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New Synthesis of 1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Derivatives

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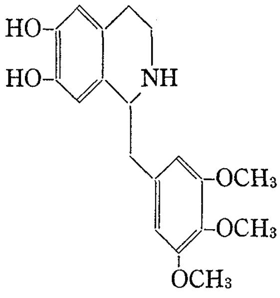
A new method is described for the synthesis of 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines starting from 3,4-dihydroxyphenylethylamine and α-formyl (or equivalent)-phenylacetic acid derivatives under Pictet–Spengler's working conditions.

Recently we reported the synthesis of 1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (VIId) hydrochloride,[2] which was proved to be a potent yet low toxic bronchodilator, of which the L-form is now widely used in practical clinics.



VIId

This compound had been synthesized by reacting 3,4-dihydroxyphenylethylamine with sodium 3-(3,4,5-trimethoxyphenyl)-glycidate according to Pictet–Spengler's method.[3] We have now succeeded to synthesize the same compound *via* an alternative route, which is also generally applicable to the synthesis of various 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines as shown in the accompanying Chart. This method may also find a wide application to the synthesis of similar 1-substituted-isoquinolines, since α-formyl esters [RCH(CHO)COOEt] may often be prepared more readily and convenient to handle than the corresponding aldehydes (RCH_2CHO).

When treated with ethyl formate in the presence of NaH ethyl phenylacetates (Ia,b,c,d) gave the corresponding α-formyl derivatives (IIa,[4,5]b,c,d), whose diethyl acetals (IIIa,[6]b,c,d) we prepared by treating them with EtOH–HCl. Alkaline hydrolysis of the latters afforded the free acids (IVa,[6]b,c,d), from which the corresponding ethoxymethylene derivatives (Va,[7] b,c,d) were obtained by the agency of $SOCl_2$ in chloroform according to the method of Strukov.[7]

All these compounds (IIa,b,c,d through Va,b,c,d) uniformly furnished 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines when reacted with 3,4-dihydroxyphenylethylamine under Pictet–Spengler's working conditions, yield ranging from 20—30%.

No effort has yet been made to find out the best working conditions to raise the maximum yield of the products. Thus at present there remains much to be desired concerning the yield of the products, but work up of the reaction mixture is simple, rendering easy isolation of the ultimate products possible.

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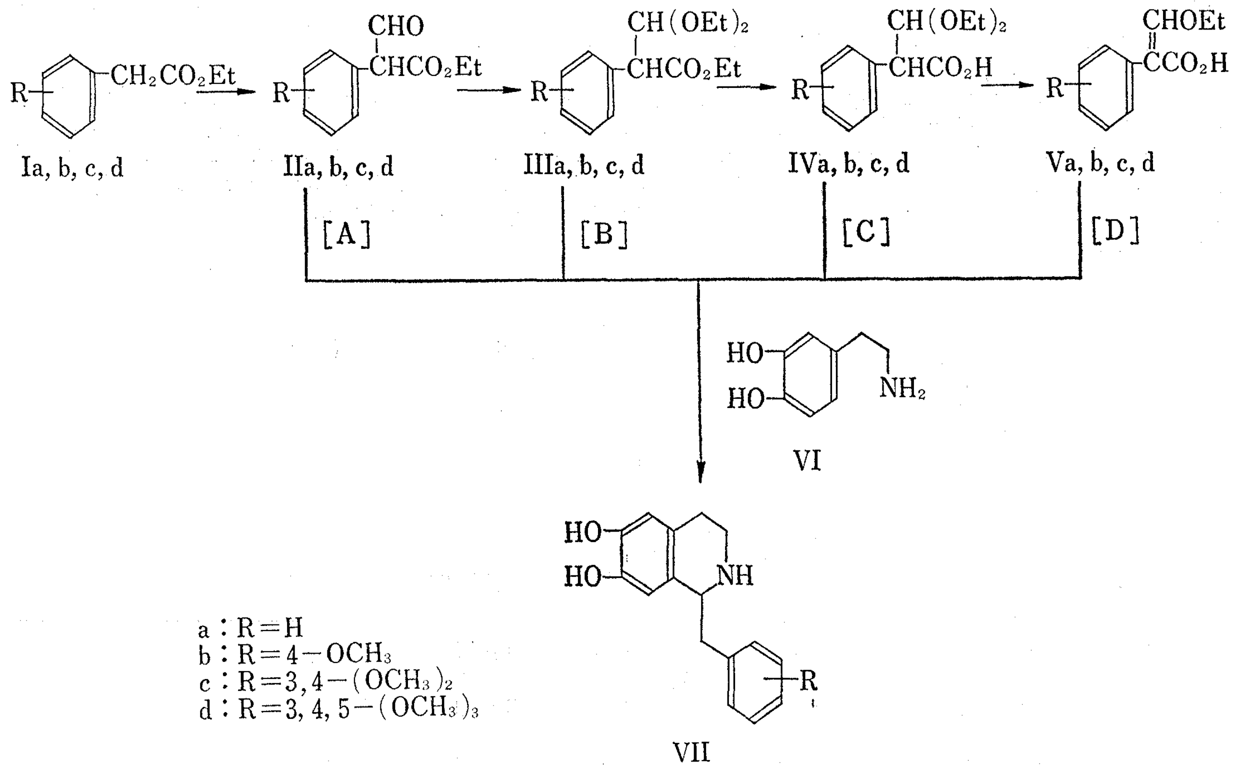


