Rearrangement of Secondary β-Dinitro Alkanes to 3,5-Dialkyl Isoxazoles

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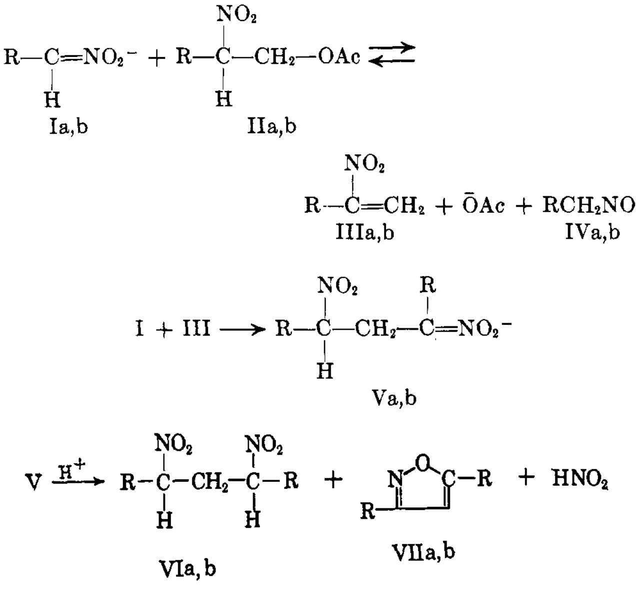
The Michael-type addition between sodium 1-alkane nitronates and α-nitro olefins, which are generated *in situ* from 2-nitroalkyl acetates leads largely to the formation of 3,5-dialkyl isoxazoles. The latter also are obtained by the demethylolation of 2-alkyl-2,4-dinitro 1-alkanols and by the rearrangement of secondary β-dinitro alkanes in weakly basic media.

The Michael-type addition between 2-alkane nitronates and α-nitro olefins generally proceeds in reasonably good yields.[2-6] In contrast, 1-alkane nitronates give the desired Michael adducts, secondary β-dinitro alkanes, only in poor yields. No explanations have been given to account for the poor yields in this reaction. There are, however, reports in the literature in which attempts to prepare phenyl-substituted β-dinitro alkanes gave rise largely to isoxazoles and isoxazoline N-oxides.[7-9] For example, Heim[7] obtained in the base-catalyzed reaction between phenylnitromethane and benzaldehyde, in addition to 1,2,3-triphenyl-1,3-dinitropropane and nitrostilbene, 3,4,5-triphenylisoxazole. Heim and other workers[8,10-12] were able to show that phenyl-substituted β-dinitro compounds were unstable in the presence of base and eliminated nitrous acid to form isoxazoline N-oxides and isoxazoles.

In a preliminary investigation of the reaction between sodium 1-propanenitronate (Ia) and 2-nitrobutyl acetate (IIa), from which 2-nitro-1-butene (IIIa) was generated *in situ*, Feuer and Miller[6] reported the formation of a mixture of low-boiling materials, in addition to the expected 3,5-dinitroheptane (VIa). The infrared spectrum of the mixture indicated the presence of a cyclic C=N linkage (6.25 μ).[13] We now have determined that the main component of this mixture was 3,5-diethylisoxazole (VIIa).



a, R = C_2H_5
b, R = CH_3

In this investigation, several attempts were made to improve the yield of VIa by carrying out the reaction between Ia and IIa in various solvents at room temperature; but in all cases the yield of VIa was low and VIIa was formed. For example, the reaction between excess (5 equivalents) Ia (sodium salt) and IIa in tetrahydrofuran (THF) afforded only a 16% yield of VIa. Similar results were obtained with Ia (lithium salt) in THF (22%) and Ia (sodium salt) in dimethyl sulfoxide (11%) and in methanol (4%). In all of these experiments, distillation of the acidified reaction mixtures gave foreruns which by vapor phase chromatography were found to contain the solvent, IVa, unchanged IIa, and the isoxazole (VIIa). 1-Methoxy-2-nitrobutane[6] was found also to be present when the solvent was methanol. All of these reactions also produced undistillable high molecular weight byproducts which were probably formed by the addition of anions such as Va to the nitro olefin (IIIa).

No 3,5-dinitroheptane (VIa) was formed at all when Ia and IIa interacted in aqueous medium. In fact, these were the conditions at which VIIa was obtained in highest yield (66%). A small amount of another substance was isolated, but there was only enough material for an infrared spectrum, which indicated the presence of hydroxyl and nitro groups.

