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SYNTHESIS OF 6,7-DIHYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES

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Abstract—Some sixty 1-substituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines were synthesized for pharmacological evaluation. 1-(3′,4′,5′-trimethoxybenzyl) derivative thus prepared was found to be the most active bronchodilator both *in vitro* and *vivo* test hitherto described in the literature.

SYNTHESIS and pharmacological studies of various isoquinoline derivatives have been ardently pursued in our laboratories.

During their work, Kiyomoto and Iwazawa found a salient bronchodilating activity in 1-(3′,4′-dihydroxybenzyl) 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (I) hydrochloride.[1] This compound was first synthesized by Pyman[2] in 1909 and its hypotensive action was reported by Laidlow[3] in the following year.

While our work was in progress, Holtz[4] demonstrated enzymatic formation of this compound from dopamine, and expressed the view that in pharmacological activity it resembled (±)-N-isopropylnoradrenaline (isoproterenol). This adrenergic β-stimulant is at present clinically used as bronchodilator. The studies of Kiyomoto *et al.* were first focused on the bronchodilator action of isoquinoline derivatives.

In order to investigate the structure-activity relationship 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (II) was prepared and tested. This also showed a distinct activity, which was found to reside only in the (−)-form. However, the (+)-form did not appreciably antagonize the action of the (−)-form. But the N-methyl, 3-methyl, 1,2-dehydro and 6- or 7-monohydroxy derivatives of this compound as well as its allied derivatives, i.e. 1-phenyl, 1-phenethyl and 1-(3-phenylpropyl) derivatives, were uniformly inactive.

In order to obtain information regarding the function of the two sets of dihydroxy groups, 1-(3′,4′-ethylenedioxybenzyl) 6,7-dihydroxy- (III) and 1-(3′,4′-dihydroxybenzyl) 6,7-ethylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV) were synthesized.

When pharmacologically tested, only the former was found to possess activity considerably stronger than that of the above mentioned 1-benzyl derivative (II). This indicated that the two hydroxy groups at 6 and 7 positions are essential for the activity, whereas those at 3′ and 4′ position appear to have a secondary role[5] and may

[1] Our compound had been prepared by Dr. Y. Kanaoka some fifteen years ago. During storage in a cork stoppered specimen tube, it changed to a dark gray crystalline powder. For the present pharmacological study it was once crystallized from dilute hydrochloric acid.

[2] F. L. Pyman, *J. Chem. Soc.* **95**, 1610 (1909).

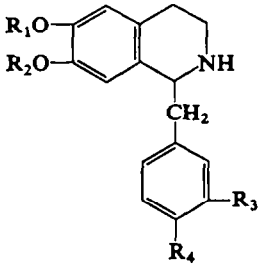
[3] P. P. Laidlaw, *J. Physiol.* (*London*) **40**, 480 (1910).

[4] P. Holtz, *Arch. exp. Path. u. Pharmak.* **248**, 387 (1964).

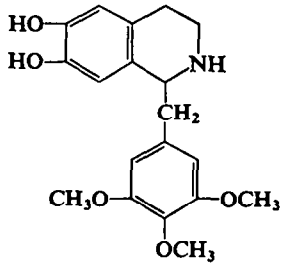
[5] For Holtz's view cf. *Pharmacol. Review* **18**(1), Part 1, 85, (1966).

advantageously be substituted by alkoxyl groups. 1-Alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline[6] is reported to manifest similar bronchodilator activity.

Based on the above experimental results, no less than sixty compounds of the 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline type were synthesized and finally the 1-(3′,4′,5′-trimethoxybenzyl) derivative (V), was found to be the most active bronchodilator hitherto described in the literature.



I: $R_1=R_2=H$; $R_3=R_4=OH$
II: $R_1=R_2=R_3=R_4=H$
III: $R_1=R_2=H$; $R_3—R_4=O\cdot CH_2—CH_2\cdot O$
IV: $R_1—R_2=\cdot CH_2—CH_2\cdot$; $R_3=R_4=OH$



V

As shown in the accompanying Table the hydrochloride of this compound is about ten times as active as isoproterenol in *in vitro* and about five times as active in *in vivo* tests, and yet the acute toxicity is very low. This compound is now under clinical investigation.

In addition to the bronchodilator activity, all the isoquinolines synthesized in our laboratory are being tested for their cardio-vascular activity and the results will be presented in detail elsewhere by Kiyomoto *et al.*

Compounds II, III and IV were prepared by the conventional Bischler-Napieralski reaction of the appropriate amides, followed by reduction and demethylation. Compound V was synthesized from 3,4-dihydroxyphenylethylamine and 3,4,5-trimethoxyphenylacetaldehyde in the nascent state under Pictét-Spengler conditions as specified in the experimental section.

