[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

5-Phenyl-2-isoxazoline-3-carboxylic Acid[1]

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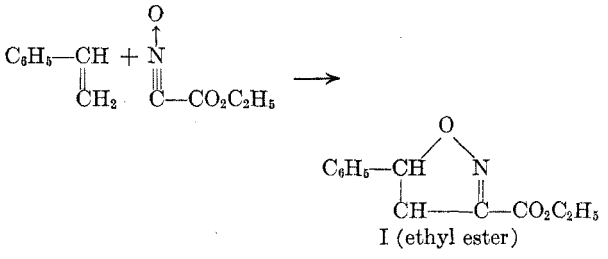
The preparation of 5-phenyl-2-isoxazoline-3-carboxylic acid by the reaction between styrene and carbethoxyformonitrile oxide, followed by hydrolysis, is described. The chemistry of this compound is discussed, and a number of derivatives are described. In addition the analogous preparation of 4-[3-hydrazido-5-phenyl-2-isoxazolinyl] carbamate from methyl styrylcarbamate and carbethoxyformonitrile oxide, followed by hydrazinolysis, is also described, and certain of its reactions are considered. The use of carbethoxyformonitrile oxide in this manner affords a useful synthetic route to various 3-substituted 2-isoxazolines.

The failure of benzylidenepyruvic acid oxime to cyclize, either to 3-hydroxylamino-5-phenyl-2-(5H)furanone by the lactoenoic tautomeric process common to imino derivatives of benzylidenepyruvic acid,[3] or to 5-phenyl-2-isoxazoline-3-carboxylic acid (I) in common with chalcone oximes,[4] has been commented upon elsewhere.[5] In view of the decided reluctance of this oxime and its derivatives to produce I, it seemed desirable to prepare I by another route and investigate its stability with respect to ring-opening as well as its general characteristics.

The reaction between benzonitrile oxide and various olefins[6] suggested that the only known nonaromatic nitrile oxide, carbethoxyformonitrile oxide,[7] might be expected to add to styrene to give the ethyl ester of I:



I (ethyl ester)

Since nitrile oxides are prone to polymerization it seemed desirable to use very mild conditions for the reaction and to generate the nitrile oxide *in situ* and slowly. The nitrile oxide is usually made by treating ethyl chlorooximinoacetate with a base,[7] and when sodium hydroxide at 0° proved unsatisfactory, sodium carbonate at room temperature was tried. Thus a solution of styrene and ethyl chlorooximinoacetate in ether was vigorously stirred while a solution of aqueous sodium carbonate was added very slowly, and a 50% yield of the desired ester was obtained. Hydrolysis by 10% sodium hydroxide, followed by acidification afforded I. Tentative assignment of the desired structure was made by analogy with the reaction between benzonitrile oxide and styrene.[6e-k] Confirmation of this assignment was obtained by oxidation of I to the known 5-phenyl-isoxazole-3-carboxylic acid,[8] with additional support from decyclization studies. The treatment of I with concentrated sulfuric acid for twenty-four hours at room temperature converted it into benzylidenepyruvic acid oxime, which had previously been shown to be stable to sulfuric acid for long periods of time.[5] Accordingly it is clear that the acyclic form is the stable one in sulfuric acid solution. Similarly treatment of the amine derived

(1) Abstracted from a portion of the Ph.D. Dissertation of John L. Spencer, University of Michigan, 1958.

(2) National Science Foundation predoctoral fellow 1956–58.

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(4) A. H. Blatt, *J. Am. Chem. Soc.*, **71**, 1861 (1949). R. P. Barnes, G. E. Pinkney, and G. McK. Phillips, *J. Am. Chem. Soc.*, **76**, 276 (1954). H. H. Blecker, Dissertation, Rutgers (1955).

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(7) G. S. Skinner, *J. Am. Chem. Soc.*, **46**, 731 (1924).

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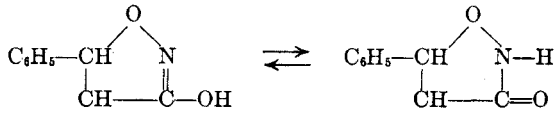
from I *via* the Curtius rearrangement (see below) with dilute hydrochloric acid afforded cinnamic acid, presumably *via* the amide oxime,[9] which also fails to cyclize in acidic media.

