New β-Adrenergic Blocking Agents. Cyclopropylphenyl Derivatives

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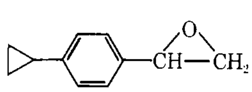
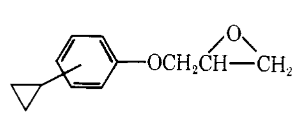
An evident structural analogy appears in known β-adrenergic blocking drugs. With very few exceptions, they are aromatic derivatives of ethanolamine as pronethalol (I, Ar = 2-naphthyl) or of oxypropanolamine as propranolol (II, Ar = 1-naphthyl). We report the synthesis and the preliminary pharmacological study of new derivatives of both types of compounds in which Ar is a cyclopropylphenyl group.

Ar—$CHOHCH_2NR_1R_2$ Ar—$OCH_2CHOHCH_2NR_1R_2$
I II

Compounds I (Ar = *p*-cyclopropylphenyl) and II (Ar = *o*- and *p*-cyclopropylphenyl) were synthesized from the corresponding epoxides III and IV by reaction with the amines R_1R_2NH. Nmr spectra of compounds obtained through opening of the epoxide rings were consistent with structures I and II.


III


IV

Epoxide III was prepared from *p*-bromocyclopropylbenzene which was readily converted through the Grignard reagent into *p*-cyclopropylbenzaldehyde. The latter was treated with dimethylsulfonium methylide according to Corey and Chaykovsky[1] to afford III. Treatment of *o*- and *p*-cyclopropylphenol with epichlorohydrin gave the corresponding epoxides IV. *p*-Cyclopropylphenol was obtained from the Baeyer–Villiger reaction of *p*-cyclopropylacetophenone with *p*-nitroperbenzoic acid and subsequent hydrolysis of the non-isolated intermediate acetate. Yields of prepared basic compounds, formulas, and physical properties of derivatives are reported in Tables I and II.

Pharmacology.—The activities of the test compounds against responses induced by isoproterenol in pharmacological and biochemical tests are given in Table III. For comparative purposes, propranolol was evaluated under the same experimental conditions. Table III also reports the intraperitoneal LD_{50} values of new derivatives.

Compound **5** exhibits the higher activity in the series. It is five- to tenfold more potent than propranolol according to the test used. The isomer **11** where the cyclopropyl nuclear substituent is *para* instead of *ortho* has only a very low activity.

Concerning the nature of amino substituent, it appears in both types of N-monosubstituted derivatives that an isopropyl chain is the more favorable for β-adrenergic blocking properties. The diethylamino derivative **9** and its quaternary ammonium salt **10** have, respectively, low and no activity. These results are in a good agreement with those obtained with pronethalol and propranolol analogs and especially with conclusions reached from a large series of substituted phenoxy compounds recently studied.[2] Further pharmacological studies on **5** are in progress.

(1) E. J. Corey, and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

Experimental Section[3]

Pharmacology.—Blood pressure was recorded on rats anesthetized with urethan (1.5 g/kg ip) from the carotid artery using a mercury Palmer manometer. Injections were made into the penis or jugular vein. The active dose of isoproterenol was determined prior to treatment and repeated 5 min after the increasing doses of the tested compound were injected. The time interval between two successive doses of compound was about 15 min.

Reversal of the inhibitory action of isoproterenol against ACh-induced bronchospasm was evaluated in guinea pigs according to the classical method of Konzett and Rössler. Assays on isolated guinea pig atria were investigated according to Burn's method. Procedures used have been described previously.[4,5]

The inhibitory effect of test compounds on isoproterenol glycogenolysis was measured in fasted rats according to Salvador, *et al.*[6] Blood samples were assayed for glucose by Hoffman's method[7] with a Technicon autoanalyzer and for lactic acid by an enzymatic method.[8]

Acute intraperitoneal toxicities were determined in groups of 10 male aggregated mice weighing from 20 to 23 g. All deaths occurring during the 48 hr following the administration of the drug were recorded for the estimation of LD_{50} values.