a : R=H
b : R=4−OCH₃
c : R=3,4−(OCH₃)₂
d : R=3,4,5−(OCH₃)₃

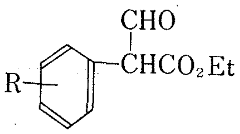
Chart 1

Experimental

All melting points are uncorrected. IR spectra were taken on a JASCO IR-E spectrometer and NMR spectra were taken on a JEOL C-60.

Ethyl α-Formyl-3,4,5-trimethoxyphenylacetate (IId)——A mixture of ethyl 3,4,5-trimethoxyphenylacetate Id (5.08 g) and ethyl formate (1.63 g) was added dropwise to a suspension of NaH (0.58 g) in dry ether (25 ml) at 25—30° with vigorous stirring. After additional stirring for 2 hr at the same temperature, the reaction mixture was shaken with cold water. The aqueous layer was acidified with 10 % HCl and a separated oil was taken up in ether. The ethereal extract was washed with saturated aqueous $NaHCO_3$, then with water and dried over Na_2SO_4. Removal of the ether left slightly yellow crystals IId (3.3 g, 59.5%).

Table I. Ethyl α-Formylphenylacetates (II)



No.	R	Yield (%)	mp or bp(°C) (mmHg)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
IIa	H	45	93 — 96[a] (3)	liquid	$C_{10}H_{12}O_3$	—	—	—	—
IIb	4-OCH_3	49.3	138 —141[b] (3—4)	liquid	$C_{12}H_{14}O_4$	—	—	—	—
IIc	3,4-$(OCH_3)_2$	43	138 —141 (0.25—0.3)	liquid	$C_{13}H_{16}O_5$	—	—	—	—
IId	3,4,5-$(OCH_3)_3$	59.5	92.5— 94	needles	$C_{14}H_{18}O_6$	59.56	6.43	59.58	6.33

a) lit. 4) bp 95—96 (1 mmHg), lit. 5) bp 89—91 (0.03 mmHg)
b) lit. 4) bp 133—139 (1 mmHg)

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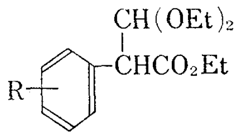
This was purified from a mixture of benzene and petroleum ether to form colorless needles, mp 92.5—94°. *Anal.* Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.58; H, 6.63. IR ν_{max}^{Nujol} cm^{-1}: 1645 (enol ester), 1700 (CHO, shoulder).

Ethyl α-Diethoxymethyl-3,4,5-trimethoxyphenylacetate (IIId)——A solution of IId (1.12 g) in 5% HCl–ethanol (5.6 ml) was refluxed for 3.5 hr. The reaction mixture was basified with 30% aqueous KOH at 0°. After filtration from the precipitated KCl, the solvent was removed *in vacuo* below 40°. The ethereal solution of the residue was washed with water and dried over Na_2SO_4. Removal of the ether left an oily product which, on distillation, gave a colorless oil IIId (1.08 g, 76.1%), bp 145—150° (0.1 mmHg), $n_D^{25.5}=1.5012$, IR ν_{max}^{film} cm^{-1}: 1730 (COOEt).

