

5-Isloxazolyhydrazines. Reduction of 5-isoxazolones to Isoxazoles

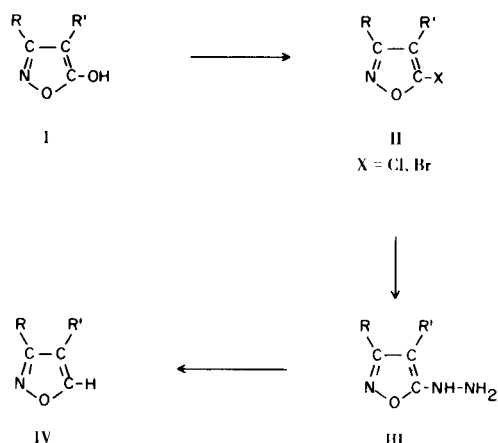
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5-Isloxazolyhydrazines III were obtained from 5-isoxazolones I, *via* the 5-haloisoxazoles II. The decomposition of the tosyl derivatives of III results in unambiguous syntheses of 3,4-disubstituted isoxazoles.

In the extensive literature in the field of isoxazoles we could find only one method of preparation of the 3,4-disubstituted compounds, namely Stork and McMurray's synthesis (1) of the 3-substituted-4-carboxylic acid. The syntheses usually employed for preparing disubstituted isoxazoles, starting from β -ketoaldehydes or from nitrile oxides, yield both 4,5- and 3,4- or 3,5- and 3,4-isomers (2,3), respectively. The resulting mixtures of products are difficult to separate and only 3,4-dimethyl- and 3,4-diphenylisoxazole are reported in the literature.

In a short communication (4) we have briefly described a new method of preparation of these compounds starting from 5-isoxazolones, according to the following scheme:



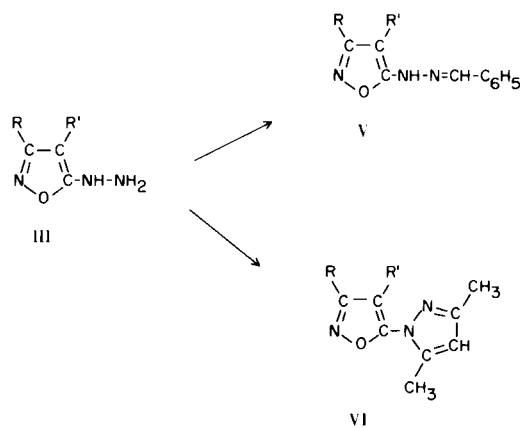
Our interest in this method is the possibility of obtaining the intermediates and the isoxazoles with indisputable structure and without isomers. Unsuccessful attempts to reduce the haloisoxazoles II (5) led us to prepare the isloxazolyhydrazines III which may then be more easily transformed into the corresponding hydrocarbons.

The 5-(3-methyl-4-carbethoxyisoxazoly)hydrazine (IIIa) can be obtained in high yield by the reaction of the corresponding chloroisoxazole with hydrazine hydrate. In this case the chlorine atom is so reactive, owing to the presence of the carboxyl group in 4-position, that the reaction is very exothermic. In other cases, only by reac-

tion of bromoisoxazole with anhydrous hydrazine was it possible to achieve 70-90% yields.

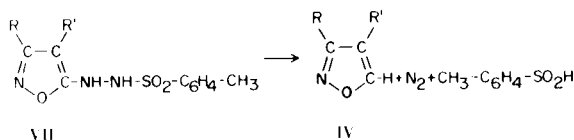
Isoxazolyhydrazines are colorless crystalline solids with properties very similar to those of the 5-aminoisoxazoles. They are weak bases, sparingly soluble in water, and take on colors on long standing in air. They react with benzaldehyde to give the corresponding benzal derivatives (V). Ultraviolet spectra show a pattern very similar to those of the corresponding 5-aminoisoxazoles (6). In fact, between 200 and 300 μ , the hydrazines IIIb and IIIc show two bands and the hydrazines IIIa and IIId only one. However, the maximum of the band at longer wave length in the hydrazines IIIb and IIIc is red-shifted compared with that of the corresponding aminoisoxazole, whereas that of hydrazines IIIa and IIId is at same wave length of the corresponding aminoisoxazole. This means that in the hydrazines IIIa and IIId the amino group does not contribute to the conjugation.

