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Isoxazole Derivatives from Acetylene and Nitrogen Oxides

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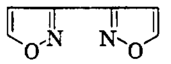
The reaction of acetylene with a mixture of nitric oxide and nitrogen dioxide in ethyl acetate at 50–65° and at 12–20 atm. provides 3,3′-biisoxazole in high yield as well as smaller amounts of two new substituted isoxazoles, *viz.* 3-cyanoisoxazole and 3-isoxazolecarboxaldehyde.

The formation of isoxazole derivatives in the reaction of acetylene with nitric acid has been reported by several workers. Mascarelli[1] in 1903 isolated unidentified crystalline compounds, probably substituted isoxazoles, with formulas $C_4H_3O_3N$ (m.p. 149°), $C_4H_2O_7N_6$, $C_6H_4O_3N_4$, and $C_6H_4O_6N_4$. Quilico[2] in 1929 found the reaction of acetylene with fuming nitric acid at room temperature to give, among other products, an acid of m.p. 149°, to which he initially assigned the structure 5-isoxazolecarboxylic acid and later[3] corrected to 3-isoxazolecarboxylic acid. These syntheses produced complex mixtures of products in slow reactions at low conversions.

We have found that acetylene reacts with a mixture of nitric oxide and nitrogen dioxide in ethyl acetate at 50–65° to give 3,3′-biisoxazole (I) in yields, based on acetylene, in the range 60–70%. Two new substituted isoxazoles, 3-cyanoisoxazole (II) and 3-isoxazolecarboxaldehyde (III) have also been obtained concurrently in yields of 5–10% each.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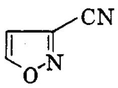
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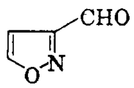
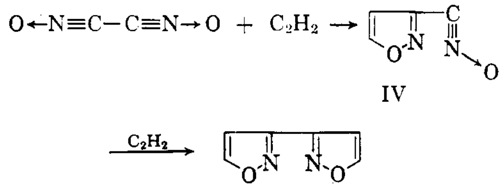

III

3,3′-Biisoxazole, whose preparation has been described by Quilico,[4] was identified by elemental analyses, by oxidation with potassium permanganate to 3-isoxazolecarboxylic acid (m.p. 149°) and by conversion of this acid to the corresponding amide. 3-Cyanoisoxazole was identified by elemental analyses, by hydrolysis to 3-isoxazolecarboxylic acid, and by examination of its infrared absorption spectrum and proton magnetic resonance, while 3-isoxazolecarboxaldehyde was identified by its infrared absorption spectrum and its proton magnetic resonance, by analysis of its 2,4-dinitrophenylhydrazone, and by oxidation to 3-isoxazolecarboxylic acid.

At higher temperatures the reaction of nitrogen oxides with acetylene was difficult to control, with the temperature flashing from 90 to 215°. Nevertheless, essentially quantitative conversion of acetylene to 3-isoxazole products was obtained. The three 3-isoxazole derivatives were produced in reduced yields through the reaction of acetylene with either nitrogen dioxide or nitric oxide alone, but in the latter case induction periods of up to nine hours were encountered, and higher temperatures (80–90°) were required.

Acetonitrile and acetic acid are satisfactory reaction media, but produced lower yields. In the absence of solvent an exothermic reaction occurred when nitric oxide and acetylene were mixed in a stainless steel vessel at 0°. The products were nitric oxide, carbon, hydrogen, and a small amount of methane.

Mechanism. It is believed that 3,3′-biisoxazole is obtained through the addition of acetylene to cyanogen-*N*,*N*′-dioxide (Eq. 1), as it is known that nitrile oxides react readily with acetylene to give isoxazoles.[5] This mechanism is supported by the fact that reduction of the two intermediates would account for two of the reaction products. Thus, 3-cyanoisoxazole would be derived from IV, and reduction of cyanogen-*N*,*N*′-dioxide would account for cyanogen which is always present in the gaseous reaction products. Nitric oxide or nitrous acid (from the synthesis of the nitrile oxide) might serve as reducing agent.



IV

(1)

The steps by which cyanogen-*N*,*N*′-dioxide is formed were uncertain. The dipseudonitrole (V) would be expected[6] to rearrange to a dinitrolic acid (VI) and thence to cyanogen-*N*,*N*′-dioxide (VII). There is no evidence to support the speculation that V might be formed by stepwise addition of nitrogen dioxide and nitric oxide to acetylene. How-

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[1] L. Mascarelli, *Gazz. chim. ital.*, **33 II**, 319 (1903).

