Synthesis and Central Nervous System Effects of Some Benzothiazinones[1]

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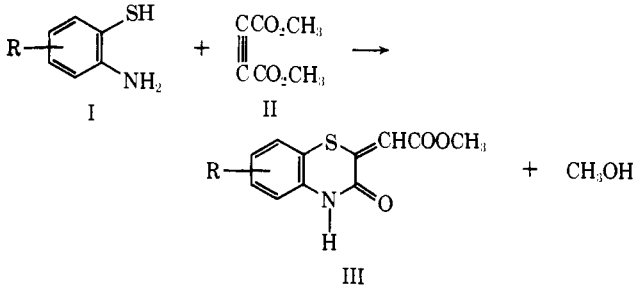
The reaction of difunctional nucleophiles with dimethyl acetylenedicarboxylate (II) has proven to be a versatile synthesis of medicinally important heterocyclics.[2-4] Although the condensation of 2-aminothiophenol with acetylenedicarboxylic acid[5] and ester[6] has been well documented in the literature, the firm basis for structural assignment of the products (as 2-carboxymethylene-3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazine derivatives) has only recently been clarified.[7] Considering the benzo-1,4-thiazine system as a norbenzo counterpart of the phenothiazine CNS agents, Japanese workers have prepared and evaluated numerous analogs and detected impressive analgetic potential in several.[8,9] We wish to report the synthesis of six 2-carbomethoxymethylene-3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazines and the evaluation of several of these in a neuropharmacological mouse profile.[10]



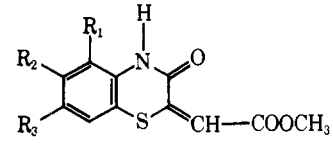
I II III

The *o*-aminothiophenols (I) were condensed with the acetylene diester II in MeOH, and the desired products pptd directly, usually with the evolution of considerable heat. Products were recrystd to anal. purity before being subjected to biological testing.

Biological Results.—Materials were administered ip in soln or suspension in H_2O–methylcellulose to 4 mice. Physiological signs were observed and recorded according to the Irwin method.[11] Compds IIIa and IIId were inactive and nontoxic at doses as high as 1000 mg/kg. The MeO analogs IIIc and IIIf displayed a low order of sedative–hypnotic activity at 1000 mg/kg, but not at 300 mg/kg, as reflected in slight depression of spontaneous motor activity and body tone and in a modest increase in passivity and pupil size. The magnitude of the effects was slightly greater for the non-Cl compd IIIc than for the Cl-containing compd IIIf. The highest order of activity was observed in the NO_2-substituted benzothiazinone, IIIe, which induced marked depression, catatonia, and reduced motor activity at doses as low as 100 mg/kg. Two of the 4 test mice gave evidence of a partial paralysis of their extremities at 100 mg/kg as reflected in a decidedly wobbly gait. This response was evidenced in all mice at the 300 mg/kg level, and the compound was nontoxic at this dose. None of the effects was of high enough magnitude to merit further investigation of this class.

TABLE I

BENZOTHIAZINONES



III a–f

Compd	R_1	R_2	R_3	Mp, °C	% yield	Formula[a]
IIIa	H	H	H	263–265[b]	44	$C_{11}H_9NO_3S$
IIIb	H	Cl	H	309–311	75	$C_{11}H_8ClNO_3S$
IIIc	H	H	OCH_3	217–219	49	$C_{12}H_{11}NO_4S$
IIId	H	H	OC_2H_5	248–249	56	$C_{13}H_{13}NO_4S$
IIIe	H	NO_2	H	312–314	29[c]	$C_{11}H_8N_2O_5S$
IIIf	OCH_3	H	Cl	224–225.5	46	$C_{12}H_{10}ClNO_4S$

[a] All compds were analyzed for C, H, and N and were within ±0.3% of theoretical values for those elements. [b] Lit. mp 264°, L. K. Mushkalo and V. A. Brezemskaya, *Ukr. Khim. Zh.*, **18**, 163 (1962); *Chem. Abstr.*, **48**, 13692 (1954). [c] Product could not be adequately purified by recrystn and was sublimed *in vacuo*. Yield reported is for purified sublimate.

Experimental Section

Combustion analyses were obtained from Dr. George I. Robertson, Florham Park, N. J. Melting points were obtained on a Mel-Temp apparatus and are reported uncorrected.

General Procedure for Benzothiazinone Synthesis.—The required 2-aminobenzenethiol and 2-amino-4-chlorobenzenethiol were obtained from commercial sources. The remaining aminothiols were prepared by lit. methods tabulated in a review article[12] with the exception of 2-amino-4-nitrobenzenethiol[13] for which an alternative synthesis was employed.

Since most of the aminothiols were utilized as their HCl salts, it was necessary to generate the free base *in situ*. A soln or suspension of 15 mmoles of the HCl salt in 15 ml of anhyd MeOH was treated with 20 mmoles of $NaOCH_3$ and warmed with stirring on a steam bath for 10 min. After filtration to remove the pptd NaCl, the filtrate was immediately treated with 15 mmoles of dimethyl acetylenedicarboxylate dissolved in 10 ml of MeOH. A yellow solid began to sep from the medium, and pptn was usually completed in 0.5 hr. The reaction mixt was chilled, and the product was filtered off and recrystd from MeOH. Yields and physical properties are reported in Table I.

(1) Supported by a grant (1 R01 MH 13562) from the National Institute of Mental Health. Previous paper in this series, N. D. Heindel and C. C. Ko, *J. Heterocycl. Chem.*, **7**, 1007 (1970).

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(10) Testing was carried out by Dr. T. O. King of Bio/dynamics Inc., East Millstone, N. J., and Dr. Richard Matthews, Pharmakon Laboratories, Scranton, Pa.

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(12) W. K. Warburton, *Chem. Rev.*, **57**, 1011 (1957).

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