and Shechter.[6] A stirred solution of 53 g (0.136 mole) of IIIc and 37 g (0.410 mole) of CuCN in 180 ml of dimethylformamide was refluxed 5 hr in a nitrogen atmosphere. The hot, dark brown mixture was poured into a warm solution of 300 ml of ethylenediamine in 900 ml of water and shaken vigorously 5–10 min in order to dissolve the copper complexes. To the still warm mixture was added 750 ml of ethyl acetate and the organic phase separated after thorough shaking. The aqueous phase was extracted with four 500-ml portions of ethyl acetate. The combined extracts were washed with two 250-ml portions each of 30% aqueous ethylenediamine, water, and brine. The tan solution was dried (Na_2SO_4), concentrated to about 600 ml, and left at ice temperature to furnish 39 g (86%) of off-white product, mp 217–219°. Further recrystallization from ethyl acetate and then absolute ethanol provided the analytical sample, mp 219.5–220.5°.

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.68; H, 5.48; N, 8.60.

Ethyl 6-Cyano-5-hydroxy-2-methylindole-3-carboxylate (IVa).—Compound IVc (18 g) was hydrogenated in 1300 ml of absolute ethanol in the presence of 2 g of 10% Pd-C. After absorption of 1 mole equiv of hydrogen the product was isolated and recrystallized from 2-propanol to give 12.5 g (94%), mp 282–284° dec. Further recrystallization furnished the analytical sample: mp 283.5–285° dec; infrared (KBr), 4.52 and 6.13 μ.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.83; H, 5.11; N, 11.56.

Ethyl 6-Aminomethyl-5-benzyloxy-2-methylindole-3-carboxylate (Va).—The benzyloxynitrile IVc (40 g) in 750 ml of acetic acid was hydrogenated in the presence of 2 g of PtO_2 at room temperature. In 24 hr 80% of the theoretical amount of hydrogen was absorbed. Fresh catalyst (2 g) was added to bring the reaction to completion (10% overreduction). The product was isolated and shaken with ethyl acetate and 10% NaOH. Concentration of the dried ethyl acetate extracts afforded 28 g (69%) of cream-colored needles, mp 150–153°. Recrystallization from 2-propanol gave 20.2 g (50%) of off-white crystals, mp 151.5–153°. The hydrochloride, mp 235.5–237° dec, was prepared by addition of alcoholic HCl to a solution of the free base in alcohol.

Anal. Calcd for $C_{20}H_{22}N_2O_3 \cdot HCl$: N, 7.47; Cl, 9.46. Found: N, 7.43; Cl, 9.40.

Ethyl 5-Benzyloxy-6-[(dimethylamino)methyl]-2-methylindole-3-carboxylate (Vb).—A mixture of 5 g (0.0148 mole) of the aminomethyl derivative Va, 3.4 g (0.074 mole) of formic acid, and 2.5 ml (0.0334 mole) of formalin was heated 12 hr on the steam bath. The brown solution was evaporated *in vacuo*, and the residue was treated with 10% NaOH and extracted with ethyl acetate. The dried extracts were concentrated, and the residue was chromatographed on 60 g of silica gel. Elution with ethyl acetate–methanol (3:1) furnished 4.5 g (83%) of off-white product, mp 152–155°. Recrystallization from aqueous ethanol produced 3.9 g of Vb (72%), mp 156–158°. This material contained a small amount of an impurity (thin layer chromatography) which could not be eliminated by crystallization or chromatography. The product was used in the next step without further purification.

Ethyl 6-[(Dimethylamino)methyl]-5-hydroxy-2-methylindole-3-carboxylate (Ia).—Compound Vb (5 g) was hydrogenated in 225 ml of ethanol in the presence of 500 mg of 10% Pd-C. The reduction was complete in 75 min. The product was isolated in good yield and characterized as the **hydrochloride**, mp 230–232° dec, after recrystallization from methanol–ether. The melting point was depressed on admixture with the 4-dimethylaminomethyl isomer IIa and their infrared spectra were different.

Anal. Calcd for $C_{15}H_{20}N_2O_3 \cdot HCl$: N, 8.96; Cl, 11.33. Found: N, 9.04; Cl, 11.52.

Compound Ia was degraded by Raney nickel in refluxing ethanol to ethyl 2,6-dimethyl-5-hydroxyindole-3-carboxylate (Ib) in 55% yield.

Ethyl 5-Hydroxy-6-[(4-hydroxypiperidino)methyl]-2-methylindole-3-carboxylate (Ic).—A mixture of 6.5 g of Ia and 25 g of 4-hydroxypiperidine was heated 24 hr at 115°. The reaction mixture was treated with 500 ml of water, and the dark insoluble solid was collected and washed thoroughly with water. Two recrystallizations from ethyl acetate with charcoal treatment yielded 2.6 g (38%) of product: mp 220–223° dec; nmr (20% DMF-d_7), 426 and 444 cps (1 H each, singlets, $J < 1$ cps).

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.96; H, 7.33; N, 8.11.