Optical resolution of (±)-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was successful with D-(−)quinic acid. Thus, from a methanolic solution of an equimolar mixture of these two components, the (−)-base: (−)-acid separated in excellent yield. The hydrochloride of the pure base showed $[\alpha]_D^{21}$ − 28·6°.

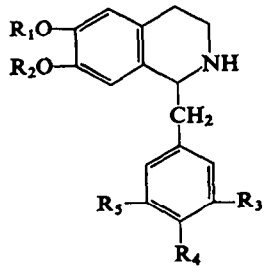
The antipodal (+)-base recovered from the original filtrate was treated with dibenzoyl-(+)-tartaric acid to separate the (+)-base: (+)-acid, which was purified and the (+)-base liberated. This was characterized as the hydrochloride salt ($[\alpha]_D^{18}$ +27·1°).

The pure (−)- and (+)-bases thus obtained were then demethylated by heating with conc. hydrochloric acid under pressure to afford (+)-(II)hydrochloride and (−)-(II)-hydrochloride respectively.

In order to prove the optical purity of these demethylated products, the (+)-(II) salt was dissolved in methanol and treated with a large excess of ethereal diazomethane

[6] P. N. Craig, F. P. Nabenhauer, P. N. Williams, E. Macko and J. Toner, *J. Amer. Chem. Soc.* **74**, 1316 (1952).

TABLE



R_1	R_2	R_3	R_4	R_5	Potency ratio
H	H	H	H	H	24
H	H	OH	OH	H	31
H	H	O—CH_2—	—CH_2—O	H	31
CH_2—CH_2		OH	OH	H	<0·01
H	H	OCH_3	OCH_3	OCH_3	20,000
Epinephrine					100
Isoproterenol					2,200

solution, and the product treated according to Eschweiler-Clark to ensure complete N-methylation. 1-Benzyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline thus obtained was identical in every respect with the N-methylated product of (−)-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. The optical stability of the original bases during the demethylation procedure was thus established.

The streochemistry of these bases was deduced from their ORD curves. (−)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, its N-methyl derivative as well as the corresponding demethylated base (II) hydrochloride all showed a negative Cotton effect, indicating 1 R-configuration[7] in this series. Therefore, the antipodal (−)-(II)hydrochloride, which only is pharmacologically active, assumes 1 S-configuration.

EXPERIMENTAL

1-*Benzyl-6,7-dihydroxy*-1,2,3,4-*tetrahydroisoquinoline* (II). A mixture of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2 g) and conc. HCl (10 ml) was heated in a sealed tube at 150–160° (oil-bath temp) for 2 hr. After cooling, the crystalline mass was collected and purified from MeOH–ether, forming colourless grouped minute prisms, m.p. 245–246° (dec), yield 1·3 g (71·5%). (Found: C, 65·9; H, 6·2; N, 4·8; Cl, 12·15. $C_{16}H_{17}O_2N.HCl$ requires: C, 65·9; H, 6·0; N, 5·1; Cl, 12·2%).

3,4-*Ethylenedioxyphenylacet*-(3,4-*dimethoxyphenyethylamide*). A mixture of homoveratrylamine (3·9 g) and ethyl 3,4-ethylenedioxyphenylacetate [8](3·3 g) was heated at 190–200° (oil-bath temp) for 3·5 hr. After cooling, the reaction product was dissolved in benzene and the soln washed with dil HCl and then with water, dried and the solvent removed. The solid residue was purified from EtOH to form colourless needles, m.p. 143–143·5°, yield 4·1 g (77·4%). (Found: C, 66·55; H, 6·2; N, 3·9. $C_{20}H_{23}O_5N$ requires: C, 67·2; H, 6·5; N, 3·9%).

[7] M. Ohta, H. Tani, S. Morizawa, S. Kodaira and K. Kuriyama, *Tetrahedron Letters* 1857 (1963). J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 401 (1965).

[8] M. Sasamoto, *Chem. Pharm. Bull. (Japan)* **8**, 324 (1960).

1-(3′,4′-*Ethylenedioxybenzyl*) 6,7-*dimethoxy*-3,4-*dihydroisoquinoline*. The above amide (1 g), dissolved in dry benzene (10 ml), was mixed with $POCl_3$ (3 ml) and the whole refluxed for 3 hr, and worked up to give the cyclized base as an orange yellow viscous oil, which was characterized as the hydrochloride salt. The latter formed very faint yellow prisms from MeOH–ether, m.p. 209–209·5° (dec). (Found: C, 64·0; H, 5·9; N, 3·8; Cl, 9·2. $C_{20}H_{21}O_4N$.HCl requires: C, 63·9; H, 5·9; N, 3·7; Cl, 9·4%).