Chemistry. *p*-Cyclopropylbenzaldehyde.[9]—To an Et_2O solution of the Grignard reagent prepared from 197 g (1 mole) of *p*-bromocyclopropylbenzene[10] and 26.7 g (1.1 g-atoms) of Mg in 550 ml of Et_2O was added 148.2 g (1 mole) of ethyl orthoformate. The mixture was refluxed for 6 hr, then Et_2O was removed *in vacuo*. A solution of 6% HCl (750 ml) was added, the upper oily layer was separated and treated for 2 hr with a boiling solution of 55 ml of concentrated H_2SO_4 in 700 ml of H_2O. After cooling and extraction with Et_2O the aldehyde was purified through its crystalline bisulfite compound, then distillation: yield 86 g (59%); bp 67–69° (0.01 mm); $n^{22}D$ 1.578 [lit.[9] bp 113° (8 mm); $n^{20}D$ 1.5549].

***p*-Cyclopropylphenyloxirane.**—Into a 1-l., three-necked flask was introduced 9.6 g (0.2 mole) of 50% NaH–oil dispersion. The oil was removed from the NaH by washing with pentane. DMSO (120 ml) was added under N_2. After heating at 70° for 1 hr the mixture was cooled, then 120 ml of THF, a solution of 40.2 g (0.2 mole) of trimethylsulfonium iodide[11] in 150 ml of DMSO, and a solution of 14.6 g (0.1 mole) of *p*-cyclopropylbenzaldehyde in 50 ml of THF were successively added. The mixture was stirred at room temperature for 1 hr, H_2O was added and the resulting mixture extracted with Et_2O. Removal of the solvent and distillation of the residue gave 12.6 g (79%) of colorless oily

(2) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. M. Smith, R. W. Turner, and T. M. Wood, *J. Med. Chem.*, **12**, 638 (1969).

(3) Melting points were determined on a Kofler hot stage microscope and are uncorrected. Boiling points are uncorrected. When analyses are indicated by symbols of the elements, analytical results obtained were within ± 0.4% of the theoretical values.

(4) J. R. Boissier, H. Schmitt, J. F. Giudicelli, and P. Viars, *Therapie*, **23**, 1371 (1968).

(5) J. F. Giudicelli, H. Schmitt, and J. R. Boissier, *J. Pharmacol. Exp. Ther.*, **168**, 116 (1969).

(6) R. A. Salvador, S. A. April, and L. Lemberger, *Biochem. Pharmacol.*, **16**, 2037 (1967).

(7) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

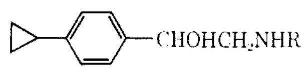
(8) H. D. Horn and F. M. Bruns, *Biochem. Biophys. Acta*, **21**, 378 (1956).

(9) R. Ya. Levina, N. M. Loim, and P. A. Gembitskii, *Zh. Obshch. Khim.*, **33**, 2074 (1963); *J. Gen. Chem. USSR*, **33**, 2020 (1963). Attempts to obtain *p*-cyclopropylbenzaldehyde following this procedure gave very low yields. An alternative method was used.

(10) R. Ya. Levina, P. A. Gembitskii, and E. G. Treshchova, *Zh. Obshch. Khim.*, **33**, 371 (1963); *J. Gen. Chem. USSR*, **33**, 364 (1963).

(11) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946).

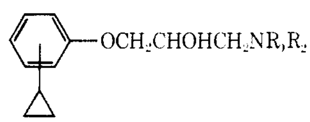
TABLE I



No.	R	Yield[a]	Derivative[b]	Mp, °C	Crystn solvent	Formula	Analyses
1	Me	33	A	128	Me_2CO	$C_{12}H_{17}NO \cdot C_6H_{13}NO_3S$	C, H, N, S
2	*i*-Pr	67	B	157	C_6H_6	$C_{14}H_{21}NO \cdot HCl$	C, H, N
3	*sec*-Bu	34	B	145	C_6H_6	$C_{15}H_{23}NO \cdot HCl$	C, H, N, Cl
4	*t*-Bu	48	B	216	C_6H_6	$C_{15}H_{23}NO \cdot HCl$	C, H, N, Cl

[a] Yield of free base obtained after distillation. [b] A, cyclohexylsulfamate; B, hydrochloride.

