oxide-isothiourea hydrobromide which formed almost immediately was filtered and weighed 18 g. (72%), m. p. 160–160.5° (dec.). Crystallization from absolute alcohol did not change the melting point.

Anal. Calcd. for $C_6H_5BrN_2OS$: C, 28.89; H, 3.22. Found: C, 28.68; H, 3.54.

A solution of 12.5 g. (0.05 mole) of the above thiourea addition compound and 10 g. of sodium carbonate in 125 cc. of water was allowed to stand four hours at room temperature. The solution was acidified with 20% hydrochloric acid and yielded 5 g. (78%) of product, m. p. 65–67°. There was no depression with an authentic sample of N-hydroxy-2-pyridinethione.

N-Hydroxy-2-pyridone.—Seven grams (0.031 mole) of 2-bromopyridine-N-oxide hydrochloride was heated on a steam-bath with 50 cc. of 10% sodium hydroxide solution for one and one-half hours. The cooled solution, after acidification with concentrated hydrochloric acid, was concentrated to dryness under reduced pressure. The residue was dissolved in water, neutralized and filtered. The addition of aqueous cupric acetate to the filtrate precipitated the copper salt of N-hydroxy-2-pyridone, 2.5 g. (53%), m. p. 283–284°, undepressed when mixed with an authentic sample.[3]

2-Benzylmercaptopyridine-N-oxide.—To a solution of 1 g. (0.043 mole) of sodium in 30 cc. of absolute alcohol were added 4.5 cc. (0.036 mole) of benzyl mercaptan and 2.5 g. (0.012 mole) of 2-bromopyridine-N-oxide hydrochloride. The mixture was warmed at 50° for one hour, then left at room temperature for two hours. After the addition of excess 10% sodium hydroxide, the solution was extracted with ethyl acetate. The organic layer was concentrated to yield 1.2 g. (46%) of product, m. p. 167–169°. After recrystallization from ethyl acetate the compound melted at 168–169°. *Anal.* Calcd. for $C_{12}H_{11}NOS$: C, 66.32; H, 5.10; N, 6.45. Found: C, 66.42; H, 5.14; N, 6.25.

2-Pyridyl Benzyl Sulfoxide.—Ten grams (0.05 mole) of 2-benzylmercaptopyridine was added to a chloroform solution containing 0.05 mole of perbenzoic acid. Since the reaction was exothermic, the reaction mixture was cooled in running water. Titration, after a few minutes, indicated that all the perbenzoic acid had reacted. The chloroform solution was washed with aqueous sodium carbonate and dried. Removal of the solvent left a crystalline residue which was recrystallized from ethyl acetate and hexane, yielding 7 g. (68%), m. p. 87–88°. *Anal.* Calcd. for $C_{12}H_{11}NOS$: C, 66.32; H, 5.10; N, 6.45. Found: C, 66.17; H, 5.10; N, 6.28.

Summary

Substituted 2-bromopyridines have been oxidized to the corresponding 2-bromopyridine-N-oxides by perbenzoic acid or peracetic acid. The labilized bromine atom was readily replaced by alkaline reagents; treatment with sodium hydroxide yielded the cyclic hydroxamic acid, while treatment with sodium hydrosulfide or sodium sulfide gave the thio analog.

The cyclic thiohydroxamic acid was also obtained by reaction of the 2-bromopyridine-N-oxide with thiourea, followed by decomposition of the addition compound with sodium carbonate.

The cyclic thiohydroxamic acids show high *in vitro* antibacterial activity against a variety or organisms.

