in rats,[9] analgetic activity in mice and rats,[10-12] antipyretic activity in mice,[13] action on rabbits' cardivascular system, action on this isolated rabbit heart,[14] local anesthetic activity,[15] antibacterial and antifungal actions,[16] and other activities. None of them showed anything worthy of note, with the exception of 4 compounds (**2**, **7**, **12**, **17**) which demonstrated inhibition of gastric secretion in the rat at doses of 50 mg/kg (MED_{50}), administered ip. Compd **7** was found to be more potent than **2**, **12**, and **17**.

Experimental Section[17]

2-(Adamantyl-1-carbonyl or -acetyl)aminobenzothiazoles.—To a soln (or suspension) of 2-aminobenzothiazole (or its derivative) (0.05 mole) in 200 ml of dry C_6H_6 was added dropwise with stirring, a soln of adamantyl-1-carbonyl (or -acetyl) chloride (0.055 mole) in 30 ml of dry C_6H_6. The mixt, after completion of the addn (15 min), was refluxed for 2 hr. The solvent was then evapd, the residue was treated with 100 ml of a satd $NaHCO_3$ soln, and the amide was extd with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), and distd. See Table I.

2-(Adamantyl-1-alkyl)aminobenzothiazoles.—A soln of the amide I (0.01 mole) in 120 ml of anhyd THF was added dropwise to a stirred suspension of LAH (0.02 mole) in Et_2O (50 ml) and the mixt was refluxed with vigorous stirring for 5–6 hr. After cooling, hydrolysis was accomplished with H_2O and 15% sol of NaOH. The white ppt formed was filtered and thoroughly washed (Et_2O). The org phase was dried (Na_2SO_4) and distd. All the amines thus obtd were solid and were characterized as their hydrochlorides (see Table II).

Nmr and Ir Spectra.[18-20]—(a) 2-(Adamantyl-1-carbonyl)-aminobenzothiazole (**1**) showed nmr ($CDCl_3$) δ 2.01 (β- and γ-H), 1.71 (δ-H) of 1-substituted adamantane.[21] Other peaks are found at δ 7.46–8.14 (m, arom protons), 9.67 (broad, NH); ir (KBr) cm^{-1} 3225 (NH), 1680 (C=O), 1590 (C=C), 1530 (C=N).

(b) 2-(Adamantyl-1-acetyl)aminobenzothiazole (**6**) showed nmr ($CDCl_3$) δ 1.32 (β-H), 1.78 (γ-H), 1.53 (δ-H).[21] Other peaks at δ 2.17 (s, $COCH_2$), 7.36–8.25 (m, arom protons), 11.90 (broad, NH); ir (KBr) cm^{-1} 3195 (NH), 1690 (C=O), 1595 (C=C), 1540 (C=N).

(c) 2-(Adamantyl-1-methyl)aminobenzothiazole (base)[22] showed nmr ($CDCl_3$) δ 1.59 (β-H), 1.95 (γ-H), 1.67 (δ-H).[21] Other peaks at δ 3.13 (s, NCH_2), 6.42 (broad, NH), 7.05–7.83 (m, arom protons); ir (KBr) cm^{-1} 3224 (NH), 1614 (broad, C=C, C=N).

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(22) The free amine was liberated from its HCl salt.

Antimicrobials. 1. Benzothiazolylbenzylamines

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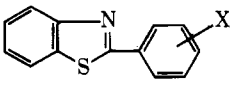
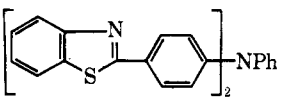
In previous publications from this laboratory, the antimicrobial properties of 2-arylbenzothiazole basic ethers[1] and of 2-arylbenzothiazolines[2] have been described. As an extension to this work, we have investigated the preparation and biological activity of a series of benzothiazolylbenzylamines. Some of the amines were also converted into dichloroacetyl amides to obtain compounds resembling the amebicide chlorbetamide.

