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AMINO ALCOHOLS. XIV. METHOXYL DERIVATIVES OF PHENYLPROPANOLAMINE AND 3,5-DIHYDROXYPHENYLPROPANOLAMINE (1)

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Mescaline, 3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$, one of the numerous bases isolated from the mescal button by Heffter (2) and later by Späth (3), possesses interesting psychological effects, usually producing supernatural and colorful visions and euphoric state of mind (4, 5, 6, 7). The relationship of mescaline to the pressor compounds depends on its structure rather than on its physiological behavior. It has been reported by Raymond-Hamet (8), Grace (9), Geesink and Jager (10), and De Nito (11) that mescaline fails to produce a rise in blood pressure in dogs, rabbits, and cats.

In view of the unique responses, which must be attributed to the presence of the three vicinal methoxyl groups on the pressor active molecule, β-phenethylamine, it was thought to be of interest to synthesize and study other compounds of this type. Unfortunately, mescaline itself is quite toxic and damaging to the tissues. Since the introduction of an alcoholic hydroxyl group into the β-phenethylamine skeleton reduces the toxicity of the molecule, the correspondingly substituted hydroxymescaline may be expected to be less toxic. Because the arylpropanolamines exhibit substantially the same pharmacodynamic behavior as do the corresponding arylethanolamines and also are more easily synthesized, a 3,4,5-trimethoxyphenylpropanolamine, 3,4,5-$(CH_3O)_3C_6H_2CH(OH)CH(NH_2)CH_3$, was prepared. In an extension of this study, other methoxyl derivatives of phenylpropanolamine were prepared.

Methoxyl ring substituted pressor amines have been investigated by Hjort (12) on N-methyl-β-phenethylamine having mono- and di-methoxy nuclear substitutions. In the phenylpropanolamine series, Hartung, Munch, Miller, and Crossley (13) have synthesized and studied 2-methoxy-, 4-methoxy-, and 2,4-dimethoxy-phenylpropanolamines. In general, the methylation of hydroxyl groups on the nucleus seems to increase the toxicity and decrease the pressor activity.

Schaumann (14) and Tainter (15) attribute to the *m*-hydroxyl group on a pressor molecule a "sympathicotropic" effect, in contrast to the *p*-hydroxyl group which exhibits more of a "musculotropic" effect. It occurred to us that it would be of interest to learn what the physiological responses would be if both available meta positions were occupied by hydroxyl groups. With this in mind, the 3,5-dihydroxyphenylpropanolamine was prepared.

The synthesis of these products depends on first obtaining the appropriate ketone, AR-CO-CH_2CH_3. This ketone is then converted into the corresponding oximino-ketone, AR-CO-$C(NOH)CH_3$, which in turn is reduced catalytically to the amino alcohol, AR-$CH(OH)CH(NH_2)CH_3$, and isolated as the hydrochloride.

EXPERIMENTAL

Preparation of ketones. 3,4,5-Trimethoxy- and 3,5-dimethoxy-4-hydroxypropiophenones. Gallic acid was methylated according to the method described by Mauthner (16) using dimethyl sulfate and alkali. This was then converted to the corresponding nitrile following the sequence of procedures outlined by Hurd and Winberg (17). After drying over phosphorus pentoxide, the 3,4,5-trimethoxybenzonitrile, m.p. 91°, was allowed to react with ethylmagnesium bromide at the refluxing temperature of toluene, following the general procedure given for the isobutyl derivative by Haller and Schaffer (18), and Hurd and Winberg. 3,4,5-Trimethoxy-, melting at 52°, and 3,5-dimethoxy-4-hydroxypropiophenone, melting at 109°, were obtained in yields of 55.8% and 14.2%, respectively. The melting points reported in the literature were 51–52° for the former and 109–110° for the latter (19, 20).

3,4-Dimethoxypropiophenone. Propionylcatechol was prepared following the method of Miller, Hartung, Rock, and Crossley (21). This ketone was then methylated according to the standard method with dimethyl sulfate in alkaline solution. The yield of 3,4-dimethoxypropiophenone, m.p. 62–63°, was 43% of the theoretical amount.

