Tetrahedron, 1959, Vol. 7, pp. 118 to 122. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF SOME ISOQUINOLINE DERIVATIVES*

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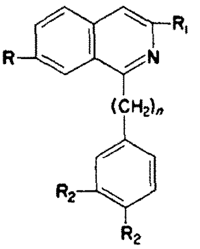
(*Received* 3 *November* 1958; *in revised form* 1 *April* 1959)

Abstract—The Bischler-Napieralski reaction has been applied to the synthesis of several isoquinoline derivatives related to papaverine but devoid of one or two methoxyl groups in positions 6 and 7.

THE isoquinoline derivatives Ia, b, c, d related to papaverine have been synthesized[1] with the object of subsequently investigating their physiological properties and to determine the influence of methoxyl groups in positions 6 and/or 7.



Ia,b,c,d

a: $R = R_1 = H, R_2 = OCH_3, n = 1$
b: $R = H, R_1 = CH_3, R_2—R_2 = O—CH_2—O, n = 1$
c: $R = H, R_1 = CH_3, R_2—R_2 = O—CH_2—O, n = 0$
d: $R = OCH_3, R_1 = H, R_2 = OCH_3, n = 1$

Ia was synthesized by condensing β-cylcohexa-1,4-dienylethylamine with 3,4-dimethoxyphenylacetyl chloride giving IIa which was cyclized forming the unstable intermediate IIIa. The latter on dehydrogenation gave IVa which was also obtained by cyclizing N-(3′,4′-dimethoxyphenylacetyl)-β-phenylethylamine. Further dehydrogenation of IVa by palladium in boiling ethyl cinnamate gave 1-(3′,4′-dimethoxybenzyl)-isoquinoline Ia. The structure of Ia is supported by the results of analyses and U.V. spectrum giving by Noller *et al.*[2] for papaverine.

Ib and Ic were synthesized by condensing 3-(cyclohexa-1′,4′-dienyl)-1′-(2-aminopropane) VII with 3,4-methylenedioxyphenylacetyl and 3,4-methylenedioxybenzoyl chlorides respectively, the products in each case being cyclized and dehydrogenated giving Ib and Ic. The amine VII was prepared by reducing 3-phenyl-3-methoxy-2 aminopropane V according to Birch,[3] and during the reaction the methoxyl group is removed. VI was therefore not obtained. VII was also prepared from propenyl-

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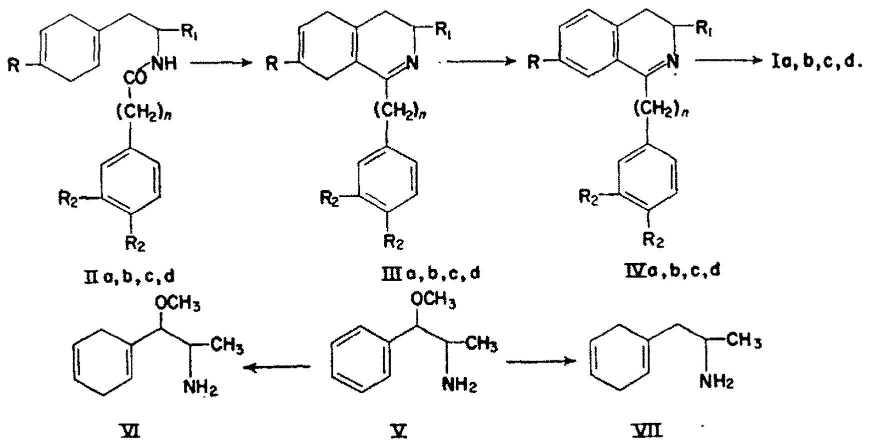
[1] S. Sugasawa and R. Tachikawa, *Tetrahedron* In press.