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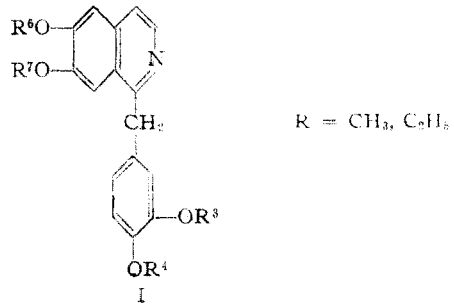
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Preparation of Some Homologs of Papaverine

BY EDWIN R. SHEPARD AND JOHN F. NOTH

Although there have been a multiplicity of synthetic papaverine-like isoquinolines reported in the chemical literature, most have been 3-methyl or 1-phenyl isoquinolines. We found that of the sixteen possible methoxy-ethoxy homologs (I) of papaverine ($R^{3,4,6,7} = CH_3$),



R = CH_3, C_2H_5

I

only three besides papaverine are known: 1, $R^{3,4,6,7} = C_2H_5$ ("Perparin"); $R^{6,7} = C_2H_5$ and $R^{3,4} = CH_3$; $R^{6,7} = CH_3$ and $R^{3,4} = C_2H_5$. Since the patents[1] revealing these three compounds and subsequent pharmacological literature[2] report varying activities and toxicities, it became of interest to prepare the entire group of homologs (I) for pharmacological evaluation.

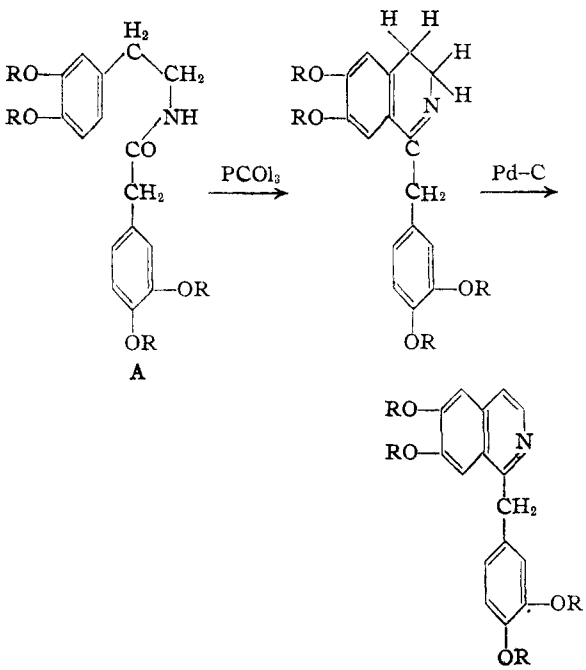
Since in our hands the Bischler–Napieralski closure and subsequent catalytic dehydrogenation have proven somewhat difficult when operating with much less than twenty to twenty-five grams of phenethylamide (A), the recorded preparative methods for several of the prerequisite amines and acids were felt to be less desirable for the larger amounts needed in this and subsequent work. For the preparation of the required benzyl alcohols from the corresponding aldehydes we preferred catalytic hydrogenation over copper chromite insofar as reliability of results and convenience of handling were concerned.

In attempting to apply the simple preparation of the benzyl chlorides by the use of anhydrous hydrogen chloride[3] excellent results were obtained

(1) German Patent 574,656; also French Patent 719,638 and U. S. Patent 1,962,224.

(2) Issekutz, Leinzinger and Divner, *Arch. exptl. Path. Pharmakol.*, 164, 158, 173 (1932); Longecker and Starkenstein, *Klin. Wchschr.*, 10, 2257 (1931).

(3) Cannizzaro and Bertagnini, *Ann.*, **98**, 191 (1856).



with veratryl alcohol and 3-ethoxy-4-methoxybenzyl alcohol. However, in the case of 3-methoxy-4-ethoxybenzyl alcohol and 3,4-diethoxybenzyl alcohol, the desired reactions failed completely, but resulted in almost complete conversion to high boiling substances. Contrary to this, Jacobs and Heidelberger[4] mention the satisfactory preparation of 3-methoxy-4-ethoxybenzyl chloride in a similar manner. Since there was no essential difference in the preparative methods, there appears to be little to offer by way of explanation for our failure. The two chlorides were obtained by treating the respective alcohols with thionyl chloride.

The hydrolysis of 3-ethoxy-4-methoxyphenylacetonitrile proceeded smoothly but some difficulty was encountered in recrystallization of the resulting acid. After each recrystallization, a sodium bicarbonate insoluble oil previously not present could be isolated from the mother liquors. Consequently in order to obtain an acid of reasonable purity the yield was lowered considerably. The oil was not investigated further.