Biological Methods. Male rats of the Charles River CD strain weighing 90–100 g were fasted 16 hr prior to test. Tail vein blood samples were assayed for blood glucose by the method of Reinicke.[9] The animals were divided into groups of five rats each on the basis of their fasting blood glucose levels. All rats were given 100 mg of glucose subcutaneously and then a single oral administration of the test agent. Blood glucose was monitored hourly from tail vein blood samples.

β-Phenoxyethylamines with Local Anesthetic and Antispasmodic Activity

PAOLO DE BIE, LUCIA VERLICCHI, AND IVO SETNIKAR

Research Division, Recordati S.A.S., Milan, Italy

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β-Phenoxyethylamine derivatives have many pharmacological activities. Bovet and Bovet-Nitti[1] who reviewed the subject until 1947 described for compounds of this type local anesthetic, adrenergic, adrenolytic, nicotinic, antihistaminic, curaremimetic, oxytocic, and antifibrillatory activities. More recently,[2–6] β-phenoxyethylamines with pronounced local anesthetic, antispasmodic, vasodilating, coronarodilating, and analgetic activities have been mentioned. For this reason an investigation was started in order to explore the pharmacological activities of β-phenoxyethylamines, N-disubstituted with different radicals in the benzene ring. Several compounds with a strong local anesthetic and with smooth muscle relaxing and antispasmodic activities were found. Particularly interesting for their local anesthetic and antispasmodic activity were 2-butyryl-β-(N,N-diisopropyl)phenoxyethylamine (**30**, ketocaine), 2-butyryl-6-amino-β-(N,N-diisopropyl)phenoxyethylamine (**34**), and 2-(α-hydroxybutyl-β-(N,N-diisopropyl)phenoxyethylamine (**36**), whose general pharmacological activities were described by Setnikar.[7] The synthesis of prototype compounds is to be found in the Experimental Section.

The results obtained in the pharmacological screening are summarized in Table I. The substances showed several pharmacological activities, but throughout, the most important in intensity were the local anesthetic and the antispasmodic activity.

Local Anesthetic Activity.—The attachment of different radicals to the phenoxyethylamino structure influenced the degree of the local anesthetic activity as follows.

(a) **Substituents in the Amino Group.**—The highest activity was obtained by substituting the hydrogens of the amino group with two isopropyl groups. The activity decreased with two ethyl and still more with two methyl groups. A further decrease of activity was

(1) D. Bovet and F. Bovet-Nitti, "Medicaments du Système Nerveux Vegetatif," Verlag S. Karger, Basel, 1948, p 229, 231.

(2) L. Beani and G. Fowst, *Arch. Ital. Sci. Farmacol.*, **5**, 287 (1955).

(3) L. Turbanti and G. F. Di Paco, *Farmaco (Pavia), Ed. Sci.*, **17**, 650 (1962).

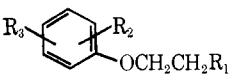
(4) S. Wiedling and C. Tegnér in "Progress in Medicinal Chemistry," A. P. Ellis and A. B. West, Ed., Butterworths and Co. (Publishers) Ltd., London, 1963, p 332.

(5) N. P. Buu-Hoï, P. Jacquignon, and M. Dufour, *Bull. Soc. Chim. France*, 23 (1964).

(6) N. P. Buu-Hoï, M. T. Richert, A. Krikorian, M. Dufour, and P. Jacquignon, *Bull. Chim. Thérap.*, **1**, 23 (1965).

(7) I. Setnikar, *Arzneimittel-Forsch.*, **16**, 1025 (1966).