TABLE II



No.	Position of cyclopropyl group	R_1	R_2	Yield,[a] %	Derivative[b]	Mp, °C	Crystn Solvent	Formula	Analyses
5	*ortho*	H	*i*-Pr	66	B	96	C_6H_6	$C_{15}H_{23}NO_2 \cdot HCl$	C, H, Cl
6	*ortho*	H	*sec*-Bu	51	B	109	C_6H_6	$C_{16}H_{25}NO_2 \cdot HCl$	C, H, N, Cl
7	*ortho*	H	*t*-Bu	61	B	123	C_6H_6	$C_{16}H_{25}NO_2 \cdot HCl$	C, H, N, Cl
8	*ortho*	H	—◁	52	A	129	C_6H_6	$C_{15}H_{21}NO_2 \cdot C_6H_{13}NO_3S$	C, H, N, S
9	*ortho*	Et	Et	75	A	103	Me_2CO	$C_{16}H_{25}NO_2 \cdot C_6H_{13}NO_3S$	C, H, N, S
10	*ortho*	Et	Et	75	C	106	EtOAc–Me_2CO	$C_{16}H_{25}NO_2 \cdot CH_3I$	C, H, I
11	*para*	H	*i*-Pr	50	B	124	C_6H_6	$C_{15}H_{23}NO_2 \cdot HCl$	C, H, N, Cl

[a] Yield of free base obtained after distillation. [b] A, cyclohexylsulfamate; B, hydrochloride; C, iodomethylate.

TABLE III

	Approx. doses[a] of antagonist vs. isoproterenol					
No.	Arterial blood pressure depression[b]	Inhibition against ACh-induced bronchospasm[c]	Hyperglycemia[d]	Hyperlactacidemia[d]	Cardiac activity[e]	LD_{50} mg/kg ip mice
1	10	2	>1	1	>10	243
2	1	1	1	1	1	103
3	10	2	>1	1	1	35
4	1	0.2	1	1	10	91
5	0.01	0.01	0.01–0.1	0.01–0.1	0.02	131[f]
6	0.1	0.1–0.2	0.1–1	0.1	0.1–1	62
7	0.1	0.05	0.01–0.1	0.01–0.1	0.1	99
8	0.01	0.2	0.1–1	0.1	0.1–1	239
9	>10	2	1	1	1	168
10	>10	5	>1	>1	>10	95
11	10	2–5	>1	>1	10	220
Propranolol	0.1	0.05–0.1	0.1–1	0.1	0.1	135[g]

[a] In these screening assays, doses were generally only in tenfold range. [b] Doses (mg/kg iv) required to suppress isoproterenol blood pressure depression. [c] Doses (mg/kg iv) required to prevent inhibitory action of isoproterenol against ACh-induced bronchospasm. [d] Doses (mg/kg sc) which injected in rats 30 min prior to isoproterenol 50% reduce blood glucose and lactic acid 1 hr after drug administration. [e] Doses (μg/ml) required to prevent chronotropic and inotropic effects of isoproterenol. [f] LD_{50} of **5** by iv and oral routes are, respectively, 32 and 382 mg/kg. [g] K. Hermansen, *Acta Pharmacol. Toxicol.*, **27**, 453 (1969). LD_{50} by iv and oral routes are, respectively, 45 and 471 mg/kg [J. W. Black, W. A. M. Duncan, and R. G. Shanks, *Brit. J. Pharmacol.*, **25**, 566 (1965)].

product; bp 66–68° (0.01 mm); $n^{25}D$ 1.549. *Anal.* ($C_{11}H_{12}O$) C, H.

***p*-Cyclopropylphenol.**[12]—To a solution of 106 g (0.66 mole) of *p*-cyclopropylacetophenone[16] in 1 l. of Et_2O was added a solution of 152 g (0.82 mole) of *p*-nitroperbenzoic acid in 650 ml of THF. The mixture was allowed to stand at room temperature for 10 days. Et_2O was then added and the organic solution was treated successively with aq solutions of KI, $Na_2S_2O_3$, and $NaHCO_3$. After drying, the solution was concentrated to dryness and the residual oil was dissolved in a solution of 71 g of KOH in 400 ml of 80% EtOH. The solution was refluxed for 3 hr, EtOH was removed *in vacuo*, the aq layer was washed with Et_2O and acidified with H_2SO_4. The product was extracted with Et_2O and after removal of the solvent *in vacuo* and distillation, 15.9 g (18%) of product was obtained which crystallized on standing: bp 110–112° (3 mm); mp 68° [lit.[13] bp 112° (8 mm); mp 65–66°].

