Some Indole and Benzo[b]thiophene Derivatives. Synthesis and Pharmacology

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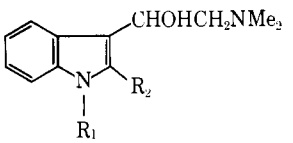
By using known methods, some derivatives of 2-dimethylamino-1-(3-indolyl)ethanol and some N-alkyl-N-(2-hydroxyethyl)-2-(3-indolyl)ethylamines have been prepared, but attempts to convert them into the corresponding 2-halogenoethylamines have failed. 5-Substituted 3-bromomethylbenzo[*b*]thiophene derivatives reacted with N-ethylethanolamine in boiling benzene to give 5-substituted N-ethyl-N-(2-hydroxyethyl)-3-aminomethylbenzo[*b*]thiophene derivatives which were isolated as their hydrochlorides. These reacted with $SOCl_2$ in dry boiling chloroform to give the corresponding 5-substituted N-(2-chloroethyl)-N-ethyl-3-aminomethylbenzo[*b*]thiophene hydrochlorides. 3-Chloroacetyl- or 3-bromoacetylbenzo[*b*]thiophene reacted with several secondary amines in benzene or a mixture of benzene and ether to give N,N-dialkyl-3-aminoacetylbenzo[*b*]thiophenes which, on reduction with $NaBH_4$ in methanol, gave the corresponding 2-dialkylamino-1-(3-benzo[*b*]thienyl)ethanol derivatives. 2-Dimethylamino-1-(3-benzo[*b*]thienyl)ethanol yielded the corresponding substituted 2-chloroethylamine in a pure state on being treated either with $SOCl_2$ or with PCl_5 in dry boiling chloroform. Preliminary pharmacological testing of the 2-chloroethylamines so prepared, together with various intermediates, showed that some of the above 2-halogenoethylamines derived from benzo[*b*]thiophene are moderately strong antagonists of 5-hydroxytryptamine *in vivo*. One or two of them showed promising activity against S180 mouse tumor.

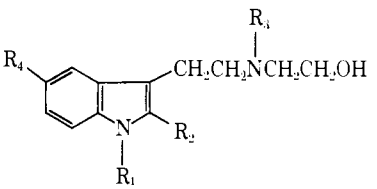
Many 2-halogenoethylamines are strong antagonists of catecholamines[1] and some of these compounds also antagonize the actions of 5-hydroxytryptamine (5-HT).[2] However, the anticatecholamine and anti-5-HT activities of these compounds do not necessarily run parallel to one another. Innes[3] has recently provided evidence that epinephrine and 5-HT act upon the same receptors in some tissues.

Gyermek[4] has shown that several quaternary salts of N,N-dimethyl- and N,N-diethyltryptamine and of N,N-dimethyl-5-hydroxytryptamine (bufotenine) are potent antagonists of the actions of 5-HT on the peripheral nervous receptors of the cat and dog, although they were only weakly active as antagonists of the actions of 5-HT on smooth muscle, and cholinergic stimulation was unaffected by the more potent members of this series of compounds in the dose range used. Thus, if a group known to give rise to compounds having a high affinity for nervous receptors is introduced into compounds related in structure to 5-HT, a new class of 5-HT antagonists is produced, capable of antagonizing the actions of 5-HT on receptors for which known antagonists of 5-HT have either very little or no affinity. By the introduction of the 2-halogenoethylamine side chain into compounds related in structure to 5-HT, a similar new class of 5-HT antagonists might be obtained. We therefore tried to prepare indole derivatives variously substituted in the 5 position and having a 2-halogenoethylamine side chain in the 3 position.

2-Dimethylamino-1-(1-ethyl-2-methyl-3-indolyl)ethanol (Ia) and 2-dimethylamino-1-(1,2-dimethyl-3-indolyl)ethanol (Ib)[5] were prepared by reduction of the corresponding glyoxylamides with lithium aluminium hydride. N-(2-Hydroxyethyl)-N-isopropyl-2-(3-indolyl)ethylamine (IIa) was prepared by the method of Frangatos, *et al.*,[6] and N-ethyl-N-(2-hydroxyethyl)-2-(1-benzyl-5-methoxy-2-methyl-3-indolyl)ethylamine (IIb), by treating 1-benzyl-3-(2-chloroethyl)-5-methoxy-2-methylindole with N-ethylethanolamine in ethanol at 80°. These indole amino alcohols reacted with thionyl chloride, phosphorus halides, or phosphoryl chloride in chloroform, ether, benzene, or dichloromethane at several temperatures to give intractable tars. DeGraw and Goodman[7] used methanesulfonyl chloride to prepare several 5-[bis(2-chloroethyl)amino]-indoles, but in our case this reagent failed to give the desired product.