TABLE I
PHARMACOLOGICAL ACTIVITIES OF PHENOXYETHYLAMINE HYDROCHLORIDES



No.	R_1	R_2	R_3	Local anesthetic activity EC_{50}, mg/ml	Antispasmodic activity, EC_{50}, mg/l. Acetylcholine	Histamine	Epinephrine	5HT	LD_{50}, mg/kg ip	Other pharmacol activities
1[i]	$(CH_3)_2N$	2-$COCH_3$	...	16	2	0.3	6	4	200[a]	*e*
2	$(CH_3)_2N$	2-$COCH_3$	5-OCH_3	10	8	2	11	11	200[a]	*e*
3[j]	$(CH_3)_2N$	2-COC_2H_5	...	6	4	0.5	4	...	150[b]	*e*
4	$(CH_3)_2N$	2-COC_2H_5	4-Br	6	9	2	7	3	140[a]	*f, g*
5[k]	$(CH_3)_2N$	2-COC_2H_5	4-CH_3	10	1	0.4	0.4	2	110[a]	*e, g*
6	$(CH_3)_2N$	2-COC_2H_5	5-OCH_3	8	22	4	13	2	140[a]	*e*
7	$(CH_3)_2N$	2-$CO(CH_2)_2CH_3$	...	1	2	0.03	0.9	0.8	50[b]	*e*
8	$(CH_3)_2N$	2-$CO(CH_2)_2CH_3$	5-OCH_3	14	5	0.7	3	0.9	130[a]	None
9	$(CH_3)_2N$	2-$COCH(CH_3)_2$	...	7	14	0.4	0.4	1.4	100[a]	*e, h*
10	$(CH_3)_2N$	2-$CO(CH_2)_4CH_3$	...	0.7	1	0.1	1	3	100[b]	*g, h*
11	$(CH_3)_2N$	2-$CHOHCH_2CH_3$	...	2	8	0.3	3	7	100[c]	*e*
12	$(CH_3)_2N$	4-$COCH_3$	3-OH	25	42	9	...	30	270[a]	*e*
13[j]	$(CH_3)_2N$	4-$COCH_2CH_3$	...	20	37	8	>250	28	240[a]	None
14	$(CH_3)_2N$	4-$CO(CH_2)_2CH_3$	3-OH	5	6	2	100	6	250[a]	*e, f*
15[j]	$(C_2H_5)_2N$	2-COC_2H_5	...	6	2	0.4	3	...	100[a]	*e*
16	$(C_2H_5)_2N$	2-COC_2H_5	5-OCH_3	2	8	4	4	17	130[a]	*f*
17	$(C_2H_5)_2N$	2-COC_2H_5	4-Br	4	3	0.8	2	4	70[a]	None
18[k]	$(C_2H_5)_2N$	2-COC_2H_5	4-CH_3	8	4	0.2	2	2	130[b]	*e, g, h*
19[l]	$(C_2H_5)_2N$	2-$CO(CH_2)_2CH_3$	...	1	5	0.4	15	1	100[a]	*e, h*
20	$(C_2H_5)_2N$	2-$CO(CH_2)_2CH_3$	6-NO_2	6	4	4	21	1	60[a]	*f*
21	$(C_2H_5)_2N$	2-$CO(CH_2)_2CH_3$	6-NH_2	0.2	30	3	>50	30	70[a]	*f*
22	$(C_2H_5)_2N$	2-$COCH_2CH(CH_3)_2$	...	0.4	1	0.04	4	4	150[a]	*e, h*
23	$(C_2H_5)_2N$	2-$CHOH(CH_2)_2CH_3$	...	2	0.8	0.1	0.8	20	250[b]	*e, h*
24[m]	$(C_2H_5)_2N$	4-$COCH_3$	3-OH	32	34	6	83	74	200[a]	*e, f*
25[j]	$(C_2H_5)_2N$	4-COC_2H_5	...	50	18	10	190	44	200[a]	*h*
26	$(C_2H_5)_2N$	4-$CO(CH_2)_2CH_3$	3-OH	21	4	1	4	7	300[a]	*e, g, h*
27	$(C_2H_5)_2N$	4-$COCH_2CH(CH_3)_2$	...	4	2	2	129	13	150[a]	*f, h*
28	$[(CH_3)_2CH]_2N$	2-$COCH_3$	...	4	0.6	0.6	100	12	90[a]	*f, h*
29	$[(CH_3)_2CH]_2N$	2-COC_2H_5	...	1	1	0.8	84	8	100[a]	*f*
30[n]	$[(CH_3)_2CH]_2N$	2-$CO(CH_2)_2CH_3$	...	0.4	0.7	0.1	21	1	102[a]	*h*
31	$[(CH_3)_2CH]_2N$	2-$COCH(CH_3)_2$	...	9	0.8	0.2	18	3	150[a]	*e, h*
32	$[(CH_3)_2CH]_2N$	2-$CO(CH_2)_2CH_3$	4-Cl	3	0.1	0.2	17	0.7	200[a]	*f, h, i*
33	$[(CH_3)_2CH]_2N$	2-$CO(CH_2)_2CH_3$	6-NO_2	20	2	2	19	2	200[a]	*f, h*
34	$[(CH_3)_2CH]_2N$	2-$CO(CH_2)_2CH_3$	6-NH_2	0.1	0.4	2	22	3	38[a]	*f*
35	$[(CH_3)_2CH]_2N$	2-$CO(CH_2)_3CH_3$	...	3	0.3	0.07	17	11	100[a]	*h*
36	$[(CH_3)_2CH]_2N$	2-$CHOH(CH_2)_2CH_3$	...	0.5	1	0.7	62	37	300[a]	*e*
37	$[(CH_3)_2CH]_2N$	3-$COCH_3$	...	55	76	19	>250	49	250[d]	*e, h*
38	$[(CH_3)_2CH]_2N$	4-$CO(CH_2)_2CH_3$	...	20	2	12	121	14	250[a]	*f, h*
39	$[(CH_3)_2CH]_2N$	4-$CO(CH_2)_3CH_3$	...	18	1	3	32	4	150[a]	*f, h*
40[o]	Morpholino	2-$COCH_3$	5-OCH_3	56	71	20	110	59	600[c]	None
41	Morpholino	2-COC_2H_5	...	14	40	11	7	35	250[d]	*e*
42	Morpholino	2-COC_2H_5	4-Br	22	12	10	42	32	300[d]	None
43	Morpholino	2-COC_2H_5	5-OCH_3	15	76	4	61	47	350[c]	None
44	Morpholino	2-COC_2H_5	4-CH_3	8	30	8	37	20	300[b]	*g*
45	Morpholino	2-$CO(CH_2)_2CH_3$	...	16	29	8	7	23	280[d]	*g, h*
46	Morpholino	2-$CO(CH_2)_2CH_3$	5-OCH_3	11	13	35	40	11	180[c]	None
47	Morpholino	2-$CO(CH_2)_3CH_3$	...	15	19	7	6	0.08	350[c]	*g*
48[p]	Morpholino	4-$COCH_3$	...	100	74	78	>250	186	600[b]	None
49	Morpholino	4-$COCH_3$	3-OH	58	67	61	195	40	850[c]	*e*
50[p]	Morpholino	4-COC_2H_5	...	250	56	30	>250	>250	750[c]	None
51	Morpholino	4-COC_2H_5	3-OH	22	35	32	70	35	850[b]	None
52	Morpholino	4-$CO(CH_2)_2CH_3$	3-OH	18	18	7	47	5	700[c]	None
53	Morpholino	4-$CO(CH_2)_2NC_6H_{10}$[q]	...	50	158	9	>250	>250	120[a]	*f*
54	Piperidino	2-COC_2H_5	...	4	3	0.8	1	35	150[a]	*e, h*
55	Piperidino	2-COC_2H_5	4-Br	7	2	0.4	11	3	150[d]	*h*
56	Piperidino	2-COC_2H_5	5-OCH_3	2	4	2	2	3	150[d]	*g, h*
57	Piperidino	2-COC_2H_5	4-CH_3	3	5	0.8	3	4	120[a]	*e, g*
58	Piperidino	2-$CO(CH_2)_2CH_3$	...	2	1	0.3	0.9	0.2	150[a]	*e, h*
59	Piperidino	2-$CO(CH_2)_2CH_3$	5-OCH_3	3	7	4	3	4	130[a]	*g*
60	Piperidino	2-$CO(CH_2)_3CH_3$	...	2	0.8	0.4	0.9	0.1	120[c]	*f, h*
61	Piperidino	4-$COCH_3$	3-OH	19	4	4	22	11	200[a]	*e*
62[p]	Piperidino	4-COC_2H_5	...	20	3	0.8	41	18	150[a]	*h*
63	Piperidino	4-COC_2H_5	3-OH	30	2	0.5	4	8	220[a]	*e*
64	Piperidino	4-$CO(CH_2)_2CH_3$	3-OH	21	0.4	0.3	13	4	200[a]	*e, h*