The use of a solvent in the preparation of the amides from the acid and amine did not offer any advantage and in fact it was disadvantageous since the high boiling solvent was very difficult to remove by two recrystallizations. Subsequently, in runs of several moles each of acid and amine it was found that the reaction in the absence of solvent was quite satisfactory provided stirring was utilized.

The reactions of the amides with phosphorous oxychloride proceeded without difficulty. Occasionally a solid would precipitate which sometimes necessitated an additional amount of benzene in order to maintain a semifluid consistency

The isoquinoline salts of this investigation were examined pharmacologically for their coronary dilator action and their acute intravenous toxicity in mice. From these results a therapeutic "index," the product of the ratios of activity and toxicity of the compound with reference to papaverine, was calculated: $I = H_t/P_t \times H_a/P_a$; where H_t and P_t are the respective intravenous toxicities (mice) of the homolog and papaverine; and where H_a and P_a are the respective coronary dilator activities of the homolog and papaverine. The values so obtained are indicated in Table III. On this basis, the 1-(3,4-dimethoxybenzyl)-isoquinolines were generally not very effective coronary dilators. However, hydrochloride no. 7 was nearly twice as active a dilator as papaverine. Unfortunately it was also the most toxic of all the isoquinolines of this group, being twice as toxic as papaverine and more than three times as toxic as all the others. As a group, the 6,7-diethoxy and the 6-methoxy-7-ethoxy isoquinolines did not have much advantage over papaverine, while the 6,7-dimethoxy and 6-ethoxy-7-methoxy isoquinolines, especially salts no. 10 and no. 15 were clearly superior as coronary dilators.

Experimental

4-Ethoxy-3-methoxybenzaldehyde.—One mole of vanillin (152 g.) suspended in 200 ml. of water was warmed on the steam-bath until melted whereupon cooling was begun as 65 g. of sodium hydroxide in 150 ml. of water and 165 ml. of diethyl sulfate were added simultaneously through separate funnels and under stirring at 65–80°. The addition was completed in fifteen minutes, and stirring was continued for one hour, maintaining the temperature at 65–80°. The reaction mixture was poured into cold water, extracted twice with benzene, and washed with a small portion of water. Distillation of the solvent gave a residue which crystallized to give 142.8 g. (79%) of light colored crystals, m. p. 62–63.5° (lit.,[5] m. p. 64–65°).

3-Ethoxy-4-methoxybenzaldehyde.—(A) Isovanillin was alkylated with diethyl sulfate in the same manner as vanillin. The crude product was distilled to give an 84% yield of aldehyde, b. p. 153–155° (10 mm.). (B) Alkylation of 4-hydroxy-3-ethoxybenzaldehyde with dimethyl sulfate in the same manner gave a 93% yield of the distilled aldehyde.

3,4-Diethoxybenzyl Alcohol.—(A) Reduction of 100 g. of 3,4-diethoxybenzaldehyde in 100 ml. of methanol under 50 lb. of hydrogen p.s.i. in the presence of 2.5 g. of 5% palladium on carbon gave an 86% yield of the alcohol, b. p. 166–171° (10 mm.). (B) The crossed Cannizzaro reaction[6] gave a 73% yield of the alcohol. (C) Three hundred eleven grams of the aldehyde in 150 ml. of ethanol was reduced at 120–140° under an initial pressure of 3000 lb. p.s.i. of hydrogen in the presence of 20 g. of copper chromite catalyst. The reduction was complete in thirty minutes. The catalyst was removed and the mixture was distilled to give 296 g. (94%) of the alcohol, b. p. 167–170° (10 mm.).

4-Ethoxy-3-methoxybenzyl Alcohol.—The crossed Cannizzaro reaction using formalin gave satisfactory results with 4-ethoxy-3-methoxybenzaldehyde. The alcohol was obtained in 90% yield, m. p. 54–56° (lit.,[7] m. p. 56–57°) without distillation.

(4) Jacobs and Heidelberger, *J. Biol. Chem.*, **20**, 680 (1915).

