TABLE I

	Intraperitoneal						Oral			
Dose (mg./kg.)	100	200	300	500	750	1000	200	500	1000	1500
Deaths—Acute	0	0	0	0	0	2	0	0	0	0
—Delayed	0	0	0	0	0	0	0	0	0	0
—Total	0/3	0/3	0/3	0/3	0/3	2/3	0/3	0/3	0/3	0/3
—Time						15–30 min.				
Atoxia	−	−	+	+	+	+ +	−	−	+	+
Decrease in observed spontaneous activity	−	−	+	+ +	+ +	+ +	−	+	+ +	+ +

α-Carbamylpropanesulfonamide (IV).—Diphenyl α-sulfopropionate (49 g.) was heated with liquid ammonia (100 ml.) in a sealed tube at 75° for 12 hr. Removal of the ammonia followed by extraction with ether left a residue which after 2 crystallizations from ethanol gave the diamide; yield 20.5 g., m.p. 174–175°.

Anal. Calcd. for $C_4H_{10}N_2O_3S$: C, 28.91; H, 6.03; N, 16.88. Found: C, 29.09; H, 6.01; N, 17.15.

The infrared spectrum in potassium bromide gave principal bands at 3 μ (NH) broad, 5.96 μ (CO), and 7.55 μ, 8.8 μ (SO_2).

α-Carbamylpropanesulfonylurea (V).—α-Carbamylpropanesulfonamide (IV) (8.95 g.) was added to a finely divided suspension of potassium cyanate (4.5 g.) in refluxing absolute ethanol (150 ml.) and the mixture was refluxed with stirring for 2 hr. The resulting mixture was cooled and the potassium salt of the ureide (11.55 g.) was collected by filtration. The salt was dissolved in water (15 ml.) and acidified with concd. hydrochloric acid (pH 2). The resulting white solid (7.2 g.), which formed after cooling, melted after recrystallization from absolute ethanol at 151–155° dec.

Anal. Calcd. for $C_5H_{11}N_3O_4S$: C, 28.71; H, 5.26, N, 20.10. Found: C, 28.47; H, 5.18; N, 19.75.

The infrared spectrum had bands at 5.80 μ ($NHCONH_2$), 5.95 μ (NH_2COCH), 6.62 μ (?), 7.60 μ, 8.67 μ (SO_2) and was practically identical with that of carbamylmethanesulfonylurea.[2]

Lutidinium 6-Ethyl-1,2,4,2H-thiadiazine-3,5(4H,6H)dione 1,1-Dioxide.—A mixture of α-carbamylpropanesulfonylurea (2.0 g.) and dry 2,6-lutidine (5 ml.) was refluxed for 30 min. At the end of this period a viscous liquid formed which solidified to a glass upon cooling. Decantation of the lutidine was followed by trituration of the glass with acetone. The crystals formed were recrystallized from absoluted ethanol; yield 0.81 g., m.p. 204–206°.

Anal. Calcd. for $C_{12}H_{17}N_3O_4S$: C, 48.20; H, 5.72; N, 14.05. Found: C, 48.32; H, 5.88; N, 14.42.

The infrared spectrum in potassium bromide contained principal bands at 5.9 μ (CO), 6.19 μ (CO), 7.24 μ, 8.8 μ, (SO_2) and resembled that for the sodium salt of 1,2,4(2H)-thiadiazine-3,5-(4H,6H)-dione 1,1 dioxide.[2]

The decanted lutidine upon treatment with ether gave an amorphous solid which when recrystallized from absolute ethanol gave 0.65 g. of α-carbamylpropanesulfonamide.

Reaction of Diphenyl α,α-Diethylsulfoacetate with Liquid Ammonia.—Diphenyl α,α-diethylsulfoacetate (19.5 g.) was sealed with liquid ammonia (40 ml.) in a glass tube and allowed to stand at room temperature for 1 day. Removal of the ammonia was followed by extraction with ether. The remaining solid was refluxed for 30 min. with 75 ml. of absolute ethanol and gave 8.8 g. of a compound melting at 223–224.5° dec.

Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 37.11; H, 7.22. Found: C, 36.77; H, 6.79.

Treatment of this salt with hydrochloric acid followed by solution in dimethylformamide and reprecipitation with ether gave a white solid melting at 218–220° dec. 4,4-Diethyl-1,2-thiazetidine-3-one 1,1-dioxide[4] is reported to melt at 63°.

