[Contribution from the Chemical Laboratory of Tufts College]

THE ACTION OF HYDROXYLAMINE AND OF HYDRAZINE ON THE ARYL MONOTHIO AMIDES OF CARBETHOXY-ETHYLMALONATE

By David E. Worrall

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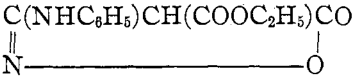
The addition products obtained by the action of phenyl mustard oil and *para* substituted mustard oils on ethyl aceto-acetate were shown in a previous communication[1] to be useful for the preparation of heterocyclic compounds of the isoxazole and pyrazole series. The reagents used were hydroxylamine and hydrazine. Similar series of reactions have been found to take place with the corresponding mustard oil addition products of malonic ester.

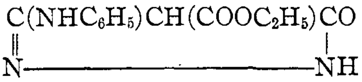
Thus, carbethoxy-ethylmalonate monothio-anilide, formed by the action of phenyl mustard oil on diethylmalonate reacts with hydroxylamine as follows: $CS(NHC_6H_5)CH(COOC_2H_5)COOC_2H_5 + NH_2OH = H_2S +$



$$\underset{N\text{————————————}O}{\overset{\|\qquad\qquad\qquad\qquad\qquad\qquad |}{C(NHC_6H_5)CH(COOC_2H_5)CO}} + C_2H_5OH.$$

The actual product obtained is the hydroxylamine salt of the above compound; consequently, it is necessary to use two equivalents of the base. The free isoxazole is obtained by decomposition of the salt with hydrochloric acid. It is less basic than the corresponding isoxazole obtained from aceto-acetic ester and does not form a salt with acids. It is insoluble even in warm concd. hydrochloric acid. It readily dissolves in dil. sodium hydroxide solution, changing to a sodium salt.

Hydrazine reacts with carbethoxy-ethylmalonate monothio-anilide to form a pyrazole: $CS(NHC_6H_5)CH(COOC_2H_5)COOC_2H_5 + NH_2NH_2 = H_2S +$



$$\underset{N\text{————————————}NH}{\overset{\|\qquad\qquad\qquad\qquad\qquad\qquad |}{C(NHC_6H_5)CH(COOC_2H_5)CO}} + C_2H_5OH.$$

The pyrazole is soluble in warm concd. hydrochloric acid solution and is also soluble in sodium hydroxide solution from which the sodium salt may be isolated.

The series of reactions starting with malonic ester and resulting ultimately in isoxazoles and pyrazoles is somewhat less restricted in scope than the series beginning with ethyl aceto-acetate. This is due to the fact that the addition products of *ortho* and *meta* substituted mustard oils to ethyl aceto-acetate undergo hydrolysis so readily to the thio amides of acetic acid that ring formation is not possible.[1] No such difficulty presents itself in the malonic ester series.

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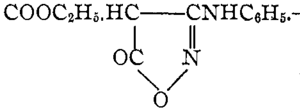
[1] Worrall, This Journal, **44**, 1551 (1922).

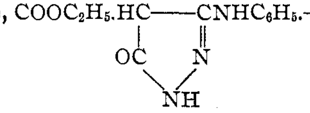
Experimental Part

3-Anilino-4-carbethoxy-5-oxy-isoxazole, —To 10 g. of carbethoxy-ethylmalonate monothio-anilide were added 2 equivalents of free hydroxylamine dissolved in approximately 80 cc. of alcohol and prepared by neutralization of the hydrochloride with potassium hydrogen carbonate. The mixture was heated under a reflux condenser for 6 hours and then poured into a beaker where it rapidly solidified to a sticky cake. This product was dried on a porous plate, stirred with 50 cc. of warm water with which it formed a thick paste, and 10 cc. of dil. hydrochloric acid was added. A gum formed as a result of the action of the acid, but it quickly changed to a compact crystalline substance, easy to manipulate; yield, 6.5 g. Finally, the isoxazole was further purified by two crystallizations from an alcohol.

Analyses. Calc. for $C_{12}H_{12}O_4N_2$: C, 58.1; H, 4.8. Found: C, 58.4; H, 4.6.

It is readily soluble in hot alcohol from which it separates in small, stout needles softening at 160° and melting at 166° with foaming, due to the evolution of carbon dioxide, accompanied by decomposition.