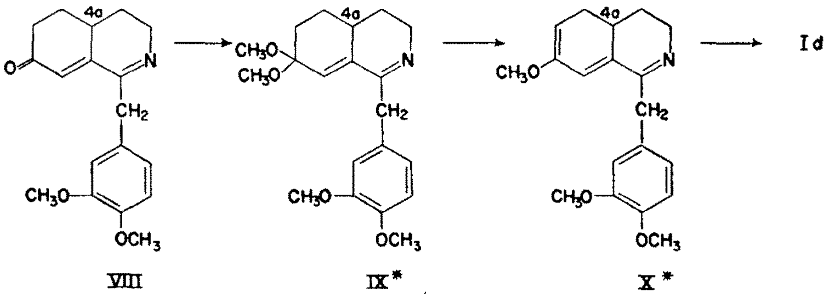
[2] R. C. Noller and R. Azima, *J. Amer. Chem. Soc.* 72, 18 (1950).

[3] A. J. Birch, *J. Chem. Soc.* 430 (1944); cf. also A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* 75, 5360 (1953).



benzene which was converted to 1-methoxy-1-phenyl-nitropropane via the nitrosite, and on reduction with lithium aluminium hydride gave V which by Birch's method gave VII.

For the synthesis of Id 4-methoxyphenylethylamine is reduced[1] to β-4-methoxy-cyclohexa-1,4-dienylethylamine, and the crude base was condensed with 3,4-dimethoxyphenylacetyl chloride yielding N-(3,4-dimethoxyphenylacetyl)-β-cyclohexa-1,4-dienylethylamine IId. Cyclization of the latter with phosphoryl chloride gave a poor yield[4] of the base IIId mixed with unchanged IId and resinous matter. Dehydrogenation of the mixture of IId and IIId gave the dihydro base IVd which was further dehydrogenated to Id. An alternative route for the synthesis of Id started from the crude base (obtained by cyclizing IId) which was treated with acid, yielding the keto-base VIII in which the presence of the conjugated keto group was indicated by the I.R. spectrum (1668 cm^{-1}). VIII was converted to the dimethylketal IX containing four methoxyl groups. Treatment of IX with aluminium t-butoxide[5] yielded with loss of one methoxyl group the unstable base X which was dehydrogenated giving Id.



EXPERIMENTAL

*N-(3′,4′-Dimethoxyphenylacetyl)-β-cyclohexa-*1,4-*dienylethylamine* (IIa)

β-Cyclohexa-1,4-dienylethylamine (6·2 g) in benzene (80 cc) during stirring and cooling was treated dropwise with freshly distilled 3,4-dimethoxyphenylacetyl chloride dissolved in 100 cc benzene

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[*] III. Communication of Extension of Bischler–Napieralksi Reaction by S. Sugasawa. II. Communication S. Sugasawa and S. Ushioda, *Tetrahedron* In press.

[†] The positions of the double bonds in these compounds are not exactly located.

[4] N. Itoh and S. Sugasawa, *Tetrahedron* **1**, 45 (1957).

[5] S. M. McElvain and G. R. McKay, *J. Amer. Chem. Soc.* 77, 5601 (1955).

in the presence of 200 cc 5% $NaHCO_3$ solution. After the addition of about 80% of the chloride the amide separated and was kept in solution by addition of ethyl acetate. After stirring a further 2 hr at room temp the supernatant layer yielded the amide (13·8 g; 91·6%) which crystallized from benzene: n-hexane as colourless needles, m.p. 111–112°. (Found: C, 71·5; H, 7·6; N, 4·55. $C_{18}H_{23}O_3N$ requires: C, 71·8; H, 7·6; N, 4·65%).