The presence of a hydrazino group in compounds III could be confirmed by condensation with acetylacetone; for example, from this reaction the pyrazolyisoxazoles VIa and VIc were obtained. An attempt to oxidize the



IIIa, Va, VIa R = CH₃, R' = COOC₂H₅
 IIIb, Vb R = C₆H₅, R' = H
 IIIc, Vc, VIc R = C₆H₅, R' = CH₃
 IIId, Vd R = CH₃, R' = C₆H₅

compound IIIa with copper sulfate resulted in complete decomposition. Hence, we preferred to decompose in alkaline medium the tosylhydrazines VII, obtained from III by tosylchloride in pyridine. However, the yield of



IVa, VIIa	R	CH ₃	R'	COOC ₂ H ₅
IVb, VIIb	R	C ₆ H ₅	R'	H
IVc, VIIc	R	C ₆ H ₅	R'	CH ₃
IVd, VIId	R	CH ₃	R'	C ₆ H ₅

this decomposition to isoxazole was never high because the isoxazole ring opens to yield a nitrilic and a ketonic compound. The purification of compounds IVa and IVb was easily achieved by fractional distillation. This operation is not sufficient to purify the compounds IVc and IVd and therefore, in both cases the raw products were treated by gas chromatography. By this method we completely separated the ketone and the nitrile byproducts, in addition to the isoxazoles. The first two compounds were identified as benzonitrile and propiophenone and acetonitrile and methylbenzylketone, respectively.

The U. V. Spectrum of compound IVa shows a maximum at the same wave length as 3-methylisoxazole (7). The introduction of a carboxyl group at 4-position of the isoxazole ring only raises the intensity of the band. Analogous behavior was found by comparison of the 3,5-dimethylisoxazole and 3,5-dimethylisoxazol-4-carboxylic acid spectra (8).

The spectra of methylphenylisoxazoles IVc and IVd are shifted towards shorter wave lengths compared with the corresponding phenylisoxazole spectra (9). The influence of the methyl group is evident in both cases.

The I. R. spectra of compound IVc and IVd show very close patterns. In particular, the occurrence of the fundamental modes of the isoxazole ring at nearly the same frequencies, suggests that they are not affected by the relative positions of the methyl and the phenyl group in the ring.

EXPERIMENTAL

All melting points are uncorrected. The infrared and ultraviolet spectra were recorded on Perkin Elmer 457 and Cary Model 14 spectrometers, respectively. The ultraviolet spectra were taken in methanol. Gas chromatography was carried out on a Wilkens Aerograph Autoprep 705 equipped with 3/8" X6m column, packed with 30% SE-30 on Chromosorb WAW 60-80 mesh.

5-(3-Methyl-4-carbethoxyisoxazolyl)hydrazine (IIIa).

To 3.2 ml. (0.066 mole) of ice-cold hydrazine hydrate was

added slowly with stirring 4 g. (0.022 mole) of 3-methyl-4-carbethoxy-5-chloroisoxazole. The resultant mixture was stirred an additional hour at room temperature. The white precipitate was filtered, washed with cold water and dried *in vacuo*. The product was purified by recrystallization from benzene to give 2.95 g. (yield 75%) of IIIa, m.p. 130-132° (dec.); infrared cm^{-1} , 3350 (m), 3320 (m), 1690 (s), 1645 (s), 1600 (m), 1542 (m), 1460 (s), 1430 (s), 1410 (s), 1375 (s), 1265 (s), 1140 (m), 1120 (s), 1100 (s), 770 (s), (nujol); U. V. (methanol) λ max (log ϵ) 252 (4.13).

