

3. These compounds react with inorganic iodides to form the corresponding compounds of the type, R_2Hg .

4. These compounds can be saponified without breaking the C-Hg linkage.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TUFTS COLLEGE]

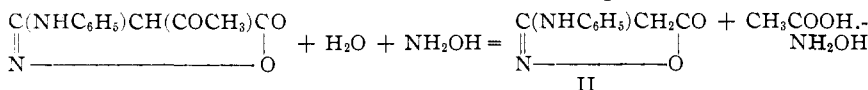
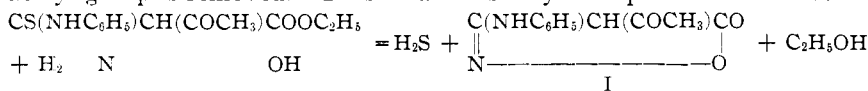
THE ACTION OF HYDROXYLAMINE AND OF HYDRAZINE ON THE ARYL MONOTHIO-AMIDES OF ETHYL ACETYLMALONATE

BY DAVID E. WORRALL

Received March 10, 1922

Sodium aceto-acetic ester reacts easily and smoothly with phenyl- and *para*-substituted phenyl mustard oils to form substituted mono-thio-amides of the general formula, $CH_3COCH(CSNHR)COOC_2H_5$. These thio-amides¹ undergo acid hydrolysis when dissolved in aqueous alkali, so that the acetyl as well as the ethoxy groups are removed. Since the resulting acids, $CH_2(CSNHR)COOH$, lose carbon dioxide when heated, a new and interesting method is offered for the preparation of thio-acetanilide and related compounds. The *ortho*- and *meta*-substituted mustard oils form addition products that are hydrolyzed to ketones in the presence of alkali but as the latter readily undergo further hydrolysis, ultimately the derivatives of thio-acetanilide are formed. Consequently, the various aromatic mustard oils can be used for the preparation of thio-acetanilides. It will be shown in this paper that the mustard oils are also useful for the preparation of certain heterocyclic compounds of the isoxazole and hydrazole series, all of which are new.

A well-known reaction of aceto-acetic ester is the condensation with hydroxylamine to form an isoxazolone. Ethyl acetylmalonate mono-thio-anilide, $CH_3COCH(CSNHC_6H_5)COOC_2H_5$, contains the same grouping and in addition the thio-anilide radical which also is known to react as in thio-acetanilide, with hydroxylamine. Consequently, a reaction would be expected between the mustard oil addition product of aceto-acetic ester and substances such as hydroxylamine. It was found that they react very readily indeed, and that it is sulfur and not oxygen which is attacked by hydroxylamine or hydrazine. The ring is closed by the subsequent elimination of the elements of ethyl alcohol; also, through hydrolysis, the acetyl group is removed. These reactions may be expressed as follows.

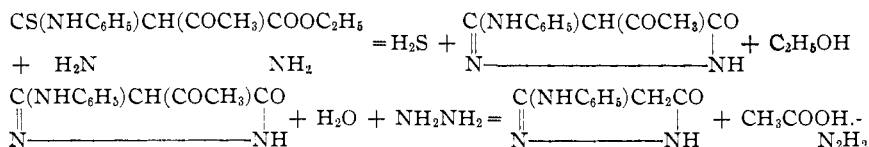


¹ Worrall, THIS JOURNAL, 40, 415 (1918).

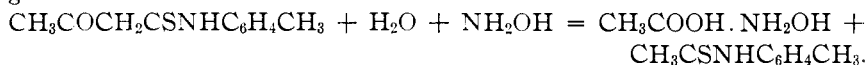
Better yields are obtained by the use of two equivalents of hydroxylamine. With one equivalent of this reagent, the acetyl isoxazole, as fast as it forms, undergoes hydrolysis. The resulting acetic acid forms a salt with unchanged hydroxylamine and, as the salt reacts only slowly with the original thio-anilide, the first reaction cannot proceed to completion. It is not feasible to push the reaction by long application of heat since the salt then decomposes the isoxazole.

The final product (II) is a well defined crystalline solid with a high melting point. It decomposes when heated near the melting point, and is soluble both in acids and in bases. It is not decomposed by prolonged heating with conc. hydrochloric acid. These facts support the view that an isoxazole is formed. The compound is easily benzoylated by the Schotten-Baumann method and acetylated by short heating with acetic anhydride. It does not react with phenyl-isocyanate. The presence of an active methylene group is indicated by the solubility in aqueous alkali, the formation of a copper salt as well as by the condensations with benzaldehyde, its reaction with nitrous acid and with benzene diazonium chloride. Permanganate solution is rapidly reduced, an unusual reaction for an isoxazole, which must be attributed in this case to the anilino group; since the substance is attacked at this point, phenyl-isonitrile is formed.