The identity of VIIa was established by an independent synthesis which followed the procedure of Harries and Haga.[14] Mono-oximation of 3,5-heptanedione gave a 63% yield of 3,5-diethylisoxazole, which had the same refractive index, infrared spectrum, and retention time (on the gas chromatogram) as VIIa.

The isolation of VIIa in varying amounts from the reaction of Ia (sodium salt) and IIa suggested that an anion of 3,5-dinitroheptane (VIa) was one of the possible intermediates in the formation of VIIa. This possibility was actually indicated by the fact that treatment of authentic VIa[6] with a weak base such as an aqueous solution of Ia (sodium salt) gave after two days a 37% yield of VIIa as established by gas chromatography. The yield of VIIa increased to 52% when the reaction mixture was allowed to stand for 2 weeks. The conversion of VIa to VIIa took place also in aqueous sodium hydroxide.

Compound VIIa was obtained also when 2-ethyl-2,4-dinitro-1-hexanol[15] (VIIIa) in a mixture of THF

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[1] From the Ph.D. thesis of S. Markofsky, Purdue University, 1962.

[2] A. Lambert and H. A. Piggott, *J. Chem. Soc.*, 1489 (1947).

[3] C. T. Bahner and H. T. Kite, *J. Am. Chem. Soc.*, **71**, 3597 (1949).

[4] H. R. Snyder and W. E. Hamlin, *ibid.*, **72**, 5082 (1950).

[5] G. L. Shoemaker and R. W. Keown, *ibid.*, **76**, 6374 (1954).

[6] H. Feuer and R. Miller, *J. Org. Chem.*, **26**, 1348 (1961).

[7] F. Heim, *Ber.*, **44**, 2016 (1911).

[8] E. P. Kohler and G. R. Barrett, *J. Am. Chem. Soc.*, **46**, 2106 (1924).

[9] D. E. Worrall, *ibid.*, **57**, 2299 (1935).

[10] A. Dornow and G. Wiehler, *Ann.*, **578**, 113 (1952).

[11] Z. Eckstein, *Roczniki Chem.*, **28**, 43 (1954).

[12] S. Umezawa and S. Zen, *Bull. Chem. Soc. Japan*, **34**, 890 (1961).

[13] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 228.

[14] C. Harries and T. Haga, *Ber.*, **32**, 1191 (1899).

[15] H. Feuer and S. Markofsky, *J. Org. Chem.*, **29**, 929 (1964).

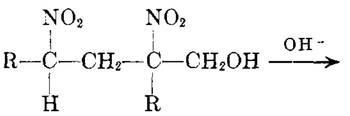
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME 3,5-DIALKYL ISOXAZOLES[a]

Isoxazole	Vinyl H	CH_2[b] of ethyl group[c]	5-CH_3	3-CH_3	CH_3[d] of ethyl group
3,5-Dimethylisoxazole	4.2		7.7	7.8	
3-Methyl-5-ethylisoxazole	4.2	7.4		7.8	8.8
3-Ethyl-5-methylisoxazole	4.2	7.4[e]	7.7		8.8
3,5-Diethylisoxazole	4.3	7.4[e]			8.8

[a] In τ values (see ref. 17; all values accurate to ±0.05). [b] Measured relative to center of quartet. [c] The difference between the τ values of 3- and 5-substituted ethyl groups is less than τ 0.05. [d] Measured relative to center of triplet. [e] Methyl singlet overlaps high field component of quartet.

and methanol was made basic by slowly extracting sodium hydroxide from the thimble of a Soxhlet apparatus.



$$R-\overset{NO_2}{\underset{H}{C}}-CH_2-\overset{NO_2}{\underset{R}{C}}-CH_2OH \xrightarrow{OH^-}$$

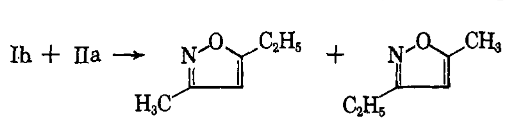
VIIIa,b
a, R = C_2H_5
b, R = CH_3

$$CH_2O + Va,b \longrightarrow VIIa,b + NO_2^-$$

In order to establish the utility of this novel preparation of isoxazoles, a number of reactions were carried out, in aqueous media, between various 1-alkane nitronates and 2-nitroalkyl acetates. Treatment of sodium ethanenitronate (Ib) with 2-nitropropyl acetate (IIb) gave 3,5-dimethylisoxazole[16] (VIIb) in 48% yield. In addition, a small amount of 3,4,5-trimethylisoxazole was isolated. This compound has been known to form directly by the rearrangement of Ib in aqueous medium.[17] A large residue of high molecular weight polymeric material was obtained also. It might have arisen from the anionic polymerization of 2-nitropropene (IIIb).