Permanganate solution is decolorized in the cold by the isoxazole, resulting in the formation of phenyl isonitrile. It reacts with bromine in glacial acetic acid solution to form a crystalline derivative, but it is changed to a tar by concd. nitric acid. It is insoluble in concd. hydrochloric acid even when warmed and sparingly soluble in hot water. Warm sodium hydroxide solution easily dissolves the substance, forming a sodium salt that separates in the form of slender needles as the solution cools. A mustard-colored copper salt is precipitated from hot water solution by copper acetate.

3-Anilino-4-carbethoxy-5-oxy-pyrazole, —Two equivalents of free hydrazine, prepared from the sulfate by neutralization with potassium hydrogen carbonate, dissolved in 80 cc. of alcohol were added to 10 g. of carbethoxy-ethylmalonate monothio-anilide. The mixture was heated under a reflux condenser for 4 to 5 hours. A dark green color developed at first but subsequently disappeared. The bulky crystalline product that formed on standing was filtered with suction, washed with a few cubic centimeters of cold water and mixed with approximately 50 cc. of water containing 10 cc. of dil. hydrochloric acid. No apparent change took place. The product was filtered by suction and recrystallized from 100 cc. of alcohol; yield, approximately 5 g.

Analyses. Calc. for $C_{12}H_{13}O_3N_3$: C, 58.3; H, 5.3. Found: C, 58.2; H, 5.2.

The pyrazole is sparingly soluble in hot water and somewhat more soluble in hot alcohol. A voluminous precipitate of fluffy white needles separated as the solution cooled. It softened at 187°, partially melting with decomposition at 194–195°. It decolorized both permanganate solution and bromine dissolved in carbon tetrachloride, and was violently acted upon by concd. nitric acid to form a black tar. A sodium salt, lustrous white leaves rapidly hydrolyzed by hot water, formed when the material was warmed with sodium hydroxide solution.

3-*o*-Toluidino-4-carbethoxy-5-isoxazole, $COOC_2H_5.C_3H_2ON.NHC_6H_4CH_3$.—A mixture of 10 g. of crude[2] carbethoxy-ethylmalonate monothio-*o*-toluide with two equivalents of hydroxylamine in alcohol solution was heated for 6 hours under a reflux conden-

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[2] The thio compound obtained by the action of *o*-tolyl mustard oil on malonic ester did not crystallize on standing; hence it had to be used without purification.

ser. The product which separated on cooling was filtered with suction, decomposed with hydrochloric acid and twice crystallized from alcohol; yield of purified substance, approximately 2 g.

Analyses. Calc. for $C_{13}H_{14}O_4N_2$: C, 59.5; H, 5.3. Found: C, 59.2; H, 5.1.

The isoxazole crystallizes from alcohol in flat needles and plates melting with decomposition at 165–167° with preliminary softening.

3-*o*-Toluidino-4-carbethoxy-5-oxy-pyrazole, $COOC_2H_5.C_2H_2ON_2.NHC_6H_4CH_3$.—A mixture of 10 g. of crude carbethoxy-ethylmalonate monothio-*o*-toluide with an alcoholic solution of two equivalents of hydrazine was heated until no further evolution of hydrogen sulfide took place. The precipitate which formed on cooling was treated with hydrochloric acid to free it from hydroxylamine, filtered off and twice crystallized from alcohol; yield, approximately 2 g.

Analyses. Calc. for $C_{13}H_{15}O_3N_3$: C, 59.8; H, 5.7. Found: C, 59.4; H, 5.5.

The pyrazole separates from alcohol in flocks of feathery, white needles. It softens at 205°, partially melting with decomposition at 215°.

3-*p*-Toluidino-4-carbethoxy-5-oxy-isoxazole, $COOC_2H_5.C_3H_2O_2N.CHNC_6H_4CH_3$.—A mixture of 10 g. of carbethoxy-ethylmalonate monothio-*p*-toluide with two equivalents of hydroxylamine in alcoholic solution was heated under a reflux condenser for 5 hours. Then 4 cc. of concd. hydrochloric acid was added directly to the hot alcoholic solution. Since the resulting precipitate contained considerable inorganic material it was twice digested with 25 cc. of warm water, cooled and filtered with suction; yield, 5.2 g. The product was finally crystallized from alcohol.

Analyses. Calc. for $C_{13}H_{14}O_4N_2$: C, 59.5; H, 5.3. Found: 59.7; H, 5.3.

