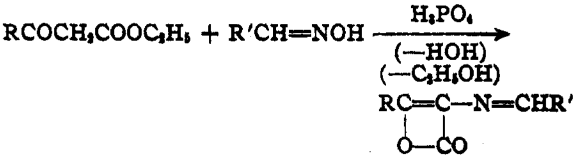
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

A Synthesis of Arylidene Isoxazolones[1]

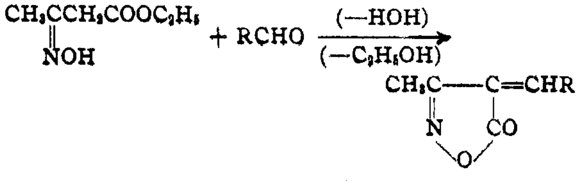
BY JOHN J. DONLEAVY AND EVERETT E. GILBERT

In 1928–1929 G. Minunni and others published a series of papers[2–4] in which a reaction between aromatic aldoximes and beta keto esters was investigated. The interaction of these substances in the presence of phosphoric acid was described as leading to the formation of alpha arylidene crotonic acid lactones in the case of acetoacetic ester, and alpha arylidene cinnamic acid lactones in the case of benzoyl acetic ester



A careful study of their conditions of experiment and a consideration of the structures assigned to the reaction products led the writers to believe that grave doubt existed as to the validity of their observations. As formulated by Minunni these products are beta lactones, which experience[5] has shown to be extremely unstable. The presence of a double bond in these products should tend toward even greater instability. The substances exhibit, however, marked stability toward acids since they are prepared in a strongly acid medium and may be recovered unchanged even after prolonged heating in concentrated sulfuric acid. Furthermore, oximes as a class show little or no tendency to form anils by loss of water in reaction with activated hydrogens. Finally, beta keto esters as a class have never been observed to condense in the sense of beta lactone formation.

As a result of these conclusions, the work of Minunni and his collaborators has been repeated in its entirety. The striking similarity of the products obtained in this way to those obtained by R. Schiff and M. Betti[6] by treating acetoacetic ester oxime or its anilide with various aromatic aldehydes led to the thought that the substances obtained by Minunni might be isoxazolones of the same type as those obtained by Schiff and Betti. The corresponding methylisoxazolones were accordingly prepared by the independent method of Schiff and Betti, and upon comparison proved to be identical with the products obtained by Minunni. In the case of the phenylisoxazolones derived from benzoylacetic ester, we have treated the aldehydes directly with 3-phenylisoxazolone-5 according to the technique developed by A. Wahl and A. Meyer.[7] These are also identical with the corresponding products obtained by Minunni from benzoylacetic ester and aromatic aldoximes.



As a result of the above observations it is now established beyond any reasonable doubt that the products described by Minunni and his coworkers as alpha arylidene amino lactones are in fact arylidene isoxazolones.

Minunni further studied the behavior of his so-called lactones with phenylhydrazine and with warm dilute alkali. By using his method of treatment we have obtained products with the properties and with the empirical formulas he has described; however, these reaction products also arise from the corresponding isoxazolones by exactly the same course of treatment. In this way we have proved that both the parent substances and the derivatives must have very different structures from those originally assigned by him.

In a typical case he treated what we now know to be 3-phenyl-4-benzylidene-isoxazolone-5 with phenylhydrazine (2 moles) and obtained what he termed α-amino-β-hydroxycinnamic acid phenylhydrazide. We have found this to be the phenylhydrazine salt of 3-phenylisoxazolone-5; it is identical with the salt obtained directly from 3-phenylisoxazolone-5 by the action of phenylhydrazine

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(1) This communication describes work done by Everett E. Gilbert in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(2) G. Minunni and S. D'Urso, *Gazz. chim. ital.*, **58**, 485 (1928); *C. A.*, **23**, 1120 (1929).

(3) G. Minunni, S. D'Urso, V. Bellecci, and I. Ottaviano, *Gazz. chim. ital.*, **59**, 32 (1929); *C. A.*, **23**, 3676 (1929).

