[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

PREPARATION OF SOME ANALOGS OF PAPAVERINE[1]

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Received December 12, 1951

The ability to dilate the coronary artery of the heart is a property possessed by certain isoquinoline derivatives of the papaverine type. A study has been in progress in an effort to relate coronary dilator activity with modifications of the papaverine structure. The first paper in this series (1) reported the preparation of all the 6,7-dialkoxy-1-(3,4-dialkoxybenzyl)isoquinolines of the ethoxy, methoxy series. It was found that the substitution of ethoxyl groups for methoxyl groups did not profoundly alter the type or the extent of the physiological action of the molecule.

It seemed desirable, not only to continue the study of the effect of alkoxyl groups other than ethoxyl and methoxyl, but also to determine what effect the absence of an alkoxyl group has upon the action of the molecule. A variety of compounds illustrating these variations is reported herein. In addition, all of the possible 6,7-dimethoxy-1-(dimethoxybenzyl)isoquinolines were prepared to determine if the position of substitution of the benzyl group was of importance.

The analogs were prepared by the classical Bischler-Napieralski isoquinoline synthesis involving the cyclization and subsequent catalytic dehydrogenation of the appropriately substituted N-β-(phenylethyl)phenylacetamide.

The amides were obtained by the condensation of the properly substituted phenylacetic acid with the required β-phenylethyl amine. The use of the well known conversion of a benzyl alcohol to its chloride and hence to the phenylacetonitrile had the unique advantage of providing an intermediate that yielded the desired phenylacetic acid on hydrolysis or the analogous β-phenylethylamine on catalytic reduction.

In some instances the benzyl alcohols were synthesized by the crossed-Cannizzaro reaction. However, 2,3-dimethoxybenzyl alcohol prepared in this manner proved to be unstable toward distillation. In this case, catalytic hydrogenation gave a definitely superior product. The 2,4- and 2,6-dimethoxybenzyl alcohols were obtained by the reduction of the corresponding benzoic acids with lithium aluminum hydride using the general procedure of Adams, Harfenist, and Loewe (2); 3,5-dimethoxybenzyl alcohol was prepared in a similar manner from methyl 3,5-dimethoxybenzoate. Attempts to isolate either 2,4-dimethoxybenzyl alcohol or its chloride were unsuccessful. Distillation *in vacuo* caused polymerization to a resin; in fact, resin formation took place on prolonged standing of either substance in petroleum ether. In spite of this, a usable yield of 2,4-dimethoxyphenylacetic acid was obtained by continuing the series of reactions without isolation of these intermediates.

[1] Presented before the Division of Medicinal Chemistry at the 118th Meeting of the American Chemical Society in Chicago on September 6, 1950.

In certain cases the required phenylacetic acid was prepared more quickly and in fewer steps by the Willgerodt reaction. However, in our hands, the conversion of 2,4-dimethoxyacetophenone to 2,4-dimethoxyphenylacetic acid by this procedure failed. This is somewhat surprising in that the conversion of the closely related 2,5-dimethoxyacetophenone to 2,5-dimethoxyphenylacetic acid was accomplished in a 54% over-all yield. Traces of sulfur proved to be detrimental in the subsequent steps of the process. However, the acids obtained by the Willgerodt reaction could be rendered sulfur-free by heating an alkaline solution of the acid with Raney nickel catalyst.

Salts of the papaverine analogs were examined for coronary dilator effects in dogs. The ratio of the extent of dilation produced by the analog to that produced by papaverine hydrochloride was determined and these results are presented in Table III. Mice were used in the determination of the acute intravenous toxicity (LD_{50}) of the compounds; these values are also reported in Table III. For purposes of comparison, the toxicity of papaverine hydrochloride is about 30 mg./kg.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

2-Ethoxy-3-methoxybenzaldehyde (3). A solution of 304 g. (2.0 moles) of *o*-vanillin in 100 ml. of Methyl Cellosolve was heated at 65–75° while 130 g. of sodium hydroxide in 300 ml. of water, and 330 ml. of ethyl sulfate were added simultaneously through separate dropping-funnels. The addition required 40 minutes. The solution was heated at 70–80° for one hour and diluted with water. The oily suspension was extracted repeatedly with benzene; the combined benzene extracts were dried over magnesium sulfate and distilled. The fraction boiling at 151–154° (22 mm.) was collected to yield 282 g. (78%); $n^{26.5}_{D}$ 1.5327.

