Benzothiazinones by Addition of *o*-Mercaptobenzamides to Acetylene Esters (1)

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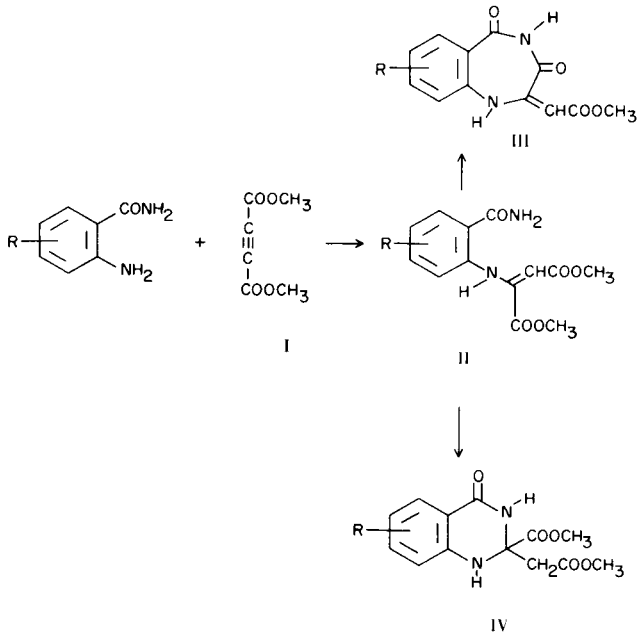
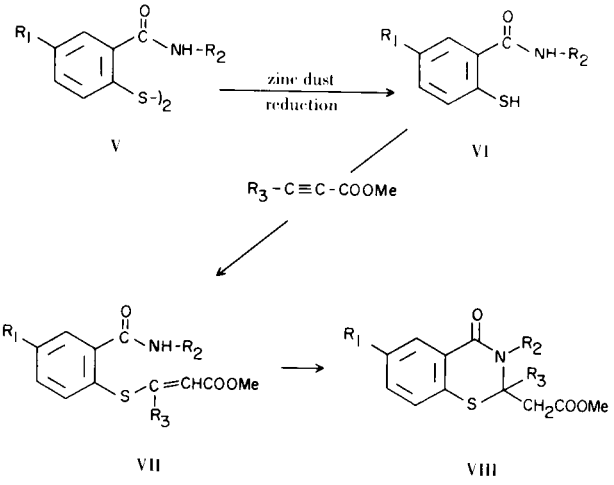
The condensation of *o*-mercaptobenzamides with methyl acetylenedicarboxylate or methyl propiolate occurs with *trans* addition of the SH to the alkyne linkage. The resulting vinyl sulfide adducts can be ring closed to 1,3-benzothiazin-4-ones in excellent yield.

In previous contributions from these laboratories we have reported the reaction of numerous nucleophiles with methyl acetylenedicarboxylate, I, and methyl propiolate as a route to new heterocycles (2). The addition of the *o*-amino function of anthranilamides to the alkyne linkage of I gave enamine adducts, II, which upon



treatment with alkoxides in xylene solvent yielded benzodiazepinediones, III, and in methanol solvent yielded quinazolinones, IV, (3). In a similar fashion, *o*-mercaptobenzamides reacted with I to produce a vinyl sulfide adduct which could be cyclized to 2-carbomethoxymethyl-2-carbomethoxy-3,4-dihydro-2*H*-1,3-benzothiazin-4-one, VIIIa (4).

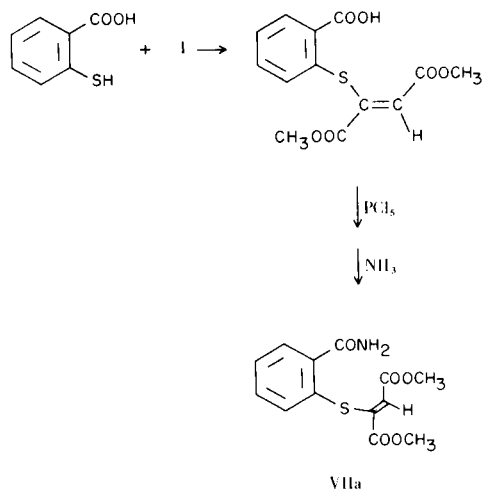
We wish to report that this *o*-mercaptobenzamide-acetylene ester synthesis serves as a general route to this novel type of benzothiazinone but unlike the parallel condensation of anthranilamides and I it cannot be directed to seven- or six-membered heterocycles by control of reaction conditions; only the latter result. The required *o*-mercaptobenzamides were synthesized from anthranilic acids by the diazotization procedure of Katz (5) which yielded the disulfides of the *o*-mercaptobenzoic acids. These were converted by the method of Reissert and Manns (6) through the bis acid chlorides to the bis amides, V. A zinc dust reduction of these disulfides provided the *o*-mercaptobenzamides. Due to the facility