(5) Tiemann, *Ber.*, **8**, 1129 (1875).

(6) "Org. Syn.," Coll. Vol. II, 590 (1943).

(7) Vavon, *Compt. rend.*, **154**, 360 (1912).

TABLE I

N-β-(PHENETHYL)-PHENYLACETAMIDES[b], R^7O—$C_6H_3(OR^3)$—$C_2H_4NHCOCH_2$—$C_6H_3(OR^4)$—R^6O

R^6	R^7	R^3	R^4	Procedure	M. p., °C.[a]	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	CH_3	C_2H_5	A	125–126	79	$C_{21}H_{27}NO_5$	67.54	67.39	7.28	7.41
CH_3	CH_3	C_2H_5	C_2H_5	A	95.5–97	72	$C_{22}H_{29}NO_5$	68.19	67.73	7.54	7.63
CH_3	C_2H_5	C_2H_5	C_2H_5	A	88–89	80	$C_{23}H_{31}NO_5$	68.80	68.84	7.78	7.99
C_2H_5	C_2H_5	C_2H_5	C_2H_5	A	106.5–107[c]	84	$C_{24}H_{33}NO_5$	69.36	69.25	8.01	8.11
				C		70					
C_2H_5	C_2H_5	C_2H_5	CH_3	B	104.5–105.5	61	$C_{23}H_{31}NO_5$	68.80	68.68	7.78	7.70
C_2H_5	C_2H_5	CH_3	CH_3	A	106–107	89	$C_{22}H_{29}NO_5$	68.19	68.15	7.54	7.71
C_2H_5	CH_3	CH_3	CH_3	A	109.5–110.5	78	$C_{21}H_{27}NO_5$	67.54	67.62	7.28	7.36
C_2H_5	C_2H_5	CH_3	C_2H_5	A	113–114	79	$C_{23}H_{31}NO_5$	68.80	68.96	7.78	7.83
C_2H_5	CH_3	C_2H_5	C_2H_5	A	114–114.5	53	$C_{23}H_{31}NO_5$	68.80	68.95	7.78	8.05
C_2H_5	CH_3	C_2H_5	CH_3	A	106.5–107	41	$C_{22}H_{29}NO_5$	68.19	68.20	7.54	7.59
C_2H_5	CH_3	CH_3	C_2H_5	A	134.5–135.5	51	$C_{22}H_{29}NO_5$	68.19	67.75	7.54	7.65
CH_3	C_2H_5	C_2H_5	CH_3	A	95.5–96.5	78	$C_{22}H_{29}NO_5$	68.19	68.12	7.54	7.49
CH_3	C_2H_5	CH_3	CH_3	A	104.5–105	73	$C_{21}H_{27}NO_5$	67.54	67.67	7.28	7.56
CH_3	C_2H_5	CH_3	C_2H_5	A	83–83.5	66	$C_{22}H_{29}NO_5$	68.19	67.86	7.54	7.99
CH_3	CH_3	C_2H_5	CH_3	A	99.5–100	72	$C_{21}H_{27}NO_5$	67.54	67.02	7.28	7.46

[a] All melting points determined on a Fisher–Johns block. [b] During the course of the investigation additional amounts of many of these amides were independently synthesized by the Monsanto Chemical Company and supplied to us for our use. [c] Also prepared by Weijlard, Swanezy and Tashjian, THIS JOURNAL, 71, 1889 (1949); m. p. 102–103°.

3-Ethoxy-4-methoxybenzyl Alcohol.—The catalytic reduction of the aldehyde in ethanol in the presence of copper chromite gave a 95–97% yield of the alcohol, b. p. 166–169° (10 mm.).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.60; H, 7.61.

4-Ethoxy-3-methoxyphenylacetonitrile.—A mixture of 150 ml. of thionyl chloride and 7 g. of calcium chloride was stirred at 30–35° while 320 g. of 4-ethoxy-3-methoxybenzyl alcohol in an equal volume of benzene was added during the course of one hour. The stirring was continued for one additional hour whereupon 400 ml. of ether and 10 g. of calcium carbonate were added, and stirring was continued for one-half hour. The mixture was stored overnight and then decomposed with excess ice and water. The organic layer was washed with water and eventually with dilute sodium bicarbonate solution. The solvents were removed *in vacuo* and the residue of the benzyl chloride was used immediately in the following reaction.

