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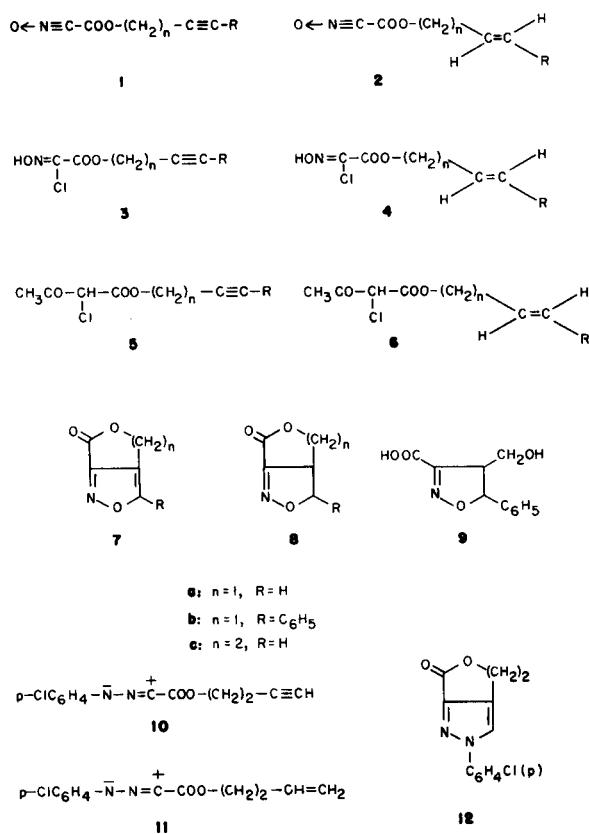
Treatment of functionalized 1-chloro-oximes (**3c** and **4a,b**) with triethylamine originates nitrile oxides (**1c** and **2a,b**) which undergo an intramolecular cycloaddition providing fused-ring isoxazole derivatives (**7c** and **8a,b**). The latter reaction was not observed for one substrate (**2c**).

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In recent years, several authors have been interested in intramolecular cycloadditions of 1,3-dipoles to multiple bonds (1,2). However, a few reports deal with the behaviour of nitrile oxides bearing an unsaturated function (3-6), particularly as concerns aliphatic nitrile oxides. In a previous paper (5), we have shown that **1a,b** are able to give the furo[3,4-c]isoxazole derivatives **7a,b**, arising from an intramolecular 1,3-dipolar cycloaddition to the acetylenic bond. On continuing this line of research, we have taken into account the structurally related substrates **2a,b** which, however, contain an olefinic bond as a potential dipolarophile. Nitrile oxides **1c** and **2c** have been also considered with the aim of studying possible effects of the longer distance between dipole and dipolarophile groups.

All nitrile oxides were generated *in situ* from the corresponding 1-chlorooximes (**3** and **4**), which in turn were available by reacting alkynyl or alkenyl 2-chloro-acetoacetates (**5** and **6**) with isoamyl nitrite. Treatment of **4a,b** and **3c** with an excess of triethylamine in boiling benzene (0.01 *M* substrate concentration) gave the bicyclic compounds **8a,b** and **7c** in 41, 37, and 25% yield, respectively. At higher concentrations, the yields of these products decreased and major quantities of uncharacterizable material were formed. Treatment of **4c** with triethylamine under the same conditions (at different concentrations) resulted in tarry mixtures from which no product could be isolated and characterized.

The structures of the above products are consistent with elemental and spectral data. Significantly, the ir absorption of the carbonyl group is at 1740 cm^{-1} in the δ -lactone **7c**, while raising at 1780 cm^{-1} in compounds **8a,b** in accord with a peculiar property of the γ -lactones (7). In the case of **8b**, the observed coupling constant of the isoxazoline protons (11.5 Hz) is not clear-cut for a stereochemical assignment: the literature data (8-11) show that the vicinal coupling constants in 2-isoxazolines are greatly dependent on the substituents and spread over wide ranges, particularly in the case of *trans* coupling ($J_{cis} = 8.0\text{-}12.3\text{ Hz}$, $J_{trans} = 1.5\text{-}12.0\text{ Hz}$). However, the isoxazoline protons of the hydroxy acid **9** (which was derived from **8b** by alkaline hydrolysis) exhibit $J = 7.3\text{ Hz}$, clearly corresponding to a *trans* configuration. This finding indicates that



the intramolecular reaction leading to **8b** proceeds with retention of stereochemistry, which is in line with a common feature of intermolecular 1,3-dipole cycloadditions (12).