Anal. Calcd. for $C_6H_{11}NO_3S$: C, 40.70; H, 6.27. Found: C, 40.71; H, 6.63.

Pharmacological Test (Table I).—Groups of 3 mice were dosed with the drug and then watched for gross symptomatology. The degree of the affect was graded from 0 to +++ by an experienced observer. No sleep was observed at any dose level. By comparison pentobarbital produces sleep at 35 mg./kg. intraperitoneally.

Acknowledgment.—The authors wish to thank the Abbott Laboratories for the pharmacological test reported.

Derivatives of 1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine

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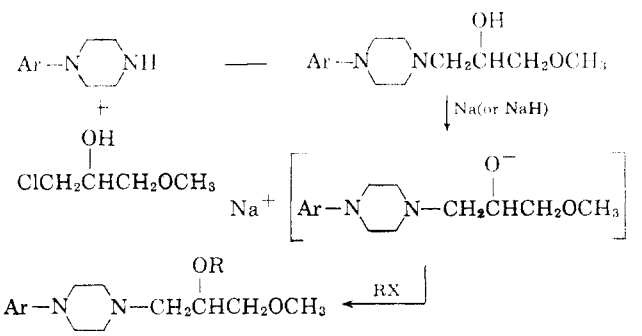
The structural relationship of the piperazines to certain other materials known to have pharmacological activity has prompted the synthesis of several series of piperazine derivatives with potential use as anthelmintic, antihistiminic, and tranquilizing agents. Amino ethers, particularly those of the ethanolamine series, are effective as antihistiminics. A wide variety of piperazine compounds have already been found to have effect upon the central nervous system. These include various dialkyl- and arylalkylpiperazines,[2–6] frequently with a 2-alkoxyethyl, 3-alkoxypropyl, 2-hydroxyethyl, or 3-hydroxypropyl group as one of the N-substituents.

The present work consists of the preparation and characterization of derivatives of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine. It also includes the synthesis of four new 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines and their use in the preparation of the respective methyl ethers. The physical and analytical data for these compounds are given in Table I. The following general procedure was used in these syntheses.

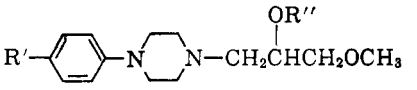


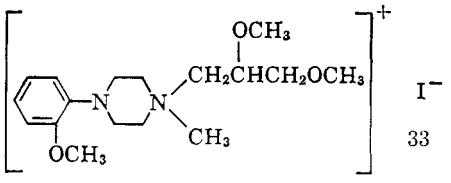
where R = —COO—alkyl or —COC_6H_5.

(1) Deceased. Formerly Professor of Chemistry, University of Florida.
(2) G.m.b.H. Nordmark-Werke, British Patent 813,473 (1959).
(3) Robert F. Parcell, U. S. Patent 2,836,594 (1958).
(4) Walter Voegtli, U. S. Patent 2,800,474 (1957).
(5) H. G. Morren, R. Denayer, R. Linz, J. Mathieu, H. Strubbe, and S. Trolin, *Ind. Chim. Belge*, **22**, 409 (1957).
(6) Armiger H. Sommers, U. S. Patent 2,891,063 (1959).