(4) G. Minunni, I. Ottaviano, and V. Spina, *Gazz. chim. ital.*, **59**, 116 (1929); *C. A.*, **23**, 3914 (1929).

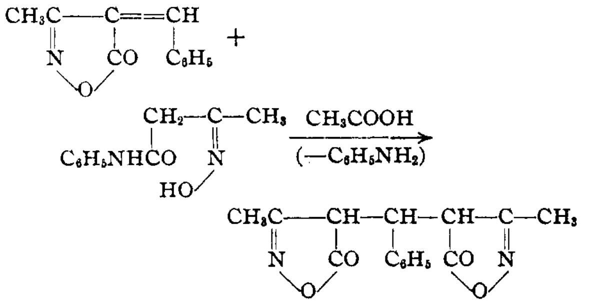
(5) H. Staudinger, "Die Ketene," Stuttgart, 1912, p. 60.

(6) R. Schiff and M. Betti, *Ber.*, **30**, 1337 (1897).

(7) A. Wahl and A. Meyer, *Bull. soc. chim.*, [4] **3**, 952 (1908).

by the method described by R. Uhlenhuth.[8] (In the case of the arylidene isoxazolones, the corresponding aldehyde phenylhydrazone was also formed.)

We have found the action of alkali on these compounds to be specific for each compound. On treating 3-methyl-4-benzylidene-isoxazolone-5 with hot aqueous 5% sodium carbonate, Minunni obtained a product which he made no attempt to analyze or identify. We have obtained a product agreeing with the physical properties he has cited. It also agrees in every way with a product originally obtained by Schiff and Betti[6] by alkaline hydrolysis of the isoxazolone. They tentatively proposed the structure I. We have also produced this compound by the action of phenylhydrazine on the parent substance under mild conditions. Minunni obtained it from the parent substance by the mild action of hydroxylamine. He also corroborated Schiff and Betti's observation that exactly half a mole of benzaldehyde was removed per mole of product formed. We have also been able to synthesize this product by treating acetoacetic ester oxime anilide with 3-methyl-4-benzylidene-isoxazolone-5 in glacial acetic acid.



I

We have also found it possible to prepare a new diethyl derivative of this substance. However, all attempts made by us to synthesize this product by the direct action of hydroxylamine on benzylidene bis-acetoacetic ester resulted in failure because of the practical impossibility of preparing the last-mentioned material in pure form.

On heating 3-phenyl-4-benzylidene-isoxazolone-5 with 10% aqueous sodium carbonate for several hours, we obtained benzaldehyde and 3-phenylisoxazolone-5, which behavior is in marked contrast to that of the methyl analog just discussed. 3-Methylanisylidene-isoxazolone-5 could be reprecipitated unchanged by mineral acid after the above treatment; in cases where Minunni observed more than the melting point, he tended to assign formulas to all the above-mentioned compounds without the support of corroborative data, and often even without analyses.

In an attempt to widen its scope, a further study of the mechanism of the above reaction was made. Condensation will occur in the presence of any strong acid. Minunni used concentrated phosphoric acid of unspecified strength; Schiff and Betti[6] used hydrogen chloride gas or strong aqueous hydrochloric acid. We have found that sulfuric acid of strength from 40 to 60% may be employed. Hydrated oxalic acid may be used to advantage because of its mildness. Concentrated sulfuric acid and concentrated hydrochloric acid tend to produce decomposition into black tarry products. Acetic acid gave no evidence of reaction; several basic catalysts were tried without success. Iodine also gave no reaction. Maximum yields of 65% were obtained in the case of acetoacetic ester by allowing the components to stand for one day at room temperature mixed with 10% of the total weight of 85% phosphoric acid. However, in the case of benzoylacetic ester, heating for three hours at 100° was necessary for condensation to occur. Prolonged heating or too high temperatures tended to reduce the yields and to produce decomposition.

Aliphatic oximes in general we have found to produce viscous glassy polymeric products when applied in the above reaction. Aliphatic and alicyclic ketoximes condensed with poor yields (20%) or not at all.