A similar series of changes takes place when ethyl acetylmalonate monothio-anilide is heated with hydrazine. An excellent yield of the corresponding pyrazolone is obtained, a substance very similar in its properties to the isoxazole, except that it is more distinctly base forming.



Ethyl acetomalonate monothio-(*ortho* or *para*)toluide has not been prepared as yet because of the ease with which it undergoes ketonic hydrolysis to give thio-aceto-acetyltoluide. This thiotoluide is extremely sensitive to bases and, with hydroxylamine, is still further hydrolyzed before any appreciable amount of it reacts in such a way as to form hydrogen sulfide.



Thio-acetyltoluide, of course, will form an oxime with hydroxylamine, but it cannot undergo internal condensation to form an isoxazole. It has not been possible, therefore, to form ring compounds from the addition products of *o*-tolyl- or *m*-tolyl-mustard oils, and the scope of the reaction is correspondingly limited.

The formation of a pyrazole by the action of phenylhydrazine on ethyl-acetylmalonate monothio-anilide has not been observed. Hydrogen sulfide is evolved, and it may be that a pyrazole is formed only to be decomposed by the unchanged phenylhydrazine. The formation of ammonia is evidence that other reactions take place. Symmetrical acetyl-phenylhydrazine is formed and can be isolated.²

That semicarbazide and guanidine bring about hydrolysis of the thio-anilide is indicated by the formation of ethyl acetate. Subsequently, hydrogen sulfide is evolved slowly. The reactions were not studied further because there was no indication of ring formation.

Experimental Part

3-Anilino-5-oxy-isoxazole, $\text{H}_2\text{C}-\text{CNHC}_6\text{H}_5$.—Two equivalents of hydroxylamine



prepared from the hydrochloride by neutralization with the calculated amount of potassium hydrogen carbonate, in alcohol solution was added to 10 g. of ethyl acetylmalonate monothio-anilide. It was found advisable to avoid long refluxing, as otherwise the product was not so pure. The mixture was heated under a reflux condenser for a few minutes and then kept at room temperature for 12 hours; yield, 4.7 g. A small fraction of a gram of decidedly less pure material was recovered by concentration of the filtrate. Addition of water to the latter precipitated several drops of a black tar.

Analysis. Calc. for $\text{C}_9\text{H}_9\text{O}_2\text{N}_2$: N, 15.9. Found: 16.2.

The new isoxazole is soluble in hot alcohol from which it separates in slender cream colored needles. It darkens in color when heated above 165° , and at 180° is changed completely to a black tar. When heated quickly it melts with decomposition and gas evolution at 186° .

The isoxazole decolorizes permanganate in the cold with the formation of isonitrile. It can be nitrated and brominated. It is readily soluble in conc. hydrochloric acid, dil. sodium hydroxide and ammonium hydroxide solutions. It is slightly soluble in hot water and rather sparingly soluble in carbon tetrachloride, glacial acetic acid, benzene and ether. A mustard colored copper derivative is precipitated from hot water solution by copper acetate. The isoxazole decomposes alkali carbonates to form soluble salts when warmed and is acid toward litmus. It does not form a salt with *p*-toluidine, a reaction that takes place with 3-phenyl-isoxazolone.³ An ammonium salt is formed.

Action of Sodium Hydroxide.—One g. of the isoxazole was rubbed with a few drops of sodium hydroxide solution. The resulting pasty mass was then pressed between filter paper; it crystallized from alcohol in lustrous plates. The alcohol solution rapidly acquired a yellow, then a deep red color. Hydrochloric acid reprecipitated the original substance. Metallic sodium appeared to be without action on the isoxazole suspended in dry ether.

Action of Hydrochloric Acid.—The isoxazole was found to be insoluble in dil. hydro-

² Acetyl phenylhydrazine is also formed by the action of phenylhydrazine on thio-diaceto-acetyl anilide, $\text{CH}_3\text{COCH}(\text{CSNHC}_6\text{H}_5)\text{COCH}_3$. This reaction has been incorrectly reported as resulting in the formation of the hydrazone of thioforanilide. Worrall, *THIS JOURNAL*, **42**, 1055 (1920).