[a] Convulsions. [b] Tremors. [c] Depression. [d] Tremors followed by depression. [e] Transient decrease of arterial blood pressure. [f] Increase of resistance of isolated heart to anoxia. [g] Inhibition of formaldehyde paw edema. [h] Protection against $CaCl_2$ ventricular fibrillation. [i] G. Di Paco and C. S. Tauro, British Patent 905,903 (Sept 12, 1962); *Chem. Abstr.*, **58**, 5576*g* (1963). [j] R. I. Meltzer and A. B. Lewis, *J. Org. Chem.*, **22**, 612 (1957). [k] Aktiebolaget Pharmacia, British Patent 872,997 (Jan 23, 1958); *Chem. Abstr.*, **56**, 2384*e* (1962). [l] R. E. Nitz, W. Persch, and A. Schmidt, *Arzneimittel-Forsch.*, **5**, 357 (1955). [m] H. Grasshof (Firma M. Woelm), German Patent 1,174,311 (July 23, 1964); *Chem. Abstr.*, **61**, 11933*g* (1964). [n] P. Da Re and I. Setnikar, *Experientia*, **20**, 607 (1964). [o] S.-C. King and C.-C. Chang, *Hua Hsueh Hsueh Pao*, **22**, 467 (1956); *Chem. Abstr.*, **52**, 10971*h* (1958). [p] H. Najer, P. Chabrier, and R. Guidicelli, *Bull. Soc. Chim. France*, 1672 (1956).

observed with the piperidino and with the morpholino radical.

(b) **Acyl Group.**—Only small and irregular differences were found between the butyryl, isovaleryl, valeryl, and caproyl groups. These groups conferred higher activity, however, than the propionyl group, and this was followed by the isobutyryl and acetyl groups. In the few instances in which the α-keto group was reduced to an alcohol group, the activity did not change significantly. The position of the acyl group is important. The *ortho* position conferred the highest activity and was followed by the *meta* and then by the *para* positions.

(c) **Other Substituents in the Benzene Ring.**—An amino group in position 6 increased markedly the local anesthetic activity, probably because it increased the polarity of the whole molecule. Chloro and bromo substituents did not affect significantly the activity, whereas the nitro group reduced the activity.

Antispasmodic Activity.—The substances investigated showed a notable musculotropic smooth muscle relaxing activity. In several instances contractions of the small intestine provoked by histamine were particularly pronounced. The antihistaminic effect, however, was not sufficiently specific to allow a clear classification of the investigated substances as antihistaminic drugs.

