SYNTHESIS OF POTENTIALLY PHYSIOLOGICALLY ACTIVE β-PHENYLETHYLAMINES

PART I. 3,4,5-TRIMETHOXY-α-AMINOMETHYLBENZYL ALCOHOL AND 4-ACETOXY-3,5-DIMETHOXY-α-AMINOMETHYLBENZYL ALCOHOL DERIVATIVES[1]

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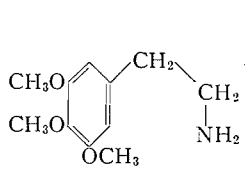
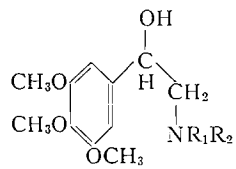
ABSTRACT

The preparation of several 3,4,5-trisubstituted-β-hydroxy-β-phenylethylamines related to mescaline, by the reduction or reductive alkylation of the corresponding nitroalcohols, is described.

Mescaline (I) has been known for many years to produce marked psychological changes in human subjects (see ref. 1 for some of the more important references), and many chemically similar substances have been prepared and examined for psychopharmacological activity (cf. ref. 2). However, little attention, so far, seems to have been given to the preparation or physiological activity of mescaline-like compounds with a hydroxyl group in the side chain on the carbon atom adjacent to the aromatic ring (i.e. as in adrenaline). As yet, only two compounds of this type have been described, but as far as the authors are aware, there are no reports in the literature of studies on the psychological activity of either of these two substances.



I



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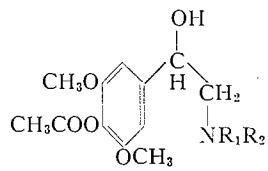

III

3,4,5-Trimethoxy-α-aminomethylbenzyl alcohol (II: $R_1 = R_2 = H$) was first prepared in 1931 by the catalytic reduction of 3,4,5-trimethoxybenzoyl cyanide (3). Twenty years later, it was shown that (II: $R_1 = R_2 = H$) could also be obtained by reduction of the corresponding aryl cyanohydrin (or aroyl cyanide) with lithium aluminum hydride (4, 5). The *N*-methyl analogue (II: $R_1 = CH_3$; $R_2 = H$) has been prepared by the catalytic hydrogenation of ω-(*N*-benzyl-*N*-methyl)-amino-3,4,5-trimethoxybenzophenone (6).

This communication describes a simple method for the synthesis of compounds of this nature by the reduction or reductive alkylation (cf. ref. 7) of suitable α-phenyl-β-nitroethanol derivatives. (These nitroalcohols are readily available by the method of Heacock, Hutzinger, and Nerenberg (8).)

The reduction of α-phenyl-β-nitroethanol derivatives with sodium amalgam and dilute acetic acid to the corresponding α-phenyl-β-aminoethanol was first described by Rosenmund (9). Later, Kanao obtained 3,4-diacetoxy-α-aminomethylbenzyl alcohol from the reduction of 3,4-diacetoxy-α-nitromethylbenzyl alcohol with zinc and dilute acetic acid