With a comparatively simple synthesis for I at hand it was of interest to determine whether 3-amino-5-phenyl-2-isoxazoline (II) accessible from derivatives of I through the Curtius rearrangement could be converted to 3-hydroxy-5-phenyl-2-isoxazoline, which should be tautomeric with 5-phenyl-3-isoxazolidinone:



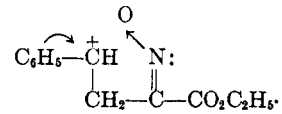
The latter substance is the 4-deamino analog of 5-phenylcycloserine,[10-12] which has been shown to possess some antibiotic activity.

To this end the hydrazide of I was prepared, converted to the azide with nitrous acid and rearranged to both the urethan (III) and the amine (II). While II may partake of the same type of tautomerism pictured for the hydroxy analog, its general behavior suggests that it exists primarily as the 2-isoxazoline rather than the 3-imino-5-phenylisoxazolidine. Thus, its acetyl derivative is base-soluble; and while II cannot be titrated potentiometrically, it is soluble in 5% aqueous hydrochloric acid, and it forms a stable hydrochloride in alcohol or ether. However, nitrous acid, nitrosyl chloride, and nitrogen tetroxide under a variety of reaction conditions afforded only untractable oils possessing none of the expected characteristics of the desired substance. Likewise attempts to hydrolyze the potential imino or amino group by conventional and unconventional (*e.g.* Bucherer, reverse Sommelet[13]) procedures afforded only starting material, cinnamic acid, or unidentifiable tars. The only clean reactions involved acetylation, which occurs readily on warming with acetic acid and even to some extent with 50% aqueous acetic acid, and exchange with hydrazine in glacial acetic acid, which affords the 3-β-acetylhydrazino analog of II; this, like the acetyl derivative of II, is base-soluble.

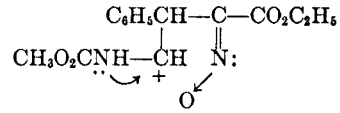
Several other potential preparations of 5-phenyl-3-isoxazolidinone from I and its derivatives were investigated. The Hunsdiecker silver salt reaction failed to afford the desired 3-bromo-5-phenyl-2-isoxazoline, and various oxidative reactions (*e.g.* periodic acid, lead tetraacetate on I or the carbinol derived from I by treatment with methyl Grignard) were entirely unsuccessful, only starting material being recovered. With a stronger oxidizing agent, permanganate, I was oxidized to the isoxazole.

In the expectation that a 4-substituent might alter the characteristics of I, the addition of carbethoxyformonitrile to several β-substituted styrenes was investigated. Cinnamic acid, methyl cinnamate, and cinnamonitrile failed to afford products, but no exhaustive study of reaction conditions was made because it was found that methyl styrylcarbamate reacted well.

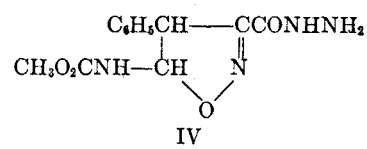
The exact nature of the reaction between styrene and a nitrile oxide is unknown, but the failure to observe reactions with methyl cinnamate and cinnamonitrile under conditions which are satisfactory for styrene suggests that the attack of the nitrile oxide is more electrophilic than nucleophilic in character, and the comparably good reaction of methyl styrylcarbamate would seem to substantiate this hypothesis. Thus in spite of one's inclination to picture the charge distribution in a nitrile oxide as $R-C\equiv N\rightarrow O$, it would seem that $R-\overset{+}{C}=\ddot{N}\rightarrow O$ is the more significant for the addition reaction. The initial reaction intermediate with styrene is accordingly



With methyl styrylcarbamate, however, the inherently greater polarizability of the p-electrons of nitrogen (compared with the π-electrons of phenyl) should provide greater stabilization of a transition state leading to



On this basis, then, the hydrazide derived from the adduct of methyl styrylcarbamate and carbethoxyformonitrile oxide is formulated as methyl 5-[3-hydrazido-4-phenyl-2-isoxazolinyl]carbamate:



IV

This is in keeping with the observation that the addition of nitrile oxides to olefins is similar to that of aliphatic diazo compounds and azides and orientation follows the Markownikoff rule.[6c]

The initial product of this reaction was not purified, but by analogy with the hydrazinolysis of the ethyl ester of I, which could be very readily converted to the hydrazide, which was more tractable, the crude product was at once converted to the above hydrazide (IV). Since the ethyl group, and

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(11) P. H. Hidy, *et al.*, *J. Am. Chem. Soc.*, **77**, 2345 (1955).