The chloride in 380 ml. of benzene was brought to reflux, and 162 g. of sodium cyanide in 750 ml. of water was added with vigorous stirring in the course of fifty minutes. The refluxing and stirring were continued for six hours. The organic layer was separated, washed with water and fractioned. The yield of nitrile was 227 g. (69%), b. p. 170–181° (3 mm.).

3-Ethoxy-4-methoxyphenylacetonitrile.—A solution of 175.4 g. of 3-ethoxy-4-methoxybenzyl alcohol in a mixture of 500 ml. of benzene and 1 liter of Skellysolve B was cooled to −10°, and dry hydrogen chloride was passed in rapidly with stirring until the precipitated alcohol dissolved. Distillation of the mixture gave 167 g. of the chloride, b. p. 117–120° (1.5 mm.).

The chloride was dissolved in 3.2 liters of acetone and 105.6 g. of potassium cyanide in 1.6 liters of water was stirred in. The solution was allowed to stand at room temperature for ten hours. The acetone was then removed *in vacuo* and the residue was extracted with ether. Distillation of the ether extract gave 141 g. (76%) of nitrile, b. p. 125–131° (0.5 mm.).

3-Ethoxy-4-methoxyphenylacetic Acid.—A mixture of 44 g. of 3-ethoxy-4-methoxyphenylacetonitrile, 28 g. of sodium hydroxide, 90 ml. of water and 30 ml. of methyl cellosolve was refluxed four and one-half hours. The resulting solution was diluted with three volumes of water and extracted with ether. The water layer was acidified and extracted twice with 200 ml. portions of benzene. The extract was concentrated by distilling approximately one-half the benzene, and the acid crystallized upon the addition of Skellysolve B. Two recrystallizations from a mixture of Skellysolve B and ethyl acetate gave 25.0 g. (51%) of acid, m. p. 70.5–72° (lit.,[8] 69–69.5°).

4-Ethoxy-3-methoxyphenylacetic Acid.—A mixture of 92 g. of 4-ethoxy-3-methoxyphenylacetonitrile, 55 ml. of ethanol, 330 ml. of water and 50 g. of sodium hydroxide was refluxed for six hours. The resulting solution was diluted with two volumes of water and extracted with ether. The last traces of ether were removed from the water layer by warming it for a short period under vacuum. The acid was precipitated from the water solution by adding a slight excess of dilute hydrochloric acid and chilling. The crystals were filtered and washed with cold water to give 91 g. (90%) of 4-ethoxy-3-methoxyphenylacetic acid, m. p. 121.5–122° (lit.,[9] m. p. 118.5–119°).

β-4-Ethoxy-3-methoxyphenethylamine.—A solution of 226 g. of 4-ethoxy-3-methoxyphenylacetonitrile in 150 ml. of absolute ethanol and 50 ml. of liquid ammonia was reduced with hydrogen at 1800 lb. p.s.i. over Raney nickel catalyst at 120–140°. The reduction was complete in forty-five minutes. The catalyst was removed and the alcoholic solution was fractioned to yield 172 g. (74%) of amine, b. p. 151–153° (8 mm.). **β-3-Ethoxy-4-methoxyphenethylamine**, b. p. 122–227° (1 mm.), and **β-3,4-diethoxyphenethylamine**, b. p. 142–145° (5 mm.), were obtained in 86 and 85% yields, respectively, by reduction of the corresponding nitriles in an analogous manner.

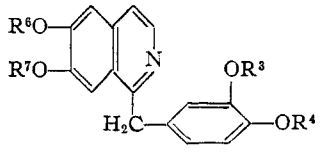
N-(β-Phenethyl)phenylacetamides.—The amides were prepared by standard procedures as illustrated by the following examples and are described in Table I.