TABLE I

DERIVATIVES OF 1-ARYL-4-(2-HYDROXYPROPYL)PIPERAZINES



	R′	R″	Yield, %	Recrystallizing solvent	B.p.°, (mm.) or M.p., °C.	Analyses C Calcd. Found	H Calcd. Found	N Calcd. Found	Neut. equiv. Calcd. Found
I	H	CO_2CH_3	25	Abs. EtOH–dry acetone	176–176.5 dec.	55.73 56.03	7.31 7.26	8.13 8.28	345 343
II	H	$CO_2C_2H_5$	29	n-C_4H_9OH	162–162 dec.	56.40 57.08	7.58 7.68	7.81 7.94	359 359
III	H	CO_2-n-C_3H_7	56	EtOH-Et_2O	161–162 dec.	57.98 58.02	7.84 7.45	7.51 7.88	373 370
IV	H	CO_2-n-C_4H_9	19	H_2O	155.5–156.5	58.98 58.92	8.08 8.13	7.24 7.40	387 386
V	H	CO_2-i-C_4H_9	7	C_6H_6	155.5–156.5	58.98 58.87	8.08 7.89	7.24 7.36	387 386
VI	H	CO_2-n-C_5H_{11}	20	H_2O	159–160	59.91 60.09	8.30 8.45	6.99 6.79	401 404
VII	H	CO_2-n-C_6H_{13}	24	H_2O	155–156	60.78 61.09	8.50 8.65	6.75 6.68	415 417
VIII	H	CH_3	45		135 (0.2)	68.15 68.47	9.15 9.54	10.60 10.01	
IX	H	C_2H_5	23		132 (0.2)	69.03 69.04	9.41 9.23	10.06 10.26	
X	H	n-C_3H_7	29		150 (0.2)	69.82 69.75	9.65 9.47	9.58 9.66	
XI	H	n-C_4H_9	14		140 (0.1)	70.55 71.04	9.87 10.11	9.14 9.28	
XII	H	i-C_4H_9	8		145 (0.2)	70.55 70.14	9.87 9.89	9.14 10.03	
XIII	H	$CH_2C_6H_5$	50		194–208 (0.1)	74.08 74.31	8.29 8.34	8.23 7.94	
XIV	2-CH_3O	H	69	Et_2O	81–83	64.26 63.98	8.63 8.70	9.99 10.07	
XV	2-C_2H_5O	H	40	C_6H_6	71–71.5	65.27 66.32	8.90 8.80	9.52 9.74	
XVI	4-C_2H_5O	H	57	C_6H_6	96–97	65.27 66.45	8.90 8.88	9.52 9.65	
XVII	2-n-C_3H_7S	H	59		177 (0.2)	62.93 62.92	8.70 8.89	8.63 8.77	
XVIII	2-CH_3O	CH_3	33		147 (0.3)	65.28 65.67	8.90 8.92	9.52 9.42	
XIX	2-C_2H_5O	CH_3	18		147 (0.3)	66.20 65.93	9.15 8.98	9.09 9.05	
XX	4-C_2H_5O	CH_3	46	(Distilled)	41–43	66.20 66.11	9.15 9.10	9.09 9.05	
XXI	2-C_2H_5S	CH_3	15		173–180 (0.3)	63.86 63.97	8.93 8.85	8.28 8.55	
XXII	H	COC_6H_5	70	Et_2O	104.5–105	71.16 70.91	7.39 7.48	7.91 7.83	
XXIII			33		164–164.5	46.79 46.66	6.70 6.72	6.42 6.21	29.09[a] 29.27

[a] Iodine analysis.

Both sodium hydride and metallic sodium were used for the preparation of the sodium salt, but in many cases it proved difficult, because of the proximity of their boiling points, to separate the final reaction product from the oil in which the sodium hydride was suspended. Consequently, with few exceptions, the compounds reported here were prepared using metallic sodium. Furthermore, the sodium alcoholate, which was soluble in benzene or toluene in which it was prepared, could be decanted from any unreacted sodium before addition of the halide to the solution.

Invariably, the crude product was contaminated with at least a small amount of the starting alcohol Purification processes were repeated in each case until the

infrared spectrum of the product showed little or no absorption below 3.0 μ. The benzoate derivative, which is a solid, was purified by recrystallization. The benzyl ether and alkyl ether derivatives were obtained as liquids. The benzyl ether was purified by a second distillation under vacuum. However, each of the alkyl ethers distilled simultaneously with the respective alcohol from which it had been prepared. An attempt to separate the ether from the crude mixture by esterification of the unreacted alcohol with phthalic anhydride resulted in incomplete reaction. The product was obtained pure by distillation under vacuum from sodium.

The use of a molar excess of methyl iodide in the preparation of 1-(2-methoxyphenyl)-4-(2,3-dimethoxypropyl)piperazine gave the quaternary ammonium iodide.

In the special case of the carbonic acid esters, the products were precipitated from solution as the amine monohydrochlorides. The hydrochlorides were recrystallized from the designated solvent until the melting point ranges and infrared spectra indicated that they were pure.

Pharmacological Evaluation.—Preliminary pharmacological testing indicated a slight to moderate adenergic blockade for compounds I, IX, and XIII at doses of 2 mg./kg. when tested for the reversal of epinephrine affect on blood pressure *in vivo*.[7] Compound I also exhibited moderate hypotensive activity at a dose of 8 mg./kg. Compounds XV and XVII exhibited moderate cerebral depressant activity when tested as anti-excitants in rats. A slight activity against schistosomiasis in mice was observed for compounds XIX and XX. Quaternization of the nitrogen in the 4-position of the piperazine ring in compound XXIII produced no significant activity. A routine antibacterial screening of all compounds failed to reveal any significant activity.