with which these mercaptans underwent air oxidation back to disulfides, they were reacted *in situ* with the acetylene ester. Most of the resulting adducts, VII, were sufficiently stable to isolate and characterize, although they could readily be cyclized to the benzothiazinones, VIII (see Table).

With commercial *o*-mercaptobenzoic acid (7) an alternative procedure was employed. The acid was converted to the known vinyl sulfide adduct (4) and thence through the acid chloride to the amide adduct VIIa in 45% overall yield.

It is interesting to note that while aromatic amines including anthranilamides react in exothermic, non-catalytic addition to acetylene esters (3,8), the corresponding phenols and salicylamides require prolonged contact in basic medium to effect addition (9,10,11).



VIIa

As previously noted (4), the addition of these thiols to I is usually exothermic and apparently proceeds in an exclusively *trans* fashion. NMR spectral studies of mixtures of geometric isomers resulting from amine additions to I have established a basis for isomer characterization: the relative chemical shift of the unit vinyl proton resonance in maleate or fumarate product (8,12,13). Thus in fumarate adducts the =C*H* experiences the deshielding of two flanking ester carbonyls and hence a downfield shift relative to the corresponding maleate vinyl flanked by a single deshielding ester.

The adducts, VIIa-d, as directly isolated from the reaction mixture, all displayed a single vinyl proton resonance at δ 6.64 ± 0.05 ppm which corresponds closely to the reported position of fumarate vinyl protons, δ 6.79 ± 0.05 ppm, in the related methyl *o*-mercaptobenzoate adducts of I (4). Although thermal geometric isomerization of vinyl sulfides is well known (14,15), it was impossible to effect in these situations since cyclization to benzothiazinones intervened. However, if pure samples of *trans* VIIa-d were allowed to stand in DMSO solutions at room temperature for three weeks they underwent slow isomerization to equilibrium mixtures containing 42 ± 3% *cis* isomer. The new maleate vinyl proton resonances appeared up-field at δ 5.84 ± 0.08 ppm vs δ 6.73 ± 0.03 ppm for fumarate vinyl resonances in the identical solvent (DMSO-d_6).

In the addition of the *o*-mercaptobenzamides, VIc and VId, to methyl propiolate, labile β-thioacrylates were obtained whose coupling constant for the vicinal protons in the β position to sulfur, was 10 Hz. A *cis* vinyl system implies a *trans* addition of the thiol (16). Truce has reported that base-catalyzed additions of thiols (*i.e.*, thiolate anions) to acetylenes proceed with overall *trans* addition (17), but the uncatalyzed addition of SH to alkyne has received scant attention.

The thiol adducts could be cyclized by heating with a small amount of sodium methoxide. Although the indicated mechanism for quinazolinone formation from anthranilamide adducts, II, involved ring-contraction of a transient benzodiazepinedione, III, through nucleophilic involvement of methanol (3) a similar mechanism was not implicated here. Identical products were obtained in either methanol or xylene solvent and were readily recognized as the benzothiazinones, VIII, by their characteristic CH_2 resonances at 3.15 to 2.93 ppm and by their saturated ester carbonyls at 1759 to 1728 cm^{-1} in the infrared.

Two of these benzothiazinones, VIIIc and VIIId, were oxidized by potassium permanganate in acetic acid to their respective 1,1-dioxides, IX and X. The CH_2 resonances in these oxidized materials appeared as a geminally split AB set (J = 17 Hz) at δ 3.09, 3.69 and 3.16, 3.78 ppm in the two respective products. The appearance of magnetically non-equivalent methylene protons adjacent to an asymmetric center is well documented (18).

Because of the structural analogy of these 1,3-benzothiazinones to a number of 1,3-benzoxazinones (19,20,21) which have shown promise as CNS depressants, VIIIa,b,d, and e and X were evaluated in an Irwin neuropharmacological mouse profile (22). No significant activity was observed, although VIIIe and X did display slight depression of alertness and reduction of spontaneous motor activity at 1000 mg/kg.