(A) N-Homoveratryl-3,4-diethoxyphenylacetamide.—A mixture of 44.8 g. (0.20 mole) of 3,4-diethoxyphenylacetic acid[10] and 36.2 g. (0.20 mole) of homoveratrylamine[11] was heated in an open flask on an oil-bath at 200 ± 10° (internal) until distillation of water ceased (approximately one hour) and for twenty minutes thereafter. The partially cooled mixture was poured into 150 ml. of

(8) Späth and Tharrer, *Ber.*, **66B**, 588 (1933).
(9) Späth and Tharrer, *ibid.*, **66B**, 590 (1933).
(10) Kindler and Gehlhaar, *Arch. Pharm.*, **274**, 377 (1936).
(11) Bide and Wilkinson, *J. Soc. Chem. Ind.*, **64T**, 85 (1945).

TABLE II

ISOQUINOLINES



No.	R⁶	R⁷	R³	R⁴	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	CH_3	CH_3	CH_3	C_2H_5	95.5–96.5	87	$C_{21}H_{23}NO_4$	71.36	71.23	6.55	6.60
2	CH_3	CH_3	C_2H_5	C_2H_5	113.5–114[a]		$C_{22}H_{25}NO_4$	71.91	71.91	6.85	7.22
					91–92[b]	64	$C_{22}H_{25}NO_4 \cdot {}^1/_4C_6H_{14}$	72.56	72.61	7.38	6.96
3	CH_3	C_2H_5	C_2H_5	C_2H_5	94.5–95	83	$C_{23}H_{27}NO_4$	72.41	72.51	7.13	7.05
4	C_2H_5	C_2H_5	C_2H_5	C_2H_5	99–100[d]	81	$C_{24}H_{29}NO_4$	72.88	72.59	7.39	7.91
5	C_2H_5	C_2H_5	C_2H_5	CH_3	113–113.5[c]	61	$C_{23}H_{27}NO_4 \cdot {}^1/_4C_6H_{14}$	73.01	73.19	7.63	7.76
							$C_{23}H_{27}NO_4$	72.41	72.55	7.13	7.43
6	C_2H_5	C_2H_5	CH_3	CH_3	106.5 108	73	$C_{22}H_{25}NO_4$	71.91	72.26	6.85	6.58
7	C_2H_5	CH_3	CH_3	CH_3	140–140.5	82	$C_{21}H_{23}NO_4$	71.36	71.46	6.55	6.66
8	C_2H_5	C_2H_5	CH_3	C_2H_5	111–112	66	$C_{23}H_{27}NO_4$	72.41	72.30	7.13	6.92
9	C_2H_5	CH_3	C_2H_5	C_2H_5	100–100.5	76	$C_{23}H_{27}NO_4$	72.41	72.60	7.13	6.91
10	C_2H_5	CH_3	C_2H_5	CH_3	136.5–137.5	79	$C_{22}H_{25}NO_4$	71.91	71.80	6.85	6.98
11	C_2H_5	CH_3	CH_3	C_2H_5	125–126	85	$C_{22}H_{25}NO_4$	71.91	71.77	6.85	6.83
12	CH_3	C_2H_5	C_2H_5	CH_3	91.5–92.5	81	$C_{22}H_{25}NO_4$	71.91	71.67	6.85	7.10
13	CH_3	C_2H_5	CH_3	CH_3	129–130.5	82	$C_{21}H_{23}NO_4$	71.36	71.15	6.55	6.70
14	CH_3	C_2H_5	CH_3	C_2H_5	127.5–128.5	82	$C_{22}H_{25}NO_4$	71.91	71.64	6.85	6.75
15	CH_3	CH_3	C_2H_5	CH_3	130–130.5	76	$C_{21}H_{23}NO_4$	71.36	71.28	6.55	6.64

[a] From dilute methanol. [b] From Skellysolve B (mixed hexanes). [c] Recrystallized successively from dilute ethanol, benzene–Skellysolve B and dilute ethanol. Dried 3 hr. at 100° (first anal.) and 3 hr. at 120° (second anal.). [d] German Patent 574,656 reports m. p. 99–101°. The base has been described by Weijlard, Swanezy and Tashjian, THIS JOURNAL, 71, 1889 (1949).