4-Isopropoxy-3-methoxybenzaldehyde (4). A solution of 304 g. (2.0 moles) of vanillin in 500 ml. of Methyl Cellosolve was caused to react with 115 g. of potassium hydroxide dissolved in 300 ml. of water. The resultant solution was heated under reflux for 68 hours with 300 g. (2.44 moles) of isopropyl bromide. The solution was diluted with 4 l. of water and extracted with benzene. The benzene extracts were washed repeatedly with dilute sodium hydroxide solution, dried over magnesium sulfate, and distilled. The fraction boiling at 120–125° (0.05 mm.) was collected; yield, 194 g. (50%); $n^{26.5}_{D}$ 1.5561.

3-Methoxy-4-n-propoxybenzaldehyde (4). A mixture of 304 g. (2.0 moles) of vanillin in 500 ml. of Methyl Cellosolve, 115 g. of potassium hydroxide in 300 ml. of water, and 300 g. of *n*-propyl bromide was heated under reflux for 48 hours. The reaction mixture was processed as above to yield 276.2 g. (71%) of product distilling at 159–162° (9 mm.).

4-Isopropoxy-3-methoxybenzyl alcohol. A mixture of 194 g. (1.0 mole) of 3-methoxy-4-isopropoxybenzaldehyde, 100 ml. of 35% formalin, and 100 ml. of methanol was added in the course of 15 minutes to 167 g. (3.0 moles) of potassium hydroxide in 250 ml. of methanol maintained at a temperature of 60–70°. The solution was heated, with mechanical stirring for three hours at this temperature. After diluting with water, the reaction mixture was extracted with two portions of benzene; the benzene extracts were washed with dilute sodium carbonate solution, dried over magnesium sulfate, and distilled. The fraction boiling at 162–164° (9 mm.) was collected to yield 158.8 g. (80%); $n^{27.5}_{D}$ 1.5288.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22.
Found: C, 67.33; H, 8.14.

3-Methoxy-4-n-propoxybenzyl alcohol. Using the crossed Cannizzaro reaction according to the above directions, 3-methoxy-4-*n*-propoxybenzaldehyde was converted in 81% yield to the corresponding benzyl alcohol, b.p. 173–178° (10 mm.), $n^{27.5}_{D}$ 1.5332.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22.
Found: C, 67.10; H, 8.03.

2-Ethoxy-3-methoxybenzyl alcohol (5). 2-Ethoxy-3-methoxybenzaldehyde was converted to the corresponding benzyl alcohol (b.p. 150–153°/11 mm., n_D^{26} 1.5262) in 89% yield following the procedure described for the preparation of 3-methoxy-4-isopropoxybenzyl alcohol.

2,3-Dimethoxybenzyl alcohol (6). *A.* 2,3-Dimethoxybenzaldehyde was converted to the alcohol by the procedure followed for the preparation of 3-methoxy-4-isopropoxybenzyl alcohol. In addition to the desired product, a large amount of a high-boiling residue was formed. Furthermore, redistillation of the 2,3-dimethoxybenzyl alcohol caused more resin formation to occur. The over-all yield of the twice-distilled benzyl alcohol was only 27%.

B. The high pressure hydrogenation at 150° of an ethanolic solution of the aldehyde in the presence of copper chromite catalyst produced 2,3-dimethoxybenzyl alcohol (b.p. 138–144°, 10 mm.) in 97% yield. The material prepared in this manner did not resinify during redistillation.

3,4-Methylenedioxybenzyl alcohol (7). A solution of 200 g. (1.33 moles) of piperonal in 200 ml. of 95% alcohol was hydrogenated at 2200 p.s.i. in the presence of 15 g. of copper chromite. The theoretical quantity of hydrogen was absorbed at 130°. The catalyst was removed and distillation of the filtrate produced 194.8 g. (96%) of material boiling at 116–122° (4 mm.).

2,4-Dimethoxyacetophenone (8). Nitroethane was purified by distillation *in vacuo* from 5% by weight of anhydrous aluminum chloride. To 150 g. (0.83 mole) of resorcinol dimethyl ether in 200 ml. of purified nitroethane was added 155 g. of anhydrous aluminum chloride at such a rate that the temperature remained at 25–35°. Then 86 g. (1.09 moles) of acetyl chloride was added slowly while maintaining the temperature at 30–37°. The reaction mixture was heated at 45° for one hour. The cooled solution was poured upon an ice-hydrochloric acid mixture and extracted with ether. The organic layer was washed twice with dilute sodium hydroxide solution and once with water. The ether layer was dried over magnesium sulfate and distilled. The fraction boiling at 156–161° (9 mm.) weighed 151 g., 77%.