Anal. Calcd. for C₇H₁₁N₃O₃: C, 45.40; H, 5.98; N, 22.70. Found: C, 45.40; H, 5.79; N, 22.69.

5-(3-Phenylisoxazolyl)hydrazine (IIIb).

A mixture of 4 g. (0.0178 mole) of 3-phenyl-5-bromoisoxazole and 17 ml. (0.534 mole) of anhydrous hydrazine was steam heated at 100° with stirring for 2 minutes. The resulting solution was poured over crushed ice. The precipitate so obtained was filtered, washed with cold water and dried *in vacuo*. Recrystallization from benzene yielded 2.85 g. (90%) of white crystals, m.p. 145-146° (dec.); infrared cm^{-1} , 3330 (w), 3235 (m), 3130 (w), 1610 (s), 1575 (s), 1530 (m), 1460 (s), 1445 (s), 1405 (s), 1020 (m), 940 (m), 760 (m), 725 (m), 680 (s), (nujol); U. V. (methanol) λ max (log ϵ) 237 (4.29), 277 (3.98).

Anal. Calcd. for C₉H₉N₃O: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.89; H, 5.16; N, 23.94.

5-(3-Phenyl-4-methylisoxazolyl)hydrazine (IIIc).

The procedure used for the preparation of this compound was similar to IIIb except that the reaction time was increased to 25 minutes. The analytical sample was recrystallized from ethanol to give a white compound, m.p. 113-114° (dec.) (yield 75%); infrared cm^{-1} , 3330 (s), 3260 (m), 1655 (s), 1465 (s), 1440 (m), 1380 (m), 1175 (m), 1170 (m), 1120 (s), 1010 (s), 770 (m), 710 (s), 695 (s), (nujol); U. V. (methanol) λ max (log ϵ) 230 (4.14), 285 (4.08).

Anal. Calcd. for C₁₀H₁₁N₃O: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.38; H, 6.04; N, 22.45.

5-(3-Methyl-4-phenylisoxazolyl)hydrazine (III d).

Compound III d was prepared by following the method described for IIIb, except that reaction time was increased to 5 minutes. After pouring on ice, III d was obtained as an oil which crystallized by rubbing. Recrystallization by dissolving in the least amount of chloroform and adding ligroin (90-120° b.p.) yielded a white product, m.p. 67-68° (dec.) (yield 70%); infrared cm^{-1} 3310 (m), 3190 (s), 1650 (s), 1608 (m), 1515 (s), 1465 (s), 1440 (s), 1380 (s), 1340 (s), 1330 (m), 1162 (m), 1155 (m), 990 (s), 710 (s), (nujol); U. V. (methanol) λ max (log ϵ) 257 (4.12).

Anal. Calcd. for C₁₀H₁₁N₃O: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.40; H, 5.81; N, 22.30.

General Procedure for the Benzylidenehydrazinoisoxazoles (V).

A solution of 0.01 mole of 5-isoxazolylhydrazines III and 0.03 mole of benzaldehyde in the least amount of methanol was heated under reflux for 1 hour. The benzylidenehydrazinoisoxazoles were separated by adding water to the cold solution.

3-Methyl-4-carbethoxy-5-benzylidenehydrazinoisoxazole (Va).

The crude product was recrystallized from methanol to give a white powder, m.p. 134-135° (yield 75%).

Anal. Calcd. for C₁₄H₁₅N₃O₃: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.60; H, 5.57; N, 15.50.

3-Phenyl-5-benzylidenehydrazinoisoxazole (Vb).

The crude product was recrystallized from 1:1 benzene-ligroin

(90-120° b.p.) to give white crystals, m.p. 157-159° (yield 80%).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.91; H, 5.00; N, 15.75.

