

A New Synthesis of Some Quinazoline-4(1H)thiones (1)

Ned D. Heindel

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

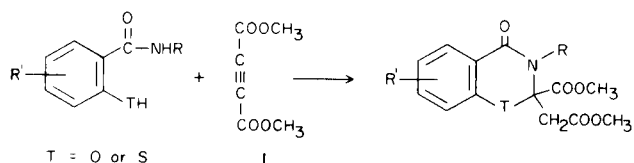
and

Maria C. Chun

Department of Chemistry, Cedar Crest College, Allentown, Pennsylvania 18104

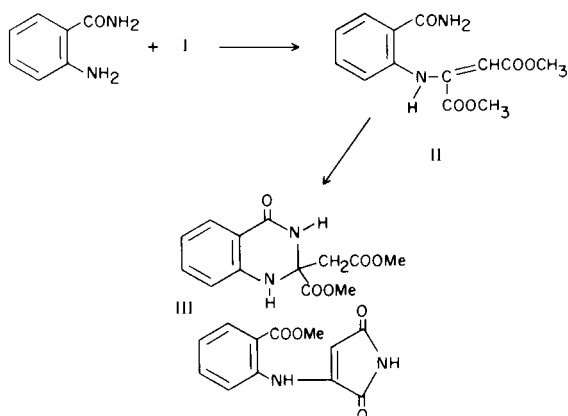
Received March 10, 1971

Quinazoline-4(1H)thiones have been the subject of considerable recent interest as pharmaceutical intermediates, anti-inflammatory agents, diuretics, antispasmodics, and analgesics (2,3,4,5). Our own efforts in heterocyclic syntheses by condensation of dimethyl acetylenedicarboxylate (I) with *ortho*-substituted (either OH or SH) benzamides have yielded 1,3-benzoxazin-4-ones (6) and 1,3-benzothiazin-4-ones (7) which have demonstrated CNS



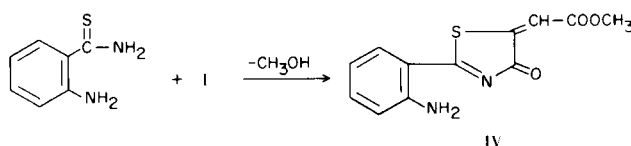
depressant potential. We should like to report our results in the application of this general synthetic method to the preparation of a new type of quinazoline-4(1H)thione.

Because the reaction of *o*-aminobenzamides with I yields dimethyl 2-carboxamidoanilnofumarates (II) which can be cyclized to quinazolinones (III), albeit difficultly separated from maleimide byproducts (8), a logical choice



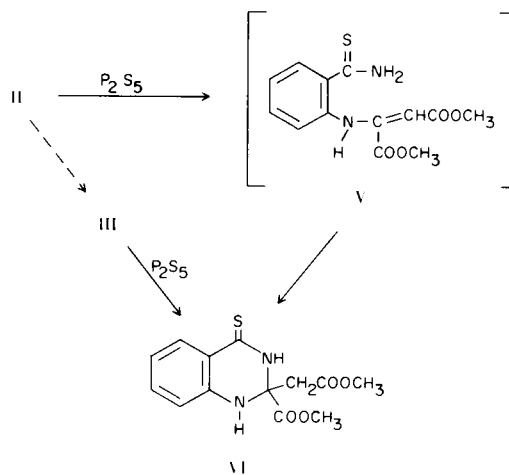
of reagents to generate the quinazoline-4(1H)thiones would appear to be *o*-aminobenzenethioamides (9) and I. This reaction, however, proceeds directly and in high yield to

an *o*-aminophenyl substituted thiazolone (IV). The acetylenedicarboxylate presumably intercepts the thiol-

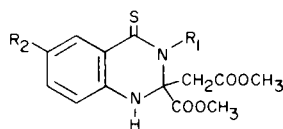


imide tautomer of the thioamide and does not involve the *o*-amino on the phenyl ring. The product IV still possessed the primary amino bands in the infrared and was characterized by elemental analysis and nmr to have lost a molecule of methanol. Hendrickson has reported several related condensations of simple thioamides and I leading to thiazolones (10).

The Taylor procedure (9) for addition of hydrogen sulfide to nitriles as a route to thioamides was investigated with the adducts (11) of anthranilonitriles and I in hopes of obtaining thioamide adducts V which could be cyclized to VI. Only complex oily mixtures, at least 5 components by tlc, resulted.