In a similar manner, *2,5-dimethoxyacetophenone* (9) (b.p. 155–159°/15 mm.) was prepared in 62% yield from hyrdoquinone dimethyl ether.

3-Methoxyacetophenone. The procedure of von Auwers (10) gave 3-methoxyacetophenone (b.p. 125–127°/14 mm.) in 79% yield. The replacement of methyl sulfate in von Auwers' procedure by ethyl sulfate produced *3-ethoxyacetophenone* (11) (b.p. 120–122°/7 mm.) in 85% yield.

Preparation of nitriles. The procedure reported previously (1) for the conversion of 4-ethoxy-3-methoxybenzyl alcohol to 4-ethoxy-3-methoxyphenylacetonitrile was followed. 2-Ethoxy-3-methoxybenzyl alcohol produced *2-ethoxy-3-methoxyphenylacetonitrile* (b.p. 111–130°/0.11 mm.) in 73% yield. Similarly, *4-isopropoxy-3-methoxyphenylacetonitrile* (b.p. 111–130°/0.12 mm.), *3-methoxy-4-n-propoxyphenylacetonitrile* (b.p. 142–160°/0.25 mm.), and *3,4-methylenedioxyphenylacetonitrile* (b.p. 134–142°/5.0 mm.) were obtained in yields of 58, 60, and 72% respectively.

Phenylacetic acids. The acids were prepared by standard procedures as illustrated by the following examples and are described in Table I.

A. 3-Methoxy-4-n-propoxyphenylacetic acid. A mixture composed of 140 g. (0.68 mole) of 3-methoxy-4-*n*-propoxyphenylacetonitrile, 71 g. of sodium hydroxide dissolved in 210 ml. of water, and 70 ml. of Methyl Cellosolve was heated under reflux for 4½ hours. The solution was diluted with water and extracted with ether. Dissolved ether was removed from the aqueous layer *in vacuo*. Acidification of the ether-free solution with dilute hydrochloric acid produced a white precipitate. After the suspension was cooled in the refrigerator, the precipitate was collected. The acid was recrystallized twice from a benzene-Skellysolve B mixture to yield 102.8 g. (67%) of analytically pure material.

B. 3-Ethoxyphenylacetic acid. A suspension of 33 g. (1.04 moles) of sulfur in 113.5 g. (0.69 mole) of 3-ethoxyacetophenone and 90 g. (1.04 moles) of morpholine was heated under

reflux for 15 hours. A solution composed of 350 ml. of acetic acid, 105 ml. of water, and 70 ml. of sulfuric acid was added and the solution was heated under reflux for 5½ hours. The reaction mixture was poured upon ice-water and stirred until crystallization took place. After the resultant suspension was cooled in an ice-bath, it was filtered. The precipitate was dissolved in dilute sodium hydroxide and heated under reflux for two hours with 30 g. of Raney nickel catalyst (Gilman Paint and Varnish Company). The spent catalyst was removed; 30 g. of fresh Raney nickel was added and the solution again was heated under reflux for two hours and filtered. The colorless filtrate was acidified with dilute hydrochloric

TABLE I

PHENYLACETIC ACIDS

PHENYLACETIC ACID	FORMULA	METHOD	YIELD, %	M.P., °C.	ANALYSES			
					Calc'd		Found	
					C	H	C	H
3,4-Diethoxy[a]	$C_{12}H_{16}O_4$	A	65	78.5–79.5				
2,3-Dimethoxy[b]	$C_{10}H_{12}O_4$	A	70	81–82				
2,4-Dimethoxy[c]	$C_{10}H_{12}O_4$	C	31	109–111				
2,5-Dimethoxy[d]	$C_{10}H_{12}O_4$	B	54	123–125				
2,6-Dimethoxy	$C_{10}H_{12}O_4$	C	22	149.5–152.5	61.21	6.17	61.47	6.23
3,4-Dimethoxy[e]	$C_{10}H_{12}O_4$	A	44	95–97				
3,5-Dimethoxy[e]	$C_{10}H_{12}O_4$	C	56	100–102				
3-Ethoxy	$C_{10}H_{12}O_3$	B	72	92–93	66.65	6.71	66.45	6.63
2-Ethoxy-3-methoxy	$C_{11}H_{14}O_4$	A	91	85.5–86.5	62.84	6.71	62.77	6.69
4-Ethoxy-3-methoxy[f]	$C_{11}H_{14}O_4$	A	51	70.5–72				
4-Isopropoxy-3-methoxy	$C_{12}H_{16}O_4$	A	61	75.5–76	64.26	7.19	64.35	7.34
3-Methoxy[g]	$C_9H_{10}O_3$	B	57	69–70				
3-Methoxy-4-*n*-propoxy	$C_{12}H_{16}O_4$	A	67	87–88	64.26	7.19	64.33	7.10
3,4-Methylenedioxy[h]	$C_9H_8O_4$	A	76	128–129				