The mechanism of this reaction appears to be as follows. First hydrolysis of the oxime occurs, liberating the parent aldehyde and hydroxylamine. Formation of the glassy polymers from the aliphatic oximes is due no doubt to the polymerization of the aldehydes in the strongly acid medium. It appears probable that the next step in the reaction is the condensation of the aldehyde with the active methylene group. We believe such to be the case since *n*-butylacetoacetic ester could not be made to take part in the above reaction, even to the extent of forming *n*-butylisoxazolone. The next step consists of the formation of the beta ketoxime by means of the hydroxylamine split out in the first stage and its ring closure to form the isoxazolone ring.

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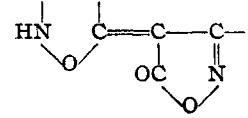
[8] R. Uhlenhuth, *Ann.*, **296**, 44 (1897). The carbonyl group in the isoxazolone ring does not condense in the sense of a ketone. Since isoxazolones as a class are strongly acidic, they form very stable salts with bases. This particular product reduces Fehling's solution, a behavior to be expected from phenylhydrazine salts, but not from phenylhydrazones.

Structure of the Alleged Methylisoxazolone.—Thinking that the methyl arylidene isoxazolones might easily be prepared by condensing an aldehyde with 3-methylisoxazolone-5 (as Wahl and Meyer[7] had done in the case of the 3-phenyl analog), we prepared what was described as this substance by several authors. It was found to be unexpectedly inert toward aldehydes, while the phenyl analog condensed easily under the same conditions. A. Hantzsch[9] had obtained the so-called methylisoxazolone by allowing acetoacetic ester to stand with an equivalent weight of hydroxylamine for several hours in strongly alkaline solution; he cites unconvincing analytical data. A product of identical physical properties was obtained by L. Knorr and B. Reuter[10] by treating acetoacetic ester oxime anilide with strong acids or with strong bases; they cite no analytical data. R. Uhlenhuth[8] prepared an exhaustive series of salts and alkyl derivative of this substance. By a long series of careful analyses (which did not include an analysis of the original substance), he proved that they were all mono derivatives of two methylisoxazolone molecules minus one molecule of water. He made no attempt to propose structures, but merely suggested that methylisoxazolone might be "dimolecular," or that when salt formation occurred, two molecules united with loss of water. A molecular weight determination made by Uhlenhuth agrees well with a dimolecular structure of some sort.

We have resynthesized this substance according to the method of Hantzsch, and on analysis have found it to correspond exactly to a molecule formed from two methylisoxazolone molecules by loss of one molecule of water. Since the alkylation of isoxazolones always occurs on the nitrogen[8] (which exhibits strongly acidic behavior), and since the formation of mono derivatives only has been observed, we have concluded that one of the two rings must lack the necessary hydrogen, and that therefore structure II is the only possible one.



II

The melting points of related isoxazolones found in the literature also preclude any monomolecular structure. 3-Methyl-4-chloroisoxazolone-5 melts at 86°,[11] 3-methyl-4-benzylisoxazolone-5 melts at 106°;[11] other cases could be cited to show that melting points of the 3-methylisoxazolones become higher with increasing molecular weight of the substituent in the 4-position. It is therefore strange that the alleged methylisoxazolone should melt at 169°, a figure higher than any of its recorded 4-substituted derivatives. Methylisoxazolone has accordingly never been prepared. The compound thought by various workers to be this substance was actually "dimethyl-diisoxazolone."

The structure and the autocondensation reaction of methylisoxazolone bear striking similarities to those of gamma-butyrolactone. This lactone is composed of a five-membered ring containing an active methylene group adjacent to an ester grouping; the same is true of the isoxazolone. Butyrolactone also condenses with itself in the presence of alkaline agents to form a "dimolecular" product, water being liberated between a keto and a methylene group. However, it might be expected that methylisoxazolone would condense even more easily in this sense, since its active methylene would be rendered even more active by the possibility of a double bond on the nitrogen (producing activity similar to that found in the methyl group of quinaldine).