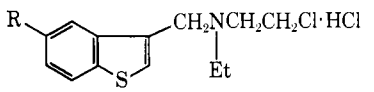


Ia, R_1 = Et; R_2 = Me
b, R_1 = R_2 = Me



IIa, R_1 = R_2 = R_4 = H; R_3 = *i*-Pr
b, R_1 = CH_2Ph; R_2 = Me; R_3 = Et; R_4 = OMe

Since benzo[*b*]thiophene is isosteric with indole,[8] and since Graham[1] has reported that several benzo[*b*]-thiophene compounds containing the 2-halogenoethylamine moiety antagonize the actions of 5-HT, this class of compound was investigated further.



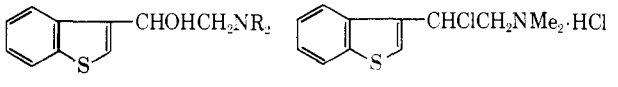
III

(1) J. P. D. Graham, *J. Med. Pharm. Chem.*, **2**, 499 (1960).
(2) L. Gyermek, *Pharmacol. Rev.*, **13**, 399 (1961).
(3) I. R. Innes, *Brit. J. Pharmacol.*, **19**, 427 (1962).
(4) L. Gyermek, *J. Med. Chem.*, **7**, 280 (1964).
(5) A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.*, 3388 (1959).
(6) G. Frangatos, G. Kohan, and F. L. Chubb, *Can. J. Chem.*, **38**, 1434 (1960).
(7) (a) J. DeGraw and L. Goodman, *J. Org. Chem.*, **27**, 1395, 1728 (1962); (b) J. DeGraw and L. Goodman, *J. Med. Chem.*, **7**, 213 (1964).
(8) M. Martin-Smith and S. T. Reid, *ibid.*, **1**, 507 (1959).

Several 5-substituted N-(2-chloroethyl)-N-ethyl-3-aminomethylbenzo[*b*]thiophene hydrochlorides (III) were prepared by a method very similar to that used earlier by Avakian and Martin,[9] and by Chapman and Tompsett[10] to prepare the unsubstituted compound (III, R = H). The 5-substituted 3-bromomethylbenzo[*b*]thiophene derivatives, prepared as described previously,[11] were treated with N-ethylethanolamine in boiling benzene, and the resulting amino alcohols reacted with thionyl chloride in dry chloroform to give the required 2-halogenoethylamines (III).

We attempted to prepare compounds more closely related in structure to epinephrine by using 3-acetylbenzo[*b*]thiophene[12] as a starting material. This was converted into 3-chloroacetylbenzo[*b*]thiophene by the method of Royer, *et al.*,[13] or into the corresponding 3-bromoacetyl compound by Tilak's[14] method. There was evidence (mainly from infrared and nmr spectra) that this last method of bromination (with bromine in carbon tetrachloride) yielded some of the ω,ω-dibromo derivative. However, recrystallization of the reaction product from benzene gave the pure 3-bromoacetylbenzo[*b*]thiophene.

Either 3-chloro- or 3-bromoacetylbenzo[*b*]thiophene reacted with each of several secondary amines to give the corresponding ketoamine in moderate yield. These compounds, which were difficult to purify, were characterized as their hydrochlorides. The ketoamines were readily reduced in good yield with sodium borohydride in methanol to the corresponding secondary alcohols (IV), which were characterized as their picrates or hydrochlorides. Reduction with aluminum isopropoxide in 2-propanol resulted in lower yields and a more difficult working-up procedure.



IV V

NR_2 = NMe_2, NEt_2, $N(CH_2Ph)_2$, piperidino, pyrrolidino, morpholino

2-Dimethylamino-1-(3-benzo[*b*]thienyl)ethanol with thionyl chloride or with phosphorus pentachloride in dry boiling chloroform yielded the pure 2-chloroethylamine (V).