[a] Kindler and Gehlhaar, *Arch. Pharm.*, **274**, 377 (1936). [b] von Krannichfeldt, *Ber.*, **46**, 4016 (1913). [c] Reference 14. [d] Reference 9. [e] Mauthner, *J. prakt. Chem.*, **110**, 125 (1925); *Chem. Centr.*, **25**, II, 1272 (1925). [f] Reference 1. [g] Pschorr, *Ann.*, **391**, 40 (1912). [h] Reference 15.

acid. The white precipitate was collected and dried; yield 90.3 g. (72%), m.p. 92–93°. The analytical sample was prepared by dissolving the acid in boiling benzene and diluting with Skellysolve B.

Attempted preparation of 2,4-dimethoxyphenylacetic acid. 2,4-Dimethoxyacetophenone was heated under reflux with morpholine and sulfur as described in the preparation of 3-ethoxyphenylacetic acid. When the hydrolysis mixture was poured into water, a tar separated. The tar was dissolved in ether and the ether solution extracted repeatedly with dilute sodium carbonate solution. The alkaline aqueous layers were desulfurized with Raney nickel as previously described. Acidification of the filtered solution produced no insoluble product of any kind.

An attempt to prepare 2,4-dimethoxyphenylthioacetylmorpholide by the procedure reported in "Organic Reactions" (12) resulted in a non-crystalline product.

TABLE II

N-β-(PHENYLETHYL)PHENYLACETAMIDES

SUBSTITUTED PHENYLACETAMIDE	FORMULA	YIELD, %	M.P., °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
N-β-(3,4-Diethoxy-phenylethyl)-3,4-methylenedioxy	$C_{21}H_{25}NO_5$	76	119–120	67.91	6.79	67.83	6.88
N-β-(4-Ethoxy-3-methoxyphenyl-ethyl)-2-ethoxy-3-methoxy	$C_{22}H_{29}NO_5$	83	105.5–106.5	68.19	7.54	68.40	7.71
N-β-(4-Ethoxy-3-methoxyphenyl-ethyl)-3,4-methylenedioxy	$C_{20}H_{23}NO_5$	71	114–115	67.21	6.48	67.10	6.39
N-(Homopiperonyl)-3,4-diethoxy	$C_{21}H_{25}NO_5$	73	105–106	67.91	6.79	67.63	6.77
N-(Homopiperonyl)-2-ethoxy-3-methoxy	$C_{20}H_{23}NO_5$	62	84–85	67.21	6.49	67.37	7.10
N-(Homopiperonyl)-4-ethoxy-3-methoxy	$C_{20}H^{23}NO_5$	64	140–141	67.21	6.49	67.26	6.53
N-(Homopiperonyl)-2,3-dimethoxy	$C_{19}H_{21}NO_5$	60	106.5–107	66.46	6.16	66.22	5.97
N-(Homopiperonyl)-3-methoxy-4-*n*-propoxy	$C_{21}H_{25}NO_5$	75	125–126	67.91	6.79	67.82	6.59
N-(Homoveratryl)-2,3-dimethoxy[a]	$C_{20}H_{25}NO_5$	77	131–132	66.83	7.01	66.69	7.18
N-(Homoveratryl)-2,4-dimethoxy	$C_{20}H_{25}NO_5$	75	131–132	66.83	7.01	67.23	6.91
N-(Homoveratryl)-2,5-dimethoxy	$C_{20}H_{25}NO_5$	89	105–106	66.83	7.01	66.51	6.91
N-(Homoveratryl)-2,6-dimethoxy	$C_{20}H_{25}NO_5$	48	113–114	66.83	7.01	66.63	7.27
N-(Homoveratryl)-3,5-dimethoxy	$C_{20}H_{25}NO_5$	87	122–123	66.83	7.01	66.60	7.10
N-(Homoveratryl)-2-ethoxy-3-methoxy	$C_{21}H_{27}NO_5$	86	115.5–116.5	67.54	7.28	67.30	7.34
N-(Homoveratryl)-3-ethoxy	$C_{20}H_{25}NO_4$	85	87.5–88	69.95	7.33	69.69	7.26
N-(Homoveratryl)-4-isopropoxy-3-methoxy	$C_{22}H_{29}NO_5$	86	96.5–97.5	68.19	7.54	68.20	7.70
N-(Homoveratryl)-3-methoxy	$C_{19}H_{23}NO_4$	93	113–114	69.28	7.04	69.00	6.82
N-(Homoveratryl)-3-methoxy-4-*n*-propoxy	$C_{22}H_{29}NO_5$	86	130.5–131.5	68.19	7.54	68.19	7.50

