EXPERIMENTAL

Method A—The procedure described by Clark *et al.* (2) was found to be adequate in most instances.

Method B—Method A was modified by reducing the reaction time to only 5 min.

Method C—Method A was modified. A methanolic solution of the amine was added dropwise over a period of 1 hr. to a stirred, refluxing solution of the other reagents. An additional hour of reflux was permitted.

Method D—The 1-substituted 1,3-diiminoisoindoline was heated with an eightfold mole excess of the corresponding amine until the evolution of ammonia had ceased. The excess of amine was removed *in vacuo*. The product was triturated with benzene–petroleum ether, collected, and recrystallized from benzene–petroleum ether.

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New Compounds: *N*-Substituted Benzothiazoline-2-thiones

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Abstract □ A series of *N*-substituted benzothiazoline-2-thiones has been synthesized for biological screening.

Keyphrases □ Mannich bases—synthesis □ Benzothiazoline-2-thiones, *N*-substituted—synthesis □ IR spectrophotometry—structure

Antibacterial (1–3) and antispasmodic (4) activity has been exhibited by benzothiazoline-2-thione and some of its derivatives. A survey of the literature revealed that 3-substituted benzothiazoline-2-thiones have not been evaluated for medicinal properties. This led the authors to synthesize a series of 3-substituted derivatives for biological screening.

EXPERIMENTAL[1]

Preparation of N-Mannich Bases (Table I)—Benzothiazoline-2-thione (0.5 mole) was suspended in 20 ml. of ethanol. To this suspension 7.5 ml. of 37% formalin was then added, followed by the appropriate secondary amine (0.05 mole). During the addition of the amine, the reaction mixture became exothermic. The reaction mixture was stirred at room temperature for 4 hr. with occasional warming on a water bath. The product obtained after cooling the reaction vessel was collected and recrystallized from a suitable solvent.

3-Hydroxymethyl-5-chloro-benzothiazoline-2-thione—To a hot solution of 5-chloro-benzothiazoline-2-thione (30 g.) in 150 ml. of ethanol was added 21 ml. of 37% formalin, The reaction mixture was refluxed for 3 hr. At the end of this period the ethanol was removed under vacuum and the desired product obtained as a solid was recrystallized from ethanol; m.p. 130–133°; yield 25 g. (72%).

Anal.—Calcd. for $C_8H_6ClNOS_2$: C, 41.48; H, 2.61; N, 6.05. Found: C, 41.20; H, 2.69; N, 5.95.

3-N-(4-Fluoroanilinomethyl)benzothiazoline-2-thione—37% formalin (7.5 ml.) was added to a mixture of benzothiazoline-2-thione (8.36 g.) and 4-fluoroaniline (5.55 g.) in 20 ml. of ethanol. The reaction mixture was stirred for 2 hr. and then kept at room temperature overnight. The product (8 g., 55%) was recrystallized from ethanol; m.p. 141–143°.

Anal.—Calcd. for $C_{14}H_{11}FN_2S_2$: C, 57.89; H, 3.82; N, 9.65. Found: C, 57.73; H, 3.98; N, 9.46.

3-(3,4,5-Trimethoxybenzoyloxymethyl)benzothiazoline-2-thione—Freshly prepared 3,4,5-trimethoxybenzoylchloride (6.9 g.) and 3-hydroxymethylbenzothiazoline-2-thione (5.9 g.) were refluxed in 50 ml. of dry benzene for 6 hr. At the end of this period, the benzene was removed under vacuum and the product triturated with 10% sodium bicarbonate solution. The ester (5 g., 42%) was recrystallized from benzene; m.p. 120–123°.

Anal.—Calcd. for $C_{18}H_{17}NO_5S_2$: C, 55.23; H, 4.38; N, 3.58. Found: C, 55.31; H, 4.50; N, 3.51.

3-Acetoxymethyl-5-chlorobenzothiazoline-2-thione—Acetic anhydride (12 ml.) and 5-chloro-3-hydroxy methylbenzothiazoline-2-thione (4.6 g.) were heated on a water bath for 6 hr. The reaction mixture was poured into 400 ml. of ice water with stirring and allowed to stand overnight. Recrystallization from ethanol yielded 4 g. (73%) of the pure product melting at 131–134°.