EXPERIMENTAL

Melting points were obtained between glass slides on a Fisher-Johns Apparatus and are reported uncorrected. Elemental analyses were provided by Dr. G. I. Robertson, Jr., Microanalytical Laboratory, Florham Park, N. J. NMR spectra were obtained in deuteriochloroform unless otherwise indicated, on a Varian A60 and Hitachi Perkin Elmer R20A Spectrometer and are reported in δ ppm units from TMS. Infrared spectra were run on a Perkin Elmer 257 Spectrometer as hydrocarbon mulls.

4,4′-Dichloro-2,2′-dicarboxamidodiphenyldisulfide (Vb).

A solution of 49 mmoles of 4,4′-dichloro-2,2′-dicarboxydiphenyldisulfide (5) and 36 ml. of thionyl chloride was refluxed until hydrogen chloride evolution ceased, evaporated to dryness *in vacuo*, treated with 30 ml. of dry benzene and the evaporation repeated. The crude yellow crystals were dissolved in 100 ml. of benzene at 45° and a steady stream of ammonia gas was passed through for 5 minutes. The resulting precipitate was doubly recrystallized from acetic acid to provide a 43% yield of Vb, m.p. 275-276.5°.

4,4′-Diiodo-2,2′-dicarboxamidodiphenyldisulfide (Vc).

Employing 5-iodoanthranilic acid in the diazotization procedure described by Katz for the 5-chloroanalog, 49% of 4,4′-diiodo-2,2′-dicarboxydiphenyldisulfide was obtained, crude m.p. 317-323°. A solution of 6.26 mmoles of this diacid and 30 ml. of thionyl chloride was reacted as described above and the crude diacid chloride was ammoniated to produce the diamide in 93% yield, m.p. 279-280°.

2,2′-Di(*N*-3,5-dichlorophenylcarboxamido)diphenyldisulfide (Vb).

The acid chloride of 2,2′-dicarboxydiphenyldisulfide (6) was

TABLE

2,2′-Dicarboxamidodiphenyldisulfides

Compound	R_1	R_2	M.p. °C	Formula	Yield	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	H	H	245 (a)	$C_{14}H_{12}N_2O_2S_2$	53						
Vb	Cl	H	275-276.5	$C_{14}H_{10}Cl_2N_2O_2S_2$	43	43.05	2.70	7.50	45.35	2.68	7.23
Vc	I	H	279-280	$C_{14}H_{10}I_2N_2O_2S_2$	93	30.23	1.81	5.08	29.91	1.52	4.85
Vd	H	3,5-$Cl_2C_6H_3$	225-228	$C_{26}H_{16}Cl_4N_2O_2S_2$	37	52.54	2.71	4.71	52.79	2.91	4.40

(a) Lit. m.p. 239°, Ref. (6). Yields based on conversions from 2,2′-dicarboxydiphenyldisulfides.

Mercaptoamide Adducts

Compound	R_1	R_2	R_3	M.p. °C	Formula	Yield	C	H	N	C	H	N
VIIa	H	H	COOMe	143.5-144.5	$C_{13}H_{13}NO_5S$	55	52.87	4.44	4.74	53.05	4.62	4.79
VIIb	Cl	H	COOMe	144.5-145.0	$C_{13}H_{12}ClNO_5S$	70	47.35	3.67	4.25	47.15	3.54	3.89
VIIc	I	H	COOMe	175.5-176.5	$C_{13}H_{12}INO_5S$	61	37.07	2.87	3.33	37.35	3.11	3.34
VIId	H	3,5-$Cl_2C_6H_3$	COOMe	162-163	$C_{19}H_{15}Cl_2NO_5S$	90	51.83	3.43	3.18	51.61	3.45	2.96
VIIf	I	H	H	158-159	$C_{11}H_{10}INO_3S$	77	36.38	2.78	3.86	36.60	2.95	3.63