2-Dibenzylamino-1-(3-benzo[*b*]thienyl)ethanol, either as the free base or as its hydrochloride, reacted with thionyl chloride or phosphorus pentachloride in dry chloroform to give mainly dibenzylamine hydrochloride. In all other cases, products were isolated which appeared from their infrared spectra and other properties to consist of intractable mixtures of the required product and amine hydrochlorides produced by decomposition of either the starting materials or the products.

Preliminary pharmacological investigations of these compounds show that the 2-halogenoethylamines derived from benzo[*b*]thiophene are quite strong antagonists of the actions of 5-HT *in vivo* when tested according to the method of Woolley.[15] They also possess significant antitumour activity when tested against the Crocker sarcoma S180, in mice.

(9) S. Avakian and G. J. Martin, U. S. Patent 2,553,495 (1951); *Chem. Abstr.*, **46**, 537e (1952).

(10) N. B. Chapman and A. J. Tompsett, *J. Chem. Soc.*, 1291 (1961).

(11) N. B. Chapman, K. Clarke, and B. Iddon, *ibid.*, 774 (1965).

(12) C. Hansch and H. G. Lindwall, *J. Org. Chem.*, **10**, 381 (1945).

(13) R. Royer, P. Demerseman, and A. Cheutin, *Bull. Soc. Chim. France*, 1534 (1961).

(14) B. D. Tilak, *J. Sci. Ind. Res. (India)*, **14B**, 11 (1955).

Experimental Section

1-Benzyl-3-(2-chloroethyl)-5-methoxy-2-methylindole was kindly donated by the Nicholas Research Institute Ltd. It can be synthesized by the method of Sletzinger, *et al.*[16]

N-Ethyl-N-(2-hydroxyethyl)-2-(1-benzyl-5-methoxy-2-methyl-3-indolyl)ethylamine.—The above chloro compound (10.4 g, 0.033 mole) and N-ethylethanolamine (8.9 g, 0.10 mole) in dry ethanol (250 ml) were heated at 80° for 6 hr in a stainless steel autoclave. After being concentrated under reduced pressure, the solution obtained was shaken with excess 2 *N* NaOH. The product was extracted with ether, and the ethereal extracts were washed with water and dried ($CaSO_4$). Distillation gave an almost colorless oil (8.0 g, 76%), bp 214–216° (0.5 mm).

The corresponding hydrochloride was obtained (~100%) by interaction of dry HCl and the base in dry ether, and crystallization from ethanol yielded white crystals, mp 168°.

Anal. Calcd for $C_{23}H_{31}ClN_2O_2$: C, 68.5; H, 7.8. Found: C, 68.6; H, 7.8.

2-Dimethylamino-1-(1-ethyl-2-methyl-3-indolyl)ethanol.—1-Ethyl-2,*N*,*N*-trimethylindole-3-glyoxylamide[17] (10.3 g, 0.04 mole) in dry tetrahydrofuran (THF) (200 ml) was added to a stirred suspension of $LiAlH_4$ (5.0 g, 0.132 mole) in dry THF (200 ml). The mixture was boiled under an atmosphere of dry nitrogen for 3 hr. After the product had been cooled, excess $LiAlH_4$ was destroyed by careful addition of wet ether followed by aqueous NaOH (50 ml of 10%), and the mixture was then filtered. Removal of the solvents under reduced pressure then gave a yellow oil, which was dissolved in the minimum of hot ethyl acetate. On being kept overnight in the refrigerator, the product (4.0 g, 41%) separated as white crystals, mp 78–80°.

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.1; H, 9.0. Found: C, 73.2; H, 8.9.

5-Substituted N-Ethyl-N-(2-hydroxyethyl)-3-aminomethylbenzo[*b*]thiophene Hydrochlorides.—3-Bromomethylbenzo[*b*]thiophene (22.7 g, 0.10 mole) and N-ethylethanolamine (18.7 g, 0.21 mole) were dissolved in dry benzene (300 ml) and the mixture was boiled for 1 hr. Ether (300 ml) was added to the cold reaction product, and the resulting mixture was then washed several times with water and dried (Na_2SO_4). The N-ethyl-N-(2-hydroxyethyl)-3-aminomethylbenzo[*b*]thiophene was obtained as an oil after distillation of the solvents under reduced pressure. The hydrochloride was prepared in the usual way and was recrystallized from dry ethanol. Details of this and other compounds prepared in a similar way are given in Table I.

