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The Synthesis of Tetrahydroisoquinolines from 1,4-Dihydro-3(2*H*)-isoquinolones

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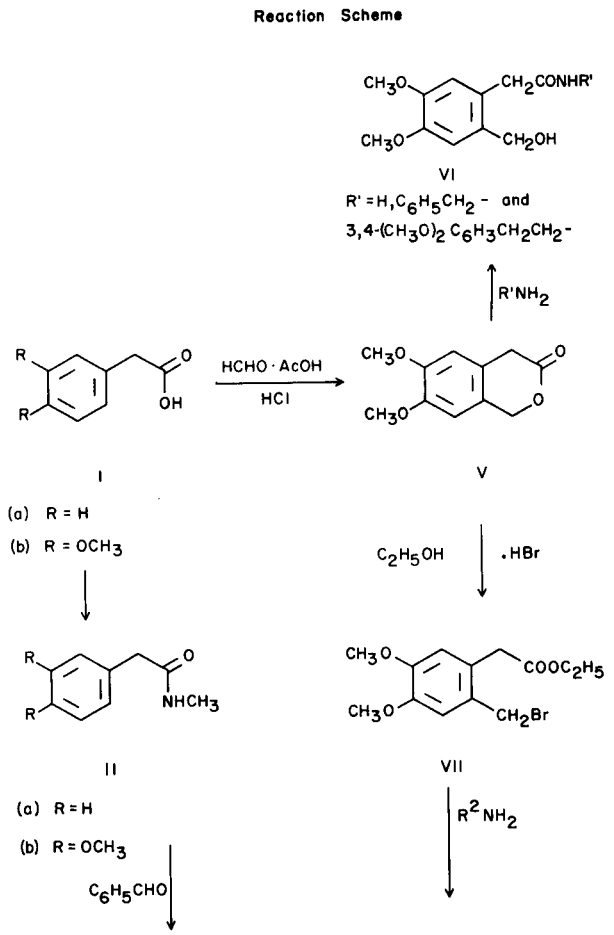
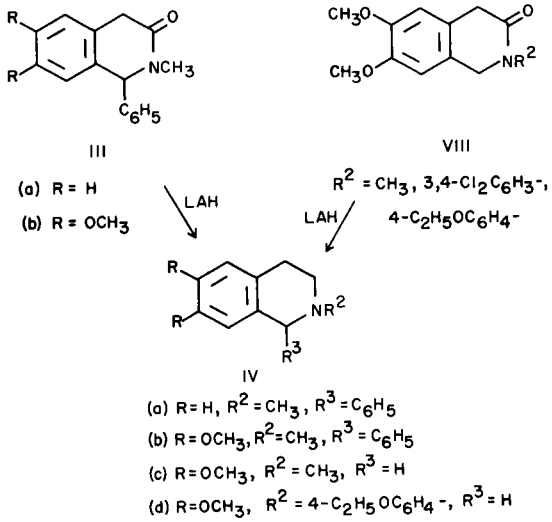
Experimental procedures are given for the facile synthesis of various types of 1,4-dihydroisoquinolones and their reduction to the corresponding 1,2,3,4-tetrahydroisoquinolines.

In the course of synthesizing certain 1,2,3,4-tetrahydroisoquinolines IV we found that they can be obtained conveniently by reduction of their corresponding 1,4-dihydro-3(2*H*)-isoquinolones. These lactams, represented by compounds III and VIII, have been prepared by the two routes shown in the following scheme.

Reaction Scheme





Phenylacetic acid Ia was converted into *N*-methylphenylacetamide (IIa) (2) which was than allowed to react with benzaldehyde in polyphosphoric acid to give 1,4-dihydro-2-methyl-1-phenyl-3(2*H*)-isoquinolone (IIIa) (3). This compound was then reduced by lithium aluminum hydride in anhydrous ether to give 1,2,3,4-tetrahydro-2-methyl-1-phenylisoquinoline (IVa) having the same melting point with that obtained by another synthesis (4), and confirmed by infrared and nmr spectral evidence.

In a similar manner, homoveratric acid Ib, via its acid chloride, was converted to *N*-methylhomoveratramide IIb, which was allowed to react with benzaldehyde in trifluoroacetic acid to give 1,4-dihydro-6,7-dimethoxy-2-methyl-1-phenyl-3(2*H*)-isoquinolone (IIIb). When IIIb was refluxed with lithium aluminum hydride in dry ether, 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (IVb) was obtained.