Benzothiazinones

Compound	R_1	R_2	R_3	M.p. °C	Formula	Yield	C	H	N	C	H	N
VIIIa	H	H	COOMe	168-169 (b)	$C_{13}H_{13}NO_5S$	55	52.87	4.44		53.01	4.60	
VIIIb	Cl	H	COOMe	218-218.5	$C_{13}H_{12}ClNO_5S$	60	47.35	3.67	4.25	47.33	3.84	3.98
VIIIc	I	H	COOMe	235-235.5	$C_{13}H_{12}INO_5S$	70	37.07	2.87	3.33	37.34	2.82	3.15
VIIId	H	3,5-$Cl_2C_6H_3$	COOMe	183-184	$C_{19}H_{15}Cl_2NO_5S$	61	51.83	3.43	3.18	51.99	3.24	2.99
VIIIe	H	3,5-$Cl_2C_6H_3$	H	119.5-120	$C_{17}H_{13}Cl_2NO_3S$	63 (c)	53.41	3.43	3.66	53.33	3.28	3.60
VIIIf	I	H	H	141.0-141.5	$C_{11}H_{10}INO_3S$	88	36.38	2.78	3.86	36.63	2.68	3.53

(b) Lit. m.p. 168-169°, Ref. (4). (c) VIIe could not be obtained in analytical purity and hence was used as an intermediate. Yield stated is for the sequence VIe to VIIIe.

dissolved in 100 ml. of benzene and treated with a two fold excess of 3,5-dichloroaniline (0.10 moles of acid chloride to 0.40 moles of aniline). The components were allowed to stand at room temperature for 24 hours. The resulting precipitate was filtered, washed with benzene and water, and recrystallized from xylene (sparingly soluble) and methanol to provide a 37% yield of Vd, m.p. 225-228°.

Preparation of *o*-Mercaptobenzamides (VIa, VIb, VIc).

The zinc dust reduction method of Boudet (23) as described for conversion of Va to VIa was similarly applied to the chloro and iodo substituted analogs. 4-Chloro-2-merceptobenzamide (m.p. 127-133°) was obtained in 43% yield and 4-iodo-2-mercapto-benzamide (m.p. 153-159°) in 30% yield, but because of a facile tendancy to oxidize to the disulfide upon attempted preparation of analytical samples they were reacted *in situ* without further purification.

Preparation of *N*-(3,5-Dichlorophenyl)-2-mercaptobenzamide (VId).

A mixture of 24.2 mmoles of Vd, 3.0 g. of fine zinc dust, and 50 ml. of ethanol was heated to reflux with stirring, and 2 ml. of concentrated hydrochloric acid was added. Reflux was continued until the organic solid had dissolved (about 15 minutes) and then for an additional 15 minute period. The medium was filtered while yet hot, the zinc dust and salts washed with ethanol, and the concentrated filtrate chilled in an ice bath to precipitate 12 g. (84% yield) of white microneedles of the amide, VId. Recrystallization from ethanol with the aid of activated carbon provided the analytical sample, m.p. 164-165°.

Anal. Calcd. for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.04; N, 4.70. Found: C, 52.60; H, 3.12; N, 4.64.

Preparation of the Mercapto-Acetylene Adducts (Vinyl Sulfides) VIIa-f).

A solution of 10 mmoles of the required *o*-mercaptobenzamide in 100 ml. of methanol was treated with an equimolar quantity of acetylene ester. In some cases considerable heat was evolved and precipitation ensued but all reactions were refluxed for 0.5 to 1 hour before concentration and recrystallization (from methanol) to obtain the analytical material. Yields and physical properties are reported on the Table. Compound VIIe was a gummy, low melting solid which could not be adequately purified and hence was ring closed to VIIIe directly.

Alternative Synthesis of VIIa.

A solution of 10 mmoles of dimethyl (2-carboxyphenylthio)-fumarate (4) in 100 ml. of dry benzene was shaken over phosphorus pentachloride for 24 hours. The unreacted phosphorus pentachloride was filtered off and ammonia gas passed at a rapid rate through the benzene solution. The tan solid was filtered off, washed with cold water, and recrystallized from methanol to produce 1.33 g. (45%) of VIIa, m.p. 144-145°.

Cyclization of the Adducts to Benzothiazinones (VIII).

To a refluxing solution of 3 to 7 mmoles of the vinyl sulfide in 50 ml. of methanol was added 0.1 g. of sodium methoxide, and reflux was continued for 2 hours. Concentration *in vacuo* and recrystallization of the crude products from methanol produced the analytical material. Yields and physical properties are given on the Table. Similar results were obtained if the reaction solvent was xylene, although larger volumes (70-100 ml.) were necessary to dissolve the reactants.