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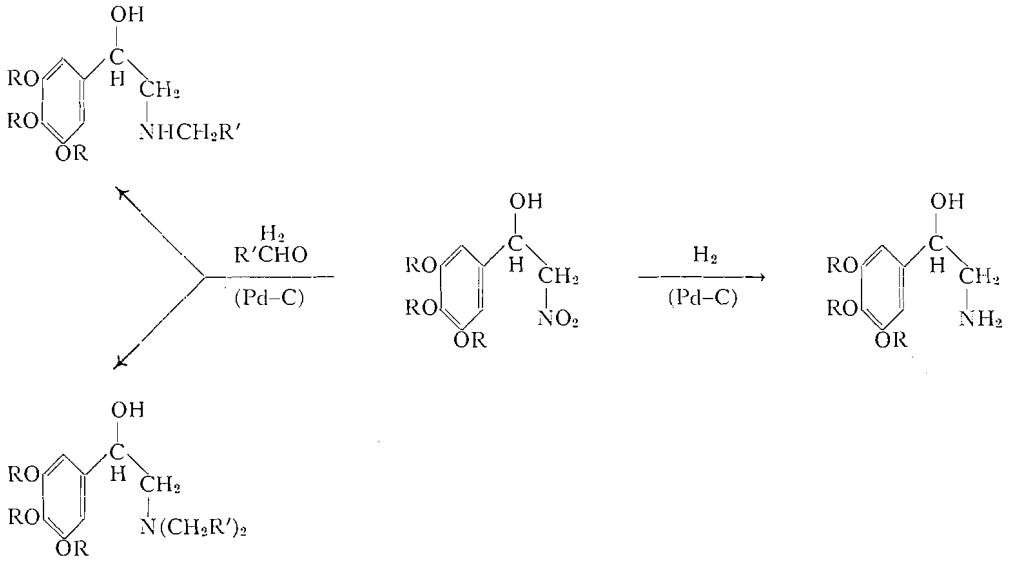


(10). This author also reported several reductive alkylations of 3,4-diacetoxy-α-nitromethylbenzyl alcohol with zinc and dilute acetic acid in the presence of about one mole of a suitable aldehyde (10). Recently, Axelrod *et al.* prepared O^4-benzylnormetanephrine by the catalytic hydrogenation of 4-benzyloxy-3-methoxy-α-nitromethylbenzyl alcohol (11). O^4-Acetylnormetanephrine and O^4-acetylmetanephrine have recently been obtained from 4-acetoxy-3-methoxy-α-nitromethylbenzyl alcohol by catalytic reduction and reductive alkylation respectively (12).

3,4,5-Trimethoxy-α-aminomethylbenzyl alcohol (II: $R_1 = R_2 = H$) has been obtained in high yield (as the hydrochloride or oxalate salt) by catalytic hydrogenation of 3,4,5-trimethoxy-α-nitromethylbenzyl alcohol in aqueous suspension. If the hydrogenation was carried out in the presence of 1 equivalent of formaldehyde, reductive alkylation occurred with the formation of the monomethylamino derivative (i.e. 3,4,5-trimethoxy-α-methylaminomethylbenzyl alcohol; II: $R_1 = CH_3$; $R_2 = H$); reduction in the presence of 3 to 4 equivalents of formaldehyde lead to the formation of the dimethylamino derivative (i.e. 3,4,5-trimethoxy-α-dimethylaminomethylbenzyl alcohol; II: $R_1 = R_2 = CH_3$). 4-Acetoxy-3,5-dimethoxy-α-aminomethylbenzyl alcohol (III: $R_1 = R_2 = H$) and the corresponding *N*-methyl (III: $R_1 = CH_3$; $R_2 = H$) and *N*,*N*-dimethyl (III: $R_1 = R_2 = CH_3$) derivative could be obtained (as the oxalates) in an analogous manner from 4-acetoxy-3,5-dimethoxy-α-nitromethylbenzyl alcohol.

In view of the possibility of an intermolecular cyclization reaction of the Pictet–Spengler type (cf. ref. 13) occurring during the reductive alkylations which would have presumably led to the formation of tetrahydroisoquinoline derivatives, a sample of the product assumed to be 3,4,5-trimethoxy-α-dimethylaminomethylbenzyl alcohol (II: $R_1 = R_2 = CH_3$) was oxidized with aqueous alkaline potassium permanganate. 3,4,5-Trimethoxybenzoic acid was obtained, indicating that cyclization had not occurred, since a phthalic acid derivative would have been expected from the permanganate oxidation products of the tetrahydroisoquinoline ring system.

Further synthetic work in this field is underway and the physiological activity of this group of substances is under investigation. The results will be reported elsewhere in due course.