5-Substituted N-(2-Chloroethyl)-N-ethyl-3-aminomethylbenzo[*b*]thiophene Hydrochlorides.—A solution of N-ethyl-N-(2-hydroxyethyl)-3-aminomethylbenzo[*b*]thiophene hydrochloride (13.6 g, 0.05 mole) in dry $CHCl_3$ (400 ml) was boiled gently and pure $SOCl_2$ (11.9 g, 0.10 mole) was added dropwise (10 min) with stirring. The mixture was boiled for a further 45 min, and the excess $SOCl_2$ and chloroform were distilled under reduced pressure. The residue was dissolved in the minimum of hot dry ethanol, excess dry ether was added, and the product separated as a white solid. Recrystallization from dry ethanol gave white sternutatory crystals. Details of this and other compounds prepared in a similar way are given in Table I.

3-Acetylbenzo[*b*]thiophene was prepared by Hansch and Lindwall's method[12] but the yield of pure product was increased from 56 to 70% by increasing the reaction time from 2 to 12 hr. The product had mp 63–65° (lit.[13] 64°) after crystallization from ethanol, and bp 112–115° (0.05 mm) [lit.[12] 135–137° (3 mm)].

3-Chloroacetylbenzo[*b*]thiophene was prepared (73%) by Royer's method and had mp 137–139° (lit.[13] 139°).

3-Bromoacetylbenzo[*b*]thiophene was prepared (84%) by Tilak's method and had mp 139–140° (lit.[14] 139°).

3-Dialkylaminoacetylbenzo[*b*]thiophenes.—The following method was used for all the compounds listed in Table II except

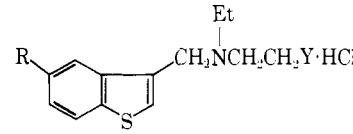
(15) D. W. Woolley, *Proc. Soc. Expl. Biol. Med.*, **98**, 367 (1958).

(16) (a) M. Sletzinger, W. V. Ruyle, and W. A. Gaines, U. S. Patent 2,995,566 (1957); *Chem. Abstr.*, **56**, 1431c (1962); (b) W. A. Gaines, M. Sletzinger, and W. V. Ruyle, U. S. Patent 3,014,043 (1957); *Chem. Abstr.*, **56**, 15486c (1962).

(17) W. C. Anthony and M. E. Speeter, U. S. Patent 2,930,797 (1960); *Chem. Abstr.*, **54**, 21129b (1960).

TABLE I

5-SUBSTITUTED N-ETHYL-N-(2-HYDROXYETHYL)- OR -(2-CHLOROETHYL)-3-AMINOMETHYLBENZO[b]THIOPHENE HYDROCHLORIDES

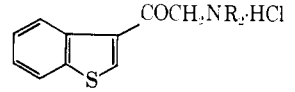


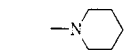
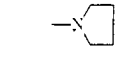
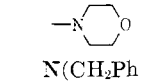
No.	Y	R	Mp, °C	Bp, °C (mm) of free base	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3	OH	H	126.5–128.5[a]	140–145 (0.03)[b]	87	$C_{13}H_{18}ClNOS$	57.4	6.7	5.2	57.8	6.4	5.0
4	OH	Me	148–150	138–142 (0.02)	66	$C_{14}H_{20}ClNOS$	58.8	7.1	4.9	58.6	7.3	4.7
5	OH	Cl	167–169	153–158 (0.03)	82	$C_{13}H_{17}Cl_2NOS$	51.0	5.6	4.6	50.8	5.8	4.4
6	OH	Br	181–182	156–160 (0.01)	78	$C_{13}H_{17}BrClNOS$	44.5	4.9	4.0	44.9	5.0	3.7
7	Cl	H	144–146[c]		97	$C_{13}H_{17}Cl_2NS$	53.8	5.9	4.8	53.5	5.7	4.7
8	Cl	Me	174–175		100	$C_{14}H_{19}Cl_2NS$	55.3	6.3	4.6	55.3	6.4	4.5
9	Cl	Cl	157–159		95	$C_{13}H_{16}Cl_3NS$	48.1	5.0	4.3	47.8	5.1	4.5
10	Cl	Br	167.5–169.5		98	$C_{13}H_{16}BrCl_2NS$	42.3	4.4	3.8	41.9	4.3	4.0

[a] Lit.[9] 129–130°. [b] Lit.[9] 185–189° (2 mm). [c] Lit.[9] 147–148°.