Chemistry.—Bromination of 2-*p*-tolylbenzothiazole with NBS gave the bromomethyl compd Ia which was treated with a series of primary and secondary aliphatic amines to afford the benzylamines Ib. The primary amine (Ib, $R_1 = R_2 = H$) was obtained from Ia by Gabriel synthesis, and the meta analog Ie was prepared similarly from Id. The ortho analog If was available in moderate yield by hydrogenation of 2-*o*-cyanophenylbenzothiazole over Raney Ni. Reaction of Ia with aniline gave the bis-substituted compd II, and with substituted anilines complex reaction mixtures were obtained. Compds Ic were therefore synthesized by

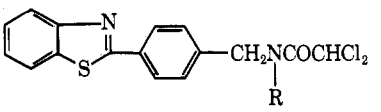


I

a, X = *p*-CH_2Br e, X = *m*-CH_2NH_2
b, X = *p*-$CH_2NR_1R_2$ f, X = *o*-CH_2NH_2
c, X = *p*-CH_2NHAr g, X = *p*-$CH_2NHCH_2CH_2NEt_2$
d, X = *m*-CH_2Br h, X = *p*-CHO



II



III

reaction of Ia with the tosyl derivative of the appropriate aniline followed by acid hydrolysis. Sommelet reaction of Ia afforded in high yield the aldehyde Ih, and this, by condensation with $Et_2N(CH_2)_2NH_2$ and subsequent LAH reduction gave the amine Ig. The dichloroacetamides III were obtained from the appropriate amine by dichloroacetylation using standard procedures.

Biological Activity.—The compounds described were all screened *in vitro* against a range of Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, *Entamoeba histolytica*, and a few representative dermatophytes. The highest antituberculous activity

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found was for the simple benzothiazolylbenzylamine **1**, but this compd was not active *in vivo*. The dichloroacetamides (**20–24, 33,** and **34**) showed no activity against any of the bacteria or fungi. They were, however, consistently active *in vitro* against *E. histolytica*, with the notable exceptions of **20** and **23**, but were not sufficiently active in the Jones' weanling rat test[3] to be of further interest. Most of the benzothiazolylbenzylamines showed some activity *in vitro* against *Streptococcus pyogenes*, the level of activity being, in most cases, considerably higher than was shown by the simple benzylamines (see Table I). The greatest enhancement of activity over that of the parent compd (**1**) was achieved by the use of an ethanolamine side chain (**10**).

TABLE I

BIOLOGICAL ACTIVITY[a] OF COMPOUNDS NOT GIVEN IN TABLES II AND III

Compd	*S. pyogenes*	*E. histolytica*	*Mycobacterium tuberculosis*
19	>200	>200	>200
27	3.1	25	25
28	100	25	100
29	>200	>200	>200
31	200	>200	>200
32	6.3[b]	100[b]	50[b]
33	>200	1.6	>200
34	>200	3.1	>200
35	>200	>200	>200
Piperonylamine·HBr	200		
p-$CH_3C_6H_4CH_2NH_2$·HCl	>200		
2,4-$Cl_2C_6H_3CH_2NH_2$·HCl	>200		
p-$HOC_6H_4CH_2NH_2$·HCl	>200		
Dequalinium chloride Chlorhexidine acetate	0.3		

[a] MIC values are in μg/ml and were detd by serial diln in nutrient broth (*S. pyogenes*), LMS medium (*E. histolytica*), and Proskauer and Beck medium (*M. tuberculosis*). Compds were tested as salts where these are described. [b] Compd tested as monocitrate.

Experimental Section[4]

General Methods for Preparing Benzothiazolylbenzylamines. A.—A soln of Ia (5.0 g) in C_6H_6 (50 ml) and an excess (3- to 5-fold) of the appropriate amine were stirred at room temp or above for a suitable time, the mixt washed with dil NaOH and H_2O, dried, and evapd, and the residue was crystd (see Table II).

B.—As above except the C_6H_6 was omitted and larger amts of amine were used as solvent.

C.—A mixt of the appropriate phthalimide (1 part) and 98% $NH_2NH_2·H_2O$ (2 parts) in EtOH (30 parts) was refluxed 1 hr, the solvent was evapd, and the residue was warmed with 2 *N* NaOH (20 parts). Extn with $CHCl_3$ gave the amines which were characterized as such or as salts (see Table II).

Dichloroacetamides.—$Cl_2CHCOCl$ (1.25 equiv) was added to a soln of the amine (1 equiv) in C_6H_6 (100 ml/g) contg K_2CO_3 (excess), the mixt was refluxed 1 hr and filtered, and the filtrate was concd and cooled to give the amides (see Table III).