[a] Tsatsas, *Compt. rend.*, **229**, 219 (1949).

C. 2,6-Dimethoxyphenylacetic acid. A slurry of 91 g. (0.5 mole) of 2,6-dimethoxybenzoic acid (13) in 2 l. of absolute ether was added in small portions by means of a dropping-funnel to a well stirred suspension of 24 g. (0.63 mole) of lithium aluminum hydride in 1 l. of anhydrous ether. The reaction mixture was heated under reflux for four hours and then stirred at room temperature overnight. Addition of 150 ml. of ice-water, dropwise initially, followed by 100 ml. of concentrated sulfuric acid in 1600 ml. of water caused the white precipitate to enter solution. The ether layer was separated and washed twice with water, twice with dilute sodium carbonate solution, and again with water. After drying over magnesium sulfate, the ether solution was treated with 6 ml. of pyridine, and with stirring, 132 g. of thionyl chloride was added in a dropwise manner. After 40 minutes at room temperature, the solution was poured into ice-water; the separated organic layer was washed with three 1-l. portions of water, two 500-ml. portions of saturated sodium carbonate, and finally with water. The ether layer was stripped to dryness *in vacuo* and the residue, diluted with 2 l. of acetone, was caused to react at room temperature with 66 g. (1 mole) of potassium cyanide in 1 l. of water. After a reaction time of 20 hours, the acetone was removed from the solution *in vacuo*. The oily aqueous layer was extracted with ether and the organic layer concentrated by distillation. The residue, diluted with 60 ml. of Methyl Cellosolve, was heated under reflux for five hours with 60 g. of sodium hydroxide in 180 ml. of water. The cooled reaction mixture was extracted with ether; the aqueous layer, after heating to expel ether, was acidified with dilute hydrochloric acid to yield 21.9 g. (22%) of a light tan precipitate; m.p. 143–151°. The analytical sample was prepared by two recrystallizations of this material from a benzene-Skellysolve B mixture (1:3).

In a similar manner, 2,4-dimethoxyphenylacetic acid (14) was obtained in a 31% over-all yield. Preliminary experiments revealed that the intermediates, *2,4-dimethoxybenzyl alchohol* and *2,4-dimethoxybenzyl chloride*, were unstable and resinified readily. However, it was possible to isolate *2,4-dimethoxyphenylacetonitrile*, m.p. 73.5–74.5°, in 28% yield by vacuum distillation of the crude nitrile at 0.5 mm., followed by recrystallization from methanol.

Anal. Calc'd for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 8.17.

3,5-Dimethoxyphenylacetic acid, m.p. 100–102°, was prepared in like manner from methyl 3,5-dimethoxybenzoate in 56% over-all yield.

Homopiperonylamine (15). A solution of 140 g. (0.86 mole) of 3,4-methylenedioxyphenylacetonitrile in a solvent composed of 150 ml. of ethanol and 150 ml. of liquid ammonia was subjected to high pressure hydrogenation in the presence of 15 g. of Raney nickel catalyst. The theoretical amount of hydrogen was absorbed in 45 minutes at 100–110°. The cooled reaction mixture was filtered and the filtrate concentrated *in vacuo*. Distillation of the residue produced 132.5 g. (92%) of the amine, b.p. 150–156° (18 mm.).

