

Preparation of the Esters.--The method used was similar to that employed in the former work, but it was found more convenient to use a solution of 1 *N* sodium hydroxide for neutralization of the acid, taking care to have the final salt solution slightly acid to prevent formation of colored by-products. The neutral equivalent of an unknown acid may thus be obtained with no additional effort.

The sodium salts of some of the dibasic acids were found to be insoluble in aqueous alcohol, and caused trouble. Mere substitution of the ethyl ammonium salt for the sodium salt did not obviate the difficulty. If, however, the acid was dissolved in a little water and neutralized with ethylamine, alcohol could be added until the salt started to come out of solution. By use of salts prepared in this way it was possible to obtain the di-esters satisfactorily; 0.0025 mole of acid and 0.005 mole of reagent were used in the experiments with dibasic acids.

Many of the esters listed below were found to be sparingly soluble in 95% alcohol, and accordingly their solubility was tested in acetone, ether and benzene.

Melting points were taken in a small beaker containing concd. sulfuric acid which was well stirred during the determination. No corrections were applied to the melting points, but the thermometer used was calibrated, and registered correctly at 0, 100 and 121.25°, the melting point of pure benzoic acid.

With but two acids were we unable to obtain satisfactory results. The ester of methylantranilic acid was a gum which could not be induced to crystallize, and the ester of trinitrobenzoic acid was a red colloid which could not be filtered. It was also found that under the conditions used in this work, no esters were obtainable from sulfonic acids.

Summary

A number of common acids have been characterized by the preparation of their *p*-phenylphenacyl esters.

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[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]
**PENTHAZOLINES. I. THE ACTION OF HALOGENS ON THE
DIMETHYL MALONATE ADDITION PRODUCT OF ALLYL
MUSTARD OIL¹**

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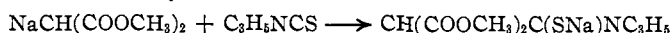
It has been shown previously that the aromatic isothiocyanates react smoothly with certain esters² containing an active methylene group, forming substituted thioamides that have been found useful for the preparation of heterocyclic ring compounds. The aliphatic derivatives have been much less studied. Ruhemann was unable to obtain a tractable³ substance from the action of allyl mustard oil on malonic ester. Methyl isothiocyanate, however, and its homologs have been observed to form

¹ Original manuscript received July 3, 1931.

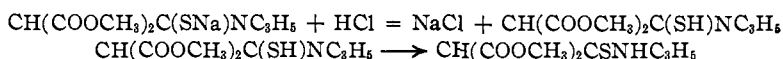
² Worrall, *THIS JOURNAL*, **44**, 1551 (1922); **45**, 3092 (1923); **46**, 2832 (1924).

³ Ruhemann, *J. Chem. Soc.*, **93**, 621 (1908).

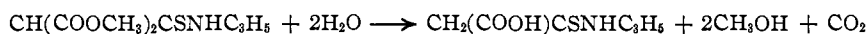
crystalline addition⁴ products with malonic ester. The resulting esters did not react smoothly with hydroxylamine or hydrazine, substances used in the aromatic series for the preparation of isoxazolones and pyrazolones;⁵ moreover, the product contained sulfur in spite of the fact that hydrogen sulfide was evolved in the reaction. Because of these facts and the meager amount of material available, the reaction was not further investigated at the time. In resuming the study of this reaction, allyl mustard oil suggested itself in spite of Ruhemann's discouraging results. The substitution of dimethyl malonate for the usual ethyl ester resulted in a crystalline product, low melting to be sure, but tractable and easily purified. The reaction may be formulated as follows



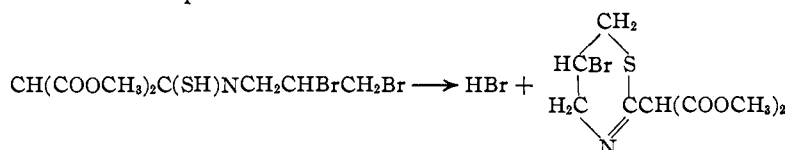
The product was precipitated from water by the addition of hydrochloric acid.



The resulting ester was found to react readily with hydrazine. Hydrogen sulfide was evolved and a small amount of a crystalline product was eventually obtained which was identified as malonic acid monothioallylamide. Hydrolysis, not condensation, takes place in the presence of this base. The presence of hydrogen sulfide is due to further decomposition of the new thioamide.