Experimental[8]

Intermediates.—N-Phenylpiperazine was commercially available from Chemopuro Manufacturing Corporation and was used without further purification. The 4-ethoxyphenylpiperazine was prepared in this laboratory by the method of Prelog, *et al.*,[9] as modified by Parcell.[10] N-(2-Methoxyphenyl)piperazine, N-(2-ethoxyphenyl)piperazine, and N-(2-propylthio-phenyl)piperazine were furnished as research samples by Parke, Davis and Co.

1-Chloro-3-methoxy-2-propanol.—The method of preparation was an adaptation of the method of Fairbourne, *et al.*,[11] for the preparation of 1-chloro-3-ethoxy-2-propanol. Concentrated sulfuric acid (20 ml.) was added to methanol (1615 ml.) and epichlorohydrin (314 ml.) was then added dropwise with stirring. The solution was refluxed overnight, cooled, and neutralized to a phenolphthalein end point with concd. aqueous sodium hydroxide. The solvent was removed by passing the solution through a steam-heated coil under vacuum from a water aspirator and the residue was distilled at 20 mm. pressure. The product which distilled between 80 and 85° was collected.

Preparation of 1-Aryl-4-(2-hydroxy-3-methoxypropyl)piperazines.—These intermediates were prepared by slight modifications of the method of Pollard and Wicker.[12] The modifications consisted of heating a mechanically stirred mixture of the reactants at 90–100° instead of heating with occasional agitation on the steam bath, and of the use of ether instead of heptane for the extraction and recrystallization of the product. These modifications resulted in increased yields of purified product and eliminated the necessity for handling the comparatively large volume of heptane which was required for solution of the product.

Preparation of the Sodium Salts of 1-Aryl-4-(2-hydroxy-3-methoxypropyl)piperazines.—The appropriate 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine (0.12 mole) and sodium (0.1 mole) were placed with toluene (200 ml.) in a flask equipped with a condenser and outlet tube which led to a rotary wet-test meter for measuring hydrogen evolution. The contents were refluxed until the calculated amount of hydrogen had evolved. The solution was cooled and, if any unreacted sodium still remained, it was either removed or the solution of the sodium alkoxide was carefully decanted.

In the alternative procedure involving the use of sodium hydride, the hydride (0.1 mole) was placed in the reaction vessel with the toluene (or benzene) and the 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine in a sclution of the same solvent was added dropwise through a pressure-equalizing funnel. The reaction was considered complete when the calculated amount of hydrogen had evolved. The solution of the sodium alkoxide was cooled to room temperature before beginning the reaction with the appropriate halogen compounds.

Reaction of the Sodium Alkoxide with Chloroformates.—The appropriate chloroformate (0.2 m.) was added, with stirring, to the solution of the sodium alkoxide at such a rate as to keep the temperature from rising above 75°. The liquid–solid mixture was stirred for several hours and the solid was then separated by filtration. In some instances, the efficiency of the separation was improved by dissolving the crude solid in aqueous sodium carbonate and extracting the resulting solution once or twice with ether. The toluene–ether solution of the carbonate ester was then concentrated to approximately 100 ml. on a rotary evaporator and the product was precipitated as the monohydrochloride with anhydrous hydrogen chloride. The crude material was recrystallized until acceptable purity was indicated by a correct value for neut. equiv. wt. of the product.

Reaction of the Sodium Alkoxides with Alkyl Halides.—The desired alkyl halide was added dropwise with stirring to a solution of the sodium alkoxide. When it appeared that no more solid was precipitating, the stirring was stopped and the reaction mixture poured into about an equal volume of water. The resulting oil layer was separated and the aqueous layer was extracted with benzene, ether, or heptane. Upon evaporation of the solvent in a rotary evaporator, a solid sometimes appeared which was removed by filtration and found to be the starting alcohol, 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine. In this case, a small amount of sodium was added to the liquid product containing the desired ether in a distillation flask and the contents heated at a temperature sufficient to melt the sodium for about 1 hr. under vacuum. The temperature was then raised and the 1-aryl-4-(2-alkoxy-3-methoxypropyl)piperazine was distilled.

When twice the equimolar amount of methyl iodide was added to the sodium salt of 1-(2-methoxy)phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine, voluminous precipitation occurrred. The precipitate was removed by filtration and partially dissolved in aqueous sodium hydroxide. The undissolved portion was again removed by filtration and recrystallized from a methanol ethyl acetate solution. Elemental analysis indicated this to be the quaternary ammonium iodide.