TABLE II

3-DIALKYLAMINOACETYLBENZO[b]THIOPHENE HYDROCHLORIDES

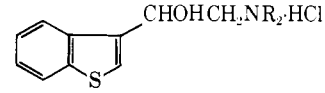


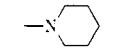
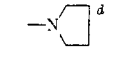
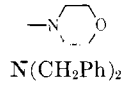
No.	NR_2	Mp, °C dec	Yield, %[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	NMe_2	233–235	80	$C_{12}H_{14}ClNOS$	56.3	5.5	5.5	56.1	5.5	5.8
12	NEt_2	203–205	42	$C_{14}H_{18}ClNOS$	59.2	6.4	4.95	58.9	6.3	5.2
13		265–267	70	$C_{15}H_{18}ClNOS$	60.9	6.1	4.7	61.1	6.0	4.5
14		252–253[b]	47	$C_{14}H_{16}ClNOS$	59.7	5.7	5.0	59.6	5.9	4.9
15		228	97	$C_{14}H_{16}ClNO_2S$	56.4	5.4	4.7	56.5	5.8	5.0
16	$N(CH_2Ph)_2$[c]	188[d]	96	$C_{26}H_{28}ClNO_2S$	68.8	6.2	3.1	68.9	5.7	3.5

[a] Yield of crude material. Except for compounds **15** and **16** severe losses resulted on recrystallization. [b] Very unstable to heat. Decomposed above 200°; increasingly so above 240°. [c] The free base had mp 82°. *Anal.* Calcd for $C_{24}H_{21}NOS$: C, 77.6; H, 5.7; N, 3.8. Found: C, 77.4; H, 5.7; N, 4.0. [d] Contains 1 molecule of ethanol of crystallization.

TABLE III

2-DIALKYLAMINO-1-(3-BENZO[b]THIENYL)ETHANOL HYDROCHLORIDES



No.	NR_2	Mp, °C	Yield, %[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
17	NMe_2[b]	163–165[b]	90	$C_{18}H_{18}N_4O_8S$	48.0	4.0	12.45	48.4	4.5	12.1
18	NEt_2[c]	122–124	64	$C_{14}H_{20}ClNOS$	58.8	7.1	4.9	58.7	7.2	5.2
19		216–217	82	$C_{15}H_{20}ClNOS$	60.5	6.8	4.7	60.9	6.8	4.7
20	 [d]	174–175	53	$C_{14}H_{18}ClNOS$	59.2	6.4	4.9	59.6	6.5	4.9
21		189–190	78	$C_{14}H_{18}ClNO_2S$	56.1	6.05	4.65	56.2	6.2	5.0
22	$N(CH_2Ph)_2$	196 dec	90	$C_{24}H_{24}ClNOS$	70.3	5.9	3.4	70.4	6.1	3.4

[a] Over-all yield from the 3-halogenoacetylbenzo[b]thiophene. [b] Free base is a liquid of bp 138–140° (0.5 mm). Characterized as the picrate, recrystallized from benzene. [c] Recrystallized from ethyl methyl ketone. [d] This hydrochloride was formed in dry $CHCl_3$, precipitated with dry ether, and recrystallized from dry ether–ethanol.

3-dibenzylaminoacetylbenzo[b]thiophene. To the 3-halogenoacetylbenzo[b]thiophene (0.10 mole) in dry benzene (500 ml) or in dry benzene (250 ml) and dry ether (250 ml) was added the appropriate amine (0.20 mole), and the mixture was stirred at room temperature. In general, the 3-chloroacetyl compounds required 12 hr while the 3-bromoacetyl compounds needed only 1 hr. Ether (300 ml) was added to the cold reaction mixture and the solution so formed was washed several times with water, and dried (Na_2SO_4). The solvents were removed and the product was obtained as an oil which was either used in subsequent stages or dissolved in dry ether and treated with dry ethereal HCl. The hydrochlorides, which usually separated as gums, solidified on being cooled and scratched; they were recrystallized from dry ethanol with charcoal to yield colorless solids. Details are given in Table II.