In another series of reactions, homoveratric acid Ib was treated with formaldehyde and hydrochloric acid in acetic acid solution to form 6,7-dimethoxy-3-isochromanone (V). When V was allowed to react with ammonia under pressure or refluxed with benzylamine and homoveratrylamine, the corresponding amides VI were obtained. These structures were confirmed by physical data, as well as by elemental analyses. Alternatively, V upon treatment with ethanolic hydrogen bromide yielded the ethyl ester VII, which reacted with methylamine, 3,4-dichloroaniline, and 4-ethoxyaniline to give the corresponding 3(2*H*)-isoquinolones VIII. When VIII (R^2 = CH_3 and 4-$C_2H_5OC_6H_4$-) was refluxed with lithium aluminum hydride, the corresponding tetrahydroisoquinolines IVc and IVd were readily obtained.

EXPERIMENTAL (5)

1,4-Dihydro-2-methyl-1-phenyl-3(2*H*)-isoquinolone (IIIa).

A mixture of 14.9 g. (0.1 mole) of *N*-methylphenylacetamide (IIa) and 10.6 g. of benzaldehyde in 400 g. of freshly prepared polyphosphoric acid was stirred under nitrogen and heated at 150° for 5 hours. The dark brown solution was poured into 1200 ml. of water, and the separated oil was extracted with chloroform. The chloroform extract was washed successively with water, a saturated aqueous solution of sodium bisulfite, water, dried, and concentrated *in vacuo* to about 50 ml. This solution was passed through a column of alumina (20 x 1.8 cm), and the eluate evaporated to leave 9.5 g. of an oil. This product was taken up in warm hexane, stirred with charcoal, filtered hot to give a light colored filtrate, which deposited beige crystals when cooled, m.p. 72–78°. Upon recrystallization from hexane, IIIa was obtained as white crystals, which were dried *in vacuo* at 70°, m.p. 93–94°, yield, 5 g. (21%).

Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 80.96; H, 6.06; N, 5.91.

1,2,3,4-Tetrahydro-2-methyl-1-phenylisoquinoline (IVa).

A mixture of 1.18 g. (0.005 mole) of IIIa and 1 g. (0.026 mole) of lithium aluminum hydride in 150 ml. of dry ether was stirred and refluxed for 3 hours. After cooling to 0° and with stirring, 1 ml. of cold water, 0.8 ml. of 20% sodium hydroxide, and 3.7 ml. of cold water were added successively. The reaction mixture was allowed to reach room temperature, and then refluxed until a solid precipitated. This was filtered, the ethereal solution was dried, evaporated *in vacuo* to give an oil, which solidified upon cooling to 0°. It was crystallized from water-ethanol mixture and further purified by passing a petroleum ether (30–60°) solution through a column of alumina (1 x 9 cm). The colorless eluate, upon evaporation at room temperature, deposited white needles of IVa, m.p. 70.5–71° (4), yield, 0.66 g. (59%).

The methiodide, prepared by adding methyl iodide to an ethereal solution of the base at room temperature, was obtained as a yellow crystalline product, m.p. 236–238° (6).

2-(3,4-Dimethoxyphenyl)-*N*-methylacetamide (IIb).

A solution of 9.8 g. (0.05 mole) of 3,4-dimethoxyphenylacetic acid (Ib) and 12 g. (0.1 mole) of thionyl chloride in 100 ml. of dry toluene was warmed until the reaction was completed, and then evaporated *in vacuo*. The residue was diluted with 100 ml. of dry toluene, and evaporated *in vacuo*, this process being done three times. The acid chloride was dissolved in 100 ml. of dry ether, and this solution was added slowly to a well-stirred solution of 15 g. of methylamine in 100 ml. of dry ether at 0°. The crystals of methylamine hydrochloride were filtered, and the filtrate evaporated *in vacuo* to a solid, m.p. 97–98°, unchanged after recrystallization from ethyl acetate, yield 6.2 g. (60%).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.10; H, 7.18; N, 6.70. Found: C, 63.33; H, 7.21; N, 6.62.

This compound can also be prepared by heating an alcoholic solution of ethyl 3,4-dimethoxyphenylacetate with methylamine at 125° for 24 hours in an autoclave.

1,4-Dihydro-6,7-dimethoxy-2-methyl-1-phenyl-3(2*H*)-isoquinolone (IIIb).

A solution of 6.3 g. (0.03 mole) of IIb and 3.5 g. (0.033 mole) of benzaldehyde in 25 ml. of trifluoroacetic acid was refluxed for 2 hours and poured onto 300 ml. of chipped ice to give a tan precipitate. It was dissolved in chloroform, washed with a sodium carbonate solution until neutral, and the solvent was evaporated. The residual oil was dissolved in ethyl acetate, washed with several portions of a saturated solution of sodium bisulfite, dried, and the solvent evaporated to give a solid, m.p. 133–139°. Recrystallization from a mixture of ethanol-petroleum ether (30–60°) raised the melting point to 140–142°. Repetition of this preparation starting with 20.9 g. of the amide gave 16 g. (54%) of IIIb.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.40; N, 4.71. Found: C, 72.44; H, 6.69; N, 4.82.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (IVb).