(12) P. A. Plattner, *Helv. Chim. Acta*, **40**, 1531 (1957); *Chem. Abstr.*, **52**, 3771 (1958).

(13) W. R. Vaughan and R. Perry, Jr., *J. Am. Chem. Soc.*, **75**, 3168 (1953).

not the methyl, was hydrazinolyzed, there can be no doubt as to the structure.

The hydrazide was converted to the azide, which then was rearranged in ethanol to give a bis-urethane, which unfortunately resisted hydrolysis under mild conditions; and under more vigorous conditions it afforded only uncharacterizable products. Consequently it would appear that introduction of a 4-substituent consisting of a functional group renders the system less tractable than without it.

The present work constitutes an introductory survey of the applicability of the nitrile oxide synthesis to 3-functionally substituted 2-isoxazolines. The method is a convenient one and should be satisfactory for the preparation of any 2-isoxazoline-3-carboxylic acid to the extent that any given olefin has been shown to react with aromatic nitrile oxides. From the work herein described it further appears that one can readily prepare derivatives of such acids and that the amines available *via* the Curtius rearrangement should also be readily accessible. However, the transformation of such amines into 3-isoxazolidinones is not at present feasible.

EXPERIMENTAL[14-16]

Ethyl chlorooximinoacetate. Ethyl chlorooximinoacetate was prepared by the action of 2 moles of nitrous acid on ethyl glycinate hydrochloride according to the procedure of Skinner.[7]

Ethyl 5-phenyl-2-isoxazoline-3-carboxylate. Carbethoxyformonitrile oxide was generated *in situ* with styrene to give the addition product. The following procedure was found to give the best yield. To a solution of 15.1 g. (0.10 mole) of ethyl chlorooximinoacetate in 220 ml. of ether was added 12.5 g. (0.12 mole) of styrene. The solution was vigorously stirred with a Hershberg stirrer while a solution of 10.6 g. (0.10 mole) of sodium carbonate in 150 ml. of water was added dropwise over a 4-hr. period at room temperature.

The layers were separated and the ether layer washed with water. Ether extraction of the aqueous layer gave essentially no ester. Evaporation of the original ether layer gave about 17 g. of crude ester. This was distilled under vacuum to yield 11.0 g. (50%) of slightly yellow colored ester, b.p. 162–163°/2.5 mm.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.02; H, 6.02; N, 6.44.

5-Phenyl-2-isoxazoline-3-carboxylic acid (I). In a separate run the 17.0 g. of crude ester was hydrolyzed to the acid. A mixture of the ester and 100 ml. of 10% sodium hydroxide was stirred until a white solid formed (about 4 hr.). This was dissolved by adding 150 ml. of water and the hydrolysis was completed by an additional 20 hr. of stirring. Nonacidic impurities were removed by ether extraction, and polymeric material was removed by filtration.

The solution of the sodium salt was acidified by dropwise addition of 10% hydrochloric acid. This yielded, after cooling, 11.0 g. of crude acid, m.p. 90–103°. Recrystallization from benzene yielded 9.5 g. (49%) of white product, m.p. 104–106°; neut. equiv. calcd.: 191, found: 190.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.89; H, 4.83; N, 7.31.

Treatment of the acid with ethereal diazomethane and, after evaporation, hydrazine in ethanol gave the same hydrazide (see below) as the original crude ester. The identity of these two compounds was shown by undepressed mixture melting point and superimposable infrared spectra.

