.2.

4-(3′,4′-Dimethoxybenzyl)-1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX). A mixture of 2.5 g. of VIII, 7.5 cc. of phosphorus oxychloride, and 15 cc. of xylene was heated at 100° for one hour. After cooling, the supernatant liquid was decanted from the yellow cake, and the latter washed with water, treated with an excess of concentrated sodium hydroxide, and extracted with benzene-ether. The solution was evaporated and the residue distilled: b.p. 242–244°/0.3 mm.; yield, 2.1 g. Recrystallization from ethyl acetate gave the pure product, m.p. 123–124°.

Anal. Calc'd for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.0; N, 3.9.
Found: C, 71.4; H, 6.9; N, 4.0.

The *hydrochloride* crystallized from isopropanol, m.p. 187°.

Anal. Calc'd for $C_{21}H_{26}ClNO_4$: C, 64.4; H, 6.6; N, 3.6.
Found: C, 64.3; H, 6.7; N, 3.8.

4-(3′,4′-Dimethoxybenzyl)-1-methyl-6,7,-dimethoxyisoquinoline (X). The dihydro-compound (IX) (1 g.) was heated in a CO_2-atmosphere with 10% Pd-charcoal catalyst (0.2 g.) until about 75% of the calculated amount of hydrogen had been liberated. The product distilled at 230–235°/0.15 mm.; yield, 0.8 g. Recrystallized from propanol-2, it had m.p. 147–149°.

Anal. Calc'd for $C_{21}H_{23}NO_4$: C, 71.4; H, 6.5; N, 3.9.
Found: C, 71.6; H, 6.3; N, 4.1.

Hydrochloride, m.p. 210–211° (from a mixture of ethanol and acetone).

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