2-*p*-Tolylbenzothiazole.—*p*-Toluic acid (256 g) was added portionwise to polyphosphoric acid (500 ml) at 100° and the mixt stirred until a smooth paste was obtd. Redistd *o*-aminothiophenol (234 g) was added in 20-ml portions (exothermic); by the time the addn was complete, the temp of the reaction mixt had reached 185°. After stirring at this temp for a further 15 min, the mixt was poured into 5 l. of vigorously stirred H_2O. The product was collected, washed with aq Na_2CO_3 and then H_2O, and air-dried to give a solid (409 g), mp 83.5–85°, which was sufficiently pure for further use. The pure compd had mp 87–88° (lit.[5] mp 85°).

4-(2-Benzothiazolyl)benzyl Bromide (Ia).—A mixt of 2-*p*-tolylbenzothiazole (240 g), NBS (189 g), and Bz_2O_2 (0.5 g) in anhyd CCl_4 (3 l.) was refluxed, while being irradiated with a W lamp, until all the NBS had been consumed. The hot suspension was filtered, and the filtrate was cooled to give a solid (153 g), mp 126–128°. Concn of the filtrate gave a further crop (161 g), mp 124–127°. Crystn (C_6H_6–hexane) gave needles, mp 130–131°. *Anal.* ($C_{14}H_{10}BrNS$) C, H, Br, N.

3-(2-Benzothiazolyl)benzyl bromide (Id) was prepd by a similar procedure from 2-*m*-tolylbenzothiazole. It had mp 100–102° (C_6H_6–hexane). *Anal.* ($C_{14}H_{10}BrNS$) H, N; C, calcd, 55.3; found, 55.8.

4-(2-Benzothiazolyl)benzylphthalimide (25).—Potassium phthalimide (9.3 g) was added to a stirred soln of Ia (15 g) in DMF (120 ml) at 25°. The reaction mixt, which warmed spontaneously, was stirred for 1 hr before adding $CHCl_3$ (200 ml) and H_2O (600 ml). The aq phase was extd with $CHCl_3$ (2 × 50 ml), and the combined $CHCl_3$ layers were washed, dried, concd to turbidity, and Et_2O (400 ml) was added. The resulting solid (16.6 g), mp 243°, was crystd ($CHCl_3$–EtOH) to give **25**, mp 247.5–248.5°. *Anal.* ($C_{22}H_{14}N_2O_2S$) C, H, N.

3-(2-Benzothiazolyl)benzylphthalimide (26) prepd in a similar manner from Id had mp *ca.* 160° and 190.5–191.5° ($CHCl_3$–MeOH). *Anal.* ($C_{22}H_{14}N_2O_2S$) H, N, C, calcd, 71.3; found, 70.7.

2-(2-Cyanophenyl)benzothiazole.—The lactamidine·HCl (2.6 g) obtd from the condn of *o*-cyanobenzaldehyde and *o*-aminobenzenethiol·HCl[6] was basified with NH_4OH, the product was extd into $CHCl_3$, and the dried soln was stirred with MnO_2 for 0.5 hr to give the nitrile, mp 94–95° (aq EtOH). *Anal.* ($C_{14}H_8N_2S$) C, H, N.

***N*-Acetyl-2-(2-benzothiazolyl)benzylamine.**—The above compd (1.0 g), NaOAc (1.0 g), Ac_2O (40 ml), and Raney Ni (W7, 0.5 g) were shaken under H_2 for 2 days at 3.16 kg/cm² and 50° to afford the amide, mp 180–182° (MeOH). *Anal.* ($C_{16}H_{14}N_2OS$) C, H, N.

2-(2-Benzothiazolyl)benzylamine·HCl (27).—The above amide (0.75 g) was hydrolyzed with boiling H_2SO_4 (100 ml; 25%) for 3 hr to give an oily base (0.65 g). The amine was charactd as a hydrochloride, mp 278–280° (2 *N* HCl). *Anal.* ($C_{14}H_{13}ClN_2S$) C, H, N, and as a picrate, mp 239–241° dec (EtOH). *Anal.* ($C_{20}H_{15}N_5O_7S$) C, H, N.