Different radicals in the phenoxyethylamino structure had the following influence on the antispasmodic activity.

(a) **Substituents in the Amino Group.**—The highest activity was found with dimethylamino or with diethylamino radicals. The diisopropylamino radical decreased the activity as much as the piperidino radical. Still less active was the morpholino radical.

(b) **Acyl Radical.**—No important difference was found in the antispasmodic activity by substituting different acylic chains, such as the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, and caproyl radicals. Reduction of the acylic radical to an alcohol group did not alter significantly the antispasmodic activity. The position of the acylic chain is again very important, the *ortho* position conferring a much stronger antispasmodic activity than the *meta* or the *para* positions.

(c) **Other Substituents in the Benzene Ring.**—The introduction of hydroxy, methyl, or an amino, chloro, or bromo group in the benzene ring did not influence significantly the antispasmodic activity. A methoxy group reduced the antispasmodic activity.

Acute Toxicity.—The intraperitoneal LD_{50} in mice was found with few exceptions in the range between 100 and 400 mg/kg. Very often the animals showed symptoms of CNS excitation, which appeared, however, only with overtly toxic doses, so that they cannot be interpreted only as a CNS action of the drugs. After a phase of excitement the animals became depressed; sometimes the excitatory phase was almost absent. In some cases the toxicity was proportional to activity. The following regression could be calculated between local anesthetic activity (EC_{50}) and LD_{50}. In the equation the regression coefficient has a statistically significant value ($P < 0.001$); the correlation between toxicity and local anesthetic activity is, however, rather small ($r = 0.54$).

$$EC_{50} = (0.040 \pm 0.008)LD_{50} + 3.8$$

Other Pharmacological Activities. Among the other pharmacological activities screened, a transient hypotensive effect appeared most commonly. Many of the compounds increased the resistance of the isolated heart to anoxia, some showed an antiphlogistic or an antifibrillatory activity. No clear relationship could be established for these activities.

Experimental Section

All melting points were determined on a Koller-Heiztischmikroskop melting point apparatus and are uncorrected.

N-Substituted acyl-β-phenoxyethylamines were prepared by condensing the corresponding hydroxyphenones with suitable β-aminoethyl chloride hydrochlorides in ethanol with sodium ethoxide or in toluene with anhydrous potassium carbonate. Some N-substituted acyl-β-phenoxyethylamines were prepared by literature procedures and analyzed for identification.

Amino derivatives were obtained by hydrogenation at normal pressure on 10% Pd-C from the corresponding nitro derivatives. N-Substituted 2,α-hydroxyalkyl-β-phenoxyethylamines were obtained by hydrogenation at 4 atm on PtO_2 from the corresponding phenones. 4,5-Piperidinopropionyl-β,N-phenoxyethylmorpholine was obtained by a Mannich reaction from 4-acetyl-β,N-phenoxyethylmorpholine.

All starting hydroxyphenones were prepared according to literature methods; 2-hydroxy-4-methoxybutyrophenone was obtained by methylation with dimethyl sulfate and anhydrous potassium carbonate in acetone from 2,4-dihydroxybutyrophenone.

N-Substituted Acylphenoxyethylamines. Method A. A solution of hydroxyphenyl alkyl ketone (0.1 mole) and sodium ethoxide (0.2 mole) in 100 ml of ethanol was added to the N,N-dialkylaminoethyl chloride hydrochloride (0.1 mole) and the mixture was refluxed for 3 hr. After cooling and filtering, the solvent was evaporated. The crude oil was dissolved in ethyl ether, washed with water, and dried. Treatment of the ethereal solution with ethanolic HCl solution gave the hydrochloride, which was filtered and recrystallized.

Method B. A mixture of hydroxyphenylalkyl ketone (0.05 mole) and anhydrous K_2CO_3 (0.07 mole) in 250 ml of anhydrous toluene was stirred, and the N,N-dialkylaminoalkyl chloride hydrochloride (0.05 mole) was added. The mixture was refluxed for 8 hr and filtered. The filtrate was washed with saturated aqueous NaCl solution and dried. After acidification with anhydrous HCl and evaporation, the residue was crystallized.

2-Butyryl-6-amino-β-(N,N-diethyl)phenoxyethylamines. Method C.—The nitro derivative hydrochloride (0.05 mole) and anhydrous HCl (0.06 mole) dissolved in 60 ml of ethanol was hydrogenated at normal pressure over 0.1 g of 10% Pd-C. After filtration the solution was evaporated. The crude product was washed with ethyl ether and crystallized.

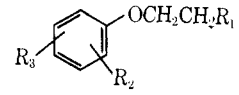
N-Substituted 2,α-Hydroxyalkyl-β-phenoxyethylamines. Method D.—The N-substituted acyl-β-phenoxyethylamine (0.02 mole) dissolved in 150 ml of methanol was hydrogenated at 4 atm of pressure over 0.25 g of PtO_2. After filtration and evaporation, the crude product was crystallized. The melting points, solvents of crystallization, and analytical data of all compounds are summarized in Table II.