In this respect the alkyl thioamides differ markedly from the corresponding arylated substances. Bromine was absorbed by the new ester, but the product contained one equivalent only of bromine. It is well known that thioamides, through the enolic form, condense with certain halogenated compounds producing thioazoline bases. Moreover, Dixon⁶ has shown that a penthiazoline is formed by the action of bromine on allyl urea. A similar reaction is probable here.



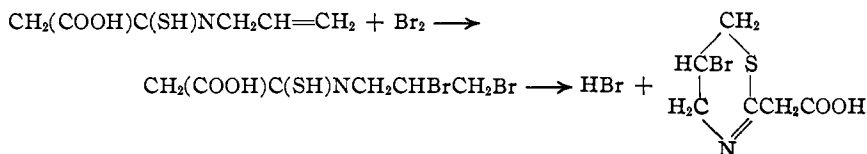
The penthiazoline ester shows only slight evidence of basic character. It readily undergoes hydrolysis when heated with water even without the addition of acid or alkali. Some evidence was found of the presence of hydroxypenthiazoline-acetic acid, but no traces of the intermediate bromo

⁴ Worrall, *THIS JOURNAL*, **50**, 1456 (1928).

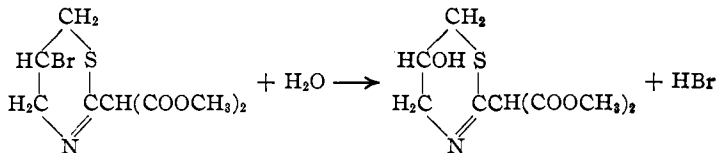
⁵ Unpublished results.

⁶ Dixon, *J. Chem. Soc.*, **69**, 24 (1896).

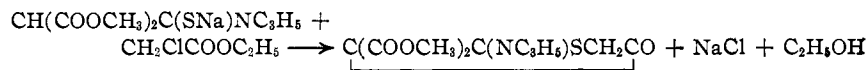
derivative. However, the latter is easily obtained by the action of bromine on malonic acid monothioallylamide.



No difficulty was experienced in replacing halogen in the penthiazoline ester with an hydroxyl group without disturbing the ester radical. Alcoholic silver nitrate quickly brought about the desired change.



The product of the action of malonic ester on allyl mustard oil reacts smoothly in the presence of sodium methylate with ethyl chloroacetate, a reaction discovered by Ruhemann, to form a thiophene derivative.



Experimental

Carbomethoxy Methyl Malonate Monothioallylamide.—To 11.5 g. of sodium suspended in 500 cc. of dry ether were added 66 g. of dimethyl malonate and (the next day) 49 g. of allyl mustard oil. The mixture was allowed to stand for some hours with occasional shaking at room temperature, after which it was heated under a reflux condenser for two hours. The entire contents was poured into ice water and the resulting aqueous layer after separation was added slowly with stirring to a freezing mixture of crushed ice and hydrochloric acid. The resulting bulky precipitate was filtered, washed free from chlorides with cold water and then extracted with a rather large volume of a mixture of approximately equal parts of ordinary ethyl alcohol and water warmed merely to room temperature. On cooling to the freezing point of water, a colorless precipitate of flat needle-like crystals quickly appeared. A yield of 77 g. or approximately 66% of the theoretical amount of fairly pure material was obtained in this manner.

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{O}_4\text{NS}$: S, 13.9. Found: S, 13.7.

The pure substance separates from alcohol-water mixtures in the form of brilliant narrow plates melting at 42–43°. It is easily dissolved by the usual organic solvents, also by aqueous sodium hydroxide, from which it may be recovered unchanged in the cold by the prompt addition of dilute acetic acid. The alkaline solution undergoes decomposition on standing at room temperature.

Malonic Acid Monothioallylamide.—Attempts to prepare this substance by the action of alkali on the ester failed. However, by the use of a less vigorous reagent, namely, hydrazine, the above acid was obtained. To 10 g. of the ester dissolved in alcohol was added the molar equivalent of hydrazine. The mixture was then heated under a reflux condenser for four to five hours and allowed to concentrate to a small

volume. The crystalline product separating on the addition of an excess of hydrochloric acid to the dark red solution was recrystallized from water; yield of crude product, approximately two grams.

Anal. Calcd. for $C_6H_9O_2NS \cdot 2H_2O$: S, 16.4. Found: S, 16.4.

It crystallizes from warm water in brilliant plates. The melting point is not sharp, the substance softening at 115° and partially melting with foaming due to the elimination of water at 120 – 121° . The new thioamide is very soluble in alcohol, although only sparingly soluble in benzene, chloroform and similar solvents.