³ Uhlenhurth, *Ann.*, **296**, 38 (1897).

chloric acid, but was soluble in conc. acid and was reprecipitated by the addition of water. A salt is formed, however, when the acid mixture is heated. Two g. of the substance was heated under a reflux condenser for 8 hours with 20 cc. of constant-boiling mixture of hydrochloric acid. Salt formation soon took place, but it was desired to observe the effect of long application of heat. The clear solution was then evaporated on the water-bath to a thick, pale yellow sirup which became crystalline on standing. The new substance was very soluble in water, but insoluble in ether and in benzene. It melted at 135° with evolution of carbon dioxide. One g. was carefully neutralized in 10 cc. of water with sodium hydrogen carbonate. The mixture remained clear, but when it was heated a bulky crystalline precipitate formed that proved to be the original isoxazole. The new substance, evidently the hydrochloric acid salt of the isoxazole, was rapidly hydrolyzed by boiling it with water.

Analysis. Calc. for $C_9H_8O_2N_2.HCl$: Cl, 16.7. Found: 16.6.

Action of Nitrous Acid.—One g. of isoxazole was dissolved in dil. sodium hydroxide solution to which was added the equivalent amount of sodium nitrite. This mixture was added dropwise to cold, dil. sulfuric acid which was stirred vigorously. The voluminous solid which separated was crystallized from hot water, in which it was sparingly soluble. This new substance, 3-anilino-4-oximino-5-oxy-isoxazole consisted of slender scarlet needles which deflagrated at 149°.

Analysis. Calc. for $C_9H_7O_3N_3$: N, 20.5. Found: 21.0.

Action of Benzene Diazonium Chloride.—One g. of the original isoxazole was dissolved in a dilute solution of sodium hydroxide cooled with ice. This solution was stirred and the molecular equivalent of freshly prepared benzene diazonium chloride was added to it. The pasty yellow mixture was filtered and the solid crystallized from hot alcohol.

Analysis. Calc. for $C_{15}H_{12}O_2N_4$: N, 20.0. Found: 20.4.

3-Anilino-4-benzene-azo-5-oxy-isoxazole crystallizes from alcohol in yellow needles melting, with decomposition, at 195–197°.

Action of Benzaldehyde.—Three g. of the isoxazole was mixed in alcohol solution with an equivalent amount of benzaldehyde and heated for an hour. The red solution, after it stood overnight, formed a scarlet conglomerate that was repeatedly crystallized from alcohol and finally separated as orange colored needles melting at 170–171°. The new compound was soluble in alkali with some decomposition, as the odor of benzaldehyde was noticeable, and was reprecipitated by acid. This substance was probably 3-anilino-4-benzal-5-oxy-isoxazole, but because of an accident no analysis was made.

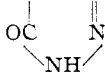
Action of Acetic Anhydride.—One g. of the isoxazole was heated for an hour with approximately 6 g. of acetic anhydride. The solution became brownish in color, though on standing white crystals separated. These were collected and purified.

Analysis. Calc. for $C_{11}H_{10}O_3N_2$: N, 12.8. Found: 13.1.

The acetyl derivative, acetyl-2 or 5-, crystallizes from alcohol in shining white plates and flat needles. It is sparingly soluble in hot water. It melts without decomposition at 145–146°. It is insoluble in a cold solution of sodium hydroxide, but rapidly undergoes hydrolysis to form the soluble sodium salt of the original isoxazole. The latter is precipitated on the addition of acid.

Action of Benzoyl Chloride.—One g. of isoxazole was dissolved in 15 cc. of a dilute solution of sodium hydroxide and then shaken with the molecular equivalent of benzoyl chloride. The white solid that formed was separated and crystallized from hot alcohol. The benzoyl-isoxazole, 2- or 5-, is sparingly soluble in hot alcohol from which it separates in clusters of silky-white needles melting at 157–158°.

3-Anilino-5-oxy-pyrazole, $\text{H}_2\text{C} \text{---} \text{CNHC}_6\text{H}_5$.—To ten g. of ethyl acetylmalonate



monothio-anilid dissolved in alcohol was added 2 equivalents of hydrazine. The mixture was heated under a reflux condenser for 4–6 hours, as long as hydrogen sulfide was freely evolved. A compact crystalline precipitate rapidly formed; at the same time the mixture became dirty green in color, subsequently changing to a clear yellow color. A strong tendency to bump became evident. The operation was interrupted and the mixture filtered. This separation had an added advantage, for the first crop of crystals was snow-white, while those formed subsequently were discolored somewhat and not easy to purify. Total yield, 5.5 g., of which the first lot accounted for approximately 3 g. The presence of acetic acid in the filtrate was confirmed.