4,5-Piperidinopropionyl-β,N-phenoxyethylmorpholine. A mixture of piperidine hydrochloride (4.88 g, 0.02 mole), paraformaldehyde (2 g), 4-acetyl-β,N-phenoxyethylmorpholine (5.71 g, 0.02 mole), and 14 ml of ethanol was refluxed. After 0.5 hr 1.4 g of paraformaldehyde was added and the mixture was refluxed for another 15 min. After cooling, the product was filtered and crystallized from ethanol-ethyl ether to yield 6 g of white crystals, mp 213–215°.

Anal. Calcd for $C_{20}H_{30}N_2O_3 \cdot 2HCl$: N, 6.68; Cl, 16.91. Found: N, 6.88; Cl, 17.15.

2-Hydroxy-4-methoxybutyrophenone.—Dimethyl sulfate (41 g, 0.3 mole) was added to a mixture of 2,4-dihydroxybutyrophenone (54 g, 0.3 mole), anhydrous K_2CO_3 (60 g), and 250 ml of acetone, and the mixture was refluxed for 8 hr. After filtration, the solvent was evaporated, and the crude oil was distilled to yield 46 g of product, bp 124–125° (2 mm). After crystallization from ligroin (bp 80–120°) it melted at 30–31°.

TABLE II



No.	Method	Mp, °C	Solvent of crystn[a]	Formula	Calcd, % N	Calcd, % Cl	Found, % N	Found, % Cl
2	A	215–216	A	$C_{13}H_{19}NO_3 \cdot HCl$	5.12	12.95	5.17	13.05
4	A	147–149	A–E	$C_{13}H_{18}BrNO_2 \cdot HCl$	4.19	10.61	4.23	10.70
6	A	182–183	A	$C_{14}H_{21}NO_3 \cdot HCl$	4.87	12.32	4.99	12.15
7	A	115–116	A–E	$C_{14}H_{21}NO_2 \cdot HCl$	5.06	13.05	5.21	13.18
8	A	101–102	A–E	$C_{15}H_{23}NO_3 \cdot HCl$	4.64	11.74	4.55	11.45
9	A	146–148	A–E	$C_{14}H_{21}NO_2 \cdot HCl$	5.06	13.05	5.36	13.26
10	A	104–106	A–E	$C_{16}H_{25}NO_2 \cdot HCl$	4.67	11.82	4.95	11.99
11	D	123–124	Ac	$C_{13}H_{21}NO_2 \cdot HCl$[b]	5.39	13.65	5.69	13.63
12	A	185–187	A	$C_{12}H_{17}NO_3 \cdot HCl$	5.39	13.65	5.41	13.61
14	A	154–156	A	$C_{14}H_{21}NO_3 \cdot HCl$	4.87	12.32	4.86	12.28
16	A	118–120	A–E	$C_{16}H_{25}NO_3 \cdot HCl$	4.43	11.23	4.49	11.36
17	A	97–99	A–E	$C_{15}H_{22}BrNO_2 \cdot HCl$	3.84	9.72	3.86	9.72
20	B	114–116	A	$C_{16}H_{24}N_2O_4 \cdot HCl$	8.12	10.28	8.22	10.22
21	C	175–177	I	$C_{16}H_{26}N_2O_2 \cdot 2HCl$	7.98	20.19	7.94	20.19
22	A	118–120	A–E	$C_{17}H_{21}NO_2 \cdot HCl$	4.46	11.29	4.23	10.99
23	D	99–101	B	$C_{16}H_{27}NO_2 \cdot HCl$[c]	4.64	11.75	4.60	11.64
26	A	155–157	A	$C_{16}H_{25}NO_3 \cdot HCl$	4.43	11.23	4.45	11.06
27	A	105–107	A–E	$C_{17}H_{27}NO_2 \cdot HCl$	4.46	11.29	4.57	11.21
28	A	142–144	A	$C_{16}H_{25}NO_2 \cdot HCl$	4.67	11.82	4.56	12.11
29	A	142–143	A	$C_{17}H_{27}NO_2 \cdot HCl$	4.46	11.29	4.36	11.08
31	A	123–124	A	$C_{18}H_{29}NO_2 \cdot HCl$	4.27	10.81	4.31	11.07
32	B	167–168[d]		$C_{18}H_{28}ClNO_2$[e]	4.30	10.88	4.44	10.90
33	B	146–147	A	$C_{18}H_{28}N_2O_4 \cdot HCl$	7.51	9.51	7.70	9.67
34	C	235–236	I	$C_{18}H_{30}N_2O_2 \cdot 2HCl$	7.38	18.70	7.32	18.91
35	A	124–126	A	$C_{19}H_{31}NO_2 \cdot HCl$	4.10	10.37	3.85	10.59
36	D	142–144	I	$C_{18}H_{31}NO_2 \cdot HCl$[f]	4.24	10.74	4.25	10.90
37	A	119–120	A	$C_{16}H_{25}NO_2 \cdot HCl$	4.67	11.82	4.63	11.70
38	A	126–128	A	$C_{18}H_{29}NO_2 \cdot HCl$	4.27	10.81	4.38	
39	A	125–127	A	$C_{19}H_{31}NO_2 \cdot HCl$	4.10	10.37	4.08	10.51
41	A	130–131	A–E	$C_{15}H_{21}NO_3 \cdot HCl$	4.67	11.83	4.70	11.88
42	A	145–146	A–E	$C_{15}H_{20}BrNO_3 \cdot HCl$	3.70	9.36	3.78	9.43
43	A	128–130	A	$C_{16}H_{23}NO_4 \cdot HCl$	4.25	10.75	4.24	10.55
44	A	130–131	A–E	$C_{16}H_{23}NO_3 \cdot HCl$	4.46	11.29	4.49	11.29
45	A	124–125	A	$C_{16}H_{23}NO_3 \cdot HCl$	4.46	11.29	4.47	11.37
46	A	152–153	A	$C_{17}H_{25}NO_4 \cdot HCl$	4.07	10.31	4.05	10.33
47	A	109–111	A–E	$C_{17}H_{25}NO_3 \cdot HCl$	4.27	10.81	4.25	10.84
49	A	175–177	A	$C_{14}H_{19}NO_4 \cdot HCl$	4.64	11.75	4.64	11.75
51	A	193–195	A	$C_{15}H_{21}NO_4 \cdot HCl$	4.44	11.23	4.41	11.23
52	A	180–182	A–E	$C_{16}H_{23}NO_3 \cdot HCl$	4.25	10.75	4.22	10.64
54	A	107–109	A–E	$C_{16}H_{23}NO_2 \cdot HCl$	4.70	11.91	4.76	11.91
55	A	132–133	A–E	$C_{16}H_{22}BrNO_2 \cdot HCl$	3.72	9.42	3.77	9.48
56	A	165–166	A	$C_{17}H_{25}NO_3 \cdot HCl$	4.27	10.81	4.30	10.85
57	A	149–151	A–E	$C_{17}H_{25}NO_2 \cdot HCl$	4.49	11.36	4.55	11.57
58	A	141–143	A	$C_{17}H_{25}NO_2 \cdot HCl$	4.49	11.36	4.52	11.55
59	A	178	A	$C_{18}H_{27}NO_3 \cdot HCl$	4.10	10.37	4.36	10.60
60	A	131–132	I	$C_{18}H_{27}NO_2 \cdot HCl$	4.30	10.88	4.63	11.23
61	A	166–168	A	$C_{15}H_{21}NO_3 \cdot HCl$	4.67	11.83	4.66	11.91
63	A	181–183	A	$C_{16}H_{23}NO_3 \cdot HCl$	4.46	11.29	4.50	11.26
64	A	145–147	A	$C_{17}H_{25}NO_3 \cdot HCl$	4.27	10.81	4.27	10.87