1-(3′,4′-*Dimethoxybenzyl*)-3,4-*dihydroisoquinoline* (IVa)

(a) The amide (IIa, 2·0 g) in 30 cc benzene mixed with 2 cc phosphoryl chloride was refluxed gently on a steam-bath for ½ hr. The solvent and the excess of phosphoryl chloride were removed *in vacuo* and the residue dissolved in dil HCl. The acid solution was basified and the liberated base taken up in benzene, washed, dried and the solvent removed. The residue (1·8 g), probably IIIa in 30 cc xylene was added to Pd-C (0·4 g of 30%) and the mixture refluxed for 3 hr in an atmosphere of N_2. The Filtrate free from catalyst was evaporated and the residue distilled *in vacuo* yielded a yellow viscous syrup (1·65 g) b.p. 194–197°/0·08 mm, U.V. $\lambda_{\max}^{\mathrm{EtOH}}$ 271 mμ (log ε 3·81), 312 mμ (log ε 3·31), 323 mμ (log ε 3·33). This was characterized as a crystalline picrate from ethanol, m.p. 154–155°. (Found: C, 56·0; H, 4·0; N, 10·7; $C_{24}H_{22}O_9N_4$: requires C, 56·5; H, 4·3; N, 11·0%).

(b) N-(3′,4′-Dimethoxyphenylacetyl)-β-phenylethylamine (6·0 g) m.p. 113–114° (Found: C, 71·9; H, 6·8; N, 4·9. $C_{18}H_{21}O_3N$ requires: C, 72·2; H, 7·0; N, 4·7%), in 200 cc xylene and phosphorus pentoxide (30 g) added in two portions during 1·5 hr was refluxed for 5 additional hr. The product purified through an alumina column, was a yellow oily substance (0·35 g) which gave a picrate m.p. 155–155·5° identical with that obtained by method (a).

1-(3′,4′-*Dimethoxybenzyl*)*isoquinoline* (Ia)

A solution of the above-mentioned base (2·0 g) in 20 cc ethyl cinnamate was heated over Pd-C (0·2 g, 30%) in an atmosphere of N_2 at 220–230° for 2·5 hr. On cooling the catalyst was filtered, washed with benzene and the combined benzene-filtrate shaken with 10% HCl. The acid solution, was basified and the liberated base, a yellowish brown syrup (1·73 g,) was again dissolved in benzene and purified through an alumina column. The product (1·52 g or 76·2%), crystallized from n-hexane as colourless needles m.p. 71–72°; U.V. $\lambda_{\max}^{\mathrm{EtOH}}$ 274 mμ (log ε 3·76), 311 mμ (log ε 3·49), 323 mμ (log ε 3·54). (Found: C, 77·3; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires: C, 77·4; H, 6·1; N, 5·0%).

The *picrate* was crystallized from ethanol, m.p. 164°. (Found: C, 56·8; H, 4·1; N, 10·8. $C_{24}H_{20}O_9N_4$ requires: C, 56·7; H, 3·9; N, 11·0%).

Propenylbenzene pseudonitrosite

Dilute sulphuric acid (410 g, 20%) was added dropwise with stirring and cooling to a mixture of propenyl benzene (30 g in 250 cc ether) and an aqueous solution of sodium nitrite (120 g). Solid pseudonitrosite separated but stirring was continued for an additional hour and the product then washed successively with water, a small amount of methanol and ether and dried, yield 26·3 g, m.p. 116–118° (decomp). (Found: C, 55·3; H, 5·2; N, 14·35. $(C_9H_{10}O_3N_2)_2$ requires: C, 55·7; H, 5·2; N, 14·4%).

1-*Methoxy*-1-*phenyl*-2-*nitropropane*

The pseudonitrosite (15 g) was added in small portions to a methanolic solution of KOH (100 cc, 10%) in a stoppered bottle and shaken into solution. Glacial acetic acid was added until the solution was neutral, the solvent evaporated *in vacuo* and sufficient water added to dissolve inorganic matter, with separation of an oily substance. The latter in benzene was washed, dried and evaporated to a yellow liquid, which distilled at 112–114°/5 mm, yielding 12·5 g (83·2%).