Bis[4-(2-benzothiazolyl)]benzylamine (28).—Compds **1** (2.5 g) and Ia (3.04 g) in C_6H_6 (50 ml) contg Et_3N (2 ml) were refluxed 6 hr, the cooled mixt was washed with 2 *N* NaOH and evapd to yield a solid (3.1 g), mp 129–160°. This was washed with warm EtOH and the residue (1.01 g), mp 159–163°, crystd from C_6H_6 to give **28**, mp 183–185°. *Anal.* ($C_{28}H_{21}N_3S_2$) C, H, N.

4-(2-Benzothiazolyl)-*N*-(4-chlorophenyl)benzylamine (29).—Compd Ia (5 g), *N*-(4-toluenesulfonyl)-4-chloroaniline (4.64 g), and K_2CO_3 (2.28 g) in tetrachloroethane (60 ml) were refluxed 24 hr, the mixt was filtered, and the filtrate was evapd to dryness. The residue was heated with concd H_2SO_4 (20 ml) for 30 min at 100°, the cooled soln was poured into ice–H_2O (400 ml) contg aq KOH (90 ml of 40%), and the solid (1.85 g), mp 121–126°, was collected. Chromatog over Al_2O_3 (60 g) and elution with C_6H_6–hexane (9:1) gave **29**, mp 149–151° (C_6H_6–hexane). *Anal.* ($C_{20}H_{15}ClN_2S$) C, H, N.

4-(2-Benzothiazolyl)-*N*-(4-methoxyphenyl)benzylamine (30).—By a similar procedure, using *N*-(4-toluenesulfonyl)-4-methoxyaniline, **30**, mp 167–168° (C_6H_6–petr ether), was obtd. *Anal.* ($C_{21}H_{18}N_2OS$) C, H, N.

Bis[4-(2-benzothiazolyl)]benzylaniline (31).—Compd Ia (3.04 g) and $PhNH_2$ (0.93 g) in EtOH (20 ml) contg NaOAc (0.82 g) and H_2O (8 ml) were refluxed for 4.5 hr to give **31**, mp 248–249° (C_6H_6). *Anal.* ($C_{34}H_{25}N_3S_2$) C, H, N.

4-(2-Benzothiazolyl)benzaldehyde (Ih).—Compd Ia (79.15 g), dissolved in hot $CHCl_3$ (150 ml), was added to a soln of hexamine (36.4 g) in hot $CHCl_3$ (500 ml), the mixt was refluxed 5 min, cooled to 0°, and the solid was collected and washed with $CHCl_3$ and Et_2O. The dry hexamine salt (110.5 g), mp 202–208° dec, was suspended in AcOH (600 ml), and the mixt was heated to reflux

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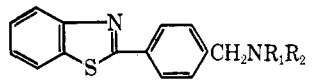
(4) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were determined with a Büchi apparatus using open capillary tubes. Ir spectra were recorded for Nujol mulls on a Perkin-Elmer 237 spectrophotometer.

(5) M. T. Bogert and M. Meyer, *J. Amer. Chem. Soc.*, **44**, 1568 (1922).

(6) G. L. Oliver, J. R. Dann, and J. W. Gates, *ibid.*, **80**, 702 (1958).