5-Phenyl-2-isoxazoline-3-carboxylic acid hydrazide. The hydrazide was prepared from the crude ester by reaction with hydrazine in ethanol. The crude ester in ethanol, 1 g. per 10 ml., was slowly added to a 10% ethanolic solution of hydrazine with swirling and cooling in an ice bath. (One milliliter of hydrazine was used per g. of ester.) After the addition the solution was allowed to warm to room temperature and filtered from an orange tar. Evaporation of the alcohol left an orange semisolid which upon trituration with water yielded the crude hydrazide, m.p. 107–114°. Recrystallization from alcohol raised the melting point to 112.5–115.5°. When 17.0 g. of crude ester was used, 100 ml. of water was used for the trituration and 40 ml. of alcohol for the recrystallization to give 10.0 g. (49% based on ethyl chlorooximinoacetate) of hydrazide, m.p. 113–115°. The analytical sample was recrystallized twice from water, m.p. 113.5–115.5°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.33; H, 5.49; N, 20.57.

5-Phenyl-2-isoxazoline-3-carboxylic acid azide. To a solution of 50 ml. of acetone and 50 ml. of 10% hydrochloric acid was added 3.0 g. (0.015 mole) of the above hydrazide. This solution was cooled in an ice bath while a solution of 1.5 g. (0.022 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. An additional 50 ml. of water was added to yield 2.8 g. (88%) of analytically pure shiny white plates, m.p. 82–83° vigorous dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.62; H, 3.82; N, 25.96.

Ethyl 3-[5-phenyl-2-isoxazolinyl]carbamate. The above azide was dissolved in ethanol, 1 g. per 100 ml., and the solution refluxed for 2 hr. Evaporation of the alcohol left a white solid. This was recrystallized from ethanol-water, m.p. 123.5–127°. When 1.3 g. of azide was used 1.2 g. (86%) of urethan was obtained. Two further recrystallizations from the same solvent pair gave the analytical sample, m.p. 126.0–127.5°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.67; H, 6.17; N, 11.93.

Hydrolysis of the urethan. (a) *In base:* A solution of 1.9 g. (0.0081 mole) of the urethan in 25 ml. of 10% sodium hydroxide was heated at 110° for 36 hr. The resulting mixture was cooled and the precipitate collected and washed with water. This was found to be 3-amino-5-phenyl-2-isoxazoline, II, m.p. 128–132°; yield 0.75 g. (56%). This product has an infrared spectrum identical with that obtained by direct rearrangement of the azide (see below) and no depression of melting point was obtained on mixing the two samples.

(b) *In water:* The urethan (100 mg., 0.00043 mole) was refluxed in 25 ml. of water for 65 hr. The resulting solution was filtered and concentrated to approximately 5 ml. Cooling yielded 45 mg. (65%) of 3-amino-5-phenyl-2-isoxazoline (II), m.p. 125–133°, as shown by identical infrared spectra and undepressed mixture melting point.

(c) *In acid:* The urethan (526 mg., 0.002 mole) was refluxed in 25 ml. of 5% hydrochloric acid for 16 hr. Cooling yielded 230 mg. (69%) of solid, m.p. 120–132°, which was shown to be *trans*-cinnamic acid by its neutral equivalent (calcd., 148; found, 148) and its infrared spectrum and failure to depress the melting point of an authentic sample of *trans*-cinnamic acid.

3-Amino-5-phenyl-2-isoxazoline (II). The above azide, (3.5 g., 0.16 mole) was slowly added to a solution of 70 ml. of trifluoroacetic acid and 17.5 ml. of water. The azide dissolved during the addition and the resulting solution was heated on a steam bath for 30 min. after the bubbling had

(14) Boiling points and melting points are uncorrected.

(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) Infrared spectra obtained from Nujol mulls or thin films by means of a Perkin-Elmer model 21 infrared spectrophotometer.

ceased. Evaporation of the solvents left a waxy solid which was dissolved in 50 ml. of 10% hydrochloric acid. The solution was filtered and made basic with 25% sodium hydroxide. After cooling, the solid, m.p. 127–130°, was collected, 2.2 g. (84%). An analytical sample was prepared by recrystallization from benzene and twice from water, m.p. 129.5–131.5°, in which it is less soluble than in 5% hydrochloric acid.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.66; H, 6.40; N, 17.29.