Table II. Ethyl α-Diethoxymethylphenylacetates (III)

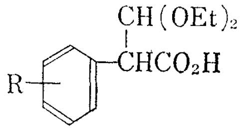


No.	R	Yield (%)	bp (°C) (mmHg)	Appearance	Formula	n_D (°C)
IIIa	H	56.6	142—145[a] (9)	liquid	$C_{15}H_{22}O_4$	—
IIIb	4-OCH_3	82	155—160 (3)	liquid	$C_{16}H_{24}O_5$	1.520 (25)
IIIc	3,4-$(OCH_3)_2$	66.4	174—178 (2)	liquid	$C_{17}H_{26}O_6$	1.4977 (25)
IIId	3,4,5-$(OCH_3)_3$	76.1	145—150 (0.1)	liquid	$C_{18}H_{28}O_7$	1.5012 (25.5)

a) lit. 6) bp 142—143 (9—10 mmHg)

α-Diethoxymethyl-3,4,5-trimethoxyphenylacetic Acid (IVd)——A solution of IIId (0.89 g) in ethanol (5 ml) containing 30% aqueous KOH (1 ml) was stirred for 2 days at room temperature (*ca.* 25°). After removal of the solvent under reduced pressure, the residue in a little water was acidified (pH 3) with 10% HCl with cooling. A separated oil was extracted with ether, and the ethereal extract was washed with water and dried over Na_2SO_4. Removal of ether left a solid which was recrystallized from a mixture of benzene and petroleum ether to give colorless needles IVd (0.5 g, 61%), mp 90—99°. This was purified from the same solvent mixture to form colorless needles, mp 106.5—107.5°. *Anal.* Calcd. for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.78; H, 7.33. IR ν_{max}^{Nujol} cm^{-1}: 1695 (COOH), 2800—2500 (COOH).

Table III. α-Diethoxymethylphenylacetic Acids (IV)



No.	R	Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
IVa	H	71.1	130 —131[a]	prisms	$C_{13}H_{18}O_4$	—	—	—	—
IVb	4-OCH_3	58.6	111 —112	needles	$C_{14}H_{20}O_5$	62.67	7.51	62.99	7.65
IVc	3,4-$(OCH_3)_2$	63.9	85.5— 87	fine needles	$C_{15}H_{22}O_6$	60.31	7.41	60.49	7.13
IVd	3,4,5-$(OCH_3)_3$	61	106.5—107.5	needles	$C_{16}H_{24}O_7$	58.52	7.37	58.78	7.33

a) lit. 6) mp 121—123°

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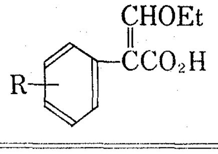
α-Ethoxymethylene-3,4,5-trimethoxyphenylacetic Acid (Vd)——A mixture of IVd (1.498 g) in dry chloroform (7.5 ml) and $SOCl_2$ (0.548 g) was kept for 19 hr at room temperature (*ca.* 25°). After removal of the solvent, the residue in a little chloroform was shaken with aqueous $NaHCO_3$. The aqueous layer was acidified (pH 3) with 10% HCl below 0°. A separated oil was taken up in chloroform, the chloroform extract was washed with water and dried over Na_2SO_4. Removal of the solvent left a product which was crystallized from a mixture of benzene and petroleum ether to yield Vd (0.343 g, 26.6%), mp 136—139°. This was purified from ether to form colorless prisms, mp 146—148°. *Anal.* Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.74; H, 6.25. IR ν_{max}^{Nujol} cm^{-1}: 1645 (COOH), 2800—2500 (COOH), 1625 (C=C). NMR ($CDCl_3$) τ: 2.20 (1H, singlet, =C$\underline{H}$OEt), 3.32 (2H, aromatic protones), 5.80 (2H, quartet, J=7 cps, $OC\underline{H}_2CH_3$), 6.12 (9H, singlet, $OC\underline{H}_3 \times 3$), 8.63 (3H, triplet, J=7 cps, $OCH_2C\underline{H}_3$).