3-*Phenyl*-3-*methoxy*-2-*aminopropane* (V)

To a cooled ethereal solution of $LiAlH_4$ (6 g) was added dropwise with cooling and stirring an ethereal solution of the foregoing nitro-compound (13·8 g). After treatment with cold water and evaporation of the ethereal solution, the yellow oily base dissolved in dilute HCl was shaken with benzene, and basified with conc NaOH solution. The base in benzene was dried, the solvent evaporated and the residue distilled *in vacuo* in an atmosphere of H_2. The amine (8·8 g, 75·3%) distilled at 93–95°/6 mm. The *hydrochloride* formed colourless needles m.p. 186–188° from ethanol–acetone. (Found: C, 59·45; H, 8·1; N, 7·05; OCH_3, 15·2; $C_9H_{12}N(OCH_3)$ HCl requires: C, 59·55; H, 7·9; N, 6·95; OCH_3, 15·4%).

3-(*Cyclohexa*-1,4-*dienyl*)-1′-(2-*aminopropane*) (VII)

The amine (V, 6·6 g) in absolute ethanol (18·3 g) mixed with 100 cc liquid ammonia was reduced by adding 2·8 g lithium in small portions and cooling in ethanol–dry ice. After addition of the metal the mixture was stirred until the blue colouration disappeared. The crude base was distilled *in vacuo* in an atmosphere of H_2, yielding 5·2 g (95·3%) of a colourless clear distillate b.p. 71–72°/5 mm, which gave a negative result on CH_3O determination.

N-(3,4-*Methylenedioxyphenylacetyl*)-β-*cyclohexa*-1,4-*dienylisopropylamine* (IIb)

This was prepared as usual and formed colourless plates from n-hexane : benzene, m.p. 108–109°. The yield was 91·5%. (Found: C, 72·2; H, 6·8; N, 4·9; $C_{18}H_{21}O_3N$ requires: C, 72·2; H, 7·0; N, 4·7%).

1-(3,4-*Methylenedioxybenzyl*)-3-*methyl*-3,4-*dihydroxyisoquinoline* (IVb)

This was obtained in a yield of 71·3% by cyclizing IIb followed by dehydrogenation as described. U.V. λ_{max}^{EtOH} 276mμ (log ε 3·80), 318 mμ (log ε 3·46), 326 mμ (log ε 3·44). *Picrate*: Yellow prisms from ethanol, m.p. 170–171° (decomp). (Found: C, 57·0; H, 4·1; N, 10·9; $C_{24}H_{20}O_9N_4$ requires: C, 56·7; H, 3·9; N, 11·0%).

1-(3,4-*Methylenedioxybenzyl*)-3-*methylisoquinoline* (Ib)

This forms colourless prisms m.p. 87–88° from n-hexane; U.V. λ_{max}^{EtOH} 278 mμ (log ε 3·89), 317 mμ (log ε 3·54), 329 mμ (log ε 3·56). The yield was 77·3% from (IVb). (Found: C, 77·7; H, 5·6; N, 5·1; $C_{18}H_{15}O_2N$ requires: C, 78·0; H, 5·4; N, 5·05%). The *picrate* separated in yellow needles from ethanol–glacial acetic acid, m.p. 180°. (Found: C, 57·0; H, 3·9; N, 11·1; $C_{24}H_{18}O_9N_4$ requires: C, 56·9; H, 3·6; N, 11·1%).

N-(3′,4′-*Methylenedioxybenzoyl*-β-*cyclohexa*-1,4-*dienylisopropylamine* (IIc)

This forms colourless needles m.p. 83–84° from n-hexane. (Found: C, 71·6; H, 6·8; N, 5·2; $C_{17}H_{19}O_3N$ requires: C, 71·6; H, 6·7; N, 4·9%).

