trum, and raised the yield to 77%. Although this material gave satisfactory carbon, hydrogen, and nitrogen analyses without further purification, a specimen was recrystallized from absolute ethanol without altering its melting point or infrared spectrum.

Anal. Calcd. for $C_6H_7N_5SO$: C, 32.42; H, 3.81; N, 37.81; S, 17.31. Found: C, 32.56; H, 3.74; N, 37.65; S, 17.37.

Addition of water to an ethanol solution caused the disappearance of the yellow color. A freshly prepared absolute ethanol solution produced absorption maxima at 253 mμ and 408 mμ and an inflection near 350 mμ.

b. Conversion to VII.—The general procedure for the preparation and isolation of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines was used in treating 185 mg. (1 mmole as XIX) of the intermediate with 139 mg. (1 mmole) of *N*-sulfinylaniline in 20 ml. of dry pyridine for 3.5 hr. 7-Amino-5-methyl[1,2,5]-thiadiazolo-[3,4-*d*]pyrimidine (VII) was isolated (96% yield based on XIX) and recrystallized from water. The purified product (80% recovery) was identical by melting point (225°), paper chromatography, and ultraviolet absorption with VII.

An experiment performed in the same way except for the omission of *N*-sulfinylaniline yielded the following fractions: (1) 10 mg. of 4,5,6-triamino-2-methylpyrimidine, identified by paper chromatography; (2) 80 mg. of a mixture, according to paper chromatography and infrared spectra, of 4,5,6-triamino-2-methylpyrimidine and VII; (3) 44 mg. of VII, identified by paper chromatography.

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Base-Catalyzed Ring Opening of *N*-Substituted 5-Isoxazolones[1]

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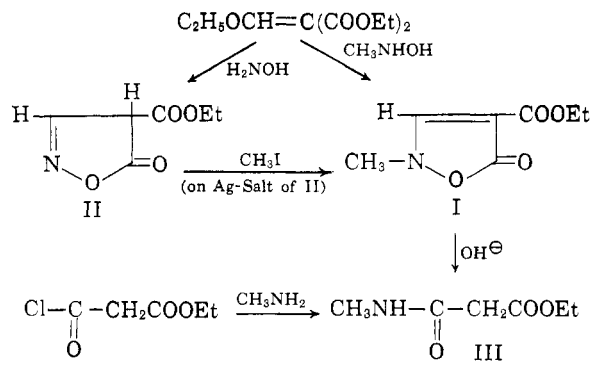
A facile ring opening of *N*-substituted 5-isoxazolones having no substituent in the 3-position is described. Reaction of 2-methyl-4-carbethoxy-5-isoxazolone (I) with dilute alkali or sodium carbonate affords the novel compound, carbethoxymethylacetamide (III). The reaction mechanism sequence probably involves abstraction of a proton from the 3-position as evidenced by the failure of 2,3-dimethyl-4-carbethoxy-5-isoxazolone (IV), also a new compound, to undergo similar ring opening in base. In the reaction of I with aqueous sodium cyanide, cyanide ions compete effectively with hydroxide ions in attack of the activated double bond, yielding ethyl 2-cyano-2-methylaminoacrylate (VI) as the major reaction product, together with some III. The reaction product of I and aqueous sodium azide, ethyl 2-azido-2-methyliminopropionate (VIII), cyclizes under the reaction conditions to ethyl 1-methyl-5-tetrazolylacetate (VII).

In 1897 Claisen[2] obtained 2-methyl-4-carbethoxy-5-isoxazolone (I) on methylation of the silver salt of 4-carbethoxy-5-isoxazolone (II) with methyl iodide. On heating of I with strong alkali, methylamine was formed, thus proving that indeed *N*-methylation had occurred. The author reported that I could be recovered from dilute alkali unchanged.

We have synthesized I from methylhydroxylamine and diethyl ethoxymethylenemalonate and, contrary to the above observations, we found that I undergoes a remarkably facile ring opening in dilute base. When I was added to 5% sodium hydroxide or aqueous sodium carbonate, an immediate exothermic reaction occurred and carbethoxymethylacetamide (III) was isolated and identified by comparison with an authentic sample.

Interestingly, the ring opening of I to III occurred on mild heating even in a weakly basic medium such as sodium acetate solution.