Amine hydrochloride. The above amine (II) (1.0 g., 0.0062 mole) was added to 25 ml. of absolute ethanol saturated with hydrogen chloride. The amine dissolved slowly and no amine salt precipitated upon standing. Evaporation of the solvent left a white solid, m.p. 163–170° dec. The melting point was very dependent on the rate of heating. Recrystallization from methanol-ether gave an analytical sample.

Anal. Calcd. for $C_9H_{11}N_2OCl$: C, 54.41; H, 5.58; N, 14.11. Found: C, 54.37; H, 5.57; N, 14.03.

The same amine hydrochloride as shown by identical infrared spectra and undepressed mixture melting point was obtained by dissolving the amine in ether, bubbling in hydrogen chloride, and collecting the precipitate.

Hydrolysis of the amine (II). (a) *In hydrochloric acid:* The amine was dissolved in 5% hydrochloric acid and heated on a steam bath for 12 hr. Cooling yielded a solid, m.p. 126–132° which had an infrared spectrum identical with *trans*-cinnamic acid and showed no depression of melting point on mixing.

(b) *In glacial acetic acid:* The amine (300 mg.) was dissolved in 7.5 ml. of acetic acid and refluxed 24 hr. The solvent was evaporated leaving a semisolid which was recrystallized from water, m.p. 95–135°. Recrystallization from water twice more gave an analytical sample of acetyl derivative, m.p. 146.5–147.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.68; H, 6.01; N, 13.80.

(c) *In 50% acetic acid:* Refluxing the amine in 50% acetic acid gave a mixture of starting material, *trans*-cinnamic acid and the acetylation product obtained from glacial acetic acid.

Attempted deamination of the amine (II). (a) *With nitrous acid:* The amine (162 mg., 0.0001 mole) was dissolved in 10 ml. of 0.1023*N* hydrochloric acid by warming. The solution was cooled in an ice bath and a solution of 69 mg. (0.001 mole) sodium nitrite in 5 ml. of water was added dropwise with swirling and continued cooling. An orange oil separated and was extracted with chloroform. The oil remaining after evaporation of the chloroform could not be crystallized. The same results were obtained when two and three times the quantity of hydrochloric acid was used, when acetic acid buffered with sodium acetate was used, and when the sodium nitrite solution was added over a 2-day period. The oil was insoluble in 5% sodium hydroxide. Its infrared spectrum had an adsorption band at 2150 cm.$^{-1}$

(b) *With nitrosyl chloride:* The amine suspended in carbon tetrachloride was treated with an equivalent amount of nitrosyl chloride dissolved in the same solvent. The mixture was warmed on a steam bath during which time an oil separated. Evaporation of the solvent left the same oil as above as shown by identity of infrared spectra. Treating the amine dissolved in chloroform and cooled in an ice bath with excess nitrosyl chloride solution gave the same results.

(c) *With nitrogen tetroxide:* A solution of 0.5 g. of nitrogen tetroxide in 20 ml. of carbon tetrachloride was cooled to 0°. Sodium acetate, 738 mg., and 486 mg. of amine were added. After standing 30 min. the mixture was poured on ice and the layers separated. The aqueous layer was extracted with ether and the combined organic layers were evaporated leaving the same oil as obtained with nitrous acid.

Nitrosation of the urethan. The procedures of White[17] for the nitrosation of amides were used.

(17) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

(a) *With nitrogen tetroxide:* Using nitrogen tetroxide, sodium acetate, and urethan, 702 mg., nothing but unchanged urethan could be obtained.

(b) *With acetic anhydride, acetic acid, and sodium nitrite:* Using 1.17 g. of urethan, 5 ml. of acetic acid, 25 ml. of acetic anhydride, and 7.5 g. of sodium nitrite gave a mixture of starting material and the same oil that was obtained by the nitrosation of the amine (II) as indicated by the infrared spectrum.

Reaction of amine (II) *with hydrazine in acetic acid.* The solution formed by adding 2.0 ml. of hydrazine to a solution of 2.0 g. of II in 20 ml. of acetic acid was allowed to stand 48 hr. The solution developed a slight yellow color after approximately half this time. The solvent was evaporated leaving an orange colored semisolid. This was treated with 20 ml. of 10% hydrochloric acid. The orange precipitate which formed was collected and washed with 10% hydrochloric acid. Trituration of this orange solid with benzene gave 0.6 g. of white solid, m.p. 152–155° dec. with great dependence on rate of heating. It was insoluble in sodium hydroxide as well as hydrochloric acid, but was not further identified.