A mixture of 1.0 g. (0.0033 mole) of IIIb and 1.0 g. (0.026 mole) of lithium aluminum hydride in 500 ml. of dry ether was stirred and refluxed for 20 hours and decomposed at 0° by the successive additions of 1.0 ml. of cold water, 0.8 ml. of 20% aqueous sodium hydroxide solution, and 3.7 ml. of water. This precipitate was filtered, and the dried ethereal filtrate was evaporated to yield approximately 600 mg. (63%) of a solid, which was recrystallized from hexane to give white crystalline product, m.p. 75–77°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.32; H, 7.42; N, 4.95. Found: C, 76.10; H, 7.71; N, 4.74.

Hydrochloride of IVb, m.p. 234–236°.

Anal. Calcd. for $C_{18}H_{21}NO_2 \cdot HCl$: C, 67.63; H, 6.93; N, 4.38. Found: C, 67.67; H, 7.05; N, 4.69.

6,7-Dimethoxy-3-isochromanone (V).

A solution of 11.7 g. (0.06 mole) of homoveratric acid (Ib) in 30 ml. of hot acetic acid was mixed with 10 ml. of concentrated hydrochloric acid and 10 ml. of 37% formalin, and heated on a steam bath for 1 hour. The cooled dark solution was poured into 300 ml. of cold water, and extracted with chloroform. The organic extract was washed with 5% sodium bicarbonate until neutral, with water, dried, and concentrated *in vacuo*. The oily residue promptly solidified and was recrystallized from ethanol, m.p. 108–109.5°, yield 10.5 g. (84%).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.59; H, 6.10.

Ethyl 2-Bromomethyl-4,5-dimethoxyphenylacetate (VII).

To a solution of 20 g. of hydrogen bromide in 300 ml. of absolute ethanol at 10°, 4.2 g. (0.02 mole) of V was added. The solid dissolved as the reaction mixture was stirred and permitted to reach room temperature. After 20 hours at room temperature, the solvent was evaporated at 3–5 mm and 20°. This material was used without purification.

1,4-Dihydro-6,7-dimethoxy-2-methyl-3(2*H*)-isoquinolone (VIII, $R^2 = CH_3$).

To 8.5 g. (0.025 mole) of VII, 75 ml. (1.7 moles) of methylamine was added, and the mixture heated at 100° for 10 hours in a rocking glass-lined autoclave under 1000 lb. pressure of nitrogen. After the amine was evaporated, the residual product was recrystallized from ethanol to give yellowish crystals, m.p. 119.5–121.5°, yield 2.5 g. (40%).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.15; H, 6.78; N, 6.33. Found: C, 65.25; H, 6.52; N, 6.37.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinoline Hydrochloride (IVc).

A mixture of 1 g. (0.0045 mole) of isoquinolone (VIII, R^2 = CH_3) and 1 g. (0.026 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether was stirred and refluxed for 20 hours. The excess lithium aluminum hydride was decomposed at 0° with ethyl acetate and the mixture was made alkaline with dilute aqueous sodium hydroxide solution. The ether solution was shaken with several portions of dilute hydrochloric acid, and the combined acid extracts, when made alkaline, gave a white precipitate. The solid was then dissolved in ether, washed with water, dried, and treated with dry hydrogen chloride, yield, 0.65 g. (64%), recrystallized from 2-propanol, m.p. 216.5–217.5° (7).

Anal. Calcd. for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.18; H, 7.39; N, 5.75. Found: C, 59.33; H, 7.67; N, 5.67.

2-(4-Ethoxyphenyl)-1,4-dihydro-6,7-dimethoxy-3(2*H*)-isoquinolone (VIII, R^2 = 4-$C_2H_5OC_6H_4$-).

A solution of VII [obtained from 4.2 g. (0.02 mole) of V] in 200 ml. of absolute ethanol and 13.7 g. (0.1 mole) of *p*-phenetidine was heated at 100° for 8 hours in a rocking glass-lined autoclave under 1000 lb. pressure of nitrogen. The ethanol was removed *in vacuo* and the black oily residue was diluted with 50 ml. of water, and extracted with chloroform. The chloroform solution was washed with water, dried, concentrated *in vacuo* to a dark brown oil, which crystallized on standing. The product recrystallized first from ethanol, and then from ethyl acetate was obtained as yellow crystals, m.p. 167–170°, yield, 2.5 g. (38%).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.99; H, 6.15; N, 4.42.