The formation of III may be explained as occurring *via* base attack on the double bond at the

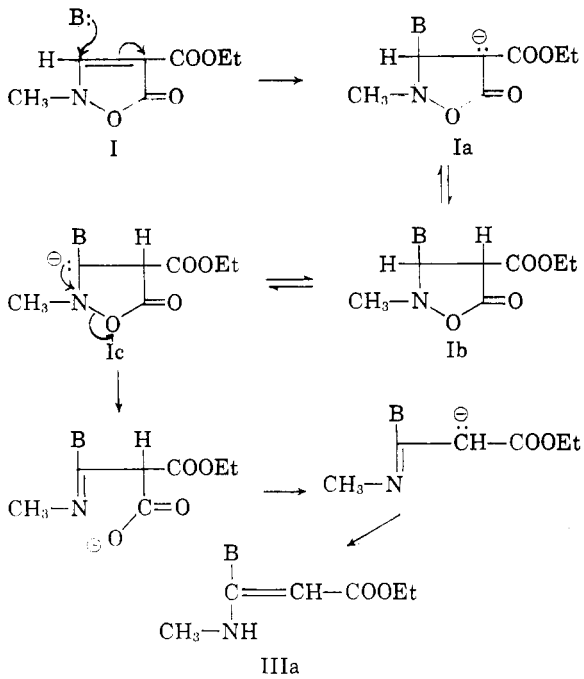


3- position forming the carbanion Ia. Ia could be in equilibrium with its conjugate acid Ib as well as with the less likely carbanion Ic. This carbanion can undergo electron shifts leading to ring opening and decarboxylation yielding the final product. When the base is hydroxide ion, the species IIIa tautomerizes to the amide III.

There are alternate possible mechanisms such as ring opening *via* carbanion Ia with formation of a ketene intermediate or direct abstraction of the proton in I with formation of a keteneimine inter-

(1) This paper was presented before the Division of Organic Chemistry at the 141st Meeting, American Chemical Society, Washington, D. C., March, 1962.

(2) L. Claisen, *Ber.*, **30**, 1480 (1897).

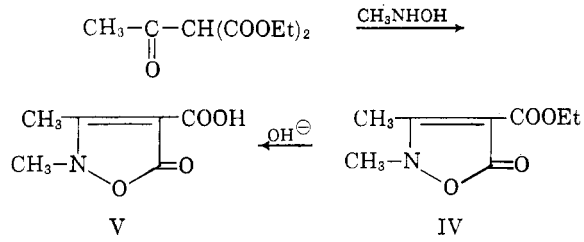


mediate. The latter is an attractive alternative since ring opening of isoxazolium salts which according to Woodward and Olofson[3] proceeds *via* a keteneimine intermediate produces similar reaction products.[4]

These alternate reaction mechanisms are apparently ruled out on the basis of infrared studies. The reaction mixture of I in either sodium hydroxide or sodium carbonate solution did not show absorption in the cumulative double-bond region,[5] as would be expected if ketene intermediates were present.

A prerequisite of the proposed reaction mechanism is the availability of a proton in the 3- position. Presumably a compound lacking this proton could not undergo the ring opening in base.

Accordingly 2,3 - dimethyl - 4 - carbethoxy - 5 - isoxazolone (IV) was synthesized from diethyl acetylmalonate and methylhydroxylamine. When IV was added to 5% sodium hydroxide solution, no immediate exothermic reaction could be observed. Unchanged IV could be recovered after fifteen minutes; however, when the mixture had been left overnight, 12% of the starting material still could be recovered, together with 2,3-dimethyl-4-carboxy-5-isoxazolone (V) formed *via* saponification of the ester group.

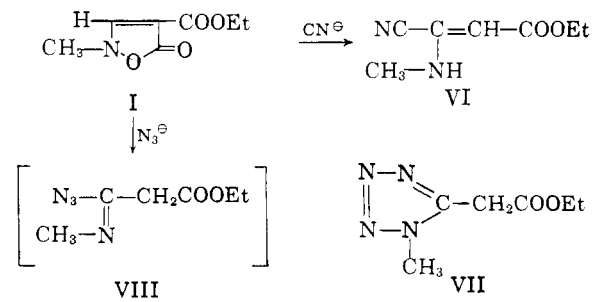


When V was refluxed in 50% sodium hydroxide, no methylamine was evolved demonstrating that even under vigorous conditions, while ring opening may occur, it does proceed in a different fashion than in the case of I.

The ease of attack of the double bond in I with subsequent abstraction of the proton in the 3- position is further demonstrated by the facile reaction of I with either cyanide or azide ion. In the case of these bases the carbanion Ic is favored because of stabilization by resonance interaction with the cyanide or azide group.

