

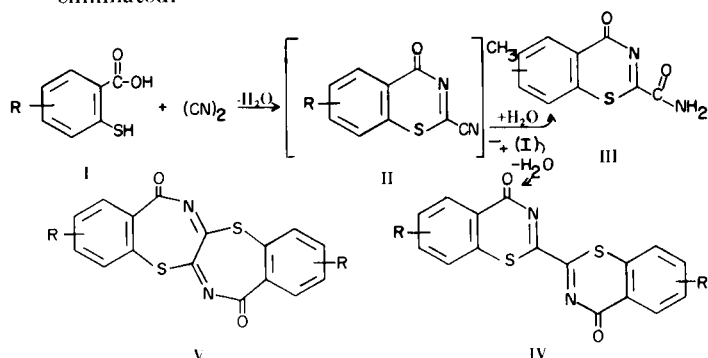
Cyanogen-2-mercaptobenzoic Acid Condensations: A Route to Bis-1,3-benzothiazin-4-ones

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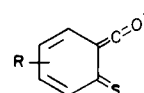
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Cyanogen has been proven to be a useful and versatile reactant for heterocyclic synthesis (1,2,3,4). It reacts in a step-wise fashion with α -mercapto acids to give first monocyclic thiazolin-4-ones and then bicyclic bis-thiazolin-4-ones (5). Our continuing interest in benzothiazinones as potential therapeutic agents (4,6,7) and the intriguing possibility that, in parallel with the results of Ketcham (5), cyanogen and 2-mercaptobenzoic acids (I) might yield bis-1,3-benzothiazin-4-ones (IV) prompted our investigation of this condensation. *A priori*, a 2:1 combination yielding a fused benzo-1,4-thiazepin-5-one (V) product can not be eliminated.



Even at a 5/1 ratio of cyanogen to the 2-mercaptobenzoic acids, the only products which could be isolated, with the exception of III, incorporated one molecule of cyanogen and two of the thiol compound. Structure proof for the major products rested in the spectral information obtained. Infrared spectra revealed no trace of nitrile or N-H absorptions but did demonstrate the presence of an intense C=O band at $1665 \pm 5 \text{ cm}^{-1}$. This frequency is more nearly in accord with that reported for 1,3-benzothiazin-4-ones, $1670\text{-}1690 \text{ cm}^{-1}$ (8) than with that reported for benzo-1,4-thiazepin-5-ones, 1650 cm^{-1} (9). The most conclusive support, however, for the six-membered bis-benzothiazinones (IV) was provided by the unique mass spectral fragmentation pattern. Each heterocyclic product in addition to a parent peak displayed a peak at half-mass (corresponding, apparently, to scission of the single bond joining the

two ring systems). A similar ion could not readily be rationalized from the alternative structure (V). Furthermore, the base peak in the fragmentation patterns of each IV was the retro Diels-Alder ion known to be characteristic of benzo-fused six-membered heterocyclics (10).



A plausible mechanism, involving the possible intermediacy of a labile cyano-1,3-benzothiazin-4-one (II), received some support in the isolation of a small amount of III from the 5-methylthiosalicylic acid (Id) condensation with cyanogen. An *in situ* hydrolysis, effected by the water generated in the cyclization to IVd, presumably produced the amide from the cyano precursor II. Carefully dried tetrahydrofuran solvent had been employed.

EXPERIMENTAL

Infrared spectra were obtained in 1% potassium bromide disks on a Perkin-Elmer Model 257 spectrophotometer. Melting points were obtained on a Mel-Temp Apparatus and are reported uncorrected. Elemental analyses were provided by George Robertson microanalytical Laboratory, Florham Park, N.J.

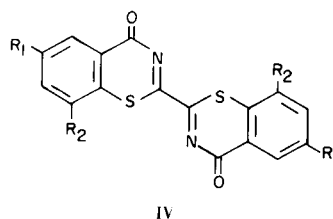
Preparation of the 2-Mercaptobenzoic Acids (Ia-d).

These compounds were prepared by literature methods (4,11, 12) and had melting points in agreement with reported values.

Preparation of the 2,2'-Bis(4-Oxo-1,3-benzothiazinyl) Compounds (IVa-d).

A solution prepared from 5.2 g. (0.10 mole) of cyanogen, 30 ml. of tetrahydrofuran, and 5 drops of triethylamine was cooled to 0° in an ice-salt bath and treated to the dropwise addition of 0.02 mole of the 2-mercaptobenzoic acid (Ia-d) dissolved in 50 ml. of tetrahydrofuran. The addition required about 30 minutes after which the reaction was stirred at 0° for 3 hours and allowed to warm to room temperature with continuous stirring for another 12 hours. Evaporation of the solvents yielded a crystalline residue which was recrystallized from DMF (sparingly soluble) to analytical purity. See Table I for the tabulated results. In the case of Id evaporation of the tetrahydrofuran mother liquors yielded 10% of a second compound (III), m.p. $266.5\text{-}268.5^\circ$ from benzene; ir

Table I



Compound	R ₁	R ₂	Formula	% yield	M.p.	C	Analysis				
							Calcd. H	N	Found C	Found H N	
IVa	H	H	C ₁₆ H ₈ N ₂ O ₂ S ₂	95	408-410°	59.24	2.49	8.64	59.10	2.43	8.35
IVb	Cl	H	C ₁₆ H ₆ Cl ₂ N ₂ O ₂ S ₂	87	470-473°	48.87	1.54	7.12	48.94	1.78	7.18
IVc	Cl	Cl	C ₁₆ H ₄ Cl ₄ N ₂ O ₂ S ₂	76	414-417°	41.58	0.87	6.06	41.56	1.16	5.86
IVd	CH ₃	H	C ₁₈ H ₁₂ N ₂ O ₂ S ₂	21 (a)	359-362°	61.34	3.43	7.95	61.54	3.48	8.09

(a) Additional monocyclic product isolated, see Experimental text.

(potassium bromide): 3400-3100 (br N-H), 1705, 1675 and 1655 cm⁻¹ (C=O).

Anal. Calcd. for C₁₀H₈N₂O₂S₂: C, 54.53; H, 3.66; N, 12.72. Found: C, 54.30; H, 3.41; N, 13.00.

Acknowledgments.

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