Reaction of 1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine with Benzoyl Chloride.—Sodium hydride was treated with 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine as described above except that the solvent used was dimethylformamide at 60–70°. Benzoyl chloride was added dropwise with stirring. The solution was then cooled and a flocculent precipitate began to separate at approximately 40°. The mixture was stirred at room temperature for 24 hr. and filtered. The product was recrystallized from a dimethylformamide–water solution, again from ethanol, and finally from ether.

Acknowledgment.—During the period in which this research was conducted, H. H. held a Parke, Davis and Co. Research Fellowship. The authors express

(7) F. P. Luduena, E. O'Malley and I. H. Oyen, *Arch. Intern. Pharmacodyn.*, **122**, 111 (1959).

(8) The elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

(9) (a) V. Prelog and G. J. Driza, *Collection Czech. Chem. Commun.*, **5**, 497 (1953); (b) V. Prelog and F. Blazek, *ibid.*, **6**, 211 (1934).

(10) Unpublished work of Robert F. Parcell, Parke, Davis & Co., Ann Arbor, Michigan.

(11) A. Fairbourne, G. P. Gibson, and D. W. Stephens, *J. Chem. Soc.*, 1965 (1932).

(12) C. B. Pollard and T. H. Wicker, U. S. Patent 2,575,122 (1950).

their appreciation for this research grant, and for the help of Parke, Davis and Co. in carrying out the pharmacological testing herein reported.

The Synthesis of Two New Metabolites of Catecholamines: 3,4-Dihydroxyphenylethyleneglycol and 4-Hydroxy-3-methoxyphenylethyleneglycol[1]

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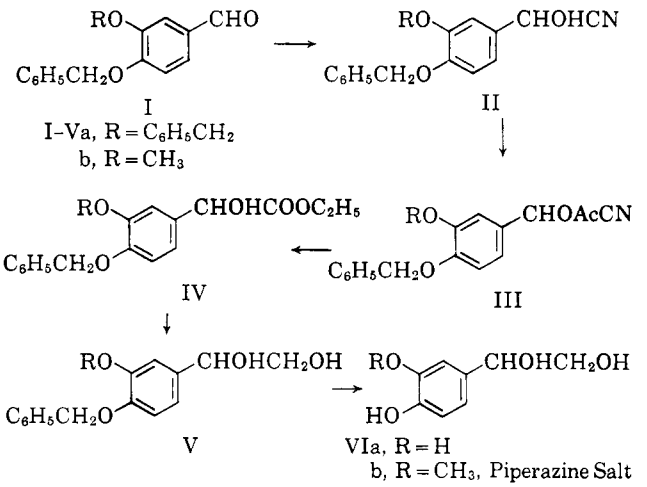
Recently two metabolites of epinephrine and norepinephrine have been identified as 4-hydroxy-3-methoxyphenylethyleneglycol[3-5] and 3,4-dihydroxyphenylethyleneglycol.[6,7] The preparation of these two metabolites was undertaken in order to complete their identification by chemical syntheses.

In the reaction sequence the benzylated aldehydes I were treated with a large excess of hydrogen cyanide to maximize their conversion to the mandelonitriles II. The mandelonitriles were unstable and difficult to separate from the starting aldehydes. Furthermore, when the crude mandelonitriles were converted to their corresponding ethyl mandelates (IV), the starting aldehydes and the esters proved to have nearly identical solubility and absorbance properties on alumina or silica gel and could not be separated. It was found that acetylation of the intermediate mandelonitriles afforded a mixture from which the acetylated mandelonitriles (III) could be fractionally crystallized. Ethanolysis of the acetylated mandelonitriles with ethanolic hydrogen chloride gave the easily purified ethyl mandelates (IV), which were reduced to the corresponding glycols (V) with lithium aluminum hydride. Hydrogenolysis of the protecting benzyl groups gave the glycols in good yield. An attempt to prepare these glycols by lithium aluminum hydride reduction of the unprotected ethyl mandelates[8] was unsuccessful.