Analysis. Calc. for $\text{C}_9\text{H}_9\text{ON}_3$: N, 24.0. Found: N, 24.4.

The pyrazole is sparingly soluble in hot alcohol, separating in tiny, shining, white plates which decompose with gas evolution at $255\text{--}256^\circ$. It is only slightly soluble in the usual organic solvents, but is easily soluble in dil. hydrochloric acid and in aqueous solutions of sodium hydroxide. It is precipitated unchanged from the latter by acid. It decolorizes permanganate and bromine solutions and is violently acted upon by conc. nitric acid. The pyrazole is soluble in warm dil. hydrochloric acid; as the solution cools as an oil separates that subsequently hardens to long flat needles. It can be benzoylated by the Schotten-Baumann method, and forms an acetyl derivative, needles melting at 101° , by heating it with acetic anhydride. An oximino derivative is formed with nitrous acid, brilliant red needles (from hot water). It reacts with benzene diazonium chloride to form an azo compound, occurring as maroon colored irregular plates decomposing at $211\text{--}212^\circ$.

3-*p*-Toluidino-5-oxy-isoxazole, $\text{H}_2\text{C} \text{---} \text{CNHC}_6\text{H}_4\text{CH}_3$.—Ten g. of ethyl acetyl-

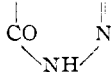


malonate monothio-*p*-toluide, heated for 10 minutes in alcohol solution with 2 equivalents of hydroxylamine and then kept at room temperature for 12 hours, gave approximately 4 g. of product.

Analysis. Calc. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{N}_2$: N, 14.7. Found: 15.0.

It separates from hot alcohol in diamond-shaped, pale yellow crystals that darken above 145° and slowly sinter to threads; it blackens and foams at $155\text{--}156^\circ$. The toluide forms salts with hydrochloric acid and with sodium hydroxide. It is changed by nitrous acid to an oximino derivative, orange colored needles that puff at 142° . A derivative is formed by heating it with acetic anhydride, silky, white, slender needles melting at $149\text{--}150^\circ$.

3-*p*-Toluidino-5-oxy-pyrazole, $\text{CH}_2 \text{---} \text{CNHC}_6\text{H}_4\text{CH}_3$.—Ten g. of ethyl acetyl-



malonate monothiotoluide was heated under a reflux condenser for 30–40 minutes with an alcohol solution of 2 equivalents of hydrazine. The crystalline precipitate was then collected and the filtrate refluxed for 4 hours longer; yield, 5 g.

Analysis. Calc. for $\text{C}_{10}\text{H}_{11}\text{ON}_3$: N, 22.2. Found: 22.5.

The pyrazole is sparingly soluble in hot alcohol, from which it separates as very small glistening square plates, which decompose and foam at $246\text{--}247^\circ$. It is soluble in alkali with development of a red color, and is reprecipitated from this solution by acid.

It forms a salt with hydrochloric acid, lustrous white plates melting at 72–73°, rapidly hydrolyzed by hot water in which the salt is readily soluble. The acetyl derivative, formed by 30 minutes' heating with acetic anhydride, separates from hot alcohol as feathery needles melting at 178–179° with preliminary softening.

3-*p*-Bromo-anilino-5-oxy-isoxazole, $\text{CH}_2\text{—CNHC}_6\text{H}_4\text{Br}$.—Ten g. of ethyl acetyl-



malonate monothio-*p*-bromo-anilide was dissolved in alcohol and treated in the usual way with twice the calculated amount of hydroxylamine; yield, slightly over 4 g.

Analysis. Calc. for $\text{C}_9\text{H}_7\text{O}_2\text{H}_2\text{Br}$: Br, 31.4. Found: 31.3.

The isoxazole crystallizes from hot alcohol in slender, cream colored needles. It darkens gradually above 150°, softening and sintering to a thread that foams and blackens at 188–189°. It separates from hot water, in which it is sparingly soluble, in hair-like needles. The bromo derivative is soluble in alkali and is reprecipitated unchanged by acid; it is soluble in conc. hydrochloric acid, and is decolorized by potassium permanganate, etc.

3-*p*-Bromo-anilino-5-oxy-pyrazole, $\text{CH}_2\text{—CNHC}_6\text{H}_4\text{Br}$.—From 10 g. of ethyl



acetylmalonate monothio-*p*-bromo-anilide heated under a reflux condenser with 2 equivalents of hydrazine nearly 6 g. of product was obtained.