The preparation of the thiazoline esters may be illustrated by the following experiment. To 30 g. of carbomethoxymethylmalonate monothioallylamide dissolved in a small volume of chloroform and cooled with a freezing mixture was added dropwise the molar equivalent of bromine mixed with chloroform. The clear mixture, after several extractions with cold water to remove hydrobromic acid, was concentrated to a small volume and alcohol added. A prompt removal of the acid is essential as otherwise the substance decomposes even when cold, eventually changing into a tar. The resulting solid after thorough washing with water was crystallized from alcohol; yield of pure material, 27 g.

TABLE I
HALOGEN DERIVATIVES OF PENTHAZOLINE-2-DIMETHYLMALONATE

	Formula	M. p., $^\circ C$.	Cryst. form	Halogen, %	
				Calcd.	Found
-5-Chloro	$C_9H_{12}O_4NSCl$	145–146	Microscopic needles	13.4	13.4
-5-Bromo	$C_9H_{12}O_4NSBr$	153–154	Flat needles	25.8	25.6
-5-Iodo	$C_9H_{12}O_4NSI$	156–157	Flat needles	35.6	35.8

A more complete analysis was made of the bromine compound. Calcd. for $C_9H_{12}O_4NSBr$: C, 34.8; H, 3.9; S, 10.3. Found: C, 35.0; H, 4.2; S, 10.3.

These halogen derivatives are sparingly soluble in hot alcohol, but very soluble in chloroform. They are insoluble in cold sodium hydroxide solution or dilute mineral acids and exhibit marked stability toward concentrated nitric acid even after short heating. Permanganate dissolved in acetone is not reduced. Cold concentrated hydrochloric and sulfuric acids dissolve the substances. On heating with water the bromine derivative gradually dissolves. Carbon dioxide is set free, also hydrobromic acid, and a non-tractable gum is formed which gives forth a pyridine-like odor on neutralization with alkali. It is not changed after several hours' heating with methyl iodide and is recovered unchanged after decomposition with water of the addition product with CH_3MgI in ether.

2-Hydroxy-pentiazoline-2-dimethylmalonate.—To 5 g. of the bromothiazoline ester dissolved in alcohol was added the molar equivalent of silver nitrate and the mixture heated for several hours. Sodium bicarbonate was then added to neutralize the nitric acid formed in the reaction and the mixture filtered. The filtrate was concentrated to a small bulk from which crystals separated on cooling; yield, 3.5 g. It was recrystallized from alcohol.

Anal. Calcd. for $C_9H_{13}O_5NS \cdot 2H_2O$: S, 11.3. Found: S, 11.3.

The hydroxy derivative is soluble in hot water and readily soluble in hot alcohol, separating in slender flat needles melting at 104 – 105° with preliminary softening.

While no satisfactory results were obtained in attempts to hydrolyze the above-mentioned esters, it was found possible to obtain the monocarboxyl derivatives by the action of halogens on malonic acid monothioallylamide as follows. To the substance dissolved in glacial acetic acid was added the appropriate amount of the halogen. A prompt precipitation of the halogen acid salt of the carboxyl derivative took place. The

salt was decomposed after filtration by trituration with water mixed with alcohol, following which the penthiazoline was recrystallized from water.

TABLE II
HALOGEN DERIVATIVES OF PENTHIAZOLINE-2-ACETIC ACID

	Formula	M. p., °C.	Cryst. form	Halogen, %	
				Calcd.	Found
-5-Chloro	$C_6H_5O_2NSCl \cdot 2H_2O$	179-180	Powder	15.5	15.3
-5-Bromo	$C_6H_5O_2NSBr \cdot 2H_2O$	188-190	Flat needles	29.2	28.5
-5-Iodo	$C_6H_5O_2NSI \cdot 2H_2O$	213-214	Feathery needles	39.6	39.8

Considerable difficulty was experienced in obtaining satisfactory results with the bromine derivative, for this substance was acted upon by the vapors of fuming nitric acid and apparently bromine was lost before the tube was sealed. After heating, the inside of the Carius tube was spattered with silver bromide. A sulfur determination was made with the following satisfactory results. Calcd. for $C_6H_5O_2NSBr \cdot 2H_2O$: S, 11.7. Found: S, 11.7.

Apparently water of crystallization is lost on standing, for the bromo derivative was observed to change to a crystalline powder.