Compound VIIb was prepared also in 58% yield from the demethylolation of 2-methyl-2,4-dinitro-1-pentanol (VIIIb) in aqueous sodium hydroxide.

The reaction between Ib and IIa gave rise to the expected mixture consisting of 3-methyl-5-ethylisoxazole (IX) and 3-ethyl-5-methylisoxazole (X). This same isomeric mixture (IX and X) was obtained from (a) the reaction between Ia and IIb and (b) the respective demethylolations[15] of 2-methyl-2,4-dinitro-1-hexanol and 2-ethyl-2,4-dinitro-1-pentanol.



IX X

It is of interest to note that vapor phase chromatographic analysis, on four different columns, of the reaction mixtures containing IX and X gave only one symmetrical peak. N.m.r. spectra, however, clearly indicated that an isomeric mixture of isoxazoles was present on comparison with an authentic sample of VIIb. The spectrum of VIIb showed two distinct methyl groups at τ[18] 7.7 and 7.8. Similarly, the mixture containing IX and X showed two distinct absorption peaks at τ 7.7 and 7.8 of approximately equal area, indicating that both 3-methyl- and 5-methyl-substituted isoxazoles were present and that IX and X had formed in about equal amounts. (The τ values of a number of 3,5-dialkyl isoxazoles are enumerated in Table I.)

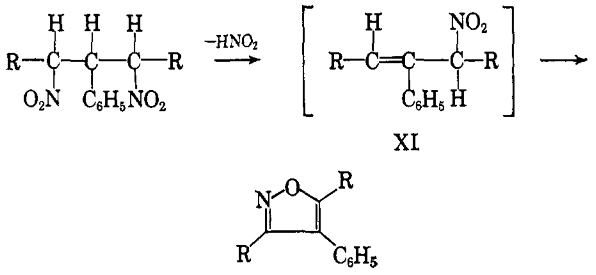
In order to assign τ values, IX and X were synthesized independently. Compound IX was prepared from acetohydroxamic chloride[19] and 1-butynylmagnesium bromide[20] by a method which followed essentially the procedure of Palazzo.[21] Similarly, X was prepared from propionohydroxamic chloride and 1-propynylmagnesium bromide.

The n.m.r. spectrum of authentic IX showed only one peak for the methyl group at τ 7.8, while X exhibited the methyl peak at τ 7.7. The n.m.r. spectrum of a synthetic mixture prepared from equal volumes of IX and X showed two absorptions at τ 7.7 and 7.8 and was superimposable on the spectrum of the mixture of isoxazoles obtained in the various experiments (*vide supra*). The synthetic mixture (IX and X) also gave only one symmetrical peak on four different gas chromatographic columns (see Experimental).

The infrared spectra of IX and X were almost identical. The main difference was that X had two bands, at 7.93 and 8.03 μ, which were absent in IX.

Discussion

The mechanism of the rearrangement of β-dinitro compounds to isoxazoles has never been established. Both Heim[7] and Dornow[10] suggested the formation of an olefinic intermediate (XI) which rearranged directly to the isoxazole. While an elimination reaction is certainly involved in this transformation, the direct loss of nitrous acid from an α,γ-dinitro compound on treatment with base is certainly not general. For instance, Keppler and Meyer[22] converted crude 1,3-dinitropropane to the monosodium salt with sodium ethoxide in absolute ethanol; also 2-methyl-2,4-dinitrohexane (XII) is apparently stable under basic conditions, since it can be prepared in high yield (87%) from the reaction of sodium 2-propanenitronate and 2-



XI

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(16) G. Speroni, P. Pino, and L. Mori, *Gazz. chim. ital.*, **82**, 269 (1952).

(17) W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.*, **59**, 410 (1891).