Analysis. Calc. for $\text{C}_9\text{H}_5\text{ON}_3\text{Br}$: Br, 31.5. Found: 31.3.

The pyrazole is very sparingly soluble in hot alcohol and in hot water from which it separates in tiny white plate-like crystals which melt with decomposition and foaming at 234–235°. It forms a rose colored solution with alkali and is reprecipitated by acid; it dissolves in hot conc. hydrochloric acid.

Action of Hydroxylamine on Thio-aceto-acetyl-*o*-toluide.—Five g. of the ketone, $\text{CH}_3\text{COCH}_2\text{CSNHC}_6\text{H}_4\text{CH}_3$, was heated for a few minutes with one equivalent of hydroxylamine. Some hydrogen sulfide was evolved but the chief reaction was hydrolysis of the ketone resulting in the formation of hydroxylamine acetate and thio-acetyl-*o*-toluide both of which were identified. The toluide separated as an oil, as the solution cooled; it quickly hardened to flat needles melting at 91–92°.

Action of Phenylhydrazine on Ethyl Acetylmalonate Monothio-anilide.—To 5 g. of the ester was added 5 g. of freshly distilled phenylhydrazine. Considerable evolution of heat took place, while the odors of hydrogen sulfide and ammonia were noticed. The mixture subsequently hardened to a thick mass which was pressed on a porous plate and repeatedly crystallized from hot alcohol. White crystals, melting at 128°, were finally obtained. The substance was identified by comparison with a known sample as acetyl-phenylhydrazide, $\text{CH}_3\text{CONHNHC}_6\text{H}_5$.

Summary

The phenyl, *p*-bromophenyl and *p*-tolyl mustard oil addition products of aceto-acetic ester react with hydroxylamine and hydrazine to form, respectively, isoxazoles and pyrazoles.

The derivatives are crystalline solids which decompose when they are heated near their melting points. Salts are formed with both acids and bases.

They are easily benzoylated and acetylated, and form condensation products with benzaldehyde. They react with nitrous acid and with benzene diazonium chloride.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TEXAS]

ISOPROPYL, MENTHYL AND BORNYL SEMICARBAZIDES. REDUCTION OF PHENYLHYDRAZONES

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Isopropyl Semicarbazide¹

Introduction

Lochte and Bailey by employing the Skita method of reduction with colloidal platinum as catalyst succeeded in preparing 2,2'-hydrazobispropane, $(\text{CH}_3)_2\text{CHNHNHCH}(\text{CH}_3)_2$, from dimethyl-ketazine, $(\text{CH}_3)_2\text{C}=\text{NN}=\text{C}(\text{CH}_3)_2$. This reaction with the use of other reducing agents had been previously attempted by other investigators with negative results.² It is evident that a successful extension of this kind of reduction will be of great preparative value, more especially in the aliphatic and hydroaromatic series, in obtaining hydrazine derivatives, since it will make available as intermediates the numerous hydrazones and azines which are easily obtained from the corresponding aldehydes and ketones. The work on hydrazopropane, azopropane, and isopropylhydrazine is being continued by Lochte in the University of Illinois as a thesis problem with Professor W. A. Noyes.³

In the Texas laboratory several lines of investigation, involving the reduction of the $\text{C}=\text{N}$ complex, are under way. In the present paper it is shown that acetone semicarbazone, $(\text{CH}_3)_2\text{C}=\text{NNHCONH}_2$, yields isopropyl semicarbazide, and a preliminary report is submitted on the reduction of camphor and menthone semicarbazones, and acetaldehyde phenylhydrazone.

An extensive investigation on the reduction of semicarbazones with sodium amalgam has recently been carried out by Rupe and Oestreicher⁴ with the purpose of preparing the corresponding semicarbazides. It developed in this work that the reduction by the method they employed takes place only in such cases where the $\text{N}=\text{C}$ complex is joined through its carbon atom to an aryl or other electronegative radical. The result

¹ By De Witt Neighbors and J. R. Bailey.

² Curtius, *J. prakt. Chem.*, [2] **44**, 163 (1891). Thiele, *Ann.*, **376**, 262 (1910). Maible, *Compt. rend.*, **170**, 1265 (1920).

³ Noyes, Lochte and Bailey, *THIS JOURNAL*, **43**, 2603 (1921). Ref. 24.

⁴ Rupe and Oestreicher, *Ber.*, **45**, 30 (1912).