1-(*o*-Cyclopropylphenoxy)-2,3-epoxypropane.—To a solution of 11.2 g (0.2 mole) of KOH in 90 ml of H_2O were added 18.9 g (0.14 mole) of *o*-cyclopropylphenol[13,16] and 12.2 ml (0.155 mole) of epichlorohydrin. The mixture was stirred at room temperature for 4 hr, then extracted with Et_2O. Removal of the solvent *in vacuo* and distillation of the residue gave 11.6 g (44%) of

(12) Synthesis was described from *p*-nitrocyclopropylbenzene, in our hands nitration of cyclopropylbenzene[13-15] afford mainly *ortho* derivatives and only a few *p*-nitro derivatives. An alternative procedure was used.

(13) Yu. S. Shabarov, V. K. Potapov, and R. Ya. Levina, *Zh. Obshch. Khim.*, **34**, 3127 (1964); *J. Gen. Chem. USSR*, **34**, 3171 (1964).

(14) Yu. S. Shabarov, R. Ya. Levina, V. K. Potapov, A. M. Osipov, and E. G. Treshchova, *Zh. Obshch. Khim.*, **30**, 3874 (1960); *J. Gen. Chem. USSR*, **30**, 3830 (1960).

(15) R. Ketcham, R. Cavestri, and D. Jambotkar, *J. Org. Chem.*, **28**, 2139 (1963).

(16) R. Ya. Levina, P. A. Gembitskii, V. N. Kostin, S. M. Shostakovskii, and E. G. Treshchova, *Zh. Obshch. Khim.*, **33**, 365 (1963); *J. Gen. Chem. USSR*, **33**, 358 (1963).

colorless oil: bp 92–94° (0.01 mm); n^{20}D 1.549. *Anal.* ($C_{12}H_{14}O_2$) C, H.

Amino Alcohols I and II.—The appropriate epoxide[17] (0.075 mole) and amine (0.1 mole) were dissolved in 70 ml of *i*-PrOH and heated in a sealed vessel at 80° for 4 hr. The solvent was removed under reduced pressure and the oily residue was distilled. Results are summarized in Tables I and II.

Acknowledgment.—The authors are indebted to Dr. P. Vaudescal for chemical cooperation, to Miss A. M. Conrard for biochemical analyses, and to Mr. P. Vassort for spectroscopic and analytical services.

(17) 1-(*p*-Cyclopropylphenoxy)-2,3-epoxypropane was prepared in a similar manner as for the *ortho* derivative and was used without distillation.

2,3,6-Trimethoxynitrostyrene and Its β-Phenethylamine

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In a report of a general synthesis of a number of β-phenethylamines, Merchant and Mountwala[1] condensed 2,3,6-trimethoxybenzaldehyde (2,4-DNP, mp 223°)[2] with $MeNO_2$ and obtained an oil. This was not further purified, and was reduced to yield an amine whose picrate melted at 166–167°. Clark, *et al.*,[3] following the above procedure, obtained a β-phenethylamine as a hydrochloride, mp 122–123°. In contrast to the other trimethoxy derivatives evaluated, these authors reported that this compound had no activity in the presence of soluble amine oxidase from rabbit liver.

We now doubt that the 2,3,6-trimethoxyphenethylamine reported in the previous two communications was the correct compound. Using a method different from that in ref 2, 2,3,6-trimethoxybenzaldehyde was prepared; its 2,4-dinitrophenylhydrazone melted at 207° which compares with that reported by Shulgin.[4]

Condensing the substituted aldehyde with $MeNO_2$ resulted in a *crystalline* substituted nitrostyrene which melted at 99–100°. The nmr signals at δ 8.60 and 8.96 were due to the ethylenic protons and a coupling constant of $J = 21$ Hz indicated[5] a *trans* configuration for this compound. The melting points of the picrate and hydrochloride of the corresponding β-phenethylamine are now given as 176 and 135°, respectively.

Biological Activity.—The compound produced hypomotility in 20-g Swiss-albino mice when administered ip as a saline solution at 16 mg/kg. At 31 mg/kg the compound induced fatal convulsions.

Following a modified monomine oxidase procedure of Wurtman and Axelrod[6] using homogenized mouse brain, the amine at a concentration of 2.5×10^{-4} *M* inhibited by 43% the production of indole-^{14}C acetic acid from tryptamine-2-^{14}C. This compound is either a competitive substrate for the monoamine oxidase or an inhibitor of that enzyme.

