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PHARMACOLOGICALLY ACTIVE BENZO[b]THIOPHENE DERIVATIVES

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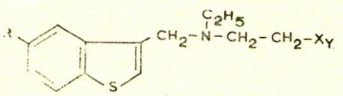
5-Substituted-*N*-ethyl-*N*-2-(hydroxyethyl)-3-aminomethylbenzo[*b*]thiophen and its chloro derivative were isolated as methane sulphonates and citrates. 5-Substituted-*N*-ethyl-3-aminomethylbenzo[*b*]thiophen reacted with 1-bromo-2-fluoroethane in ethylmethyl ketone to give 5-substituted-*N*-ethyl-*N*-2-(fluoroethyl)-3-aminomethylbenzo[*b*] thiophen. Pharmacological testing of 5-bromo-*N*-ethyl-*N*-2-(fluoroethyl)-3-aminomethylbenzo[*b*]thiophen showed that there is an activity in the compound both at cytoplasmic as well as nuclear level.

Alkylating agents of various types probably constitute the largest single group of antitumour agents, and of these nitrogen mustards have re-received most attention. This pharmacological activity has been shown in a number of substituted benzo[*b*]thiophenes particularly in case of 5-bromo-*N*-ethyl-*N*-(2-chloroethyl)-3- aminomethyl-benzo[*b*]thiophene hydrochloride.[1] However, very low solubility of the compound necessiated the preparation of some soluble salts. It was also decided to substitute chlorine by flourine in the side-chain, which could be confidently predicted to be immobile.

The compounds of the general structure which were prepared were limited to the derivatives of 5-*H* and 5-bromobenzo[*b*]thiophene. Methane-sulphonic acid and citric acid were used for the salt formation of I.



I

X=OH, Cl
R=Br, H

The products were isolated as colourless plates in 80% yield.

Synthesis of the fluoro compounds proved more difficult. Condensation of 5-bromo-3-(bromomethyl) benzo[*b*]thiophene with an excess of anhydrous ethylamine gave *N*-ethyl-3-(aminomethyl) benzo[*b*]thiophenes in 70–80% yield. These secondary amines were then converted into the required fluorine containing *t*-amines by condensation with 0.5 moles of 1-bromo-2-fluoroethane in boiling ethyl methyl ketone. Treatment of the *t*-amine with ethereal solution of hydrogen chloride gave the crystalline salts in 40% yields.

Experimental

5-*Bromo*-N-*ethyl*-N-(2-*chloroethyl*) -3- *aminomethyl-benzo* [*b*] *thiophene Methanesulfonate.*—5-Bromo-*N*-ethyl-*N*-(2-hydroxyethyl)-3-aminomethylbenzo[*b*]-thiophene and its corresponding 2-chloroethyl derivative were prepared as described in the litrature.[2]

To a solution of the free base (5 g) in dry ether (100 ml) was added an ethereal solution of methanesulfonic acid (1.5 g). An oil separated out, which solidified on standing. The product was filtered off, washed with water and crystallised from dry ethanol to give the corresponding salt as colourless plates. Similarly, citrate and methane-sulfonate salts of 5-bromo-*N*-ethyl-*N* (2-hydroxy ethyl)-3 aminomethylbenzo[*b*]thiophene were prepared. Details are given in Table 1.

5-*Bromo*-N-*ethyl* -3- *aminomethylbenzo* [b] *thio-phene Hydrochloride.*—5-Bromo-3-(bromomethyl) benzo [*b*]thiophene (27.4 g) and an excess of ethyl-amine (21.9 g) were dissolved in dry benzene (200 ml), and the mixture was boiled for 30 min. Ether (300 ml) was added to the cold reaction product and the precipitated solid was filtered off. The filtrate was washed several times with water and dried ($MgSO_4$). The product 5-bromo-*N*-ethyl-3-aminomethylbenzo[*b*]thiophene was ob-tained as an oil after distillation of the solvent under reduced pressure. The hydrochloride was prepared in the usual way and was crystallised from dry ethanol as colourless needles, m.p. 203–204°C, yield 70%. Found: C, 43.3; H, 4.5; N, 4.2. $C_{11}H_{13}NSBrCl$; requires: C, 43.1; H, 4.2; N, 4.5). *N*-Ethyl-3-aminomethylbenzo[*b*] thiophene was prepared in a similar way. It melted at 185–86°, yield 70%. (Found: C, 57.9; H, 5.9; N, 5.9. $C_{11}H_{14}SNCl$; requires: C, 58.0; H, 6.1; N, 6..1)