Preparation of 6-Iodo-2-carbomethoxymethyl-3-carbomethoxy-3,4-dihydro-2*H*-1,3-benzothiazin-4-one 1,1-Dioxide (IX).

A solution of 30 ml. of acetic acid and 2.4 mmoles of VIIIc was added portionwise to a second solution of 0.63 g. of potassium permanganate in 10 ml. of water. The mixture was heated on a steam bath for 1 hour, diluted with 100 ml. of water and the brown solids collected by filtration. The oxidized product was found to be entrained in the manganese dioxide from which it was extracted by repeated washing with hot methanol. Evaporation of the methanol extracts and recrystallization (2X) from methanol gave 0.54 g. (51%) of IX, m.p. 163-164°.

Anal. Calcd. for $C_{13}H_{12}INO_7S$: C, 34.45; H, 2.67; N, 3.09. Found: C, 34.54; H, 2.73; N, 3.04.

Preparation of 2-Carbomethoxymethyl-2-carbomethoxy-3-(3,5-dichlorophenyl)-3,4-dihydro-2*H*-1,3-benzothiazin-4-one 1,1-Dioxide (X).

A solution of 3.4 mmoles of VIIId in 55 ml. of acetic acid was treated portionwise with a solution of 5.6 mmoles of potassium permanganate dissolved in 20 ml. of water. After 2 days of stirring at room temperature the precipitated solids were filtered off, washed well with hot benzene and the organic phase dried (magnesium sulfate) and concentrated. The product was recrystallized from 1:1 acetic acid:water to provide 0.80 g. (50%) of X, m.p. from methanol, 196.5-197.5°.

Anal. Calcd. for $C_{19}H_{15}Cl_2NO_7S$: C, 48.32; H, 3.20; N, 2.97. Found: C, 48.55; H, 3.43; N, 2.72.

REFERENCES

(1) Supported by Grant Number 1R01 MH013562 from the National Institute of Mental Health.

(2) See N. D. Heindel, P. D. Kennewell, and V. B. Fish, *J. Heterocyclic Chem.*, 6, 77 (1969) and N. D. Heindel, P. D. Kennewell and M. Pfau, *J. Org. Chem.*, 35, 80 (1970) and papers cited therein.

(3) N. D. Heindel, V. B. Fish, and T. F. Lemke, *ibid.*, 33, 3997 (1968).

(4) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *ibid.*, 32, 2678 (1967).

(5) L. Katz, L. S. Karger, W. Schroeder, and M. S. Cohen, *ibid.*, 18, 1394 (1953).

(6) A. Reissert and E. Manns, *Chem. Ber.*, 61, 1308 (1928).

(7) Generous commercial samples were provided by Evans Chemical Co.

(8) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 99, 2526 (1966).

(9) N. D. Heindel and L. A. Schaeffer, *J. Org. Chem.*, 35 2445 (1970).

(10) N. D. Heindel, *ibid.*, 35, 0000 (1970).

(11) E. Winterfeldt and H. Preuss, *Chem. Ber.*, 99, 450 (1966).

(12) J. E. Dolfini, *J. Org. Chem.*, 30, 1298 (1965).

(13) E. C. Taylor and N. D. Heindel, *ibid.*, 32, 3339 (1967).

(14) E. P. Kohler and H. Potter, *J. Am. Chem. Soc.*, 57, 1316 (1935).

(15) W. E. Truce and R. J. McManimie, *ibid.*, 76, 5745 (1954).

(16) Although the protons *alpha* to sulfur were buried in the aromatic multiplet the *beta* protons were clearly delineated as doublets at δ 5.81 and 5.95 in VIc and VId, respectively.

(17) W. E. Truce in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, pp. 112-120.

(18) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1969, p. 199.

(19) J. Finkelstein and E. Chiang. *J. Med. Chem.*, 11, 1038 (1968).
(20) R. Kadatz, *Arzneimittel-Forsch.*, 7, 651 (1957).
(21) N. D. Heindel and L. A. Schaeffer, *J. Med. Chem.*, 13, 0000 (1970).
(22) Evaluation was carried out by Dr. Ted O. King, Bio/dynamics Labs and Dr. Richard Matthews, Pharmakon Labs. Original mouse testing method was described by S. Irwin, "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Seigler, Ed., Year Book Medical Publishers, Inc., Chicago, Ill., 1964.

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