[a] A = ethanol, E = ethyl ether, I = 2-propanol, Ac = acetone, B = 2-butanone. [b] *Anal.* Calcd: C, 60.11; H, 8.54. Found: C, 60.19; H, 8.79. [c] *Anal.* Calcd: C, 63.66; H, 9.35. Found: C, 63.53; H, 9.44. [d] Bp, °C (1 mm). [e] *Anal.* Calcd: C, 66.34; H, 8.66. Found: C, 66.31; H, 8.70. [f] *Anal.* Calcd: C, 65.53; H, 9.78. Found: C, 65.58; H, 9.56.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.80; H, 7.02.

Pharmacological Methods. Acute Toxicity.—LD_{50} values were determined on Swiss "SMZ" mice, intraperitoneally, and the mortality within 24 hr was recorded. The animals were also observed for qualitative signs of intoxication following the Irwing scheme.

Local Anesthetic Activity.—All compounds were tested for subcutaneous local anesthetic activity on the mouse tail according to Bianchi's method.[8]

Antispasmodic Activity.—Smooth muscle antispasmodic activity was tested *in vitro* by the Magnus[9] method on the small intestine of the guinea pig stimulated by 0.025 mg/l. of histamine dihydrochloride, small intestine of the mouse stimulated by 0.15 mg/l. of acetylcholine chloride, seminal vesicle of the rat stimulated by 2 mg/l. of epinephrine hydrochloride, and ascending rat colon stimulated by 0.05 mg/l. of 5-hydroxytryptamine, according to Leith, *et al.*[10]

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Other Tests.—The substances were screened also for their actions on the isolated rabbit heart, following the method of Setnikar, *et al.*,[11] changes in amplitude of contractions, rate of contractions, coronary flow, and resistance to anoxia[12] were recorded. Furthermore the substances were screened for their actions on blood pressure and respiration in rats anesthetized with 1.0 g/kg ip of urethan, on formaldehyde paw edema in rats, on electroshock convulsions in mice, and on $CaCl_2$-induced ventricular fibrillations in rats.