5-*Bromo*-N-*ethyl*-N-(2-*fluoroethyl*) -3- *aminomethy-lbenzo*[b]*thiophene.*—1-Bromo-2-fluoroethane (12.7g 0.1 mole) and 5-bromo-*N*-ethyl-3-aminome-thylbenzo[*b*]thiophene (54 g, 0.20 mole) were heated under reflux in ethyl methyl ketone (100 ml) for 16 hr. The mixture was cooled, filtered and to the filtrate was added dry ether (100 ml). It was again filtered and the filtrate was dried ($MgSO_4$). The solvents were removed, the residue was dissolved in 6N HCl and the insoluble material extracted with methylene chloride. The residue was made alkaline with sodium hydroxide,

TABLE 1

Y	X	M.p	Yield	Found	Formula	Required
CH_3SO_3	Cl	111–12°	70%	C, 38.9; H, 4.3 N, 3.24; S, 15.3	$C_{14}H_{19}NO_3S_2BrCl$	C, 39.2; H, 4.4 N, 3.27; S, 15.0
CH_3SO_4	OH	119–20°	70%	C, 40.6; H, 4.9 N, 3.7	$C_{14}H_{20}NO_4S_2Br$	C, 40.9; H, 4.9 N, 3.4
$C_6H_8O_5$	OH	124–25°	80%	C, 44.8; H, 5.0 N, 3.0	$C_{19}H_{25}NO_6SBr$	C, 45.0; H, 4.7 N, 2.7

TABLE 2

Y	X	R	a	b	c	d	e	Anti-writhing 256 mg/kg	Anti-5-HT rat fundus	Serial No
HCl	F	Br	500	1000	1000	1000	500	—	80% at 4×10^{-6}	I
HCl	F	H	Inactive		—	—	—	—	—	II

a = *Staphylococcus aureus*; b = *Escherichia coli*; c = *Proteus vulgaris*; d = *Gandida alficans*; e = *Aspergillus niger*.

the oil formed extracted with ether and dried ($MgSO_4$.) The hydrochloride was precipitated directly by the addition of an ethereal HCl and the hydrochloride was crystallised from dry ethanol–ether. The product 5-bromo-*N*-ethyl-*N*-(2-fluoroethyl) -3- aminomethylbenzo[*b*]thiophene hydorchloride crystallised as colourless plates, m.p. 169–70°C yield 40%. (Found: C, 44.5; H, 4.9; N, 4.1 S, 9.1; F, 5.2. $C_{11}H_{16}$ NSBrFcl requires: C,44.25; H, 5.0; N, 4.1; S, 9.1; F, 5.0).

N-Ethyl-*N*-(2-fluoroethyl)-3-aminomethylbenzo [*b*] thiophene hydrochloride was prepared in a (smilar way. It melted at 102–103°C, yield 45%. Found: C, 57.0; H, 6.4; N, 5.3; S, 12.0; F, 6.9 $C_{13}H_{17}$NSFcl requires: C, 57.0; H, 6.2; N, 5.1; S, 11.7; F, 7.0).

Pharmacology.—The antimicrobial and antifungal activities of the fluoro compounds are given in Table 2. Compound I is active on all the bacteria and fungi tested but with high doses i.e. 500 μg/ml in case of *Staphlylococcus aureus* and *Aspergillus niger* and 1000 μg/ml in case of *Escherichia coli*, *Proteus vulgaris* and *Bandida albicans*. This compound also showed 80% activity of anti-5-hydroxytryptamine at 4×10^{-6} and no activity at 256 mg/kg (antiwrithing). Because the killing of the bacteria with high doses and fungi with low doses with the relaxation of smooth muscles seems to indicate that there is an activity in the compound both at cytoplasmic as well as nuclear level.

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References

1. K. Hellman, P.G. Marshall and S. Stayt, Biochem. Pharmacol., **16,** 681 (1967).
2. N.B. Chapman, K. Clarke and B. Iddon, J. Med. Chem., **9,** 819 (1966).