Treatment of I with aqueous sodium cyanide resulted in an immediate exothermic reaction. Upon cooling, ethyl 2-cyano-2-methylaminoacrylate (VI) crystallized from the reaction mixture. Extraction of the reaction mixture with chloroform afforded III. Apparently the hydroxide ions present compete with the cyanide ions in the attack of the double bond. The structure VI was elucidated by analysis and infrared spectroscopy. The NH-stretching at 3.05 μ and the conjugated C=C absorption at 6.18 μ are proof for the structure VI rather than the also possible imine structure. In the reaction of *N*-substituted isoxazolium salts with potassium cyanide Mumm and co-workers[4] obtained similar products; however, a different reaction mechanism applied for this ring opening as demonstrated by Woodward and Olofson.[3]

In the reaction of aqueous sodium azide with I at room temperature, the isoxazolone derivative was completely converted to ethyl 1-methyl-5-tetrazolylacetate (VII) within three hours. The intermediate ethyl 2-azido-2-methyliminopropionate (VIII) immediately cyclizes to the end product VII.



Jacobson and Amstutz[6] have synthesized several 1-substituted-5-tetrazolyl acetates by treating *N*-

(3) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(4) O. Mumm and G. Munchmeyer, *Ber.*, **43**, 3335 (1910); O. Mumm and C. Bergell, *ibid.*, **45**, 3040 (1912); O. Mumm and C. Bergell, *ibid.*, **45**, 3149 (1912).

(5) Infrared examination of the aqueous systems was accomplished through the use of a pair of supported polyethylene films, appropriately compensated, for the absorption cell. Into this were inserted reaction samples which were then examined in the cumulative double-bond absorption region. Although an aqueous sodium azide solution, used as a control, demonstrated by strong absorption at 4.9 μ that sufficient response was thereby obtainable, the alkaline reaction solutions of I were free of absorption in this region.

(6) C. R. Jacobson and E. D. Amstutz, *J. Org. Chem.*, **21**, 311 (1956).

substituted malonamates with phosphorus pentachloride and subsequently treating the amide chlorides with hydrazoic acid; however, the authors noted that the main difficulty in this synthesis is the preparation of the necessary *N*-substituted malonamates.

Although no attempts have been made to obtain maximum yields in this remarkably mild reaction of I with sodium azide, such reaction of sodium azide with *N*-substituted isoxazolones having no substituent in the 3- position may constitute a facile and generally applicable method for the synthesis of 1-substituted-5-tetrazolyl acetates.

When either sodium cyanide or sodium azide reacted in excess with 2,3-dimethyl-4-carbethoxy-5-isoxazolone, only recovered starting material was obtained, a result which would be expected on the basis of the proposed reaction mechanism.

Experimental[7]

2-Methyl-4-carbethoxy-5-isoxazolone (I).—(a). To 6 g. of methylhydroxylamine hydrochloride[8] 15.5 g. of diethyl ethoxymethylenemalonate (Eastman) and 3.8 g. of anhydrous sodium carbonate were added. After standing overnight the sodium chloride was filtered off and the remaining oil was heated at 100–130° for 60 min. when 5.1 g. of ethanol (theor. 6.6 g.) was removed by distillation. The crude reaction product was recrystallized from ethanol yielding 6.7 g. (60%) of I, m.p. 94–95°.

(b). To 21.6 g. (0.1 mole) of diethyl ethoxymethylenemalonate and 8.4 g. (0.1 mole) of methylhydroxylamine hydrochloride in 100 ml. of ethanol was added 5.5 g. (0.055 mole) of anhydrous sodium carbonate, and the reaction mixture was refluxed for 5 hr. Filtration and evaporation afforded 8 g. (51%) of I, m.p. 95–96°.

Recrystallization from benzene afforded well defined crystals, m.p. 96–97° (lit.,[2] m.p. 96–97°); $\lambda_{max}^{CHCl_3}$ (infrared) 5.6, 5.88, 6.28, 9.23, 9.75 μ.[9]

Anal. Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.06; H, 5.38; N, 8.30.

Ring Opening of 2-Methyl-4-carbethoxy-5-isoxazolone (I) in Base (a). **Aqueous Sodium Hydroxide.**—To 5 ml. of 5% sodium hydroxide was added 1 g. of I. An immediate exothermic reaction was observed and all the material went into solution. After cooling to room temperature the reaction mixture was extracted with ether. Evaporation of the ether afforded 0.5 g. (54%) of carbethoxymethylacetamide (III). After acidification of the reaction mixture and extraction, another 60 mg. of III was obtained.

(b). **Aqueous Sodium Acetate.**—On heating of a sample of I with a slight excess of aqueous sodium acetate, decarboxylation was observed. Extraction with chloroform afforded carbethoxymethylacetamide (III) as the only reaction product.