1-(3′,4′-*Ethylenedioxybenzyl*) 6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. The above hydrochloride salt (1 g) in aq EtOH (EtOH 25 ml + H_2O 5 ml) was hydrogenated over Adams Pt-catalyst, 1 molar equiv of H_2 being absorbed. The product was obtained as a colourless solid, which was purified from MeOH–ether to form colourless needles, m.p. 204–206°, yield 0·9 g. (Found: C, 63·8; H, 6·2; N, 4·2; Cl, 9·1. $C_{20}H_{23}O_4N$.HCl requires: C, 63·6; H, 6·4; N, 3·7; Cl, 9·4%).

1-(3′,4′-*Ethylenedioxybenzyl*) 6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline* (III). The aforementioned hydrochloride salt (3·5 g) was heated with conc. HCl (14 ml) in a sealed tube at 150–160° (oil-bath temp) for 2 hr. After cooling, the solid was collected, dissolved in water, decolourized with charcoal and the filtrate evaporated *in vacuo* to dryness. The residue was purified from MeOH–benzene to form colourless prisms, m.p. 221·5–222° (dec), yield 2·2 g (68·8%). (Found: C, 61·6; H, 5·7; N, 4·1; Cl. 9·95. $C_{18}H_{19}O_4N$.HCl requires: C, 61·8; H, 5·8, N, 4·0; Cl, 10·1%).

3,4-*Dimethoxyphenylacet*-(3,4-*ethylenedioxyphenethylamide*). This was prepared from 3,4-ethylenedioxyphenethylamine[9] and ethyl 3,4-dimethoxyphenylacetate as mentioned above. It formed colourless fine needles from benzene, m.p. 115–116°, yield 55·7%. (Found: C, 67·2; H, 6·25; N, 3·9. $C_{20}H_{23}O_5N$ requires: C, 67·2; H, 6·5; N, 3·9%).

1-(3′,4′-*Dimethoxybenzyl*) 6,7-*ethylenedioxy*-3,4-*dihydroisoquinoline*. The foregoing amide was cyclized with $POCl_3$ in boiling benzene. The crude base formed orange yellow viscous oil, yield 83·4%. This was characterized as the picrate, which formed yellow minute plate from EtOH, m.p. 206–207° (dec). (Found: C, 54·9; H, 4·1; N, 9·7. $C_{20}H_{21}O_4N.C_6H_3O_7N_3$ requires: C, 54·9; H, 4·25; N, 9·9%).

1-(3′,4′-*Dimethoxybenzyl*) 6,7-*ethylenedioxy*-1,2,3,4-*tetrahydroisoquinoline*. The crude hydrochloride salt of the above base was dissolved in EtOH and reduced over Adams Pt-catalyst. The product, a colourless solid, was purified from EtOH to give colourless plates, m.p. 240–242° (dec). (Found: C, 63·1; H, 6·35; N, 3·7; Cl, 9·7. $C_{20}H_{23}O_4N$.HCl requires: C, 63·6; H, 6·4; N, 3·7; Cl, 9·4%).

1-(3′,4′-*Dihydroxybenzyl*) 6,7-*ethylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* (IV). The above hydrochloride salt was demethylated with conc. HCl and the crude (IV)-HCl was dissolved in water and decolourized with charcoal. The filtrate was saturated with HCl with cooling yielding a colourless crystalline solid (ca. 50%). This was purified from MeOH–ether, forming colourless prisms, m.p. 259–261° (dec). (Found: C, 61·6; H, 5·6; N, 3·8; Cl, 10·7. $C_{18}H_{19}O_4N$.HCl requires: C, 61·8; H, 5·8; N, 4·0; Cl, 10·1%).

Methyl 3-(3,4,5-*trimethoxyphenyl*) *glycidate*. A soln of 3,4,5-trimethoxybenzaldehyde (3·1 g) and methyl chloroacetate (2·6 g) in anhydr. MeOH (4 ml) was added dropwise to methanolic MeONa soln (0·55 g Na dissolved in 17 ml anhydr MeOH) with cooling (−8 ~ −10°) and stirring. After addition stirring was continued at −5 ~ 0° for 2 hr, and at 20–23° for additional 3 hr. The reaction mixture was then poured onto crushed ice acidified with 0·3 ml AcOH and the resulting solid was collected, washed and dried. This formed colourless crystals, m.p. 61–65°, good enough for the next stage, yield 2·8 g (66·8%). For analysis this was purified from MeOH to form colourless pillars, m.p. 67·5–68·5°. (Found: C, 58·3; H, 5·8. $C_{13}H_{16}O_6$ requires: C, 58·2; H, 6·0%).