The aqueous acid filtrate from above was made neutral with 10% sodium hydroxide. This yielded a light tan solid which was recrystallized from water. It was then heated in *ca.* 60 ml. of benzene and the mixture was cooled. This yielded 0.5 g. of white solid, m.p. 145–150°. It was found to be soluble in both 5% hydrochloric acid and 5% sodium hydroxide, but insoluble in sodium bicarbonate. An analytical sample, m.p. 155–157°, was prepared by recrystallization from benzene.

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.49; H, 5.93; N, 19.40.

5-Phenylisoxazole-3-carboxylic acid. 5-Phenyl-2-isoxazoline-3-carboxylic acid (I) was oxidized with permanganate to the corresponding aromatic isoxazole. To a solution of 4 ml. of concd. sulfuric acid in 40 ml. of water was added 1.9 g. (0.01 mole) of 5-phenyl-2-isoxazoline-3-carboxylic acid (I). With mechanical stirring 3.0 g. (0.02 mole) of potassium permanganate was added in small portions. After the addition 4 g. of sodium bisulfite was added to reduce any manganese dioxide formed. The mixture was cooled in an ice bath and yielded 1.0 g. of light tan solid. This was recrystallized from benzene to give 0.8 g. (43%) of white solid, m.p. 153–161° dec. The analytical sample was prepared by recrystallization from water andaga in from benzene, 156–161° dec. The reported[8] m.p. is 162°. Neut. equiv.: Calcd., 189. Found, 191.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.52; H, 3.65; N, 7.51.

Decyclization of 5-phenyl-2-isoxazoline-3-carboxylic acid (I). 5-Phenyl-2-isoxazoline-3-carboxylic acid (100 mg.) was dissolved in 1 ml. of concd. sulfuric acid. After standing 24 hr. the solution was poured onto 5 g. of ice to yield 100 mg. of slightly yellow solid, m.p. 125–135° dec. Recrystallization from ethanol-water gave 65 mg. of white solid, m.p. 156–158° dec. There was no depression of the melting point when mixed with a sample of benzylidenepyruvic acid oxime[5] and the two samples had identical infrared spectra.

Dimethyl-3-[5-phenyl-2-isoxazoline]-methanol. Methylmagnesium iodide was prepared from 2.4 g. (0.1 g.-atom) of magnesium and 14.1 g. (0.1 mole) of methyl iodide, and a solution of 5.5 g. (0.025 mole) of ethyl 5-phenyl-2-isoxazoline-3-carboxylate in 100 ml. of ether was added in small portions, the reaction being allowed to subside after each addition. A brownish oil separated and the mixture was stirred an additional hour.

The complex was decomposed with saturated ammonium chloride, approximately 15 ml. being required. With continued stirring the ammonium chloride solution was added dropwise at such a rate as to maintain reflux and in amount necessary to change the cloudy mixture to a clear solution with precipitated solid. The ether layer was decanted and

the ether evaporated leaving an oil which solidified on prolonged cooling. Recrystallization from a small quantity of carbon tetrachloride gave 2.4 g. (46%) of white solid, m.p. 58–60°. Further recrystallizations from the same solvent gave an analytical sample, m.p. 59–61°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.29; H, 7.38; N, 6.93.

Methyl styrylcarbamate. Methyl styrylcarbamate was prepared by a Hofmann rearrangement on cinnamamide according to the procedure of Weermann.[18]

Methyl 5-[3-carbethoxy-4-phenyl-2-isoxazolinyl]carbamate. A solution of 17.7 g. (0.10 mole) of methyl styrylcarbamate in 400 ml. of ether was added to a solution of 18.2 g. (0.12 mole) of ethyl chlorooximinoacetate[7] in 100 ml. of ether. With vigorous mechanical stirring 12.7 g. (0.12 mole) of sodium carbonate in 180 ml. of water was added dropwise over a 7-hr. period at room temperature. After the addition the mixture was stirred an additional hour. The layers were separated; the ether layer was washed with water and dried over magnesium sulfate. Filtration and evaporation of the ether left a semisolid residue, 31 g. The ester was not purified but converted directly to the hydrazide.