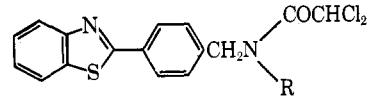
TABLE II



No.	R_1	R_2	Method	Yield, %	Mp, °C	Cryst	Formula[f]	Salts	MIC[b] *S. pyogenes*	MIC[b] *E. histolytica*	MIC[b] *M. tuberculosis* ($H_{37}RV$)
1	H	H	C	81	113.5–114.5	*a*		HCl, mp 289–290° dec (EtOH); *Anal.* ($C_{14}H_{13}ClN_2S$) C, H, Cl; N[a]	25	25	2.2
2[c]	H	H	C	87		*c*		Citrate, mp 200° dec (Me cellosolve Et_2O); *Anal.* ($C_{20}H_{20}N_2O_7S$) C, H, N	3.1	100	50
3	H	Me	A, 25°, 16 hr[d]	83	75.5–76.5	Hexane	$C_{15}H_{14}N_2S$	HBr, mp 276–277° (EtOH); *Anal.* ($C_{15}H_{15}BrN_2S$) H, Br, N; C[e]	12.5	100	50
4	H	Et	A, 25°, 16 hr	83	53–55	Hexane	$C_{16}H_{16}N_2S$	HBr, mp 281.5–282.5° (DMF–EtOH); *Anal.* ($C_{16}H_{17}BrN_2S$) C, H, Br, N	50	100	25
5	H	*n*-Pr	A, 50°, 1 hr	73	88–89	Hexane	$C_{17}H_{18}N_2S$		6.3	25	50
6	H	*i*-Pr	A, 25°, 16 hr	67	54.5–55.5	Hexane	$C_{17}H_{18}N_2S$	HCl, mp 275–276° (EtOH); *Anal.* ($C_{17}H_{19}ClN_2S$) C, H, Cl, N	6.3	25	12.5
7	H	*n*-Bu	A, reflux, 3 hr	67	72–73	Hexane	$C_{18}H_{20}N_2S$		3.1	25	100
8	H	*sec*-Bu	A, 25°, 24 hr	78	Oil			HCl, mp 207–208° (EtOH); *Anal.* ($C_{18}H_{21}ClN_2S$) C, H, N	3.1	25	25
9	H	*tert*-Bu	A, 25°, 24 hr	72	62.5–63.5	Hexane	$C_{18}H_{20}N_2S$		6.3	25	12.5
10	H	CH_2CH_2OH	A, 25°, 16 hr	90	112.5–113.5	C_6H_6	$C_{16}H_{16}N_2OS$	HCl, mp 256.5–258° (EtOH); *Anal.* ($C_{16}H_{17}ClN_2OS$) C, H, Cl, N	1.6	100	200
11	H	C_6H_{11}	A, 25°, 20 hr	72	90–91	Hexane	$C_{20}H_{22}N_2S$		6.3	50	50
12	Me	Me	A, 25°, 16 hr	75	87.5–88	Hexane	$C_{16}H_{16}N_2S$	HCl, mp 284–285° (EtOH); *Anal.* ($C_{16}H_{17}ClN_2S$) C, H, Cl, N	12.5	50	12.5
13	Et	Et	A, 25°, 16 hr	63	53–54	Hexane	$C_{18}H_{20}N_2S$	HCl, mp 228–231° (EtOH); *Anal.* ($C_{18}H_{21}ClN_2S$) C, H, Cl, N	12.5	200	100
14	*i*-Pr	*i*-Pr	A, reflux, 96 hr	98	84.5–85	EtOH	$C_{20}H_{24}N_2S$		6.3	25	12.5
15	$(CH_2)_2OH$	$(CH_2)_2OH$	B, 95°, 0.5 hr	79	111–112	MeOH	$C_{18}H_{20}N_2O_2S$	HCl, mp 217–219° (aq MeOH); *Anal.* ($C_{18}H_{21}ClN_2O_2S$) C, H, N	12.5		
16	$-(CH_2)_5-$		B, 140°, 1 hr	65	103–104	Hexane	$C_{19}H_{20}N_2S$		6.3	50	50
17	$-(CH_2)_2O(CH_2)_2-$		B, 160°, 5 hr	41	107–108	Hexane	$C_{18}H_{18}N_2OS$		12.5	>200	>200
18	$-(CH_2)_2N(CH_3)(CH_2)_2-$		B, 160°, 1 hr	64	96.5–98	Aq EtOH	$C_{19}H_{21}N_3S$		12.5	25	12.5

[a] Compd carbonates rapidly; characterized as HCl salt; *N*-acetyl deriv, mp 200.5–202.5° (MeOH). *Anal.* ($C_{16}H_{14}N_2OS$) C, H, N. [b] See footnote *a*, Table I. [c] Benzene ring meta substituted; compd difficult to crystallize; characterized as citrate. [d] Using aq $MeNH_2$ for prepn of **3** gave mostly *N*,*N*-bis[4-(2-benzothiazolyl)]benzylmethylamine (**19**), mp 145–145.5° (C_6H_6). Anal. ($C_{29}H_{23}N_3S_2$) C, H, N. [e] C: calcd, 53.7; found, 54.5. [f] All compds except **1**, **2**, **8** were analyzed for C, H, N.