1-(3′,4′,5′-*Trimethoxybenzyl*) 6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline*. (V). To a soln of the foregoing glycidate (9·9 g) in pure benzene (45 ml), methanolic MeONa soln (0·84 g of Na dissolved in 14 ml anhydr MeOH) was added dropwise with cooling (4–6°) and stirring, followed by addition of water (0·8 ml).[10] After 10 min stirring, ether (25 ml) was added and the whole stirred for an additional 3 hr to separate the corresponding Na-glycidate, which was collected, washed with ether and dried, furnishing colourless powder, yield 7·2 g (70%).

The Na-glycidate (86 g) was dissolved in water (3·6 l), to which was added an aq soln of 3,4-dihydroxyphenethylamine hydrochloride (52·9 g dissolved in 0·9 l. water). The soln was acidified to pH 2·3 by adding HCl (109 ml of 10%) and AcOH (130·6 g), and the resultant mixture stirred at 20–26° for 115 hr. The solid which separated was removed by filtration and the filtrate adjusted to pH 3·8 by adding $NaHCO_3$, and concentrated *in vacuo* under N_2 to a vol of ca. 1·5 l. The ppt formed was again

[9] M. Tomita and T. Takahashi, *Yakugaku Zasshi* (*Japan*) **77**, 478 (1957).

[10] Cf. Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (*Japan*) **6**, 574 (1958).

removed and the filtrate after decolourization with charcoal was again evaporated as above to 450 ml yielding a crystalline solid, which was collected as the first crop. When the filtrate was stored in an ice chest overnight, a second crop separated which was combined with the first and purified from MeOH–ether to form faint yellow crystals, yield 33·8 g (31·6%). For analysis this was again purified from the same solvent mixture to give colourless prisms, m.p. 224·5–226° (dec). (Found: C, 59·7; H, 6·3; N, 4·0; Cl, 9·2. $C_{19}H_{23}O_5N$.HCl requires: C, 59·8; H, 6·3; N, 3·7; Cl, 9·3%).

(–)-1-*Benzyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. (±)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6·90 g) was dissolved in water and basified with ammonia. The separated free base was taken up in ether, washed, dried and the solvent evaporated. To the residue, MeOH (30 ml) and D(–) quinic acid (4·40 g) were added and the mixture warmed to give a clear soln. On cooling ether was added carefully to the soln until incipient turbidity and the mixture then allowed to stand for 2 days. The separated solid was collected and washed with MeOH–ether, yield 4·93 g, m.p. 192–193·5°. This was the D(–)quinic acid salt of (–)-base, $[\alpha]_D^{21}$ −30·5° (c = 1·01, in MeOH). (Found: C, 63·0; H, 6·9; N, 3·3. $C_{25}H_{33}O_8N$ requires: C, 63·1; H, 7·0; N, 2·95%).

From the above salt (4·06 g) the (–)-base was liberated and converted to the hydrochloride salt, which formed minute needles from EtOH–ether, m.p. 191·5–192·5°(yield 2·5 g. $[\alpha]_D^{21}$ −28·6° (c = 1·0, in MeOH). (Found: C, 67·8; H, 6·6; N, 4·6. $C_{18}H_{21}O_2N$.HCl requires: C, 67·6; H, 6·9; N, 4·4%).

(+)-1-*Benzyl*-6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline*. The foregoing hydrochloride salt (1·0 g) was demethylated as above and the product purified from MeOH–ether to afford colourless minute needles, m.p. 244–245·5° (dec), yield 0·775 g. $[\alpha]_D^{21}$ +26·8° (c = 1·00 in MeOH). (Found: C, 65·85; H, 5·9; N, 4·7; $C_{16}H_{17}O_2N$.HCl requires: C, 65·7; H, 6·2; N, 4·8%).

(+)-1-*Benzyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. To the filtrate of the quinic acid salt water was added, followed by enough ammonia to ensure the alkalinity of the soln. The base liberated was extracted with chf, washed, dried and the solvent removed. MeOH (15 ml) and dibenzoyl-(+)-tartaric acid (4·60 g) were added to the residue. The mixture warmed to give a clear soln, which was allowed to stand overnight. The separated solid was collected and purified from MeOH–ether to furnish prisms of (+)-base: (+)-acid, m.p. 162–163° (dec), yield 6·12 g, $[\alpha]_D^{21}$ −60·9° (c = 1·00 in MeOH). (Found: C, 67·2; H, 5·4; N, 2·4; $C_{36}H_{35}O_{10}N$ requires: C, 67·3; H, 5·5; N, 2·2%).