1,2,3,4-Tetrahydro-2-(4-ethoxyphenyl)-6,7-dimethoxyisoquinoline (IVd).

A mixture of 9.6 g. (0.03 mole) of VIII (R^2 = 4-$C_2H_5OC_6H_4$-) and 4.5 g. (0.12 mole) of lithium aluminum hydride in 500 ml. of tetrahydrofuran was stirred and refluxed for 3 hours. After decomposing the excess lithium aluminum hydride with water, and filtering, the filtrate was evaporated *in vacuo* to give a solid residue, which was recrystallized from ethanol, m.p. 114–119°. The product, dissolved in benzene, was passed through a short column of alumina, evaporated to dryness, and recrystallized from ethanol; m.p. 117–119°, yield, 6.0 g. (57%).

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.34; N, 4.47. Found: C, 72.81; H, 7.23; N, 4.47.

2-(3,4-Dichlorophenyl)-1,4-dihydro-6,7-dimethoxy-3(2*H*)-isoquinolone (VIII, R^2 = 3,4-$Cl_2C_6H_3$).

As described for VIII above, 32 g. (0.1 mole) of crude VII in 1000 ml. of absolute ethanol was allowed to react with 65 g. (0.4 mole) of 3,4-dichloroaniline in an autoclave. The reaction mixture was concentrated *in vacuo* to give a solid, which was suspended in water, and extracted with chloroform. This extract was washed with dilute hydrochloric acid, water, dried, and passed through a column of alumina. The eluate was evaporated to give a solid, which was recrystallized from ethanol, m.p. 147.5–150°, yield 24 g.

Anal. Calcd. for $C_{17}H_{15}Cl_2NO_3$: C, 57.95; H, 4.26; N, 3.97. Found: C, 57.68; H, 4.17; N, 4.08.

2-Hydroxymethyl-4,5-dimethoxyphenylacetamide (VI, R′ = H).

In a rocking glass lined autoclave, 3.4 g. (0.016 mole) of V was allowed to react for 8 hours at 130° with 150 ml. of a 14% ethanolic ammonia solution under 1000 lb pressure of nitrogen. The reaction mixture was concentrated *in vacuo* to a solid, yield, 3 g. (83%). Upon recrystallization from 2-propanol, the pure product was obtained as beige crystals, m.p. 168–170°. The nmr spectrum (δ) showed: (DMSO-d_6) 3.42, singlet (CH_2CO); 3.75, singlet (2 CH_3O); 4.48, doublet (CH_2O); 5.17, triplet (OH); 6.90 and 7.02, singlets (2 aromatic H); 6.95 and 7.48, broad (NH_2); after exchange with deuterium oxide, 5.17 disappears and 4.48 becomes a sharp singlet. The IR showed: ν max (KBr), 3380, 3180, 1660, 1605, 1516, 1270 and 1230 cm^{-1}.

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.66; N, 6.22. Found: C, 58.50; H, 6.34; N, 6.15.

N-Benzyl-2-hydroxymethyl-4,5-dimethoxyphenylacetamide (VI, R′ = $C_6H_5CH_2$).

A solution of 2.0 g. (0.01 mole) of V in 25 ml. (0.23 mole) of benzylamine was refluxed for 17 hours. The solution was cooled, acidified with 3 *N* hydrochloric acid and extracted with ether. The aqueous layer deposited a solid substance upon standing at room temperature. The solid was filtered, washed with water, and recrystallized from ethyl acetate to give 1.5 g. (47%) of the product, m.p. 124–125.5°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.57; H, 6.66; N, 4.44. Found: C, 68.33; H, 6.71; N, 4.52.

N-(3,4-Dimethoxyphenethyl)-2-hydroxymethyl-4,5-dimethoxyphenylacetamide (VI, R′ = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2$-).

A solution of 6.2 g. (0.03 mole) of V and 6.6 g. (0.036 mole) of homoveratrylamine in 100 ml. of ethanol was refluxed 18 hours and evaporated to dryness *in vacuo*. The residual solid was recrystallized from ethanol to give the pure product; yield 9.0 g. (64%), m.p. 123.5–126°.

Anal. Calcd. for $C_{21}H_{27}NO_6$: C, 64.78; H, 6.94; N, 3.59. Found: C, 64.45; H, 6.91; N, 3.63.

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on 10–15% (w/v) solutions with TMS as internal standard. All melting points are corrected and were taken on a Uni-Melt Thomas-Hoover Capillary melting point apparatus. Woelm Grade I neutral alumina was used wherever the absorbant name was mentioned.

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