Experimental

Preparation of 3-Methyl-4-benzylidine-isoxazolone-5.—One-half mole each of benzaldoxime (60.5 g.) and acetoacetic ester (65 g.) were mixed, and 10% of the total weight of phosphoric acid (12.5 g.) was added with gentle shaking. The mixture was allowed to stand overnight at room temperature. The solid product which separated was then filtered, and successive crops were obtained from the sirupy filtrate by allowing it to stand further. The pure product was obtained in the form of yellow crystals upon recrystallization from benzene. It melted to a clear yellow liquid at 146–147° (corr.). The yield of recrystallized product was 65% of the theoretical (94 g.).

Anal. Calcd. for $C_{11}H_9O_2N$: N, 7.49. Found: N, 7.53, 7.30.

The same isoxazolone was then made by the method of Schiff and Betti[6] from benzaldehyde and acetoacetanilide oxime; glacial acetic acid was used instead of hydrochloric as they suggest. The melting point and physical properties were found to be the same as those of the above compound, and a mixed melting point showed no depression.

3-Phenyl-4-benzylidene-isoxazolone-5.—Equivalent amounts of benzoylacetic ester (19.2 g.) and benzaldoxime (12.1 g.) were condensed in the presence of phosphoric acid (5 g.) by heating for three hours at 100° with occasional shaking. The combined crops of crystals were

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(9) A. Hantzsch, *Ber.*, **24**, 498 (1891).

(10) L. Knorr and B. Reuter, *ibid.*, **27**, 1174 (1894).

(11) R. Schiff and G. Viciani, *ibid.*, **30**, 1159 (1897).

recrystallized from ethanol, and melted to a clear yellow liquid at 193–194° (corr.). The yield of pure product was 48% (12.8 g.).

Anal. Calcd. for $C_{16}H_{11}O_2N$: N, 5.62. Found: N, 5.42, 5.32.

The same isoxazolone was synthesized from phenylisoxazolone and benzaldehyde, using the method described by Wahl and Meyer,[7] 3-phenylisoxazolone-5 being first made by the method of Hantzsch.[8] The crystals were exactly similar to those obtained above. A mixed melting point showed no depression.

3-Phenyl-4-anisylidene-isoxazolone-5.—This compound was synthesized by heating equivalent amounts of benzoylacetic ester (19.2 g.) and anisaldoxime (15.1 g.) with phosphoric acid (5.0 g.) at 100° for three hours. Lemon-yellow needles were obtained from ethanol in a yield of 60% of the theoretical (17.0 g.); it melted at 164–165° (corr.) to a clear yellow liquid.

Anal. Calcd. for $C_{17}H_{13}O_3N$: N, 5.02. Found: N, 5.07, 5.17.

Yellow crystals exactly similar to those just described were obtained by the method of Wahl and Meyer used above; in this case phenylisoxazolone was condensed with anisaldehyde. A mixed melting point showed no depression. The products were identical.

3-Methyl-4-anisylidene-isoxazolone-5.—Acetoacetic ester (13.0 g.) and anisaldoxime (15.1 g.) condensed in 75% (16.1 g.) yield by being allowed to stand at room temperature in the presence of phosphoric acid (5 g.). On recrystallization from alcohol yellow needles were obtained melting to a clear liquid at 180–181° (corr.). This product has never before been described as such in the literature.

Anal. Calcd. for $C_{12}H_{11}O_3N$: N, 6.45. Found: N, 6.38, 6.68.

3-Methyl-4-isopropylidene-isoxazolone-5.—Acetone oxime (7.3 g.) and acetoacetic ester (13.0 g.) condensed in 20% yield (2.6 g.) on being allowed to stand at room temperature with phosphoric acid. On recrystallization from ethanol white flakes were obtained from ethanol which melted to a clear liquid at 120–121° (corr.). Attempts to obtain further crops failed in this case. This product is identical in properties with that obtained by Schiff and Betti from acetoacetic ester oxime and acetone.[6]

Anal. Calcd. for $C_7H_9O_2N$: N, 10.08. Found: N, 10.03, 10.00.

Cyclohexanoneoxime, acetaldoxime, and heptaldoxime could not be condensed in the above sense. In the last two cases viscous glasses were obtained on allowing the oximes to stand with acetoacetic ester and phosphoric acid. *n*-Butylacetoacetic ester gave no reaction in the above sense even when heated to 120° for one hour; some starting material and its hydrolytic products were recovered.