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The Sulfur Analog of Serotonin[1]

E. CAMPAIGNE, T. BOSIN, AND E. S. NEISS

Chemistry Laboratories of Indiana University, Bloomington, Indiana 47401

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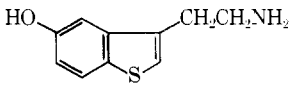
A number of structural analogs of serotonin (5-hydroxytryptamine) have been prepared.[2] Due to isoelectronic and steric relationships, the benzo[*b*]thiophene analog has been of particular interest as a possible agonist or antagonist of serotonin. The synthesis of this compound has proved to be refractory.[3] We wish to report the synthesis of 3-(β-aminoethyl)-5-hydroxybenzo[*b*]thiophene (I), and preliminary pharmacological evaluation.



I

3-Methyl-5-hydroxybenzo[*b*]thiophene,[4] prepared by the cyclization procedure[5] from *m*-hydroxyacetophenone, followed by decarboxylation of the resulting 3-methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic acid, was converted to its benzoate ester. This ester was subsequently converted to 3-bromomethyl-5-benzoyloxybenzo[*b*]thiophene by the procedure of Chapman, *et al.*,[6] and the corresponding carboxaldehyde was prepared in satisfactory yield *via* the Sommelet reaction,[7] without hydrolysis of the ester linkage. The 5-benzoyloxybenzo[*b*]thiophene-3-carboxaldehyde was then condensed with nitromethane, employing ammonium acetate as catalyst. Two products were isolated, the major product being 5-benzoyloxy-3-(2-nitrovinyl)-benzo[*b*]thiophene, and the minor product being 5-hydroxy-3-(2-nitrovinyl)benzo[*b*]thiophene. 5-Benzoyloxy-3-(2-nitrovinyl)benzo[*b*]thiophene was reduced with lithium aluminum hydride and the reaction was worked-up according to the method of Martin-Smith, *et al.*[2c] Compound I was isolated as the hydrochloride.

The central nervous system effect of I and 5-hydroxytryptophan (II) was studied by amplitude analysis of the cortical electroencephalogram (EEG) of male albino rabbits.[8] It has been demonstrated that animals given intravenous doses of II have significant increases of brain serotonin.[9,10] Administration of 400 μg/kg of I or II resulted in desynchronization of the EEG, indicative of a highly stimulated state; I caused a drop of the mean energy content (MEC) to 32.5% below control levels and II a drop of 41.0%. No peripheral effects were observed in rabbits treated with I. Animals pretreated with pentobarbital (3 mg/kg) showed a very similar polyphasic response to both I and II: at 50 μg/kg both were synergistic to the sedative, maximally stimulated at 200 μg/kg, and again sedative at 500 μg/kg. The barbiturate effect was 50% reversed (RD_{50}) at a dose of 160 μg/kg of I and 140 μg/kg of II.

Further studies on the synthesis and biological activity of benzo[*b*]thiophene analogs of biologically active indole derivatives are currently under investigation.

Experimental Section[11]

5-(α-Methyl-3-hydroxybenzylidene)rhodanine.—Rhodanine (67 g, 0.5 mole) was added to a solution of 4 g of ammonium acetate and 12 ml of glacial acetic acid in 400 ml of dry benzene and boiled for a few minutes. *m*-Hydroxyacetophenone (68 g, 0.5 mole) was added to the hot reaction mixture and the flask was connected to a Dean-Stark trap. The reaction mixture was refluxed vigorously until solid began to separate, cooled to room temperature, and filtered. The yellow precipitate was washed with two 100-ml portions of water and air dried. Recrystallization from dioxane–water gave 100 g (80%) of product which melted at 201–202°. An analytical sample melted sharply at 207°.

Anal. Calcd for $C_{11}H_9NO_2S_2$: S, 25.52. Found: S, 25.64.

β-Methyl-β-(3-hydroxyphenyl)-α-mercaptoacrylic Acid.—5-(α-Methyl-3-hydroxybenzylidine)rhodanine (50 g, 0.20 mole) was added to a stirred solution of 1 l. of 10% NaOH at 60°. The amber solution was heated to 80° and stirred for 1 hr prior to saturation with NaCl and filtration through a Norit pad. The solution was cooled to 10° and slowly poured into 400 ml of 6 *N* HCl which was saturated with NaCl and cooled to 10°. The yellow solid was collected and dried to yield 39 g (75%) of product which melted 128–129° after recrystallization from propanol: λ_{max}^{KBr} 3.00 (intermolecular H bonded OH), 3.4 (OH of acid), 3.95 (very weak) (SH), 5.95 (C=O), 6.25 (aryl conjugated C=C), 12.63, 14.2, and 14.45 μ (1,3-disubstituted benzene).

Anal. Calcd for $C_{10}H_{10}O_3S$: S, 15.25. Found: S, 15.11.

3-Methyl-5-hydroxybenzo[*b*]thiophene-2-carboxylic Acid.—β-Methyl-β-(3-hydroxyphenyl)-α-mercaptoacrylic acid (20 g, 0.095 mole) and 30 g of I_2 were allowed to gently reflux for 15 hr in 500 ml of dry dioxane. The solution was reduced to half its volume under reduced pressure and poured into 2 l. of cold

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