

New Compounds: New 1,3-Diiminoisoindolines

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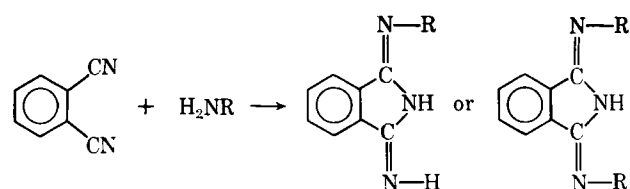
Abstract □ The synthesis of eleven 1,3-diiminoisoindolines is reported. These compounds were evaluated for their pharmacological properties and found to be inactive.

Keyphrases □ 1,3-Diiminoisoindolines—synthesis □ Pharmacological activity—1,3-diiminoisoindolines

In a search for new compounds with central nervous system activity, a series of substituted 1,3-diiminoisoindolines has been prepared for pharmacological evaluation (Table I).

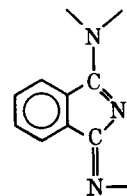
It has been reported that phthalonitrile condenses with primary amines to yield 1-substituted and 1,3-disubstituted 1,3-diiminoisoindolines (1-4) (Scheme I).

These compounds may very likely exist in the tauto-

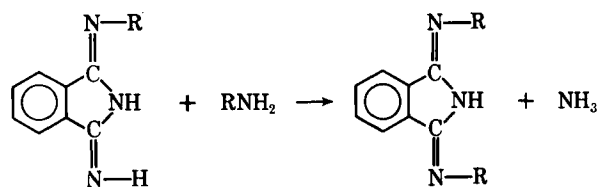


Scheme I

meric isoindolenine form (2).



The disubstituted compound may also be obtained by treating the monosubstituted compound with an excess of the corresponding amine (2) (Scheme II).



Scheme II

In the present work the generality of these reactions has been further demonstrated. In some instances it was found necessary to modify the procedures described in the literature.

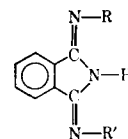


Table I—Substituted 1,3-Diiminoisoindolines

No.	R	R ¹	M.p., °C.	Yield, %	Method	Formula	Mol. Wt.	Anal., %	
								Calcd.	Found
I	H	C ₆ H ₁₁ —	185-186	57.2	A	C ₁₄ H ₁₇ N ₃	227.29	C, 73.98 H, 7.54 N, 18.49	C, 73.72 H, 7.61 N, 18.51
II	H	CH ₂ (HOCH ₂) ₂ C—	171-172	40	A	C ₁₂ H ₁₃ N ₃ O ₂	233.26	C, 61.78 H, 6.48 N, 18.01 O, 65.09	C, 61.59 H, 6.53 N, 18.23 O, 65.14
III	H	O—(CH ₂ CH ₂) ₂ N—CH ₂ CH ₂ —	128	15.7	B	C ₁₄ H ₁₉ N ₄ O	258.31	H, 7.02 N, 21.69 C, 71.33	H, 6.95 N, 21.83 C, 71.20
IV	H	CH ₂ =CH—CH ₂ —	145-145.5	5.0	C	C ₁₁ H ₁₁ N ₃	185.22	H, 5.98 N, 22.69 C, 77.08	H, 6.21 N, 22.50 C, 76.81
V	H	C ₆ H ₅ CH ₂ CH ₂ —	171-173	46.2	A	C ₁₈ H ₁₆ N ₃	249.30	H, 6.06 N, 16.85 C, 69.32	H, 5.92 N, 16.77 C, 69.53
VI	H	O—CH=CH—CH=C—CH ₂ —	182-183	49	B	C ₁₃ H ₂₂ N ₃ O	225.23	H, 14.92 N, 18.66 C, 66.79	H, 15.06 N, 18.88 C, 66.96
VII	H	<i>o</i> -ClC ₆ H ₄ CH ₂ —	158-162	48.4	A	C ₁₅ H ₁₂ N ₃ Cl	269.71	H, 4.45 Cl, 13.14 N, 15.58 C, 77.61	H, 4.56 Cl, 13.17 N, 15.85 C, 77.57
VIII	C ₆ H ₁₁ —	C ₆ H ₁₁ —	163-165	52	D	C ₂₀ H ₂₇ N ₃	309	H, 8.80 N, 13.58 C, 53.32	H, 8.79 N, 13.84 C, 53.49
IX	S—CH=CH—N=C—	S—CH=CH—N=C—	228	4.7	A	C ₁₄ H ₁₃ N ₃ S ₂	315.35	H, 4.13 N, 22.21 C, 70.80	H, 4.20 N, 22.16 C, 70.70
X	O—CH=CH—CH=C—CH ₂ —	O—CH=CH—CH=C—CH ₂ —	118-119	52	D	C ₁₅ H ₁₅ N ₃ O ₂	305.32	H, 4.95 N, 13.76 C, 67.01	H, 4.97 N, 13.82 C, 67.25
XI	<i>o</i> -ClC ₆ H ₄ CH ₂ —	<i>o</i> -ClC ₆ H ₄ CH ₂ —	162-164	45	D	C ₂₂ H ₁₇ N ₃ Cl ₂	394.28	H, 4.34 N, 10.66	H, 4.38 N, 10.78

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.

- (1) Farbenfabriken Bayer, Indian pat. 43,679 (1952).
- (2) P. F. Clark, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, **1953**, 3593.
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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.

EXPERIMENTAL¹

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 C₈H₈ClNOS₂: C, 41.48; H, 2.61; N, 6.05. Found: C, 41.20; H, 2.69; N, 5.95.

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.

3-*N*-(4-Fluoroanilino)methyl)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 C₁₄H₁₁FN₂S₂: C, 57.89; H, 3.82; N, 9.65. Found: C, 57.73; H, 3.98; N, 9.46.

3-(3,4,5-Trimethoxybenzoyloxy)methyl)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 C₁₈H₁₇NO₆S₂: C, 55.23; H, 4.38; N, 3.58. Found: C, 55.31; H, 4.50; N, 3.51.

3-Acetoxyethyl-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 C₁₀H₈ClNO₂S₂: C, 43.87; H, 2.94; N, 5.12. Found: C, 43.67; H, 3.05; N, 5.30.

3-*N*-(4-Fluoroanilino)methyl)-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 C₁₄H₁₀ClFN₂S₂: C, 51.76; H, 3.10; N, 8.63. Found: C, 51.68; H, 3.29; N, 8.56.

3-*N*-Anilinoethyl-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 C₁₄H₁₁ClN₂S₂: C, 54.80; H, 3.61; N, 9.13. Found: C, 54.67; H, 3.70; N, 9.08.