(18) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

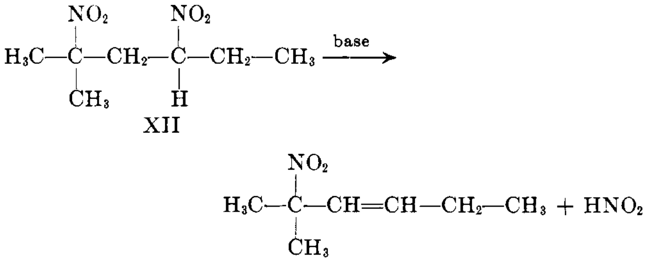
(19) H. Wieland, *Ber.*, **40**, 1676 (1907).

(20) T. Y. Lai, *Bull. soc. chim. France*, **53**, 682 (1933).

(21) G. Palazzo, *Gazz. chim. ital.*, **77**, 214 (1947).

(22) F. Keppler and V. Meyer, *Ber.*, **25**, 1709 (1892).

nitrobutyl acetate.[6] According to the suggestion of Heim and Dornow, XII should be unstable to base and lose nitrous acid.



$$H_3C-\overset{NO_2}{\underset{CH_3}{C}}-CH_2-\overset{NO_2}{\underset{H}{C}}-CH_2-CH_3 \xrightarrow{base} H_3C-\overset{NO_2}{\underset{CH_3}{C}}-CH=CH-CH_2-CH_3 + HNO_2$$

XII

In order to gain more insight into the conversion of an α,γ-dinitro alkane to an isoxazole, a basic solution of 3,5-dinitroheptane (VIa) was tested by gas chromatography for the presence of 3,5-diethylisoxazole (VIIa). The characteristic peak of VIIa was completely absent even after 2 weeks, but acidification with glacial acetic acid or carbon dioxide resulted in the formation of VIIa and the evolution of nitrous acid. The latter was detected by the fact that it turned starch iodide paper blue and that a red azo dye formed on addition of sulfanilic acid and α-naphthylamine[23] to the reaction mixture.

This experiment did not rule out the possibility that some precursor of the isoxazole had formed already in the strongly basic solution[24] and .on subsequent acidification was converted to the isoxazole. Therefore, the disodium salt of VIa was prepared first by adding a solution of VIa in methanol to a solution of sodium hydroxide. The salt was found to be highly hygroscopic and difficult to purify. Therefore the elemental analysis is only in fair agreement with the calculated values (see Experimental).

Subjecting the disodium salt of VIa to the same treatment as VIa (*vide supra*) gave the same results; VIIa was formed only after acidification of the aqueous solution of the salt.[25] It seems, therefore, that at least a mono-*aci* form of the dinitro compound must be involved in the rearrangement to the isoxazole[26] and not a direct elimination of nitrous acid as was suggested by Heim and Dornow.

Experimental

3,5-Diethylisoxazole (VIIa). A. From 2-Nitrobutyl Acetate and Sodium 1-Propanenitronate.—To a stirred solution of 55 g. (0.495 mole) of anhydrous sodium 1-propanenitronate in 75 ml. of water was added 16.15 g. (0.10 mole) of 2-nitrobutyl acetate. The mixture was stirred for 18 hr. at room temperature and acidified with 30 ml. of glacial acetic acid. After more water was added to dissolve the sodium acetate which was formed in the neutralization reaction, the mixture was extracted with ether until the extract was colorless, and the ethereal solution was dried over anhydrous magnesium sulfate and evaporated in an air stream. Distillation at 58° and 5 mm. afforded a 66% yield of **3,5-diethylisoxazole**. The infrared spectrum and gas chromatogram of the material were superimposable with those of an authentic sample of the isoxazole prepared by procedure B.

B. From 3,5-Heptanedione and Hydroxylamine Hydrochloride.—A solution of 1.63 g. (23.5 mmoles) of hydroxylamine hydrochloride dissolved in 7 ml. of water was carefully mixed with 2.5 g. (29.8 mmoles) of sodium bicarbonate dissolved in 6 ml. of water. This mixture was added to a stirred solution of 3 g. (23.5 mmoles) of 3,5-heptanedione dissolved in a mixture of 14 ml. of methanol and 6 ml. of water; then 5% hydrochloric acid was added to reach a pH of 6. The methanol was boiled off on a steam bath, the aqueous solution was extracted with six 50-ml. portions of ether, and the extract was dried over anhydrous magnesium sulfate. Distillation at 65° and 11 mm. afforded a 63% yield of VIIa, $n^{20}\text{D}$ 1.4490.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.80; H, 9.05; N, 11.25.