Experimental Section[7]

2,3,6-Trimethoxy-β-nitrostyrene.—A mixture of 4.5 g (0.025 mole) of 2,3,6-trimethoxybenzaldehyde, 1.3 g of NH_4OAc, 1. 7 ml of $MeNO_2$, and 15 ml of AcOH was refluxed for 1.5 hr. On cooling, yellow crystals were separated. Recrystallization from EtOH gave 3.2 g (54%) of mp 99–100°; nmr ($CHCl_3$) δ 4.12, 4.16, 4.20 (s, 9, OCH_3), 7.08, 7.48 (AB pattern, 2, aromatic), 8.60, 8.96 (AB pattern, 2, $J = 21$ Hz, HC=CH); ir spectra as expected. *Anal.* ($C_{11}H_{13}NO_5$) C, H, N.

2,3,6-Trimethoxy-β-phenethylamine.—To a stirred suspension of 2.0 g of LAH in 120 ml of anhyd Et_2O was added slowly a soln of 2.9 (0.012 mole) of the nitrostyrene in 100 ml of Et_2O–C_6H_6. The mixture was refluxed 2 hr, excess of LAH was decomposed (wet Et_2O), and 6 *N* HCl was added until pH 6. Then it was treated with 29 g of potassium sodium tartrate followed by 25% NaOH soln until pH 9. The mixture was extracted with CH_2Cl_2 upon evaporation the free amine was obtained as a faintly yellow syrup.

Two drops of the free amine were added to a boiling solution of picric acid in EtOH, after 48 hr large, yellow crystals, mp 176° (sharp) were obtained. Merchant and Mountwala[1] reported mp 166–167°.

The rest of the syrup was dissolved in Et_2O and HCl gas was bubbled through the solution until saturation. On evaporation, a syrup was obtained which was crystallized from *i*-PrOH–EtOAc (1:3); 1.35 g (47%) of white needles, mp 130–133° were obtained.

Recrystallization from the same solvent gave mp 134–135°; tlc (on silica gel IB-F, developed with 1-BuOH–AcOH–H_2O, 4:1:1, and visualized by spraying with ninhydrin) R_f 0.65; nmr (D_2O) δ 3.05–3.22 (m, 4, aliphatic H), 3.82, 3.88 (s, 9, OCH_3), 9.90, 7.14 (AB pattern, 2, aromatic H); ir spectra as expected. *Anal.* ($C_{11}H_{18}ClNO_3$) C, H, N.

Acknowledgments.—We wish to thank Dr. R. S. deRopp for valuable discussion and Mrs. Lena Kastl for her help with the biological testing. This work was supported by National Institute of Mental Health Grant 5 RO1 MH13687-03.

(1) J. R. Merchant and A. J. Mountwala, *J. Org. Chem.*, **23**, 1774 (1958).

(2) J. R. Merchant, R. M. Naik, and A. J. Mountwala, *J. Chem. Soc.*, 4142 (1957).

(3) L. C. Clark, F. Beningnon, and R. D. Morin, *J. Med. Chem.*, **8**, 353 (1965).

(4) A. Shulgin, *ibid.*, **9**, 445 (1960).

(5) D. W. Mathieson, *Nucl. Magn. Resonance Org. Chem.*, 187 (1967).

(6) R. J. Wurtman and J. Axelrod, *Biochem. Pharmacol.*, **12**, 1439 (1963).

(7) Melting points were taken on a Nalge-Axelrod micro hot stage and are corrected. Analytical results where indicated by symbols of the elements were within ±0.2 of theoretical values. The ir spectra were measured with a Perkin-Elmer Model 337 spectrophotometer, and nmr spectra with a Varian A-60 spectrometer.

Synthesis of B/C *trans*-Fused Morphine Structures. V.[1] Pharmacological Summary of *trans*-Morphine Derivatives and an Improved Synthesis of *trans*-Codeine

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Preceding papers[1,4,5] from this laboratory presented the synthesis of B/C *trans*-morphine and related compounds. The present paper concerns the evaluation of the analgetic activities of these compounds and

(1) Part IV: H. Inoue, M. Takeda, and H. Kugita, *Chem. Pharm. Bull.*, in press.

(2) Present address: Research and Development Division, Tanabe Seiyaku Co., Ltd. (Osaka).

(3) To whom correspondence should be addressed.

(4) H. Kugita, M. Takeda, and H. Inoue, *Tetrahedron*, **25**, 1851 (1939).

(5) H. Kugita and M. Takeda, *Chem. Pharm. Bull.*, **13**, 1422 (1965).