3-Dibenzylaminoacetylbenzo[b]thiophene.—A solution of 3-bromoacetylbenzo[b]thiophene (12.75 g, 0.05 mole) and dibenzylamine (19.7 g, 0.10 mole) in dry benzene (500 ml) was boiled for

90 min. Dibenzylamine hydrobromide was filtered off from the cold reaction product and the benzene was distilled under reduced pressure. The residue was shaken with ether (300 ml), and the resulting mixture was filtered to remove the remaining dibenzylamine hydrobromide (the total yield of which indicated the extent of the reaction). 3-Dibenzylaminoacetylbenzo[*b*]-thiophene was obtained as a solid by distilling the ether, and was recrystallized several times from petroleum ether (bp 40–60°) with charcoal. An almost quantitative yield of the product was obtained as white plates, mp 82°.

Anal. Calcd for $C_{24}H_{21}NOS$: C, 77.6; H, 5.7; N, 3.8. Found: C, 77.4; H, 5.7; N, 4.0.

The hydrochloride was obtained in the usual manner and crystallized from dry ethanol. It was shown to contain 1 mole of ethanol of crystallization (see Table II).

2-Dialkylamino-1-(3-benzo[*b*]thienyl)ethanols.—The crude amino ketone (0.10 mole) prepared as described above, was dissolved in methanol (250 ml), and $NaBH_4$ (1.9 g, 0.05 mole) in water (18 ml) and NaOH solution (2 ml of 2 *N*) was added dropwise at room temperature. The mixture was stirred for a further 45 min at room temperature, the methanol was distilled under reduced pressure, and the residue was shaken with water. The product was extracted with ether, the ethereal extracts were washed with water and dried (Na_2SO_4), and, after removal of the ether, the product was obtained as an oil by distillation under reduced pressure (except for the morpholino and dibenzylamino compounds which were converted directly into their hydrochlorides without prior distillation). The hydrochlorides were obtained in the usual manner and were recrystallized from dry ethanol. Details are given in Table III.

2-Chloro-N,N-dimethyl-2-(3-benzo[*b*]thienyl)ethylamine hydrochloride (23) was obtained (~100°C) from the corresponding amino alcohol hydrochloride by the action of $SOCl_2$ in dry chloroform. The product was recrystallized several times from dry ethanol–ether and had mp 146–148° dec.

Anal. Calcd for $C_{12}H_{15}Cl_2NS$: C, 52.2; H, 5.5; N, 5.1. Found: C, 52.1; H, 5.7; N, 4.9.

Pharmacology

The toxicities of the compounds are recorded as approximate LD_{50} values estimated from a preliminary pharmacological evaluation in mice (intraperitoneally) (see Table IV).

Antiserotonin activity was assessed *in vivo* by using essentially the method of Woolley.[15] This method makes use of the reduction of 5-HTP-induced diarrhea in groups of mice caused by the previous intraperitoneal injection of the stated dose of the compound.

For the inhibition of monoamine oxidase *in vivo* the method of Lessin[18] was used. This assesses the effect of the compound on the tremors induced in groups of mice by a subthreshold dose of 5-HTP. *In vitro*, the method of Weissbach, *et al.*,[19] was adopted. The results show the percentage inhibition of the oxidation of kynuramine by guinea pig liver homogenate caused by the stated concentration of the compound.

An antiwrithing test based on the work of Siegmund, *et al.*,[20] and of Hendershot and Forsaith[21] was also performed on groups of ten mice. The number protected by the stated dose from the writhing induced by the intraperitoneal injection of a standard dose of 2-phenyl-1,4-benzoquinone is recorded.

The methods of testing tumor inhibition were based upon those used by the U. S. National Cancer Institute.[22] A comparison was made of the growth of transplanted tumors in a group of mice being treated with the compound under test with the growth in a control group of mice (see Table V).