[2] A. Quilico and M. Freri, *Gazz. chim. ital.*, **59**, 930 (1929).

[3] A. Quilico and L. Panizzi, *Gazz. chim. ital.*, **75**, 2753 (1945).

[4] A. Quilico, G. Gaudiano, *Gazz. chim. ital.*, **87**, 638 1957).

[5] C. Weygand and E. Bauer, *Ann.*, **459**, 123 (1927).

[6] E. H. Rodd, *Chemistry of the Carbon Compounds*, Elsevier, New York, 1951, Vol. I, pp. 362 and 370.

TABLE I

CONDITIONS FOR PREPARING CERTAIN ISOXAZOLE DERIVATIVES

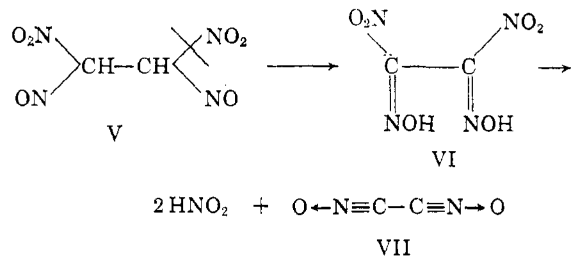
Reactants, Moles				Reaction Conditions			Moles of Residual Gas			Products, Moles (Grams)			%[b]	
C_2H_2	NO	NO_2	Solvent	Temp.	Time, hr.	Pressure, atm.[a]	C_2H_2	NO	N_2	Biisoxazole (I)	Nitrile (II)	Aldehyde (III)	Yield	Conversion
0.56	0.35	0.25	Ethyl acetate	65°	5.5	26/18	0.114	0.001	0.022	0.104(14.2)	0.02 (1.9)	0.002(1.9)	88	70
0.46	0.35	0.25	Ethyl acetate	60°	7	18/10	0.041	0.003	0.053	0.097(13.2)	0.01 (1.0)	0.019(1.8)	83	76
0.56	0.46	0.25	Ethyl acetate	60°	6	18/15	0.083	0.010	0.066	0.10 (13.5)	0.012(1.2)	0.027(2.5)	80	68
0.56	0.35	0.33	Ethyl acetate	90°–215°	[c]					0.121(16.5)	0.035(3.4)	0.055(5.2)	—	97
0.77	1.0	—[d]	Ethyl acetate	85°	4.5	40/30	0.063	0.020	0.180	0.114(15.5)	0.034(3.3)	0.040(3.8)	70	65
0.77	0.95	—[d]	Acetonitrile	85°	3.5	40/26	0.090	0.036	0.240	0.097(13.2)	0.021(2.0)	0.026(2.4)	57	50
0.56	0.93	—[d]	Acetic acid	88°	3.5	40/30	0.008	0.012	0.210	0.077(10.5)	0.019(1.8)	0.033(3.1)	61	60
0.33	0.44		None	[e]			—	—	—	—	—	—		

[a] The maximum and final pressure figures are given. [b] Yields and conversions based on acetylene in accordance with equations:

$$\% \text{ conversion} = 100 \times \frac{3 \times \text{moles of I} + 2 \times \text{moles of II} + 2 \times \text{moles of III}}{\text{moles of } C_2H_2 \text{ charged}}$$

$$\% \text{ yield} = 100 \times \frac{3 \times \text{moles of I} + 2 \times \text{moles of II} + 2 \times \text{moles of III}}{\text{moles of } C_2H_2 \text{ charged} - \text{moles of } C_2H_2 \text{ recovered}}$$

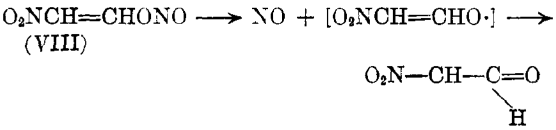
[c] In this experiment there was a temperature flash from 90° to 215°. The reaction product was cooled as soon as possible after the flash. [d] In this experiment, the reactor was purged with oxygen at atmospheric pressure after addition of the solvent. The acetylene was added next and finally the nitric oxide, which was added portionwise. Each time the pressure dropped to 30–34 atm. the reactor was repressured to a 40-atm. level with nitric oxide until there was no further pressure drop. [e] Temperature flashed to 240° on adding nitric oxide at 0°. Essentially complete decomposition of acetylene to carbon and hydrogen occurred. There was also a small amount of methane formed. The nitric oxide was unchanged.