3,5-Dimethoxypropiophenone. This ketone, m.p. 33.5° (literature, 32.5°, 34–35°), was prepared in good yields by following the method of Suter and Weston (22), starting from benzoic acid.

Preparation of isonitroso ketones. By employing the general nitrosation procedure of Hartung and Munch (23), the foregoing ketones were converted into their corresponding isonitroso ketones. The appropriate ketone was dissolved in a suitable amount of ether, dry hydrogen chloride was bubbled through the stirred solution and an equimolar quantity of freshly distilled *n*-butyl nitrite was slowly added. After completion of the nitrosation reaction the ethereal solution was extracted with dilute alkali and the alkaline extract slowly stirred into concentrated hydrochloric acid containing ice. The crystals which separated out were removed, dried, and recrystallized from the proper solvents. The experimental data on the various oximino ketones are shown in Table I.

Catalytic reduction. It has been found (24) that in those cases where the aromatic portion of the isonitroso ketone molecule is substituted by a phenolic hydroxyl, or its methyl ether, the reduction stops at the amino ketone stage; the resulting compound may be isolated and purified as its salts, and then reduced to the corresponding amino alcohol in aqueous solution.

(a) *Amino ketones.* The reduction of the isonitroso ketones to the amino ketones was carried out exactly in the manner described elsewhere (23, 24, 25), using both the normal and active palladinized charcoal catalyst.[1] The absorption of hydrogen stopped when approximately two equivalents were taken up. The catalyst was removed, and the clear filtrate placed in a vacuum desiccator over concentrated sulfuric acid and calcium chloride. The product was isolated as its hydrochloride salt. The aqueous solution of all of the amino ketones reduced Fehling's solution, and all melted with decomposition or effervescence, forming a red melt. The amino ketones synthesized are described in Table II.

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[1] The activity of palladium-charcoal catalysts depends greatly on their method of preparation, the previous history of the catalyst, and also on the type of charcoal used. Since the investigations with these catalysts have not yet reached the stage where results merit publication it may be well at this time to indicate that a much more active palladium-charcoal catalyst may be obtained if it is prepared in sodium acetate solution. For example, in a hydrogenator, 3 g. of Nuchar (Industrial Chemical Sales, N. Y. C.), 0.3 g. of palladium chloride, and 100 cc. of 1 *N* sodium acetate solution were shaken until no more hydrogen was taken up; the catalyst was then filtered off, washed with distilled water, finally once with ethanol, and was kept in a vacuum desiccator over concentrated sulfuric acid for at least overnight before use. A catalyst so prepared is frequently active where the normal catalyst is much less active, or inert (26).

(b) *Amino alcohols.* Using a fresh catalyst, the amino ketone salts in aqueous solution were further reduced to the corresponding amino alcohols. After the removal of the catalyst, the clear filtrate was evaporated to dryness over concentrated sulfuric acid and calcium chloride. The residue was dissolved in the least quantity of absolute alcohol and white crystals (except 3,5-dimethoxy-4-hydroxyphenylpropanolamine which was tan colored) were forced out by dilution with dry ethyl ether, except in the case of 3,5-dimethox-

TABLE I

ISONITROSO KETONES

AR = AR—CO—C(NOH)—CH₃	PURIFICATION SOLVENT	M.P., °C (UNCOR.)	YIELD, %	NITROGEN[a]	
				Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	Toluene	145–146	80		
3,5-Dimethoxy-4-hydroxyphenyl-	Benzene	160–164	37	5.85	5.80 5.82
3,4-Dimethoxyphenyl-	95% Ethanol	163	82	6.28	6.20 6.23
3,5-Dimethoxyphenyl-[b]	Benzene or 20% Ethanol	107–108	74		

[a] All nitrogen analysis was made by Kjeldahl (Hengar technique).

[b] Prepared by Bockmühl, Ehrhart, and Stein, German Patent, 613,215, May 14, 1935; *Chem. Abstr.*, 29, 5602 (1935).