β-3,4-Diethoxyphenylethylamine and *β-4-ethoxy-3-methoxyphenylethylamine* were prepared by the method of Shepard and Noth (1). Homoveratrylamine was supplied by the Monsanto Chemical Company.

Preparation of amides. The procedure for the preparation of *N-(homopiperonyl)-3,4-diethoxyphenylacetamide* illustrates the general method used in preparing all of the amides. The properties of the amides are presented in Table II.

A mixture of 24.7 g. (0.15 mole) of freshly distilled homopiperonylamine and 33.6 g. (0.15 mole) of 3,4-diethoxyphenylacetic acid was heated at 180–200° for 45 minutes. The reaction mixture was dissolved in 75 ml. of boiling benzene and diluted by the gradual addition of one liter of Skellysolve B with vigorous stirring to induce crystallization. The precipitate was stored in the refrigerator overnight and collected. The material was recrystallized from a methanol-water (5:4) mixture; white starry clusters of needles were obtained.

Preparation of isoquinolines and their hydrochlorides. The isoquinolines and their salts were prepared by the method previously described (1). These compounds are tabulated in Table III.

TABLE III

ISOQUINOLINES AND THEIR HYDROCHLORIDES

ISOQUINOLINE	FORMULA	YIELD, %	M.P., °C.	ANALYSES						CORONARY DILATOR ACTIVITY	LD_{50} mg./kg.
				Calc'd			Found				
				C	H	N	C	H	N		
6,7-Diethoxy-1-(3′,4′-methylenedioxybenzyl)	$C_{21}H_{21}NO_4$	60	118.5–119.5	71.78	6.02		71.50	5.96			
Hydrochloride	$C_{21}H_{22}ClNO_4$	90	193–195	65.03	5.72	3.61	65.11	6.24	3.64	0.6	91.3 ± 4.6
1-(3′,4′-Diethoxybenzyl)-6,7-methylenedioxy	$C_{21}H_{21}NO_4$	66	65–67	71.78	6.03		71.44	6.28			
Hydrochloride	$C_{21}H_{22}ClNO_4$	96	215–217	65.03	5.72	3.70	64.82	6.00	3.55	0.6	111.1 ± 4.5
6,7-Dimethoxy-1-(2′,3′-dimethoxybenzyl)[a]	$C_{20}H_{21}NO_4$		102.5–103.5	70.78	6.24		70.70	6.48			
Hydrochloride[a]	$C_{20}H_{22}ClNO_4$	68[b]	188–194	63.91	5.90	3.73	63.99	6.31	3.76	0.6	75.3 ± 2.4
6,7-Dimethoxy-1-(2′,4′-dimethoxybenzyl)	$C_{20}H_{21}NO_4$	53	139–140	70.78	6.24		70.65	6.44			
Hydrochloride	$C_{20}H_{22}ClNO_4$	76	219–221	63.91	5.90		63.70	6.22		0.5	62.8 ± 2.8
6,7-Dimethoxy-1-(2′,5′-dimethoxybenzyl) isoquinoline hydrochloride·0.5 ethanolate[c]	$C_{20}H_{22}ClNO_4 \cdot 0.5C_2H_5OH$	77[b]	155–163	63.23	6.32		63.29	6.86		0.6	39.9 ± 0.9
6,7-Dimethoxy-1-(2′,6′-dimethoxybenzyl) isoquinoline hydrochloride·ethanolate·0.5 etherate[c]	$C_{20}H_{22}ClNO_4 \cdot C_2H_5OH \cdot 0.5(C_2H_5)_2O$	12[b]	186–187	62.80	7.25	3.05	62.43	7.36	2.99	0.5	34.9 ± 2.4
6,7-Dimethoxy-1-(3′,5′-dimethoxybenzyl isoquinoline hydrochloride·0.5 ethanolate[c]	$C_{20}H_{22}ClNO_4 \cdot 0.5C_2H_5OH$	34[b]	203–204.5	63.23	6.32	3.51	62.96	6.69	3.48	0.5	61.9 ± 2.4
6,7-Dimethoxy-1-(3′-ethoxybenzyl)isoquinoline hydrochloride[c]	$C_{20}H_{22}ClNO_3$	70[b]	194–196	66.75	6.16		66.79	6.26		1.0	49.5 ± 1.6
6,7-Dimethoxy-1-(2′-ethoxy-3′-methoxybenzyl)	$C_{21}H_{23}NO_4$	62	106.5–107	71.36	6.55		71.29	6.54			
Hydrochloride·ethanolate	$C_{23}H_{30}ClNO_5$	89	164.5–166	63.37	6.94		63.55	6.98		0.6	95.1 ± 5.0