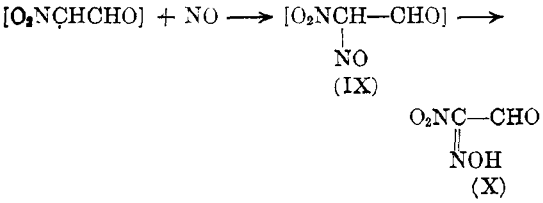
ever, the existence of an induction period when nitric oxide alone is used indicates nitrogen dioxide is necessary, and the higher yields obtained with a mixture of nitrogen dioxide and nitric oxide suggest that the intermediate contains both nitroso and nitro or nitrite groups.

Formation of 3-isoxazolecarboxaldehyde would follow from reactions 2–6. Reaction 2 is analogous to an established reaction of olefins and certain acetylenes.[7] Reaction 3 would be assisted by resonance stabilization of the intermediate radical, and reactions 3 and 4 might occur through a cyclic intermediate in which NO is transferred from an O-atom to the unsaturated carbon carrying the nitro group. The pseudonitrole (IX) is expected[6] to rearrange immediately to the nitrolic acid (X), and this would provide the nitrile oxide (Equation 5) to combine with acetylene to form 3-isoxazolecarboxaldehyde (Equation 6). Nitrolic acids have also been observed to react directly with acetylenes to give isoxazole derivatives.[8] It seems likely, however, that a nitrile oxide is formed as an intermediate in this reaction.

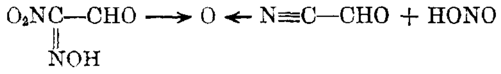
$$HC{\equiv}CH + N_2O_4 \longrightarrow O_2NCH{=}CHONO \qquad (2)$$



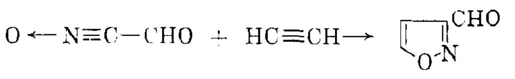
$$\underset{\text{(VIII)}}{O_2NCH{=}CHONO} \longrightarrow NO + [O_2NCH{=}CHO\cdot] \longrightarrow O_2N{-}CH{-}\underset{\diagdown H}{C}{=}O \qquad (3)$$



$$[O_2N\underset{\cdot}{C}HCHO] + NO \longrightarrow \underset{\text{(IX)}}{[O_2N\underset{NO}{CH}{-}CHO]} \longrightarrow \underset{\text{(X)}}{O_2N\underset{\|\atop NOH}{C}{-}CHO} \qquad (4)$$



$$O_2N\underset{\|\atop NOH}{C}{-}CHO \longrightarrow O \leftarrow N{\equiv}C{-}CHO + HONO \qquad (5)$$



$$O \leftarrow N{\equiv}C{-}CHO + HC{\equiv}CH \longrightarrow \qquad (6)$$

Chemical and physiological properties. Like other isoxazoles with a substituent in the 3-position,[9] 3,3′-biisoxazole is resistant to ring opening by hydrolysis with aqueous alkali or acid. Hydrogenation gives a mixture of amines, some of which are resinous.

It has been noted that the isoxazoles described here have allergenic properties which may result in headache, sternutating action, sinus flow, or more serious symptoms in the sensitized person.

EXPERIMENTAL

Typical conditions for preparing the isoxazole compounds are detailed below. Other preparations are summarized in Table I.[10] Preferred molar ratios of reactants are $1C_2H_2$: 0.6–0.8 NO: 0.45–0.6 NO_2.

A 400-ml. stainless steel reactor was charged with 100 ml. of ethyl acetate, 14.5 g. (0.56 mole) of acetylene, 10.5 g. (0.35 mole) of nitric oxide, and 11.5 g. (0.25 mole) of nitrogen dioxide at 0°. Under conditions of shaking, the reactor was heated to 65° over a period of 2 hr. The maximum pressure developed was 28 atm. at 59°. On reaching 65° the pressure was 27 atm. The reactor was held at 65° for 6 hr., but the pressure had leveled off at a value of 18 atm. after the first 20 min. of this 6-hr. period. The gaseous product contained 0.022 mole of nitrogen, 0.114 mole of acetylene, 0.008 mole of carbon dioxide, and small amounts of nitric oxide, nitrous oxide, cyanogen, hydrogen cyanide, and carbon monoxide, according to mass spectrometric analysis. The liquid product was distilled through a 40-in. spinning band column. A 1.9 g. sample, b.p. 60°/40 mm., was identified as *3-isoxazolecarboxaldehyde.*

Anal. Calcd. for $C_4H_3NO_2$: C, 49.5; H, 3.1; N, 14.4. Found: C, 48.9; H, 3.4; N, 14.4; n_D^{20} 1.463.