TABLE II

AMINO KETONES

AR = AR—CO—CH(NH₂·HCl)—CH₃	M.P., °C (COR.)	YIELD, %	NITROGEN	
			Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	248–249 dec.	71	5.08	5.01 4.99
3,5-Dimethoxy-4-hydroxyphenyl-	209.4 dec.	75	5.36	5.34 5.47
3,4-Dimethoxyphenyl-	214.2 dec.	63	5.70	5.65 5.68
3,5-Dimethoxyphenyl-	204.5 dec.	71	5.70	5.66 5.64

yphenylpropanolamine hydrochloride, where a 50% mixture of isopropyl and ethyl ethers was used. These amino alcohol salts are summarized in Table III.

The amount of nitrogen for the reduction product from the hydrochloride of 3,5-dimethoxy-4-hydroxyphenyl-α-aminoethyl ketone was found to be 7.80, 7.77, and 7.51%; calculated for the corresponding amino alcohol, 5.32%. However, in view of the previous supporting data, (a) that the amino ketone absorbed the theoretical one equivalent of

hydrogen, (b) that the product does not reduce Fehling's solution, and (c) that the nitrogen analysis was correct for the amino ketone, it is believed that the desired amino alcohol was actually formed. However, during the process of isolation it must have undergone change, and accordingly characterization and analysis could not be made. Due to lack of product and intermediate these conclusions have not been substantiated.

Demethylation of 3,5-dimethoxyphenylpropanolamine. In a Carius tube, 2.0 g. (0.008 mole) of 3,5-dimethoxyphenylpropanolamine hydrochloride and 10 cc. of concentrated hydrochloric acid were placed, and the tube was sealed and wrapped in towels. It was placed in the steam-bath for a period of six to eight hours. After thorough cooling, the tube was carefully opened, and the dark brown mixture emptied into an evaporating dish and the excess hydrochloric acid removed under vacuum over sodium hydroxide pellets. The resulting syrupy residue was finally dried over phosphorus pentoxide under vacuum. In this manner, almost quantitative yield of a tan colored product was obtained. A portion of this product was dissolved in the least quantity of pure *n*-butyl alcohol and a white precipitate forced out with dry ethyl ether. After centrifuging, the solvent was decanted

TABLE III

AMINO ALCOHOLS

AR = AR—CHOH—CH—CH_3 (NH_2·HCl)	M.P., °C (COR.)	YIELD, %	NITROGEN	
			Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	221.0–221.5	70	5.05	5.01 5.07
3,5-Dimethoxy-4-hydroxyphenyl-	96 dec.	60	5.32	See "Amino Alcohols"
3,4-Dimethoxyphenyl-	212.6–213.0	80	5.65	5.54 5.67
3,5-Dimethoxyphenyl-	169.5–170.0	66	5.65	5.60[a] 5.65

[a] This product has been previously prepared by Bockmühl, Ehrhart, and Stein, as melting at 165–167°. Since the product obtained here melted above that previously described, it was analyzed to confirm its composition.

and the white residue dried over phosphorus pentoxide. The product was very hygroscopic. An aqueous solution gave a dark violet coloration with ferric chloride test solution and did not reduce Fehling's solution. The melting point showed unusual behavior. The product did not liquefy, but passed from the crystalline state to the frothing stage without change of color at 195–200°. It decomposed to a carbonaceous mass at a temperature above 250°. Kjeldahl: nitrogen calculated for $C_9H_{13}O_3N$·HCl, 6.38%; nitrogen found, 6.15 and 6.25%.

SUMMARY

1. For the purpose of eventual pharmacological study a mescaline analog of phenylpropanolamine was synthesized.

2. Also to permit a more comprehensive study of the effect of methoxyl substitution in the phenyl nucleus of phenylpropanolamine, several additional new compounds were prepared, the complete list being: 3,4,5-trimethoxy-, 3,4-dimethoxy-, and 3,5-dimethoxy-4-hydroxyphenylpropanolamines.

3. In view of the unique physiological properties conferred on a molecule containing a single *meta* hydroxyl substitution, it appeared desirable to prepare a molecule containing two hydroxyl groups on its meta positions. The 3,5-dihydroxy compound was prepared by demethylation of 3,5-dimethoxyphenylpropanolamine hydrochloride.

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