The *p*-toluidino-isoxazole separates from alcohol in needles and plates melting with decomposition at 172–173°.

3-*p*-Toluidino-4-carbethoxy-5-oxy-pyrazole, $COOC_2H_5.C_3H_2ON_2.NHC_6H_4CH_3$.—A mixture of 10 g. of carbethoxy-ethylmalonate monothio-*p*-toluide with two equivalents of hydrazine in alcoholic solution was heated under a reflux condenser for four hours; 5 cc. of concd. hydrochloric acid was added to the mixture while it was still warm. The product was thoroughly washed with water and then was crystallized from alcohol; yield of purified substance, 4 g.

Analyses. Calc. for $C_{13}H_{15}O_3N_3$: C, 59.8; H, 5.7. Found: C, 60.0; H, 5.7.

The pyrazole separates from alcohol as a bulky precipitate of feathery needles. When heated above 200° it undergoes slow decomposition without melting.

3-*p*-Bromo-anilino-4-carbethoxy-5-oxy-isoxazole, $COOC_2H_5.C_3HO_2N.NHC_6H_4Br$.—Five g. of carbethoxy-ethylmalonate monothio-*p*-bromo-anilide was treated in the customary manner with hydroxylamine, the product decomposed with acid and purified by crystallization from alcohol; yield of purified compound, 2.4 g.

Analysis. Calc. for $C_{12}H_{11}O_4N_2Br$: Br, 24.5. Found: 24.1.

The bromo-anilino-isoxazole separates from alcohol in slender needles which slowly sinter together and melt with decomposition at 163–170°.

3-*p*-Bromo-anilino-4-carbethoxy-5-oxy-pyrazole, $COOC_2H_5.C_3H_2ON_2.NHC_6H_4Br$.—Five g. of carbethoxy-ethylmalonate monothio-*p*-bromo-anilide was heated in alcohol solution with two equivalents of hydrazine, the product treated with acid and recrystallized from alcohol.

Analysis. Calc. for $C_{12}H_{12}O_3N_3Br$: Br, 24.5. Found: 24.2.

The new pyrazole separates from alcohol in small fluffy needles, which soften at 212° and melted at 217°.

Summary

The addition products obtained by the action of phenyl, *o*-tolyl, *p*-tolyl and *p*-bromo mustard oils on diethylmalonate condense with hydroxylamine and hydrazine to form, respectively, isoxazoles and pyrazoles.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE KETENIC DECOMPOSITION OF KETONES. KETENE AND METHYL KETENE

BY CHARLES DEWITT HURD

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Undoubtedly, the best way to prepare ketene is to decompose acetone vapors at high temperatures. Recently, it has been demonstrated that ketene may be prepared in a similar manner, but with poorer yields, from methylethyl ketone. It was considered probable that methyl ketene would also be formed in this reaction, but there seemed to be no positive evidence for such an occurrence.[1]

Ketene was identified as acetanilide, its reaction product with aniline. Methyl ketene would have formed propionanilide. This was not isolated, but there was found an unidentified crystalline product that melted at 80°, about 25° lower than the melting point of propionanilide. A similar low-melting toluidine reaction product was observed. One purpose of the present investigation was to establish the identity of these substances.

A second problem with which this paper deals was to ascertain whether or not methyl ketene was decomposed by heat. An opinion was expressed by Hurd and Kocour[2] that methyl ketene may actually have been prepared in their experiment, but that it may have decomposed at the temperature to which it was exposed. In order to answer this question, it was approached from two angles. First, an apparatus was built which heated the ketone vapors for a briefer period of time than formerly. The heating unit of this consisted of an electrically heated platinum filament, described below. If methyl ketene is susceptible to heat, an apparatus of this type should result in an augmented yield of methyl ketene. It seems probable that a short combustion furnace instead of the long one employed formerly, might also produce an increased yield of methyl ketene. This idea has not been tried experimentally as yet, however.

In the second place, a study was made of the ketenic decomposition of diethyl ketone. Because of its symmetrical structure, this ketone should

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[1] (a) Hurd and Kocour, THIS JOURNAL, **45**, 2167 (1923). For the preparation of ketene from acetone, see (b) Hurd and Cochran, *ibid.*, **45**, 515 (1923); also, a footnote to the article by Hurd and Kocour.

[2] Ref. la, p. 2168.