Preparation of Compound I. Alkaline Hydrolysis of the Isoxazolones.—3-Methyl-4-benzylidene-isoxazolone-5 (15.0 g.) was suspended in 200 cc. of aqueous sodium carbonate solution. This was kept at 70° until solution was complete (about one hour). During this time benzaldehyde collected on the surface in an oily layer. The solution was cooled, and ether extracted to remove benzaldehyde. It was then acidified strongly with dilute hydrochloric acid. A gum separated which always crystallized on trituration with the acid. The crystals were filtered and washed with dilute acid. The yield of crude product was 90% of the theoretical (9.6 g.). It may be recrystallized from hot water, observing precautions to carry out the operation at maximum speed since the compound decomposed to red products if heated for a prolonged period at the temperature of boiling water. It was a yellow powder, melting with decomposition and effervescence to a red liquid at 150–151° (corr.). If it was recrystallized from ethanol, it separated as a white powder which turned pink and then yellow on exposure to the air. However, the compound crystallized only with difficulty from this solvent. The product was soluble in bases and could be reprecipitated on acidification with mineral acids. It was slightly soluble in cold water, quite soluble in hot water. Its water solution was acid toward litmus.

Anal. Calcd. for $C_{15}H_{14}O_4N_2$ (as in formula I): N, 9.79. Found: N, 9.82, 9.82.

The same hydrolysis product was obtained from samples of 3-methyl-4-benzylidene-isoxazolone-5 made both by Minunni's method and by the method of Schiff and Betti. A mixed melting point showed no depression.

A compound identical with the hydrolysis product just described was prepared by a new and independent method. One gram of 3-methyl-4-benzylidene-isoxazolone-5 was dissolved in glacial acetic acid and 1 g. of acetoacetanilide oxime was then added with shaking. It went into solution with evolution of heat and on standing for several hours yellow prisms formed. One recrystallization from glacial acetic acid and one from hot water gave a product melting as above. The yield was 1.1 g. or 69% of the theoretical. A mixed melting point with the above compound showed no depression.

To prepare its diethyl derivative, 10 g. of the above compound was dissolved in 5% aqueous sodium carbonate. Slightly more than two molecular quantities of diethyl sulfate (11.0 g.) were added and the mixture was shaken at room temperature for twelve hours. It was then extracted three times with ether. On evaporation of the ether, white prisms were obtained, which were recrystallized from alcohol. It melted to a clear colorless liquid at 159–161° (corr.). The yield was 50% of the theoretical (6.0 g.).

Anal. Calcd. for $C_{19}H_{22}O_4N_2$: N, 8.19. Found: N, 8.0, 8.04.

3-Phenyl-4-benzylidene-isoxazolone-5 was dissolved in excess 10% aqueous sodium carbonate and heated for three hours on a boiling water bath. On acidification a gum formed, which crystallized on trituration. Recrystallized from benzene, the product showed no definite melting point, but began to soften at 120°, finally melting with decomposition to a red liquid at about 155°. A mixture of phenylisoxazolone and phenylbenzylideneisoxazolone showed the same melting phenomena. Final proof that the product was a mixture of the two was obtained by refluxing it with excess benzaldehyde in glacial acetic acid solution. The solid which formed on pouring into water was washed with a little ethanol. Without further purification it melted at 191–192°, forming a clear yellow liquid, showing that it was pure 3-phenyl-4-benzylidene-isoxazolone-5. Minunni obtained 3-phenylisoxazolone-5 from 3-phenyl-4-benzylidene-isoxazolone-5, but he considered it to be alpha-aminocinnamolactone, a compound which would have the same empirical formula.