C. From 3,5-Dinitroheptane (VIa) in the Presence of Base.—A solution of 1.45 g. (13 mmoles) of sodium 1-propanenitronate dissolved in 2 ml. of water was added to 0.62 g. (3.26 mmoles) of 3,5-dinitroheptane (VIa). After the mixture was stirred vigorously for 48 hr. at room temperature, it was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIa. The yield, which was estimated by a comparison of the peak area with that of known samples of isoxazole, was 37%. After the reaction mixture had been allowed to stand for 2 weeks, the yield increased to 52%. The vapor phase analyses were carried out on a G.E.–S.F. 96 on Chromsorb W column.

The reaction mixture was then acidified with 1 ml. of glacial acetic acid, water was added to dissolve the salts, and the aqueous solution was extracted with three 7-ml. portions of ether. The extract was dried over anhydrous magnesium sulfate and evaporated on a steam bath. The residue was injected into a G.E.–S.F. 96 on Chromosorb W gas chromatographic column, and pure VIIa was collected with $n^{20}\text{D}$ 1.4492. The infrared spectrum of this compound was superimposable on the spectrum of VIIa, which was prepared by procedure B.

B. From a Basic Solution of Disodium 3,5-Heptanedinitronate after Acidification.—A solution of 0.4 g. (10 mmoles) of sodium hydroxide in 2 ml. of water was added to 0.47 g. (2.47 mmoles) of VIa, and the reaction mixture was stirred at room temperature for 2 weeks. Analysis of the mixture on a G.E.–S.F. 96 on Chromosorb W column indicated that no 3,5-diethylisoxazole was present.

One drop of the reaction mixture was then acidified with glacial acetic acid and the resulting solution was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIa but no 3,5-dinitroheptane was found to be present. Similar results were obtained on acidification of the reaction mixture with carbon dioxide.

E. From Disodium 3,5-Heptanedinitronate after Acidification.[25]—In a 10-ml. round-bottomed flask equipped with a magnetic stirrer were placed 0.0317 g. of disodium 3,5-heptanedinitronate and 2 ml. of degassed water. The resulting solution (pH 9) was stirred for 3 hr. at room temperature. Analysis as indicated in procedure D indicated that no 3,5-diethylisoxazole (VIIa) was present.

Four drops of the solution was acidified then with 4 drops of glacial acetic acid, and aliquots of the acidified solution were analyzed at intervals of 15 and 25 min. by gas chromatography. In the case of both samples, a peak was obtained which had the same retention time as an authentic sample of VIIa. The area of the peak was approximately the same with both samples.

F. From Demethylolation of 2-Ethyl-2,4-dinitro-1-hexanol (VIIIa).—The thimble of a Soxhlet extractor was charged with 0.5 g. (12.25 mmoles) of sodium hydroxide. Into a flask, connected to the Soxhlet apparatus, was placed 2.51 g. (11.14 mmoles) of VIIIa dissolved in a mixture of 7 ml. of methanol and 63 ml. of tetrahydrofuran. After the solution had been refluxed for 46 hr., the solvents were evaporated in an air stream, the residue was suspended in 50 ml. of ether and acidified with 1 ml. of glacial acetic acid. Then, water was added to dissolve the nitronate salt and to insure its complete acidification. The aqueous phase was extracted with three 100-ml. portions of ether; the extract was dried over anhydrous magnesium sulfate and evaporated on a rotating evaporator. Distillation of the residue at 60° and 10

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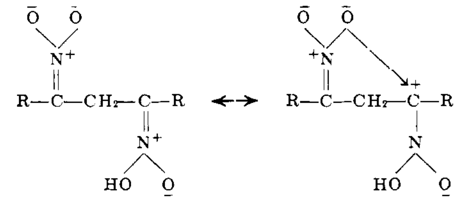
[23] F. Feigl, "Qualitative Analysis by Spot Tests," 3rd. Engl. Ed., Elsevier Publishing Co., Inc., New York, N. Y., 1946, p. 248.

[24] This possibility was pointed out to us by one of the referees.

[25] We are indebted to A. M. Hall for the preparation of the salt and for performing this experiment.

[26]



mm. afforded a 21% yield of VIIa. The infrared spectrum of this material, as well as its gas chromatogram, were essentially superimposable on those of an authentic sample of VIIa.