Bands in the infrared are at 3.47 and 5.82 μ (for aldehyde-CHO), 3.16 μ (for =CH), 6.44 μ (for conjugated C=C and/or C=N), 6.97, 9.02, 9.60, 10.76, and 12.66 μ (probably associated with the isoxazole ring), 7.85 and 13.40 μ (unassigned).

The H^1 magnetic resonance spectrum of the pure aldehyde shows 3 peaks in a 1:1:1 intensity ratio. Each peak is split into a quadruplet. The chemical shifts from a benzene reference are -2.89 p.p.m. (aldehyde H), -1.54 p.p.m. (H on C_4), and $+0.41$ p.p.m. (H on C_5). The J values are 1.9 ± 0.3 c.p.s. for the interaction between the hydrogens on C_5 and C_4, 0.65 ± 0.2 c.p.s. for the interaction between the aldehyde hydrogen and hydrogen on C_4, and 0.3 ± 0.1 c.p.s. for the interaction between the aldehyde hydrogen and hydrogen on C_5.

Oxidation with silver oxide gives 3-isoxazolecarboxylic acid, neut. equiv., 113, m.p. 149°. The 2,4-dinitrophenylhydrazone, m.p. 203–206°, was prepared.

Anal. Calcd. for $C_{10}H_7N_5O_5$: C, 43.4; H, 2.6; N, 25.3. Found: C, 43.5; H, 2.8; N, 23.8.

A second fraction, 1.9 g., b.p. 70° at 25 mm., was identified as *3-cyanoisoxazole.*

Anal. Calcd. for $C_4H_2N_2O$: C, 51.1; H, 2.2; N, 29.8. Found: C, 51.6; H, 2.6; N, 28.6; n_D^{20} 1.453.

Bands in the infrared are at 4.41 μ (for C≡N), 3.15 μ (for =CH), 6.48 μ (for conjugated C=C and/or C=N), 7.17, 8.96, 9.54, 10.67, 11.05, and 12.73 μ (probably associated with isoxazole ring), 10.07 μ and 13.50 (unassigned). The H^1 magnetic resonance spectrum for the pure liquid shows 2 peaks in a 1:1 intensity ratio. Each peak is split into a doublet. The chemical shifts from a benzene reference for these peaks are -1.84 p.p.m. (H on the C_4) and $+0.13$ p.p.m. (H on C_5). The J value is 2.3 ± 0.3 c.p.s.

A third fraction, 14.2 g., b.p. 85° at 5 mm., solidified on cooling. Large transparent, colorless crystals, m.p. 80–

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(7)(a) N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1093 (1946). (b) J. P. Freeman and W. D. Emmons, *J. Am. Chem. Soc.*, 79, 1712 (1957).

(8) A. Quilico and M. Simonetta, *Gazz. chim. ital.*, 76, 200 (1946).

(9) E. H. Rodd, *Chemistry of the Carbon Compounds*, Elsevier, New York, 1951, Vol. IV, p. 336.

(10) See also R. D. Cramer, U. S. Patent 2,855,402, Oct. 7, 1958.

80.5°, obtained on recrystallization of this solid, were identified as 3,3′-biisoxazole.

Anal. Calcd. for $C_6H_4N_2O_2$: C, 53.0; H, 2.9; N, 20.6. Found: C, 53.8; H, 3.2; N, 20.7.

Bands in the infrared are at 3.17 μ (for $=$CH), 6.0 and 6.4 μ (for conjugated C$=$C and/or C$=$N), 7.15, 9.09, 9.64, 10.72, 10.93, and 12.71 μ (probably associated with isoxazole ring), 7.26 μ, 7.36 μ, 8.59 μ, 11.57 μ, and 12.87 μ (unassigned). The H^1 magnetic resonance spectrum for a 40% solution of I in $CDCl_3$ shows two kinds of hydrogen in a 1:1 intensity ratio. Each peak is split into a doublet. The chemical shifts from a benzene reference are -1.92 p.p.m. (H on C_4) and $+0.20$ p.p.m. (H on C_5). The J value is 2.0 ± 0.3 c.p.s. Oxidation of 3,3′-biisoxazole with acidic potassium permanganate by the method described by Quilico[3] gave an acid which melts at 149° and has a distribution ratio, ether/water, of 0.52. Quilico[3] reports 149° as the melting point of 3-isoxazolecarboxylic acid.