6,7-Dimethoxy-1-(4′-isopropoxy-3′-methoxybenzyl)	$C_{22}H_{28}NO_4$	77	117–118	71.91	6.85		71.79	6.67			
Hydrochloride	$C_{22}H_{26}ClNO_4$	95	195–199	65.42	6.49	3.47	65.01	6.13	3.43	1.0	78.4 ± 2.8
6,7-Dimethoxy-1-(3′-methoxybenzylisoquinoline hydrochloride[c]	$C_{19}H_{20}ClNO_3$	58[b]	179–182	65.99	5.83		65.98	5.74		0.6	44.0 ± 2.5
6,7-Dimethoxy-1-(3′-methoxy-4′-*n*-propoxybenzyl)	$C_{22}H_{28}NO_4$	71	134.5–135.5	71.91	6.85		71.86	6.88			
Hydrochloride	$C_{22}H_{26}ClNO_4$	100	155–163	65.42	6.49	3.47	65.13	7.04	3.39	0.7	85.3 ± 4.1
1-(2′,3′-Dimethoxybenzyl)-6,7-methylenedioxy	$C_{19}H_{17}NO_4$	54	135.5–136.5	70.57	5.30		70.30	5.46			
Hydrochloride	$C_{19}H_{18}ClNO_4$	96	200–208	63.42	5.04	3.89	63.24	5.40	4.12	0.6	62.8 ± 3.8
7-Ethoxy-1-(2′-ethoxy-3′-methoxybenzyl)-6-methoxy	$C_{22}H_{28}NO_4$	78	125–125.5	71.91	6.85		71.67	6.78			
Hydrochloride	$C_{22}H_{26}ClNO_4$	95	198–201	65.42	6.49	3.47	65.13	6.64	3.69	0.6	79.1 ± 5.1
7-Ethoxy-6-methoxy-1-(3′,4′-methylenedioxybenzyl)	$C_{20}H_{19}NO_4$	64	120–120.5	71.20	5.68		71.10	5.72			
Hydrochloride	$C_{20}H_{20}ClNO_4$	99	202–204	64.25	5.39		64.19	5.61		0.6	113.0 ± 4.6
1-(2′-Ethoxy-3′-methoxybenzyl)-6,7-methylene dioxyisoquinoline hydrochloride[c]	$C_{20}H_{20}ClNO_4$	79[b]	220–221	64.25	5.39		63.95	5.76		0.3	129.0 ± 8.8
1-(4′-Ethoxy-3′-methoxybenzyl)-6,7-methylenedioxy	$C_{20}H_{19}NO_4$	65	106–107	71.20	5.68		71.20	5.72			
Hydrochloride	$C_{20}H_{20}ClNO_4$	90	200[e]	64.25	5.39		64.00	5.36		0.8	104.9 ± 8.0
1-(3′-Methoxy-4′-*n*-propoxybenzyl)-6,7-methylenedioxy	$C_{21}H_{21}NO_4$	76	86–88	71.78	6.03		71.20	5.79			
Hydrochloride[d]	$C_{21}H_{22}ClNO_4$	88	219–220	65.03	5.72		64.86	5.82		1.0	110.1 ± 5.2

[a] Tsatsas, *Compt. rend.*, **229**, 219 (1949). [b] Over-all yield, calculated from amide. [c] Free base did not crystallize. [d] Tested as phosphate due to limited solubility of the hydrochloride. [e] Resolidifies and remelts at 225°.

Acknowledgment. The authors are indebted to W. L. Brown, H. L. Hunter, and W. J. Schenck for microanalytical data and to Dr. R. E. Shipley, Dr. K. K. Chen, and R. C. Anderson for pharmacological evaluation.

SUMMARY

A series of compounds related to papaverine has been prepared and the pharmacological properties of these compounds have been evaluated. In the limited number of cases studied, it was found that the presence of an ethoxyl or propoxyl group in either the 3 or 4 position of the benzyl substituent decreases the toxicity of the compound. The 6,7-dimethoxy-1-(dimethoxybenzyl)isoquinoline isomers of papaverine have markedly decreased coronary dilator properties.

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