The free base liberated from the foregoing tartarate salt (3·50 g) was collected in chf, washed, dried and the solvent removed. The residue was dissolved in EtOH, acidified with HCl and the acid and solvent evaporated. The residue was purified from EtOH–ether to give prisms of hydrochloride salt, m.p. 191–192·5°, yield 1·56 g, $[\alpha]_D^{18}$ +27·1° (c = 1·02 in MeOH). (Found: C, 67·55; H, 6·7; N, 4·6. $C_{18}H_{21}O_2N$.HCl requires: C, 67·6; H, 6·9; N, 4·4%).

(–)-1-*Benzyl*-6,7-*dihydroxy*-1,2,3,4-*tetrahydroisoquinoline*. The foregoing hydrochloride salt (1·06 g) was heated with conc. HCl and the crude product purified from MeOH–ether to form colourless minute needles, m.p. 242–244°, yield 0·82 g, $[\alpha]_D^{18}$ −26·3° (c = 1·00 in MeOH). (Found: C, 65·7; H, 6·1; N, 4·8. $C_{16}H_{17}O_2N$.HCl requires: C, 65·7; H, 6·2; N, 4·8%).

(–)-1-*Benzyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. (i) (–)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was purified by distillation to form a faint yellow viscous oil (b.p. 166–172°/0·5 mm, $[\alpha]_D^{22}$ 0·0° (c = 2·30 in MeOH), ORD (c = 0·016 in MeOH), $[\alpha]_{340}$ −120°, $[\alpha]_{290}$ −1060° (trough), $[\alpha]_{268}$ +750° (peak), $[\alpha]_{242}$ −1250° (trough), $[\alpha]_{225}$ 0°.

A mixture of this base (283 mg), HCOOH (1 ml of 85%) and aq. formaldehyde soln (1 ml of 37%) was gently refluxed for 3 hr. The reaction mixture was then evaporated *in vacuo* nearly to dryness. The residue was dissolved in dil HCl and after once shaken with ether the aq layer was basified with soda soln. The base liberated was taken up in ether, washed, dried and ether evaporated. The residue, which gave a negative Liebermann test, was dissolved in anhydr ether. When dry HCl–gas was introduced in this soln, the hydrochloride salt separated first as a viscous oil, which on treatment with MeOH–ether formed prisms, m.p. 194–195°, yield 253 mg. (Found: C, 67·6; H, 7·2; Cl, 10·25. $C_{19}H_{23}O_2N$.HCl requires: C, 68·35; H, 7·25; Cl, 10·6%). $[\alpha]_D^{22}$ −111·2° (c = 1·00 in MeOH).

The free base, purified by distillation (b.p. 200–210° (bath temp)/1 mm, showed $[\alpha]_D^{22}$ −116·3° (c = 1·16 in MeOH), ORD (c = 0·013 in MeOH), $[\alpha]_{340}$ −690°, $[\alpha]_{292}$ −2500° (trough), $[\alpha]_{270}$ −230° (peak), $[\alpha]_{237}$ −5800° (trough), $[\alpha]_{218}$ 0°.

(ii). Finely powdered (+)-(II) hydrochloride (350 mg) was suspended in MeOH (5 ml) and added to an ethereal diazomethane soln (generated from 1·5 g of nitrosomethylurea). Methylation proceeded with gas evolution and a clear soln was obtained in 1 hr. After standing for 48 hr at room temp, excess diazomethane was decomposed by adding AcOH. The resultant soln was repeatedly shaken with dil

HCl to extract basic substances and the combined acid soln basified with dil NaOH aq. The base liberated was taken up in ether, washed, dried and the solvent evaporated. The residue was mixed with HCOOH (1 ml of 85%) and aq. formaldehyde soln (1 ml of 37%) and the mixture heated under reflux for 2 hr. The methylated base was obtained as the hydrochloride salt, m.p. 193–195° alone or admixed with the specimen obtained above. The identity of both compounds was also supported by IR spectral data, $[\alpha]_D^{22}$ −111·4° (c=1·00 in MeOH). Optical data of the free base are as follows: $[\alpha]_D$ −115·8° (c=1·24 in MeOH), ORD (c=0·0135 in MeOH), $[\alpha]_{340}$ −740°, $[\alpha]_{292}$ −2800° (trough), $[\alpha]_{270}$ −300° (peak), $[\alpha]_{238}$ −6900° (trough), $[\alpha]_{218}$ 0°.

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