TABLE III

ISOQUINOLINE SALTS

Salt of base no.	M. p., °C.	Salt	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Coronary dilator action (average value)	Therapeutic index
1	182–184	Hydrochloride	64.69	64.44	6.20	6.47	1.0	2.7
2	177–179[b]	Hydrochloride	65.42	65.26	6.49	6.48	1.0	2.0
3	165–173	Hydrochloride	66.09	66.21	6.75	6.86	1.0	2.4
4	186–188	Hydrobromide	60.11	59.87	6.66	6.69	0.9	1.4
5	180–184	Hydrochloride	66.09	66.36	6.75	7.21	0.75	2.2
6	194.5–196.5	Hydrobromide hemihydrate	57.76	57.86	5.92	6.12	0.9	1.6
7	196–217	Hydrochloride	64.69	64.79	6.20	6.38	1.6	0.8
8	171.5–181.5	Hydrochloride	66.09	66.20	6.75	7.07	1.0	1.6
9	189–193	Hydrochloride	66.09	66.14	6.75	7.11	1.0	2.5
10	168–170	Hydrochloride	65.42	65.12	6.49	6.47	1.15	3.7
11	198–202	Hydrochloride	65.42	65.66	6.49	6.72	1.1	2.0
12	179–182	Hydrochloride	65.42	65.20	6.49	6.45	0.65	1.3
13	200–204	Hydrochloride	64.69	64.61	6.20	6.47	0.65	1.4
14	120–121	Hydrochloride hydrate	62.62	63.01	6.68	6.89	0.65	1.3
15	191.5–198	Hydrochloride	69.69	64.84	6.20	6.47	1.15	3.2
Papaverine phosphate							1.0	1.0

[a] Dried *in vacuo* at 100° for a minimum of two hours. [b] German Patent 574,656 gives m. p. 190°.

methanol, and 100 ml. of water was added. Crystals were obtained on cooling. The suspension of crystals was held at 10° for one hour, filtered, and washed with cold 50% (vol.) methanol. Recrystallization from dilute methanol gave 56.0 g. (72%) of white crystals, m. p. 95.5–97°.

(B) **N-β-(3,4-Diethoxyphenethyl)-3-ethoxy-4-methoxyphenylacetamide.**—A mixture of 28.2 g. of 3-ethoxy-4-methoxyphenylacetic acid and 28.1 g. of 3,4-diethoxyphenethylamine was heated in an open flask at 190–200° until thirty minutes after the evolution of water ceased. The cooled reaction mixture was taken up in a small amount of benzene and crystallization was induced on the addition of Skellysolve B. The crude product was recrystallized from 65% (vol.) methanol after decolorization with car-

boil. The product was filtered and washed with 50% (vol.) methanol to give 33.1 g. (61%) of white crystals, m. p. 104.5–105.5°.

(C) N-β-(3,4-Diethoxyphenethyl)-3,4-diethoxyphenylacetamide.—A mixture of 35.5 g. of 3,4-diethoxyphenethylamine and 38 g. of 3,4-diethoxyphenylacetic acid suspended in 250 ml. of diphenyl ether was heated at 210° ± 5° for one-half hour. The crude amide was precipitated by adding Skellysolve B to the cooled reaction mixture. Two recrystallizations from dilute methanol yielded 49.5 g. (70%) of white crystals, m. p. 106.5–107°.

All the amides in Table I were treated substantially as in the following examples to obtain the isoquinolines as listed in Table II, and their salts, Table III.