TABLE IV
COMPARATIVE BIOLOGICAL ACTIVITIES

No.	Approx LD_{50}, mg/kg ip	Anti-5-HT or ress. Dose, mg/kg	Anti-5-HT or ress. No. protected	Antiwrithing Dose, mg/kg	Antiwrithing No. protected	MAO inhib. *in vitro*[a]
IIa	200	32	3/10	32	7/10	†
IIb	200	16	10/10	64	10/10	†
3	200	128	2.5/10	128	3/10	†
4	250	128	6/10	128	3/10	†
		32	1.5/10			
5	300	64	1/10	256	1/10	†
6	400	64	8.5/10	128	3/10	†
		16	7.5/10			
7	100	32	10/10	32	1/10	†
		1	5/10			
8		16	10/10			†
9	150	64	10/10	64	3/10	†
		16	7/10			
10	500	128	10/10			†
		16	8/10			
11	200	64	5/10	64	5/10	†
12		64	1.0.5			
13	200	64	9/10	32	1/10	†
14	128	64	1.5/10	64	10/10	†
15	500	16	6/10	64	5/10	†
16		16	7.5/10			†
17	300	16	10/10	64	2/10	†
18		64	1.5.5			
19	100	128	9.5/10	32	7/10	
		16	7.5/10			
20	200	128	9/10	64	8/10	Slight
21	300	16	1.5/10	128	6/10	†
22	500	16	8.5/10	256	0/10	†
23[b]	250	128	8/10	128	10/10	†
BAS	250	64	5.5	64	1/6	
		16	1.5	32	3/6	
				16	1/6	
Cyproheptadine	64	8	6/6			
		4	2/6			
Chlorpromazine	64	16	10/10	32	5/5	
		4	6.5/10	4	1/5	

[a] Percentage monoamine oxidase inhibition *in vitro* (concentration 300 μM unless otherwise stated): **2**, 15%; **9**, 63% at 30 μM, 12% at 3 μM; **11**, 87%; **19**, 24%; **20**, 24%. [b] No. **23** is 2-chloro-N,N-dimethyl-2-(3-benzo[*b*]thienyl)ethylamine hydrochloride.

TABLE V
ACTIVITY AGAINST S180 MOUSE TUMOR[a]

No.	$(T/C)_1$	$(T/C)_1(T/C)_2$	$(T/C)_1(T/C)_2 \times (T/C)_3$
7	0.50	0.21	0.09
3	1.3	...	...
9	0.71	...	...
5	0.94	...	...
10	0.43	0.14	0.06
6	0.72	...	...
8	0.51	0.39	...

[a] Taken from K. Hellmann, P. G. Marshall, and S. Stayt, *Brit. J. Pharmacol.*, in press. T/C = mean weight of treated tumors/mean weight of untreated tumors. For significance $T/C \leq 0.53$; $(T/C)_1(T/C)_2 \leq 0.19$; $(T/C)_1(T/C)_2(T/C)_3 \leq 0.07$, where $(T/C)_1$, $(T/C)_2$, $(T/C)_3$ are the T/C values of three successive tests.

The number of compounds tested was insufficient to permit extensive conclusions to be drawn concerning structure–activity relationships. However, it appears that 2-halogenoethylamines (**7**–**10**) containing the benzo[*b*]thiophene nucleus are quite strong serotonin antagonists and also show some activity as monoamine oxidase inhibitors. The corresponding alcohols (**3**–**6**) are much less toxic but are also less active both as serotonin antagonists and as monoamine oxidase

(18) A. W. Lessin, *Biochem. Pharmacol.*, **2**, 290 (1959).
(19) H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop, and S. Udenfriend, *J. Biol. Chem.*, **235**, 1160 (1960).
(20) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).
(21) L. C. Hendershot and J. Forsaith, *J. Pharm. Exptl. Therap.*, **125**, 237 (1959).
(22) *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

inhibitors. The ketoamines (**11–16**) show some serotonin antagonism and are mild analgesics. Both these effects are more pronounced with the corresponding amino alcohols (**17–22**).

The observation of significant antitumor activity in these halogenoethylamines is of considerable interest as it is usually assumed[23] that "one-armed" mustards possess little antitumor activity. However, the low activity of the aminoethanols (**3**, **5**, and **6**) show that the β-halogenoethylamine moiety is essential to this antitumor activity. Variation of the substituent in the 5 position of the benzo[*b*]thiophene nucleus also produces marked changes in antitumor activity although much more evidence will be required before any rationalization can be attempted.

(23) (a) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962, p 113; (b) D. J. Triggle, *J. Theoret. Biol.*, **7**, 241 (1964).