TABLE



Compound	R ₁	R ₂	Method	% Yield	Formula	M.p. °C	C	Analysis				
								Calcd.	Found	C	H	N
VIa	H	H	A	25	C ₁₃ H ₁₄ N ₂ O ₄ S	124-126	53.05	4.79	9.52	53.26	4.69	9.31
			B	33								
VIb	H	Cl	A	31	C ₁₃ H ₁₃ ClN ₂ O ₄ S	142-143	47.49	3.98	8.52	47.48	4.04	8.49
VIc	CH ₃	H	B	38	C ₁₄ H ₁₆ N ₂ O ₄ S	122-124	54.53	5.23	9.08	54.28	5.01	8.83
VI d	H	CH ₃	B	34	C ₁₄ H ₁₆ N ₂ O ₄ S	144-145	54.53	5.23	9.08	54.77	5.21	8.88

Our successful pathways to the quinazoline-4(1H)-thiones (VI) involved thiolation with phosphorus pentasulfide of either the *o*-aminobenzamide adducts of I (*i.e.*, II) or of the related quinazolinones III. Identical materials were obtained by either pathway and yields of analytical grade material and physical properties are given on the Table. The nmr spectra clearly revealed the pendant carbomethoxymethyl moiety on C-2 by virtue of a characteristic methylene geminal coupled quartet, $J = 16$ Hz, at 3.16 to 3.36 ppm. The appearance of magnetically non-equivalent methylene protons adjacent to an asymmetric center has been well documented (7,12).

In reactions of phosphorus pentasulfide with *o*-aminobenzamide adducts II it was not possible to spectrally detect or isolate the plausible thioamide adduct intermediate V. Thus a prior cyclization of II to III with subsequent thiolation to VI cannot be eliminated. Interestingly enough, while the yields on the reaction are modest, the synthesis is facile and highly workable. The principal experimental difficulty comes in freeing the organic product, without hydrolysis, from entrainment in the phosphorus pentasulfide. Since in the related systems CNS depression was optimum for chloro-containing compounds (6,7), we subjected VIb to evaluation in the Irwin neuropharmacological mouse profile (13). No significant physiological signs of depression were observed at doses up to 300 mg./kg. and at this level evidence of toxicity began to appear (25% mortality in the test mice within 20 minutes postinjection).

EXPERIMENTAL (14)

2-(*o*-Aminophenyl)-5-carbomethoxymethylidene-thiazolin-4-one (IV).

A solution of 1.52 g. of 2-aminobenzenethioamide (10 mmoles) in 50 ml. of anhydrous methanol was added to 1.42 g. (10 mmoles)

of dimethyl acetylenedicarboxylate in 10 ml. of methanol. Considerable heat was evolved and the solution turned light orange in color. The reaction mixture was heated on a steam bath for 2 hours, concentrated *in vacuo* and the crude crystals purified by recrystallization from methanol, 1.83 g., 70%. The analytical sample, m.p. 227-228°, was prepared by a second recrystallization from methanol; ir (Nujol): 3460 and 3370 (amino) and 1705 cm^{-1} (conjugated ester).

Anal. Calcd. for C₁₂H₁₀N₂O₃S: C, 54.96; H, 3.84; N, 10.68; S, 12.22. Found: C, 55.07; H, 3.63; N, 10.44; S, 11.87.

Preparation of the 2-Carbomethoxy-2-carbomethoxymethylidene-thioquinazolin-4(1H)-thiones (VIa-d).

A suspension of 25 mmoles of phosphorus pentasulfide and 14 mmoles of either the 2-carboxamidoanilino-fumarates (II) (15) or the quinazolines (III) (15) in 15 ml. of anhydrous benzene was refluxed with stirring for 2 hours. The solution was separated by filtration from the gummy suspended solid which was washed with dry benzene. The benzene phase, evaporated under reduced pressure, gave yellow crystals which were recrystallized to analytical purity from benzene. The yields and physical properties are reported on the Table. Method A refers to synthesis from the adducts (II) while Method B employs the quinazolinones (III).

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(13) Testing performed by Pharmakon Labs., Scranton, Pa.

(14) Combustion analyses provided by Dr. G. I. Robertson, Florham Park, N. J.

(15) Prepared as described in ref. 8.