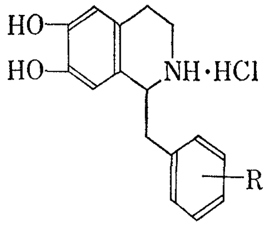
Table IV. α-Ethoxymethylenephenylacetic Acids (V)



No.	R	Yield (%)	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
Va	H	10.9	133—135[a]	needles	$C_{11}H_{12}O_3$	—	—	—	—
Vb	4-OCH_3	27.4	120—122	needles	$C_{12}H_{14}O_4$	64.85	6.35	64.95	6.42
Vc	3,4-$(OCH_3)_2$	17.4	136—137.5	prisms	$C_{13}H_{16}O_5$	61.89	6.39	62.39	6.52
Vd	3,4,5-$(OCH_3)_3$	26.6	146—148	prisms	$C_{14}H_{18}O_6$	59.56	6.43	59.74	6.25

a) lit. 7) mp 133—135°

Table V. 1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines (VII) Hydrochloride



No.	R	Yield (%) [Route] [A]	[B]	[C]	[D]	mp (°C)
VIIa	H	53.4	31.3	56.7	33.1	240 —242 (decomp.)
VIIb	4-OCH_3	59.4	29.1	48.6	62.8	218.5—220 (decomp.)
VIIc	3,4-$(OCH_3)_2$	63.1	61.3	52.0	76.1	275 (decomp.)
VIId	3,4,5-$(OCH_3)_3$	19.1	25.3	22.6	29.3	226 (decomp.)

No.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
VIIa	$C_{16}H_{17}O_2N \cdot HCl \cdot \frac{1}{2}H_2O$	64.87	6.17	4.73	11.97	65.14	6.31	4.83	12.18
VIIb	$C_{17}H_{19}O_3N \cdot HCl$	63.43	6.27	4.35	11.02	63.54	6.24	4.30	11.08
VIIc	$C_{18}H_{21}O_4N \cdot HCl$	61.44	6.30	3.98	10.08	61.17	6.09	4.14	10.06
VIId	$C_{19}H_{23}O_5N \cdot HCl$	59.76	6.34	3.67	9.23	59.37	6.30	3.51	9.09

1-(3,4,5-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (VIId) Hydrochloride——Route [A]: A mixture of 3,4-dihydroxyphenylethylamine (VI) hydrochloride (0.75 g) ,IId (1.24 g), 10% HCl (10 ml) and methanol (10 ml) was refluxed for 25 hr. After removal of the solvent, the residue in water was shaken with ether. The aqueous layer was evaporated to dryness under reduced pressure. The resulting product solidified on trituration with 10% HCl. The solid thus obtained was filtered off and washed with acetone. This was purified from 2% HCl to form colorless fine prisms VIId (0.29 g, 19.1%), mp 226° (decomp.). The identity of this compound with an authentic sample[2] was supported by both IR spectral data and undepressed mixed melting point test, mp 224—225° (decomp.). *Anal.* Calcd. for $C_{19}H_{23}O_5N \cdot HCl$: C, 59.76; H, 6.34; N, 3.67; Cl, 9.23. Found; C, 59.37; H, 6.30; N, 3.51; Cl, 9.09.

Route [B]: A mixture of VI hydrochloride (0.378 g), IIId (0.784 g) and 10% HCl (4 ml) in methanol (6 ml) was refluxed for 91 hr. Colorless prisms VIId (0.193 g, 25.3%), melting at 218—220° (decomp.), were obtained by treating the reaction mixture as described above.

Route [C]: A mixture of VI hydrochloride (0.643 g) in 10% HCl (8 ml) and IVd (1.21 g) in methanol (6 ml) was refluxed for 70 hr. Colorless prisms VIId (0.29 g, 22.6%), melting at 224.5—226° (decomp.), were obtaiend by treating the reaction mixture as described above.

Route [D]: A mixture of VI hydrochloride (0.209 g) in water (2.1 ml) and Vd (0.34 g) in methanol (16 ml), containing 10% HCl (2 ml) and AcOH (0.3 ml), was refluxed for 54 hr. Colorless prisms VIId (0.123 g, 29.3%), melting at 220—222° (decomp.), were obtained by treating the reaction mixture as described above.

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