3,4-Dihydroxyphenylethyleneglycol (VIa) is a crystalline solid which is stable on standing. However, in one attempt at purification a polymeric substance resulted. It is known that phenolic benzyl alcohols can be quite sensitive to acids, bases, and heat, giving phenol–formaldehyde type condensation products.[9]

4-Hydroxy-3-methoxyphenylethyleneglycol (VIb) has been reported[3] to be an oil, and numerous attempts on our part to obtain a solid product failed. However, a crystalline piperazine salt[10] complex formed which had several notable physical characteristics. It was easier to handle and more stable than the free phenolic-glycol. Furthermore, paper and thin layer chromatograms of the free glycol, the salt, and an acidified sample of the salt showed identical R_f values, a char acteristic of significance to biochemical investigations.



Experimental

Melting points were taken on a Hoover Uni-Melt capillary apparatus and are corrected. Ultraviolet spectra were determined in 95% ethanol using a Perkin–Elmer spectrophotometer Model 202. Infrared spectra were determined in chloroform using a Perkin–Elmer Infracord Model 137. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana.

3,4-Dibenzyloxymandelonitrile Acetate (IIIa).—To a mixture of 31.8 g. (0.1 mole) of 3,4-dibenzyloxybenzaldehyde,[11] 40 g. (0.6 mole) of potassium cyanide, 225 ml. of dioxane, and 55 ml. of water was added with stirring 33 ml. (0.4 mole) of hydrochloric acid. The mixture was stirred and refluxed for 1 hr., after which time it was cooled to room temperature. Benzene was added to the dark mixture, and the aqueous layer discarded. The organic layer was diluted with 200 ml. of benzene and dried over sodium sulfate. To the dark filtered solution was added 125 ml. (1.2 moles) of acetic anhydride and 50 ml. of pyridine, and the solution allowed to stand at room temperature overnight. The mother liquor was removed under reduced pressure, fresh benzene was added to the oil, and it again was evaporated to dryness. The oil was dissolved in 200 ml. of ethanol whereupon 24.4 g. (42%) of IIIa crystallized. A white crystalline product, m.p. 67–68°, was obtained on recrystallization from ethyl acetate and hexane.

Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.47; N, 3.62. Found: C, 74.59; H, 5.58; N, 3.52. Infrared: 5.72 μ (C=O). The nitrile absorptions in this series were not detected in our study.

Ethyl 3,4-Dibenzyloxymandelate (IVa).—A solution of 28.0 g. (0.72 mole) of 3,4-dibenzyloxymandelonitrile acetate (IIIa), 300 ml. of ethanol, and 200 ml. of ethanolic hydrogen chloride was allowed to stand under nitrogen at room temperature for 16 hr. The mixture was evaporated under reduced pressure to an oil, which was covered with water and extracted with ether and twice with benzene. The extracts were combined, dried over sodium sulfate, and evaporated. The resulting oil was covered with hexane and allowed to crystallize. There resulted 24 g. (84%) of product, m.p. 58–61°. Two recrystallizations from ethyl acetate and hexane gave a white crystalline solid, m.p. 68–70°.

Anal. Calcd. for $C_{24}H_{24}O_5$: C, 73.46; H, 6.16. Found: C, 73.72; H, 6.05. Infrared: 2.80 μ (OH), 5.80 μ (C=O).

(1) This work was supported by the Psychopharmacology Service Center of the National Institutes of Mental Health under contract No. SA-43-ph 3021.

(2) To whom inquiries should be addressed.

(3) J. Axelrod, I. J. Kopin, and J. D. Mann, *Biochem. Biophys. Acta*, **36**, 576 (1959).

(4) J. Axelrod, Abstracts of the Eight National Medicinal Chemistry Symposium of the American Chemical Society, University of Colorado, Boulder, Colorado, June 18–20, 1962, p. 4a .

(5) E. H. LaBrosse, J. Axelrod, I. J. Kopin, and S. Kety, *J. Clin. Invest.*, **40**, 253 (1961).

(6) I. J. Kopin and J. Axelrod, *Arch. Biochem. Biophys.*, **89**, 148 (1960).

(7) I. J. Kopin, J. Axlerod, and E. Gordon, *J. Biol. Chem.*, **236**, 2109 (1961).

(8) The corresponding ethyl 3,4-dihydroxy- and 4-hydroxy-3-methoxymandelate esters have been reported by E. F. Recondo and H. Rinderknecht, *J. Org. Chem.*, **25**, 2248 (1960), and K. N. F. Shaw, A. McMillan, and M. D. Armstrong, *ibid.*, **23**, 27 (1958).

(9) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1954, pp. 501–505.

(10) F. W. Short and E. F. Elslager, *J. Med. Pharm. Chem.*, **5**, 642 (1962).

(11) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 522 (1951).