A fraction (0.2 g.), which distilled at 80° and 30 μ, was also obtained. The infrared spectrum of this substance was similar to that of the starting material (VIIIa).

Disodium 3,5-Heptanedinitronate.[25]—To a stirred solution of 0.902 g. (22.55 mmoles) of sodium hydroxide in methanol was added dropwise (1 hr.) at 3° a solution of 2.32 g. (12.54 mmoles) of VIIa in 50 ml. of methanol. After stirring for 1 hr. at 3° and for an additional 12 hr. at room temperature, the solution was concentrated *in vacuo* to a slurry; then 500 ml. of ether was added and the mixture was allowed to stir overnight. Filtering under dry nitrogen pressure and drying *in vacuo* gave 2.26 g. (77.0% yield) of tan-colored salt which charred at 180° but did not explode; $\lambda_{\max}^{\text{Nujol}}$ 6.2 μ (C=N stretch of alkyl nitronates).[27]

Anal. Calcd. for $C_7H_{12}N_2Na_2O_4$: C, 35.90; H, 5.13; N, 11.96; Na, 19.66; neut. equiv., 117. Found: C, 32.15; H, 5.41; N, 10.96; Na, 20.90; neut. equiv., 113.[28]

3,5-Dimethylisoxazole (VIIb). A. From Sodium Ethanenitronate and 2-Nitropropyl Acetate.—The experimental procedure used was essentially the same as for the preparation of VIIa (procedure A) except that anhydrous sodium ethanenitronate and 2-nitropropyl acetate were employed. Distillation at 130° and 760 mm. afforded a 48% crude yield of VIIb, $n^{20}\text{D}$ 1.4400. Injection into a Carbowax 20 M gas chromatographic column gave a pure sample of 3,5-dimethylisoxazole, b.p. 141° at 760 mm., $n^{20}\text{D}$ 1.4406; lit.[16] b.p. 142° at 748 mm., $n^{20}\text{D}$ 1.4416. In addition, a small amount 3,4,5-trimethylisoxazole was collected, m.p. 3°, lit.[17] m.p. 3.5°; $n^{20}\text{D}$ 1.4510, lit.[16] $n^{20}\text{D}$ 1.4529; b.p. 171° at 762 mm.

B. From Demethylolation of 2-Methyl-2,4-dinitro-1-pentanol (VIIIb).—A heterogeneous mixture of 173 mg. (0.9 mmole) of pure VIIIb in 1 ml. of 10% aqueous sodium hydroxide was boiled over a flame for 1 min., the solution was cooled to Dry Ice temperatures and acidified with 1 ml. of 10% hydrochloric acid. The solution was allowed to warm slowly to room temperature, and 1 ml. of chloroform was added *via* a pipet. The mixture was stirred vigorously and then the chloroform layer was analyzed by gas chromatography. A peak was obtained which had the same retention time as an authentic sample of VIIIb prepared by procedure A. The yield, which was estimated by a comparison of the peak area with that of a known standard of approximately the same concentration of isoxazole, was 58%. A small amount of VIIIb was isolated on a Carbowax 20 M preparative column and had $n^{20}\text{D}$ 1.4413.

3-Methyl-5-ethylisoxazole (IX) and 3-Ethyl-5-methylisoxazole (X). A. From 2-Nitrobutyl Acetate and Sodium Ethanenitronate.—The experimental procedure used was essentially the same as for the preparation of 3,5-diethylisoxazole (procedure A), except that 78 g. (0.8 mole) of sodium ethanenitronate in 150 ml. of water and 64.4 g. (0.4 mole) of 2-nitrobutyl acetate were employed. The work-up procedure was the same except that the acidified reaction mixture was made basic again by the addition of 40 g. (1 mole) of sodium hydroxide in 150 ml. of water and extracted with six 800-ml. portions of chloroform. Distillation at 80° and 40 mm. afforded a 37% yield of a mixture consisting of IX and X. The mixture of isoxazoles gave only one symmetrical peak on a G.E.–S.F. 96 on Chromosorb W column, a Ucon polar column, a Craig polyester (succinate) column, and a Carbowax 20 M column. A pure sample of the isoxazole mixture was isolated on the Carbowax Column and had $n^{20}\text{D}$ 1.4453.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.21; N, 12.67.