3-Phenyl-4-methyl-5-benzylidenehydrazinoisoxazole (Vc).

The crude product was recrystallized from benzene to give white crystals, m.p. 157-158° (yield 90%).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.75; H, 5.44; N, 15.10.

3-Methyl-4-phenyl-5-benzylidenehydrazinoisoxazole (Vd).

By adding a few drops of petroleum ether to an ethyl ether solution of the oily product, a white powder was obtained. This was crystallized from 1:1 benzene-ligroin (90-120° b.p.) to give crystals, m.p. 148-150° (yield 80%).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.33; H, 5.37; N, 14.86.

General Procedure for the Pyrazolyliisoxazoles (VI).

A solution of 0.01 mole of isoxazolyhydrazine, 0.03 mole of acetylacetone and 1.2 ml. of glacial acetic acid in 50 ml. of ethanol was refluxed for 2 hours. The solvent was removed by evaporation under reduced pressure. The residue was digested with crushed ice.

3-Methyl-4-carbethoxy-5-(3,5-dimethyl-1-pyrazolyl)isoxazole (VIa).

The aqueous suspension was extracted with ether. The ethereal solution was dried with sodium sulfate, filtered and evaporated. The oily residue was distilled at 0.06 mm to give a product boiling at 88-96°, which solidified in a white mass. This was purified by sublimation (0.05 mm at 38°); m.p. 44-45° (yield 65%); U. V. (methanol) λ max (log ϵ) 260 (3.89).

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.64; H, 6.09; N, 17.07.

3-Phenyl-4-methyl-5-(3,5-dimethyl-1-pyrazolyl)isoxazole (VIc).

The residue was filtered, dried and purified by sublimation (0.05 mm at 60°); m.p. 69-71° (yield 85%); U. V. (methanol) λ max (log ϵ) 234 (4.17), 240 sh (ca 4.1).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.00; H, 6.02; N, 16.66.

General Procedure for the Tosylhydrazinoisoxazoles (VII).

To 0.01 mole of 5-isoxazolyhydrazine dissolved in 7 ml. of anhydrous pyridine, under cooling with ice, was added 0.012 mole of tosyl chloride. After 3 hours the solution was poured over crushed ice. The oily product was washed with cold water and solidified to a brown mass. This was dissolved in 80:20 ethanol-water, decolorized with charcoal, filtered and cooled to give a pale colored powder.

3-Methyl-4-carbethoxy-5-tosylhydrazinoisoxazole (VIIa).

The powder was recrystallized from benzene to give white crystals, m.p. 187-188° (yield 70%).

Anal. Calcd. for $C_{14}H_{17}N_3O_5S$: C, 49.56; H, 5.05; N, 12.38; S, 9.43. Found: C, 49.36; H, 5.04; N, 12.60; S, 9.35.

3-Phenyl-5-tosylhydrazinoisoxazole (VIIb).

The powder was recrystallized from ethanol to give white crystals, m.p. 179-180° (yield 60%).

Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.36; H, 4.59; N, 12.76; S, 9.73. Found: C, 58.20; H, 4.67; N, 12.74; S, 10.00.

3-Phenyl-4-methyl-5-tosylhydrazinoisoxazole (VIIc).

The powder was recrystallized from 80:20 ethanol-water to

give white crystals, m.p. 141-142° (yield 60%).

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.47; H, 4.99; N, 12.24; S, 9.33. Found: C, 59.38; H, 5.00; N, 12.27; S, 9.46.

3-Methyl-4-phenyl-5-tosylhydrazinoisoxazole (VIIId).

The powder was recrystallized from benzene to give white crystals, m.p. 138-139° (yield 55%).

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.47; H, 4.99; N, 12.24; S, 9.33. Found: C, 59.36; H, 4.94; N, 12.25; S, 9.60.

3-Methyl-4-carbethoxyisoxazole (IVa).