1-(3,4-*Methylenedioxyphenyl*)-3-*methyl*-3,4-*dihydroisoquinoline* (IVc)

This is obtained as a yellow syrup in 76·4% yield from IIc by cyclization and dehydrogenation. U.V. λ_{max}^{EtOH} 259 mμ (log ε 3·95), 293 mμ (log ε 3·83). The *picrate* forms yellow prisms from ethanol, m.p. 175–176° (decomp). (Found: C, 55·6; H, 3·6; N, 11·3; $C_{23}H_{18}O_9N_4$ requires: C, 55·9; H, 3·6; N, 11·3%).

1-(3′,4′-*Methylenedioxyphenyl*)-3-*methylisoquinoline* (Ic)

This was obtained in 72·5% yield by dehydrogenation of IVc and formed colourless needles m.p. 74–75° from n-hexane. U.V. λ_{max}^{EtOH} 285 mμ (log ε 3·96), 333 mμ (log ε 3·87). (Found: C, 77·3; H, 5·1; N, 5·3; $C_{17}H_{13}O_2N$ requires: C, 77·6; H, 4·9; N, 5·3%). The *picrate* forms yellow needles from ethanol, m.p. 184°. (Found: C, 55·85; H, 3·4; N, 11·4; $C_{23}H_{16}O_9N_4$ requires: C, 56·1; H, 3·25; N, 11·4%).

β-4-*Methoxycyclohexa*-1,4-*dienylethylamine*

4-Methoxyphenethylamine was reduced according to Birch's method and yielded a colourless liquid (92·1%) b.p. 78–78·5°/1 mm after distillation in an atmosphere of H_2. U.V. λ_{max}^{EtOH} 277 mμ (log ε 1·72). This base is fairly unstable and discolourizes gradually.

N-(3,4-*Dimethoxyphenylacetyl*)-β-*cyclohexa*-1,4-*dienylethylamine* (IId)

The foregoing base was treated with 3,4-dimethoxyphenylacetyl chloride to form IId (90·2%) which separated from benzene : n-hexane in colourless needles m.p. 91–93°. (Found: C, 68·6; H, H, 7·9; N, 4·1; $C_{19}H_{25}O_4N$ requires: C, 68·9; H, 7·55; N, 4·2%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxy*-3,4-*dihydroisoquinoline* (IVd)

A mixture of the amide (IId, 2 g) in benzene (50 cc) and phosphoryl chloride (2 cc) was gently refluxed on a steam-bath for 10–15 min. To the cooled mixture sufficient dry petroleum-ether was added to cause a reddish oil to separate. After standing the supernatant layer was discarded and the base extracted with benzene (ca. 100 cc), and addition of 100 cc 10% NaOH with vigorous shaking. The benzene layer was dried over K_2CO_3, the solvent evaporated *in vacuo* in an atmosphere of N_2 leaving a brown syrup, which in absolute xylene was refluxed over 30% Pd-C (0·5 g) in an atmosphere of N_2 for 4 hr. Filtered free from the catalyst the solvent was removed *in vacuo* and the residue in 10% HCl extracted with benzene, basified with NaOH solution, and the benzene, washed, dried and evaporated *in vacuo*. A brown residue dissolved in a mixture of n-hexane and benzene was filtered through an alumina column yielding a yellow syrup (0·21 g, 11·2%). U.V. $\lambda_{\max}^{\mathrm{EtOH}}$ 277 mμ (log ε 3·83), 310 mμ (log ε 3·37), 321 mμ (log ε 3·89). This was characterized as a crystalline *picrate*, m.p. 159–161° (decomp) from acetone. (Found: C, 55·3; H, 4·2; N, 10·0; $C_{25}H_{24}O_{10}N_4$ requires: C, 55·6; H, 4·4; N, 10·4%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxyisoquinoline* (Id)