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Structure–Activity Relationship in a Series of Adrenergic β-Blocking Agents Related to 1-(4-Nitrophenyl)-1-hydroxy-2-isopropylaminoethane (INPEA)[1]

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Several new structural analogs of the adrenergic β-blocking agent, *dl*-1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane (INPEA) were synthesized. The adrenergic β-blocking activity of these compounds was investigated in the isolated rabbit heart preparation. Substitution with a single nitro group in the *para* position of the phenyl ring yields the most active compound in this series, and the activity is decreased by moving the nitro group to *meta* or *ortho* positions. The adrenergic β-blocking activity is also decreased by substitution with two nitro groups in 2,4 and 3,5 positions in the phenyl ring and also by substitution with *p*-amino or *p*-methylsulfonyl groups in these compounds.

It is generally accepted that optimum adrenergic activity is present in the catecholamines with the basic structure of phenethylamine. A substitution with methyl, propyl, or other alkyl radicals on the primary amino nitrogen results in a decrease in the responses mediated through the adrenergic α receptors[2] without any change in the responses due to β-receptor activation. Thus, norepinephrine is the prototype of α-receptor stimulants, while isoproterenol, with N-isopropyl substitution, is the most powerful β-receptor stimulant agent in this series. The presence of a hydroxyl group in the phenolic ring is also critical for activity on the adrenergic receptors,[2a] and the substitution with two phenolic hydroxyls, especially in the catechol structure, yields compounds with optimal sympathomimetic activity.[2d,e] In the case of a single phenolic hydroxyl group, it has been demonstrated that the activity is increased as the hydroxyl group is moved from the *ortho* to the *meta* to the *para* position.

Recently, Powell and Slater[3] reported that compounds which selectively blocked the adrenergic β receptors were obtained when the phenolic OH groups were replaced by two chlorine atoms in the catecholamine nucleus. It was also demonstrated that optimal β-blocking activity was present if chlorine substitution was in the 3,4 positions in the phenyl ring and the ethanolamine side chain had the isopropyl radical (dichloroisoproterenol). The strong adrenergic β-blocking activity of pronethalol,[4] 1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane (INPEA),[5] 4-(2-isopropylamino-1-hydroxyethyl)methanesulfonanilide,[6] and other derivatives[7] also supports the view that substitution in the 3,4 or 4 positions in the phenyl ring is important for adrenergic β-blocking activity. However, compounds with substitutions in other positions of the phenyl ring of 2,3-(propranolol),[8] 2,5-(N-iso-

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(2) (a) H. D. Dakin, *Proc. Royal Soc.* (London), **76B**, 498 (1905); (b) G. Barger and H. H. Dale, *J. Physiol.* (London), **41**, 19 (1910); (c) A. M. Lands, *Pharmacol. Rev.*, **1**, 279 (1949); (d) R. A. McLean in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 592; (e) E. J. Ariëns, "Molecular Pharmacology," Vol. 1, Academic Press Inc., New York, N. Y., 1964; (f) R. P. Ahlquist, *Am. J. Physiol.*, **153**, 586 (1948); (g) P. Pratesi, E. Grana, L. Lilla, A. LaManna, and L. Villa, *Farmaco* (Pavia), *Ed. Sci.*, **18**, 920, 932 (1963); (h) E. Grana, L. Lilla, P. Pratesi, A. LaManna, and L. Villa, *ibid.*, **21**, 4 (1965).

(3) C. E. Powell and I. H. Slater, *J. Pharmacol. Expil. Therap.*, **122**, 480 (1958).

(4) J. W. Black and J. S. Stephenson, *Lancet*, II, 311 (1962).

(5) P. Somani and B. K. B. Lum, *J. Pharmacol. Exptl. Therap.*, **147**, 194 (1965).

(6) (a) A. A. Larsen and P. M. Lish, *Nature*, **203**, 1283 (1964); (b) P. M. Lish, J. H. Weikel, and K. W. Dungan, *J. Pharmacol. Exptl. Therap.*, **149**, 161 (1965); (c) P. Somani, J. G. Fleming, G. K. Chan, and B. K. B. Lum, *ibid.*, **151**, 32 (1966).

(7) (a) H. Corrodi, H. Persson, A. Carlsson, and J. Roberts, *J. Med. Chem.*, **6**, 751 (1963); (b) J. H. Biel and B. K. B. Lum, *Arzneimittel-Forsch.*, in press.

(8) J. W. Black, A. F. Crowther, R. G. Shanks, L. H. Smith, and A. C. Dornhorst, *Lancet*, I, 1080 (1964).