TABLE I

3,4,5-Trimethoxy-α-aminomethylbenzyl alcohol derivatives[a]

Substance prepared			Reagent employed[b]		Properties		
				Formaldehyde solution in water	Yield[c]		
R_1	R_2	Salt	Acid component	(36%)	g	%	M.p. (°C)
H	H	Oxalate[d]	—	—	—	—	190–191 (decomp.)
H	H	Hydrogen oxalate[d]	—	—	—	—	188–189 (decomp.)
H	H	Hydrochloride[e]	3.8 ml *N* HCl	—	0.75	73	202–203
H	CH_3	Hydrogen oxalate	0.5 g oxalic acid[f]	0.33 ml (≡ 1 mole)	0.5	39	202 (decomp.)
H	CH_3	Hydrochloride	3.8 ml *N* HCl	0.33 ml (≡ 1 mole)	0.5	46	172
CH_3	CH_3	Hydrogen oxalate	0.5 g oxalic acid[f]	1 ml (≡ 3 moles)	0.4	30	154–155 (decomp.)
CH_3	CH_3	Hydrochloride	3.8 ml *N* HCl	1 ml (≡ 3 moles)	0.8	70	201

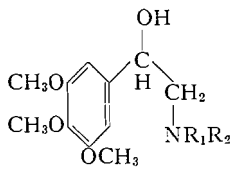
[a]In all cases, the preparation and properties of the DL-mixture of optical isomers are described.
[b]The hydrogenations were carried out in water (150 ml). The quantities of reagents given are for the reduction or reductive alkylation of 1 g of the nitroalcohol.
[c]The yields given are based on the reduction or reductive alkylation of 1 g of the nitroalcohol.
[d]Prepared from base and calculated amounts of oxalic acid. (Hydrogenation in the presence of 1 or 2 moles of oxalic acid invariably led to the formation of mixtures of the neutral and acid oxalates, which proved to be difficult to separate by recrystal-

TABLE II

4-Acetoxy-3,5-dimethoxy-α-aminomethylbenzyl alcohol derivatives[a]

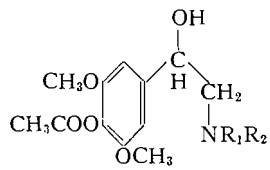
Substance prepared			Reagent employed[b]		Properties	
				Formaldehyde solution in water	Yield[c]	
R_1	R_2	Salt	Acid component	(36%)	g	%
H	H	Oxalate	0.22 g oxalic acid[d]	—	0.4	38
H	H	Hydrochloride	3.4 ml *N* HCl	—	0.8	78
H	CH_3[e]	Oxalate	0.22 g oxalic acid[d]	0.3 ml (≡ 1 mole)	0.8	73
CH_3	CH_3	Hydrogen oxalate	0.44 g oxalic acid[d]	0.9 ml (≡ 3 moles)	0.4	76
CH_3	CH_3	Hydrochloride	3.4 ml *N* HCl	0.9 ml (≡ 3 moles)	0.6	53

[a]In all cases, the preparation and properties of the DL-mixture of optical isomers are described.
[b]The hydrogenations were usually carried out in an ethanol/water (1:2) mixture (150 ml). The quantities of reagents given are for the reduction or reductive alkylation of 1 g of the nitroalcohol.
[c]The yields given are based on the reduction or reductive alkylation of 1 g of the nitroalcohol.
[d]Oxalic acid dihydrate was used in all these preparations.



of purified product		Analysis							
		Found				Calculated			
Crystalline form	M.p. reported in literature (°C)	C	H	N	Cl	C	H	N	Cl
Colorless needles from 95% ethanol	—	52.85	6.76	5.17	—	52.93	6.66	5.14	—
Colorless needles from ethanol	—	49.35	6.00	4.43	—	49.21	6.04	4.41	—
Colorless plates from ethanol	189–192 (4) 203 (3)	50.10	6.98	5.41	—	50.09	6.88	5.32	—
Small colorless plates from 95% ethanol	—	50.69	6.39	4.29	—	50.57	6.39	4.23	—
Colorless prisms from isopropanol	168–169 (6)[g]	51.89	7.12	4.91	12.72	51.89	7.25	5.05	12.77
Colorless prisms from 5% light petroleum (b.p. 60–80°) in ethanol	—	52.14	6.71	4.05	—	52.17	6.71	4.06	—
Colorless prisms from isopropanol	—	53.36	7.39	4.66	11.95	53.51	7.60	4.81	12.15