Anal. Calcd. for $C_4H_3NO_3$: N, 12.4; C, 42.5; H, 2.7; neut. equiv., 113. Found: N, 12.4; C, 42.3; H, 2.7; neut. equiv. 115.

The acid was converted to an amide by reaction with thionyl chloride and alcoholic ammonia. After recrystallization from ethanol, the product melted at 134–135° as compared with melting points of 143.5–144° (amide of 3-osoxazolecarboxylic acid) and 173–174° (amide of 5-isoxazolecarboxylic acid) reported by Quilico.[3]

The viscous, black distillation residue (4.3 g.) changed to a brittle resin on cooling. It was noted that a resin was obtained on redistillation of 3-cyanoisoxazole. In the redistillation there was a strong odor of hydrogen cyanide at the vacuum pump exhaust, and the amount of resinous product obtained corresponded to 10–12% of the original 3-cyanoisoxazole.

Acknowledgment. Helpful suggestions in connection with this work made by B. W. Howk are gratefully acknowledged.

WILMINGTON 98, DEL.

Notes A department for short papers of immediate interest.

ortho-Substitution Rearrangement of Benzyltrimethylammonium-benzyl-C^{14} Iodide

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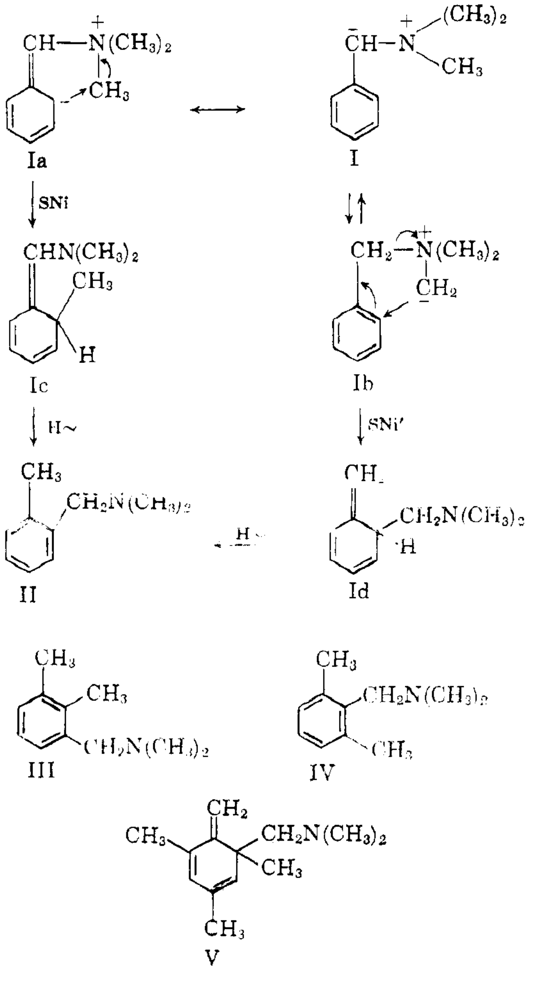
Received January 12, 1961.

In the original paper[2] on the *ortho*-substitution rearrangement of benzyltrimethylammonium ion by amide ion in liquid ammonia, two mechanisms were considered (Scheme A). One involved an SNi displacement within resonance form Ia of the more predominant carbanion I, and the other SNi′ displacement within the less predominant carbanion Ib. The initial product in each mechanism underwent a prototropic shift to form the rearranged amine II.

Although these two mechanisms were not distinguished for the parent benzyltrimethylammonium ion, the SNi′ but not the SNi mechanism would account for the further rearrangement of the methiodide of amine II to form amine III, not IV[2]. Furthermore, rearrangement of the 2,4,6-trimethylbenzyltrimethyl ammonium ion[3] gave *exo*-methyleneamine V, corresponding to intermediate Id in Scheme A.

Evidence is now presented to show that the SNi′

SCHEME A



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[1] National Science Foundation Co-operative Fellow, 1960–1961.

[2] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, 73, 4122 (1951).

[3] C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, 79, 5512 (1957).