Methyl 5-[3-hydrazido-4-phenyl-2-isoxazolinyl]carbamate (IV). The above 31 g. of crude ester in 250 ml. of ethanol was slowly added to a solution of 25 ml. of hydrazine in 250 ml. of ethanol cooled in an ice bath. After the addition the solution was allowed to warm to room temperature over a 30-min. period. The solution was filtered from the reddish solid and tars and the solvent evaporated, leaving a solid.

The residual solid was dissolved in 100 ml. of chloroform and extracted with 100 ml. of 5% hydrochloric acid. The acid extract was washed twice with 50 ml. of chloroform, partially neutralized with 50 ml. of 10% sodium hydroxide, and made basic with 50 ml. of 5% sodium bicarbonate. This yielded, after cooling, 13 g. [47% based on methyl styrylcarbamate] of light tan solid, m.p. 127–137° sl. dec. Two recrystallizations from methanol only raised the melting point slightly, 130–140° sl. dec. Further recrystallizations from methanol-water did not raise the melting point further.

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot 1/2H_2O$: C, 50.18; H, 5.25; N, 19.49. Found: C, 50.27, 50.17; H, 5.22, 5.29; N, 19.48, 19.59.

The analytical sample was recrystallized from benzene-cyclohexane and dried at 0.03 mm. for 48 hr. without change. However, drying at 100° and atmospheric pressure removed the water.

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.73; H, 5.07; N, 20.11.

Methyl 5-[3-carbazido-4-phenyl-2-isoxazolinyl]carbamate. A solution of 0.50 g. (0.0072 mole) of sodium nitrite was added dropwise to a solution of 1.0 g. (0.0036 mole) of the above hydrazide (IV) in 50 ml. of 5% hydrochloric acid cooled in an ice bath. This yielded 0.94 g. (90%) of white solid, m.p. 115° vigorous dec.

A sample for analysis was prepared by dissolving in ethanol, filtering and reprecipitating with water, m.p. 120° vigorous dec.

Anal. Calcd. for $C_{12}H_{11}N_5O_4$: C, 49.83; H, 3.83; N, 24.21. Found: C, 50.10; H, 4.16; N, 24.11.

Ethyl methyl 3,5-[4-phenyl-2-isoxazolinyl]dicarbamate. The above azide (0.90 g., 0.0030 mole) was dissolved in 50 ml. of ethanol and the solution refluxed for 30 min. The solution was decolorized with Norit and evaporated to dryness. The residue was triturated with a very small amount of ether to give 0.60 g. (65%) of white solid, m.p. 173–183°. Recrystallization from ethanol-water gave an analytical sample, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.68; H, 5.59; N, 13.82.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

2,6-Disubstituted 3,5-Thiomorpholinediones and Related Compounds[1]

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Methods suitable for the synthesis of α,α'-dialkylthiodiacetamic acids including those with unlike radicals and their conversion to 2,6-dialkyl-3,5-thiomorpholinediones are described. The diacetamic acids could be separated into racemates but attempts to resolve the racemates to their optical isomers were unsuccessful. In the synthesis of 2,2-dialkyl-3-thiomorpholones by a previously unreported process, the intermediate dialkyl(2-aminoethylmercapto)acetic acids were isolated.

Previous workers have reported the synthesis of unsubstituted 3,5-thiomorpholinedione,[2] symmetrical 2,6-di- and 2,2,6,6-tetrasubstituted analogs,[3,4] unsymmetrical 2,2-disubstituted analogs[4–7] and unsymmetrical 2,2,6-trisubstituted analogs.[7,8]

The present series of 2,6-disubstituted 3,5-thiomorpholinediones was prepared by the scheme outlined in Fig. 1, which is equally well suited for the synthesis of compounds with unlike radicals.

5-Monoalkyl-2-imino-thiazolidinones (Series I) were prepared in yields of 80–90% which is about twice that obtained for the geminal dialkyl compounds. One previously unreported member of Series I, 5-(2-secpentyl)-2-imino-4-thiazolidinone, was prepared from its hydrobromide salt and hydrolyzed to its 2-keto derivative.

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