6-Methoxy-7-ethoxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline.—A mixture of 45 g. of N-β-(3-methoxy-4-ethoxyphenethyl)-homoveratramide, 200 ml. of thiophene-1 free benzene, and 10 ml. of phosphorus oxychloride was refluxed two and one-half hours. The cooled solution was decomposed with excess dilute sodium hydroxide solution and washed with water. The operation from the time of addition of phosphorus oxychloride until beginning of dehydrogenation was carried out in an atmosphere of nitrogen. The washed benzene layer was distilled to remove the last of the water and most of the benzene, at which point 100 ml. of decalin was added. The distillation of solvent was continued under stirring until the flask contents reached 180°. One and one-half grams of 5% palladium on carbon suspended in 50 ml. of decalin was added. The dehydrogenation of the dihydroisoquinoline to isoquinoline was completed in five hours under total reflux. The reaction temperature varied from 184 to 196°. The hot solution was filtered to remove the catalyst and Skellysolve B was eventually added to complete the precipitation of the isoquinoline. The solid was filtered, washed well with Skellysolve B, and dried at 70° overnight to remove most of the residual decalin. The base was dissolved in hot 50% (vol.) ethanol, decolorized with carbon and allowed to cool. The solid was filtered, washed with dilute alcohol and dried. A second recrystallization gave 35.0 g. of a white solid, m. p. 129–130.5°.

6-Methoxy-7-ethoxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline Hydrochloride.—Thirty grams of the isoquinoline was dissolved in 100 ml. of absolute ethanol and 5 g. of dry hydrogen chloride was added. The salt was precipitated by the addition of ether. The white crystals were filtered and recrystallized from 95% ethanol, three volumes of ether being added to complete crystallization. Thirty-two grams (96%) of the hydrochloride was obtained, m. p. 200–204°.

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Summary

Fifteen ethoxy-methoxy homologs of papaverine have been prepared and their therapeutic value as coronary dilators has been determined. A minimum correlation of action and structure has been found.

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Condensation of Acetoacetic Ester with Some Unsymmetrical Epoxides

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No completely satisfactory explanation of the direction of ring-opening in S_N2 attack on unsymmetrical epoxides has yet been offered. It is becoming increasingly apparent,[2] however, that steric factors may be mainly responsible for the fact that attack by the nucleophilic agent has generally been found to occur preferentially at the unsubstituted or primary carbon of terminal epoxides. On the other hand, recent evidence[3] indicates that in the reaction of such epoxides as styrene oxide and 3,4-epoxy-1-butene with certain bases the effect of allylic resonance[3a] in lowering the energy of the transition state involved in nucleophilic attack at the secondary carbon atom may outweigh the steric factors which favor attack at the primary carbon.

In an attempt to shed further light on the relationship between steric and electronic factors and the direction of ring opening of unsymmetrical epoxides in S_N2 reactions, we have studied the base catalyzed condensation of acetoacetic ester with three representative epoxides, propylene oxide, styrene oxide and 3,4-epoxy-1-butene. Choice of acetoacetic ester was dictated by the facts that its reactions with epoxides should certainly be expected to proceed, like those of malonic ester,[4] by the S_N2 mechanism, but that steric requirements should be slightly less for acetoacetic than for malonic ester. In addition, the expected products of the condensation reactions themselves should be compounds of considerable chemical interest.

Only a few isolated studies of the condensation of acetoacetic ester with specific epoxides have been reported.[5] In each case the product isolated was a substituted α-acetyl-γ-butyrolactone, presumably formed by inner transesterification of the expected β-hydroxyalkylacetoacetic ester.

Results

The sole product isolated in the base-catalyzed condensation of the saturated epoxide propylene

(1) American Chemical Society Fellow 1946–1947. Geneva College, Beaver Falls, Pennsylvania.

(2) See Brown and Eldred, THIS JOURNAL, **71**, 445 (1949).

(3) See (a) Bartlett and Ross, *ibid.*, **70**, 926 (1948); (b) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949); (c) Trevoy and Brown, *ibid.*, **71**, 1675 (1949); (d) Guss, *ibid.*, **71**, 3160 (1949).

(4) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2606 (1942).

(5) See Traube and Lehmann, *Ber.*, **34**, 1971 (1901); Knunyantz, Chilintzev and Osetrova, *Compt. rend. acad. sci. U. R. S. S.*, **1**, 315 (1934); Chelintsev and Osetrova, *J. Gen. Chem. (U. S. S. R.)*, **7**, 2373 (1937).