To a solution of 2.9 g. (0.021 mole) of potassium carbonate in 40 ml. of water, 4 g. (0.0118 mole) of VIIa was added. The mixture was heated with stirring on the steam bath for 15-20 minutes. After cooling the brown solution was extracted with ether. The ethereal solution was evaporated under reduced pressure and the residue was distilled at 0.08 mm to give a product boiling at 30° (lit. b.p. \sim 110° at 3 mm (1) (yield 30%); infrared cm^{-1} , 3115 (w), 2982 (w), 2938 (w), 1725 (s), 1587 (m), 1485 (m), 1443 (m), 1400 (m), 1372 (m), 1305 (s), 1288 (s), 1240 (m), 1224 (m), 1163 (w), 1125 (s), 1095 (s), 1010 (w), 908 (w), 845 (w), 830 (w), 770 (m), (liquid); U. V. (methanol) λ max (log ϵ) 211 (3.75), 271 (2.88).

Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.92; H, 5.88; N, 9.30.

By treatment of IVa with an ice-cold ethanolic solution of potassium hydroxide, the potassium salt of 3-methyl-4-carboxyisoxazole was obtained. This, dissolved in a minimum amount of water and acidified with concentrated hydrogen chloride, gave the corresponding acid in almost quantitative yield, m.p. 184-185° (lit. 183-183.5° (1)).

3-Phenylisoxazole (IVb).

Compound IVb was prepared following the method described for IVa (yield 50%). Its infrared spectrum is identical with that of an authentic sample.

3-Phenyl-4-methylisoxazole (IVc).

The procedure for the preparation of this compound was similar to IVa except that reaction time was increased to 25-30 minutes. The oily residue was distilled at 0.25 mm and the liquid boiling between 50-70° was collected. By gas chromatography (1° column 150°) three fractions were isolated, of which the first two were identified as benzonitrile and propiophenone, respectively, by their infrared spectra and their retention time.

The third fraction was the 3-phenyl-4-methylisoxazole, b.p. 268° at 717 mm (yield 25%); infrared cm^{-1} ; 3110 (w), 3060 (w), 3036 (w), 2960 (w), 2930 (w), 2870 (w), 1605 (m), 1575 (m), 1455 (s), 1378 (s), 1270 (m), 1225 (m), 1178 (w), 1155 (w), 1110 (s), 1073 (w), 1045 (w), 1017 (m), 1003 (m), 918 (m), 888 (s), 820 (m), 770 (s), 695 (s), 648 (w), 588 (m), (liquid); U. V. (methanol) λ max (log ϵ) 236 (4.03).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.75; H, 5.64; N, 8.64.

3-Methyl-4-phenylisoxazole (IVd).

The procedure for the preparation of this compound was similar to IVa except that reaction time was decreased to 7-8 minutes. The oily residue was distilled at 0.1 mm and the liquid boiling at 58-62° was collected. This was gas chromatographed under the same conditions used for compound IVc.

Acetonitrile, methyl benzyl ketone and 3-methyl-4-phenylisoxazole were obtained. The first two were identified by infrared spectra and retention time. Compound IVd (yield 25%) boils at

259° at 717 mm; infrared cm^{-1} , 3120 (w), 3065 (w), 3040 (w), 2940 (w), 1618 (m), 1595 (m), 1575 (w), 1505 (m), 1470 (w), 1456 (m), 1437 (m), 1398 (s), 1370 (m), 1332 (w), 1300 (w), 1280 (w), 1225 (m), 1182 (w), 1160 (w), 1125 (s), 1080 (m), 1040 (w), 1018 (w), 1010 (m), 995 (m), 915 (w), 878 (s), 840 (m), 765 (s), 700 (s), 655 (m), 595 (w), 525 (m), (liquid); U. V. (methanol) λ max (log ϵ) 228 (4.0).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.16; H, 5.69; N, 8.71.

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