Reaction with Phenylhydrazine.—The salt was prepared directly from 3-phenylisoxazolone and phenylhydrazine by the method described by Uhlenhuth.[8] It can be recrystallized in the form of white flakes from methanol; it melts with decomposition to a red liquid at 153–154°. The yield was quantitative. It easily reduced Fehling's solution, showing it to be a phenylhydrazine salt and not a phenylhydrazone. The same salt (plus the corresponding aldehyde phenylhydrazone) was obtained by mixing warm methanol solutions of 3-phenyl-4-benzylidene-isoxazolone-5 (1 mole) and phenylhydrazine (2 moles); the same was done with 3-phenyl-4-anisylidene-isoxazolone-5. The aldehyde phenylhydrazones were separated from the salt in each case by taking advantage of the greater solubility of the former in warm benzene. Mixed melting points showed no depression, and salts from the varying sources showed identical analyses.

Anal. Calcd. for $C_{15}H_{15}O_2N_3$: N, 15.61. Found: N, 15.52, 15.76.

When 3-methyl-4-benzylidene-isoxazolone-5 was treated as above, a 50% yield of compound II was obtained, plus benzaldehyde phenylhydrazone.

Preparation of Dimethyl-diisoxazolone.—The method of Hantzsch[9] was employed using 65.0 g. acetoacetic of ester. On recrystallization from ethanol a 33% yield (17.1 g.) of white flakes was obtained. It melts with decomposition to a red liquid at 168–169° (corr.).

Anal. Calcd. for $C_8H_8O_3N_2$: N, 15.56. Found: N, 15.58, 15.58.

Summary

1. It is shown that aromatic aldoximes and beta keto esters react in the presence of acids to form arylidene isoxazolones, and not arylidene amino lactones as previously reported.[2–4]

2. The action of phenylhydrazine and of an alkaline hydrolytic agent has been studied, and the earlier work has been corrected and extended.

3. The optimum conditions for condensation have been found. The probable mechanism of the reaction is discussed. It has been found that reaction occurs in the presence of strong acids in general.

4. An unsuccessful attempt was made to extend the reaction to aliphatic and alicyclic aldoxime and ketoximes. Acetone oxime did condense, however.

5. It is shown that the compound reported as 3-methylisoxazolone-5 in the literature has actually never been prepared. The product reported as such was actually dimethyldiisoxazolone. Its structure is demonstrated.

NEW HAVEN, CONN. RECEIVED MARCH 27, 1937

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Two Forms of Anhydrous *l*-Rhamnose and a New Method for the Preparation of Crystalline β-Tetraacetyl-*l*-rhamnose[1]

BY ERNEST L. JACKSON AND C. S. HUDSON

l-Rhamnose usually crystallizes as a monohydrate of its α-modification having an initial specific rotation in water of −7.7°, which becomes constant at +8.9° after mutarotation is complete. This form is usually regarded as the configurational analog of α-*d*-mannose of initial rotation +30°, its final value being +14°. In 1895 Emil Fischer[2] crystallized a new form of rhamnose, anhydrous crystals of initial rotation about +31° which is regarded as β-rhamnose, the analog of β-*d*-mannose of initial rotation −17°. Minsaas[3] on repeating Fischer's preparation recently found "about +44°" as the initial rotation, and mentioned that the yield of this anhydrous form is small. We also had been engaged in studying this form and in devising methods for obtaining it in higher yields; our β-rhamnose showed +38° as the initial specific rotation.[4] After the publication of Minsaas' article we repeated our work and again obtained +38° for crystals which by appearance seemed to be of one form only. In the course of the preparation of these β-rhamnose crystals another anhydrous form of quite different crystalline appearance frequently separated. This third form of the sugar shows an initial rotation of about +14°, mutarotating in water at the

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(1) Publication authorized by the Surgeon General, U. S. Public Health Service. Presented before the Division of Organic Chemistry, at the Pittsburgh meeting of the American Chemical Society, Sept. 7–11, 1936.

(2) Fischer, *Ber.*, **28**, 1162 (1895); **29**, 324 (1896); Tanret, *Compt. rend.*, **122**, 86 (1896); Purdie and Young, *J. Chem. Soc.*, **89**, 1194 (1906).

(3) Minsaas, *Kgl. Norske Videnskab. Selskabs Forh.*, **6**, 177 (1933); *Chem. Zentr.*, **105**, I, 2738 (1934).

(4) Except where otherwise specified, all rotations in this article are specific rotations at 20° for sodium light.