(c). **Aqueous Sodium Cyanide.**—A solution of 0.4 g. of sodium cyanide in 5 ml. of water was added to 1 g. of I. An immediate exothermic reaction was observed with formation of an oily material which solidified on cooling. Recrystallization from methanol afforded 0.3 g. (31.5%) of ethyl 2-cyano-2-methylaminoacrylate (VI), m.p. 57–58°; $\lambda_{max}^{CHCl_3}$ (infrared) 3.05, 3.4, 4.45 (v.w.); 6, 6.18, 7.85, 8.48, 9.6 μ.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.41; H, 6.79; N, 18.23.

Extraction of the reaction mixture with chloroform afforded 0.15 g. (16.5%) of carbethoxymethylacetamide (III).

(d). **Aqueous Sodium Azide.**—A solution of 1 g. of sodium azide in 10 ml. of water was added to 1.5 g. of I. After 90 min. the material went into solution and the infrared spectrum of an aliquot showed that I was mainly unchanged. Stirring for three additional hours at room temperature, followed by extraction with chloroform gave 0.4 g. (26.5%) of ethyl 1-methyl-5-tetrazolylacetate (VII), m.p. 71–72° after recrystallization from methanol; $\lambda_{max}^{CHCl_3}$ (infrared) 3.4, 5.72, 6.75, 7.26, 7.48, 8.36, 9.73 μ.

Anal. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.60; H, 5.95; N, 33.01.

Carbethoxymethylacetamide (III).—With good cooling, 4.6 g. of ethylmalonyl chloride[10] was added dropwise to 5 g. of 40% aqueous methylamine. Extraction of the reaction mixture with ether and chloroform, washing of the extracts with dilute hydrochloric acid and water, followed by evaporation and distillation, afforded 1.2 g. (28%) of carbethoxymethylacetamide (III), b.p 101–103° (1.0 mm.); $n^{22}D$ 1.4408. The assigned structure was verified by the infrared spectrum in chloroform: bands at 3 μ for NH-stretching; 3.4 μ for CH-stretching; 5.78 μ for ester C=O; 5.96 μ for amide C=O; 6.45 μ for NH-deformation. The infrared spectrum was identical with the infrared spectrum of III isolated from the reaction mixtures of I in base.

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.77; H, 7.84; N, 9.63.

2,3-Dimethyl-4-carbethoxy-5-isoxazolone (IV).—To 5 g. of diethyl acetylmalonate[11] and 2.5 g. of methylhydroxylamine hydrochloride in 30 ml. of ethanol was added 1.6 g. of anhydrous sodium carbonate. The reaction mixture was refluxed for 5 hr. Filtration and evaporation of part of the ethanol yielded 2.7 g. (59%) of IV, m.p. 135–137°. Recrystallization from methanol afforded white crystals, m.p. 138°; $\lambda_{max}^{CHCl_3}$ (infrared), 5.68, 5.88, 6.42, 8.4 μ.

Anal. Calcd. for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56 Found: C, 51.91; H, 5.85; N, 7.48.

2,3-Dimethyl-4-carboxy-5-isoxazolone (V).—To 0.5 g. of IV was added 2 ml. of 5% sodium hydroxide; no exothermic reaction was observed. After standing overnight at room temperature almost all of the material went into solution. Extraction with chloroform afforded 60 mg. (12%) of IV, m.p. 134–135°. Acidification with concd. hydrochloric acid afforded 0.3 g. (66.5%) of the 2,3-dimethyl-4-carboxy-5-isoxazolone (V), m.p. 237–238° dec. Recrystallization from ethanol gave white crystals, m.p. 242–243° dec.; λ_{max}^{KBr} (infrared) 3.3–3.9, 5.55–5.65, 5.95, 6 05, 6.3, 6.55, 8.25, 10.35, 12.65, 13.1 μ.

Anal. Calcd. for $C_6H_7NO_4$: N, 8.92. Found: N, 8.98.

(7) Melting points are uncorrected (Fisher-Johns); analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; infrared absorption spectra were determined using a Perkin-Elmer Model 21 spectrophotometer.

(8) E. Beckman, *Ann.*, **365**, 205 (1909).

(9) The infrared absorption spectra of a series of 5-isoxazolones has been reported by A. J. Boulton and A. R. Katritzky, *Tetrahedron*, **12**, 41 (1961).

(10) H. Staudinger and H. Becker, *Ber.*, **50**, 1016 (1917).

(11) H. Lund, *ibid.*, **67B**, 935 (1934).