Anal. Calcd. for $C_6H_5O_2NSBr$: C, 30.5; H, 3.4. Found: C, 30.3; H, 3.5.

These halogen derivatives soften before the melting point is reached and partially decompose with foaming at the melting point. They are very soluble in glacial acetic acid, moderately so in water and insoluble in alcohol, ether, etc. The addition of hydrogen chloride to a glacial acetic acid solution of these substances precipitates the corresponding salt. They are slowly decomposed by hot water, liberating the corresponding halogen acid and forming a gum similar to that obtained by the hydrolysis of the penthiazoline ester.

2-Allylimino-3-dicarbomethoxy-4-ketotetrahydrothiophene.—A solution of 10 g. of carbomethoxy methylmalonate monothioallylamide in methyl alcohol was mixed with the equivalent amount of sodium methylate and ethyl chloroacetate. Considerable heat developed and on standing a dark green color developed. After an hour or so, a small amount of dilute acid was added to decolorize the solution, which was then poured into water. A bulky precipitate of slender lustrous needle-like crystals formed. It was recrystallized from water containing approximately 10% alcohol.

Anal. Calcd. for $C_{11}H_{13}O_5NS$: S, 11.8. Found: S, 11.8.

It is very sparingly soluble in hot water, from which it separates in long snow-white needles melting at 78-79°. On separation from alcohol the substance retains a yellow color which is not removed by repeated crystallization.

Methylcarbomethoxymethylmalonate Monothioallylamide.—Ten grams of methyl dimethylmalonate was condensed in the customary manner with allyl mustard oil and the product shaken with ice water. Then the water extract was slowly run into a freezing mixture of crushed ice and hydrochloric acid. The crude product was recrystallized by shaking with alcohol at room temperature, cooling with ice, and adding a few drops of water. An oil separated out, but on pouring off the turbid liquid and seeding, small colorless crystals resulted. The substance, which melted on warming to room temperature, was not further examined but was allowed to react in chloroform solution cooled to 0° with bromine. Then water was added to extract the hydrobromic acid. However, the solid product quickly changed to a tar on standing. Apparently a penthiazoline was formed, but it subsequently decomposed.

Summary

Allyl mustard oil forms addition products with dimethyl malonate and methyl dimethylmalonate.

The first addition product undergoes hydrolysis in the presence of hydrazine into methyl malonate monothioallylamide.

It forms addition products with halogens which through the loss of halogen hydride are immediately converted into penthiazolines.

Carbomethoxymethylmalonate monothioallylamide in the presence of sodium methylate forms a thiophene derivative with ethyl chloroacetate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

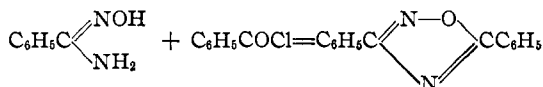
THE FORMATION OF FURO- α,β' -DIAZOLES FROM ACYL IMIDOTHIOCARBONATES AND ACYL PSEUDOTHIUREAS¹

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A review of the literature of the chemistry of furo- α,β' -diazoles or 1,2,4-oxdiazoles reveals the fact that there are essentially two different methods which are available for the synthesis of representatives of this type of heterocyclic compounds, namely, (1) by interaction of amidoximines with acyl chlorides or acid anhydrides according to Tiemann's well-known reaction expressed below, and which has been extensively studied and applied,³ and (2) by the action of hydroxylamine on acyl imidothiocar-



bonates and acyl pseudoureas, or reactions which were reported by Johnson and Menge in 1904.⁴ This latter method of synthesis has never been carefully studied since its discovery; furthermore, the structures of the resulting diazoles were by no means definitely settled in the original contribution. In this paper we shall describe experimental methods which permit us to decide definitely the constitution of the heterocyclic condensation products obtained by the application of Johnson and Menge's reaction.

Johnson and Menge described one experiment illustrating the behavior of hydroxylamine toward an acyl imidothiocarbonate. They observed that hydroxylamine interacted with diethyl benzoylimidothiocarbonate I at ordinary temperature with formation of a compound to which they as-

¹ Constructed from a dissertation presented by Shao Tseng Yang to the Faculty of the Graduate School of Yale University, June, 1931, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

² Holder of a Rockefeller Foundation foreign fellowship, 1929-1931.

³ Tiemann and Krüger, *Ber.*, **17**, 1685 (1884); and many co-workers between 1884 and 1895.

⁴ Johnson and Menge, *Am. Chem. J.*, **32**, 362 (1904).