Anal.—Calcd. for $C_{10}H_8ClNO_2S_2$: C, 43.87; H, 2.94; N, 5.12. Found: C, 43.67; H, 3.05; N, 5.30.

3-N-(4-Fluoroanilinomethyl)-5-chlorobenzothiazoline-2-thione—4-Fluoroaniline (2.8 g.) was treated with 5-chlorobenzothiazoline-2-thione (5.04 g.) in 20 ml. of ethanol and 4 ml. of formalin. The product obtained was recrystallized from ethanol–acetone, yield 5.5 g. (67%); m.p. 188–190°; mixture melting point with 5-chlorobenzothiazoline-2-thione, 166–171°.

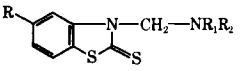
Anal.—Calcd. for $C_{14}H_{10}ClFN_2S_2$: C, 51.76; H, 3.10; N, 8.63. Found: C, 51.68; H, 3.29; N, 8.56.

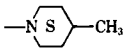
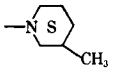
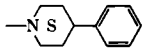
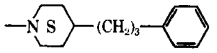
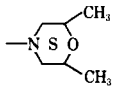
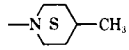
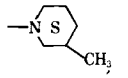
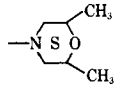
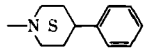
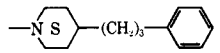
3-N-Anilinomethyl-5-chlorobenzothiazoline-2-thione—Aniline (2.32 g.) was added to a suspension of 5-chlorobenzothiazoline-2-thione (5.04 g.) in ethanol (10 ml.). To this mixture there was added 4 ml. of 37% formalin. The reaction mixture was stirred at room temperature for 2 hr. and then was allowed to remain at this temperature overnight. The product was filtered and washed with ether. An analytical sample was prepared by four successive recrystallizations from ethanol; m.p. 139°; yield, 5.0 g. (65%).

Anal.—Calcd. for $C_{14}H_{11}ClN_2S_2$: C, 54.80; H, 3.61; N, 9.13. Found: C, 54.67; H, 3.70; N, 9.08.

[1] Melting points are uncorrected and were observed in capillaries on a Thomas-Hoover apparatus. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were determined on a Perkin-Elmer model 137 spectrophotometer and were as expected.

Table I—*N*-Mannich Bases



Compd.	—NR_1R_2	M.p., °C.	Yield, %	Formula	Analyses	
					Calcd.	Found
		R = H				
1		102–104	65	$C_{14}H_{18}N_2S_2$	C, 60.39 H, 6.52 N, 10.06	60.28 6.40 9.85
2		101–103	60	$C_{14}H_{18}N_2S_2$	C, 60.39 H, 6.52 N, 10.06	60.54 6.42 9.91
3		132–135	50	$C_{19}H_{20}N_2S_2$	C, 67.02 H, 5.92 N, 8.23	66.91 5.96 8.11
4		100–103	55	$C_{12}H_{14}N_2S_2$	C, 57.58 H, 5.64 N, 11.19	57.33 5.55 11.03
5		79–80	48	$C_{22}H_{26}N_2S_2$	C, 69.07 H, 6.85 N, 7.32	69.20 6.88 7.39
		R = Cl				
6		111–113	55	$C_{14}H_{18}N_2OS_2$	C, 57.12 H, 6.16 N, 9.52	56.94 6.03 9.32
7		144–145	64	$C_{14}H_{17}ClN_2S$	C, 53.72 H, 5.48 N, 8.95	54.00 5.40 8.91
8		126–127	67	$C_{14}H_{17}ClN_2S_2$	C, 53.72 H, 5.48 N, 8.95	54.00 5.29 8.77
9		148–150	60	$C_{14}H_{17}ClN_2OS_2$	C, 51.11 H, 5.21 N, 8.52	51.29 5.17 8.43
10		169–171	57	$C_{19}H_{19}ClN_2S_2$	C, 60.87 H, 5.11 N, 7.47	60.62 4.97 7.52
11		103–105	76	$C_{22}H_{25}ClN_2S_2$	C, 63.36 H, 6.04 N, 6.72	63.49 6.12 6.65
12		120–122	57	$C_{14}H_{17}ClN_2S_2$	C, 53.72 H, 5.48 N, 8.95	53.61 5.51 8.82

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