TABLE III



No.	R	Yield, %	Mp, °C	Cryst	Formula[d]	MIC[b]
20	H	76	199–199.5	EtOH	$C_{16}H_{12}Cl_2N_2OS$	>400
21	Me	90	105–106.5	Aq EtOH	$C_{17}H_{14}Cl_2N_2OS$	2.5
22	Et	99	120–121	EtOH	$C_{18}H_{16}Cl_2N_2OS$	2.5
23	*i*-Pr	76	115.5–117	EtOH	$C_{19}H_{18}Cl_2N_2OS$	>400
24	CH_2CH_2OEt	62[a]	137–138	EtOH	$C_{20}H_{20}Cl_2N_2O_2S$[c]	0.5

[a] After chromatog on SiO_2 using C_6H_6–EtOAc; [b] MIC in μg/ml against *E. histolytica*. [c] Cl: calcd, 16.75; found, 17.45. [d] All compds were analyzed for C, H, Cl, N.

during 1 hr. Refluxing was contd for 1.5 hr, concd HCl (75 ml) was added, and the soln was refluxed for a further 0.25 hr before pouring onto ice. Extn with $CHCl_3$ gave a solid (53.1 g), mp 128–132°. Crystn (C_6H_6–EtOH) and then prep tlc gave Ih, mp 136.5–137°. *Anal.* ($C_{14}H_9NOS$) C, H, N. The semicarbazone had mp 282–284° (aq DMF). *Anal.* ($C_{15}H_{12}N_4OS$) C, H, N. The thiosemicarbazone had mp 248–250° (aq DMF). *Anal.* ($C_{15}H_{12}N_4S_2$) C, H, N.

***N*-[4-(2-Benzothiazolyl)]benzyl-*N'*,*N'*-diethylethylenediamine (32).**—A mixt of Ih (3.4 g) and $Et_2N(CH_2)_2NH_2$ (1.8 g) in C_6H_6 (200 ml) was refluxed 5 hr, and the solvent was evapd to give a yellow oil which, on crystn from hexane, gave a solid (3.92 g), mp 65–65.5°. This solid (1.0 g) in Et_2O (10 ml) was added to LAH (0.2 g) in Et_2O (20 ml), the mixt was refluxed 0.5 hr, and the resulting oily amine was characterized as its dipicrate, mp 158–162° (DMF–EtOH). *Anal.* ($C_{32}H_{31}N_9O_{14}S$) C, N; H, calcd, 4.4; found, 3.9.

***N*-[4-(2-Benzothiazolyl)]benzyl-*N*-(2-hydroxyethyl)dichloroacetamide (33).**—Compd **1** (2.0 g) and Cl_2CHCO_2Me (4.0 ml) were heated 4 hr at 95°, the soln was kept overnight at 25°, dild with C_6H_6, and chromatogd on SiO_2 (100 g). Elution with C_6H_6–EtOAc (3:1) gave **33** (1.86 g), mp 121–122° (C_6H_6). *Anal.* ($C_{18}H_{16}Cl_2N_2O_2S \cdot 0.5C_6H_6$) C, H, Cl, N.

***N*-[4-(2-Benzothiazolyl)]benzyl-*N*-dichloroacetyl-2'-(dichloroacetoxy)ethylamine (34).**—$Cl_2CHCOCl$ (1.0 ml) was added to **10** (1.0 g) in DMF (15 ml), the mixt was stirred 15 min and poured into H_2O (100 ml) to give **34** (1.0 g), mp 122–124° (C_6H_6–hexane). *Anal.* ($C_{20}H_{16}Cl_4N_2O_3S$) C, H, Cl, N.

***N*-Ethyl-*N*-trifluoroacetyl-4-(2-benzothiazolyl)benzylamine (35).**—$(CF_3CO)_2O$ (6 ml) in Et_2O (10 ml) was added dropwise to an ice-cold stirred soln of **4** (9.72 g) in Et_2O (250 ml). After stirring at 25° for 1 hr, the reaction mixt was filtered, and the filtrate was evapd to dryness. The residue was crystd from EtOH to give the product (6.89 g), mp 98.5–99.5°. *Anal.* ($C_{18}H_{15}F_3N_2OS$) C, H, F, N.

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