This was obtained by dehydrogenation of IVd and formed colourless needles m.p. 85–86° from n-hexane, yield 60·4%, U.V. $\lambda_{\max}^{\mathrm{EtOH}}$ 277 mμ (log λ 3·85), 313 mμ (log ε 3·61), 323 mμ (log ε 3·63). (Found: C, 74·0; H, 6·3; N, 4·6; OCH_3, 29·85; $C_{19}H_{19}O_3N$ requires: C, 73·8; H, 6·15; N, 4·5; OCH_3, 30·1%). The *picrate* crystallizes in yellow prisms from ethanol : acetic caid, m.p. 171°. (Found: C, 55·45; H, 4·2; N, 10·6; $C_{25}H_{22}O_{10}N_4$ requires: C, 55·8; H, 4·1; N, 10·4%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*oxo*-3,4,4a,5,6,7-*hexahydroisoquinoline* (VIII)

The crude reddish oil, obtained by cyclizing IId with phosphoryl chloride was acidified with 10% HCl and undissolved matter was removed by extraction with benzene. The acid solution with benzene was warmed (steam-bath) for several min, cooled and basified with Na_2CO_3 solution and the benzene, washed, dried and part of the solvent evaporated. The residual solution was filtered through an alumina column and a yellow syrup obtained on evaporation of the solvent. The base (39·8%) solidified and crystallized from n-hexane: acetone in pale yellow prisms m.p. 176–178°. I.R. $\upsilon_{\max}^{\mathrm{Nujol}}$ 1668 cm^{-1} ($>C{=}C{-}C{=}O$). (Found: C, 71·9; H, 6·8; N, 4·7; OCH_3, 20·3; $C_{16}H_{15}ON(OCH_3)_2$ requires: C, 72·2; H, 7·0; N, 4·7; OCH_3, 20·7%).

The 2:4-*dinitrophenylhydrazone sulphate* crystallized as red needles m.p. 212–214° (decomp) from ethanol. (Found: C, 49·55; H, 4·8; N, 12·0; $C_{24}H_{25}O_8N_5H_2SO_4$ requires; C, 49·9; H, 4·7; N, 12·1%).

1-(3′,4′-*Dimethoxybenzyl*)-7,7-*dimethoxy*-3,4,4a,5,6,7-*hexahydroisoquinoline* (IX)

To a well cooled mixture of the oxo-compound (VIII, 0·6 g) and methyl orthoformate (4 cc) dry hydrogen chloride was bubbled and the mixture refluxed (steam-bath) for 2·5 hr. Excess formate was distilled off and the dark brown residue well kneaded with powdered K_2CO_3 (2 g), covered with ether and dilute K_2CO_3 solution (20 cc, 5%) added with cooling.

The aqueous layer was extracted with ether and the ethereal solution dried (K_2CO_3) and evaporated. The resultant brown residue in benzene : n-hexane was filtered through an alumina column and 0·32 g (46·2%) of a yellow syrup obtained. (Found: OCH_3, 35·3; $C_{16}H_{15}N(OCH_3)_4$ requires: OCH_3, 35·9%). The methiodide was prepared as usual and formed yellow prisms m.p. 198–201° (decomp) from ethanol. (Found: C, 51·5; H, 5·9; N, 3·1; $C_{21}H_{31}O_4NI$ requires: C, 51·6; H, 6·2; N, 2·9%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxyisoquinoline* (Id)

The ketal (IX, 0·25 g) in a small amount of benzene was well mixed with a few drops of aluminum t-butoxide in benzene and the residue obtained by evaporation of the solvent was heated (oil-bath) at 200–220° in an atmosphere of N_2 for 2 hr. The product was extracted with benzene, mixed with n-hexane, and filtered through an alumina column. On evaporating the filtrate the reddish oil (0·11 g) was dehydrogenated in boiling ethyl cinnamate over Pd-C. The product (0·05 g, 22·3%) m.p. 85–86° was not depressed on admixture with Id obtained by the alternative method.

Acknowledgement—The author wished to express his hearty appreciation to Prof. S. Sugasawa for his interest in this work. Thanks are also due to Messrs. G. Chihara and K. Tanigawa for IR spectral data and to E. Ohki for U.V. spectra.