B. From 2-Nitropropyl Acetate and Sodium 1-Propanenitronate.—The experimental procedure used was exactly the same as procedure A except that sodium 1-propanenitronate and 2-nitropropyl acetate were employed. Distillation at 65° and 37 mm. afforded a mixture of IX and X in 31% yield. The gas chromatogram and the infrared and n.m.r. spectra of this material were superimposable on the mixture of isoxazoles obtained from procedure A.

C. From the Demethylolation of 2-Methyl-2,4-dinitro-1-hexanol.—A heterogeneous mixture of 1 g. (4.85 mmoles) of 2-methyl-2,4-dinitro-1-hexanol[15] in 10 ml. of 10% aqueous sodium hydroxide was boiled over a flame for 1 min. until the solution became homogeneous. After boiling the solution for 1 min. more, it was cooled to 0–5° and acidified with 12 ml. of 10% hydrochloric acid. The solution was allowed to stand overnight at room temperature, cooled to 0–5°, and made basic by the slow addition of 10% aqueous sodium hydroxide. The aqueous solution then was extracted with five 50-ml. portions of chloroform; the extract was dried over anhydrous sodium sulfate and evaporated on a steam bath. Distillation at 65° and 75 mm. afforded 0.22 g. (41% yield) of a mixture of IX and X. The n.m.r. and infrared spectra as well as the gas chromatogram of the isoxazole mixture were superimposable on those of the mixture of isoxazoles prepared by procedure A. The isomeric mixture of isoxazoles was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}\text{D}$ 1.4459.

D. From Demethylolation of 2-Ethyl-2,4-dinitro-1-pentanol.—The experimental procedure used was essentially the same as for the demethylolation of 2-methyl-2,4-dinitro-1-pentanol.[15] When the products were analyzed on a Carbowax 20 M gas chromatographic column, a peak was obtained which had the same retention time as the mixture of isoxazoles prepared in procedure A.

3-Methyl-5-ethylisoxazole (IX).—A 500-ml. three-necked flask, equipped with a Dry Ice condenser, addition funnel, thermometer, and magnetic stirrer, was charged with an ethereal solution (220 ml.) of 1-butynylmagnesium bromide which had been prepared from 208 mmoles of ethylmagnesium bromide and excess 1-butyne by the method of Lai.[20] (The titer of the ethylmagnesium bromide was determined by adding a 1-ml. aliquot of it to 50 ml. of 0.25 *N* hydrochloric acid and back titrating with aqueous sodium hydroxide.) The mixture was cooled to 0°, and a dry ethereal solution (20 ml.) of acetohydroxamic chloride, which had been prepared by the method of Wieland[19] from 10 g. (169 mmoles) of acetaldoxime and 12 g. of chlorine, was added dropwise over a period of 1 hr. After stirring for 5 min. more at 0°, the mixture slowly was acidified with 180 ml. of 10% sulfuric acid and stirred for another hour. The reaction mixture was extracted with four 300-ml. portions of ether, and the extract was washed three times with a dilute solution of sodium hyposulfite. Then the ether extract was stirred with 400 ml. of a 20% solution of sodium hydroxide for 30 min., separated from the aqueous phase, filtered to remove a solid brown precipitate, dried over anhydrous magnesium sulfate, and finally evaporated on a steam bath. Distillation of the residue at 83° and 45 mm. afforded an 18% yield of **3-methyl-5-ethylisoxazole (IX)**. The isoxazole was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}\text{D}$ 1.4458.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.42; H, 8.47; N, 12.48.

3-Ethyl-5-methylisoxazole (X).—The experimental procedure was exactly the same as for the preparation of IX except that 1-propynylmagnesium bromide and propionohydroxamic chloride were employed. 1-Propynylmagnesium bromide was prepared from 208 mmoles of ethylmagnesium bromide and excess 1-propyne by the procedure developed by Lai.[20] Propionohydroxamic chloride was prepared by the procedure of Wieland[19] by adding 12 g. of chlorine to 12.4 g. (170 mmoles) of propionaldoxime in dilute hydrochloric acid.

Distillation of the reaction product at 90° and 73 mm. afforded an 18% crude yield of 3-ethyl-5-methylisoxazole. The isoxazole was purified on a G.E.–S.F. 96 on Chromosorb W gas chromatographic column and had $n^{20}\text{D}$ 1.4450.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.39; H, 8.48; N, 12.66.

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