lization.)
[e]The corresponding free base (i.e. 3,4,5-trimethoxy-α-aminomethylbenzyl alcohol) was prepared by treating a solution of the hydrochloride with strong alkali, extracting with benzene, and recrystallizing the product from toluene, m.p. 141°. (Previously reported m.p.'s: 138° (4), 141–142° (5), 144° (3). Analysis: Found: C, 58.20; H, 7.66. Calc. for $C_{11}H_{17}O_4N$: C, 58.13; H, 7.54%.)
[f]Oxalic acid dihydrate was used in all these preparations.
[g]Incorrectly named as 3,4,5-trimethoxy-α-aminomethylbenzyl alcohol hydrochloride in Chem. Abstr. 47, 8036 (1953).



of purified product		Analysis							
		Found				Calculated			
M.p. (°C)	Crystalline form	C	H	N	Cl	C	H	N	Cl
182 (decomp.)	Small colorless plates from 95% ethanol	52.18	6.11	4.60	—	52.00	6.05	4.67	—
197	Small colorless prisms from ethanol	49.18	6.22	4.55	12.18	49.40	6.22	4.81	12.15
211–212 (decomp.)	Small colorless prisms from ethanol	53.36	6.36	4.18	—	53.50	6.41	4.45	—
172 (decomp.)	Colorless needles from ethanol	51.36	6.28	3.71	—	51.47	6.21	3.75	—
177–178	Colorless prisms from MEK[f]	52.49	6.91	4.14	10.83	52.58	6.94	4.38	11.08

[e]It was not possible to prepare a pure sample of the hydrochloride salt of 4-acetoxy-3,5-dimethoxy-α-methylaminomethylbenzyl alcohol, either from attempts to prepare the salt directly by hydrogenation in the presence of hydrochloric acid or by treatment of the corresponding oxalate with calcium chloride. Two different substances, m.p.'s 207–209° and 150–151° respectively, were obtained, but in neither case could a completely satisfactory analysis for the desired product be obtained.
[f]MEK = methyl ethyl ketone.

EXPERIMENTAL

*General Procedure for Reduction and Reductive Alkylation**

A suspension of the nitroalcohol (prepared by the method of Heacock, Hutzinger, and Nerenberg (8)) containing one third of its weight of a palladium catalyst (5% on charcoal), an acid component, and formaldehyde (where applicable, see tables), was shaken in the presence of hydrogen at atmospheric pressure until the calculated amount was taken up. After filtration of the reaction mixture, the product was concentrated to dryness *in vacuo* (below 40°) and the residue was recrystallized from a suitable solvent.

Oxidation of 3,4,5-Trimethoxy-α-dimethylaminomethylbenzyl Alcohol Hydrochloride

A solution of 3,4,5-trimethoxy-α-dimethylaminomethylbenzyl alcohol hydrochloride† (0.2 g) in 1% aqueous sodium hydroxide (10 ml) was oxidized with potassium permanganate (0.6 g), the solution being maintained at 90° C for 2 hours. The reaction mixture was acidified with dilute sulphuric acid, after filtration, and the white solid which separated was recrystallized from aqueous ethanol. Colorless needles, m.p. 171–172°, were obtained, which were identical in all respects (no depression of melting point and identical infrared spectra) with an authentic sample of 3,4,5-trimethoxybenzoic acid.

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**The specific quantities of reagents used in each case are given in Tables I and II.*

†*One example of a substance prepared by reductive alkylation of the nitroalcohol was chosen arbitrarily for oxidation. It was assumed that the other compounds prepared in this fashion would behave similarly on oxidation.*