The differences in behaviour within the series of the investigated nitrile oxides merit some comment. Although it is reasonable to think that the propensity to an intramolecular cycloaddition might decrease when increasing the distance between the reacting groups, the lack of intramolecular pathway (within the experimental detection limits) in the case of **4c** is somewhat surprising if compared with the formation of **7c** from **3c**. In fact, the dipolarophilic reactivity toward nitrile oxides in intermolecular cycloadditions is greater for ethylenes than for acetylenes bearing the same substituents (13). On the

Table I
Preparation of 1-Chloro-oximes **3** and **4**

Compound No.	Yield %	M.p., °C	Ir, cm ⁻¹ (nujol)	Nmr, δ (deuteriochloroform)	Anal.	
					Calcd.	Found
3c	57	65 (Carbon tetrachloride)	3340	2.05 (1H, t, J = 2.5 Hz), 2.65 (2H, dt, J = 7 and 2.5 Hz), 4.44 (2H, t, J = 7 Hz), 9.5 (1H, broad s)	C, 41.04	41.31
			1730		H, 3.45	3.55
4a	52	60 (Carbon tetrachloride)	3350	4.75-4.95 (2H, m), 5.2-5.6 (2H, m), 5.7-6.4 (1H, m), 9.8 (1H, broad s)	N, 7.98	7.83
			1750		C, 36.71	36.87
4b	65		3320	4.80 (2H, d, J = 6 Hz), 6.30 (1H, dt, J = 16 and 6 Hz), 6.7-7.5 (6H, overlapping signals), 8.8 (1H, broad s)	H, 3.71	3.71
			1750		N, 8.57	8.69
4c	67		3330	2.3-2.7 (2H, m), 4.40 (2H, t, J = 7 Hz), 5.0-5.4 (2H, m), 5.5-6.2 (1H, m), 8.5 (1H, broad s)		
			1740			

Table II
Preparation of Isoxazole Derivatives **7** and **8**

Compound No.	Yield %	M.p., °C	Ir, cm ⁻¹ (nujol)	Nmr, δ (deuteriochloroform)	Anal.	
					Calcd.	Found
7c	25	89 (cyclohexane)	1740	3.04 (2H, dt, J = 6 and 1 Hz), 4.60 (2H, t, J = 6 Hz), 8.55 (1H, t, J = 1 Hz)	C, 51.80	51.72
					H, 3.62	3.62
8a	41	82 (cyclohexane)	1780	4.2-5.1 (overlapping signals)	N, 10.07	9.98
					C, 47.25	47.03
8b	37	119 (benzene)	1780	4.2-4.8 (3H, overlapping signals), 5.73 (1H, d, J = 11.5 Hz), 7.45 (5H, s)	H, 3.97	3.85
					N, 11.02	10.92
					C, 65.02	65.20
					H, 4.46	4.41
					N, 6.89	6.73

other hand, it is to be considered that the intermolecular reactions of nitrile oxides with monosubstituted ethylenes and acetylenes result preferably in 5-substituted isoxazole derivatives (13-16). For the substrates here studied, the usual orientation is precluded intramolecularly by geometric restraints; as a consequence, the propensity to the intramolecular cycloaddition should be dependent, *inter alia*, on the ability of the dipolarophile to react with the "reversed" orientation. Such an ability is greater for acetylenes than for ethylenes, as shown experimentally and rationalized on theoretical grounds (11, 16-18).

It is interesting to note that the observed change in behaviour on going from **3c** to **4c** closely parallels a previous finding concerning similarly functionalized nitrile imines: in fact, while **10** gave **12** in 49% yield (19), no product of intramolecular cycloaddition was obtained from **11** (20).

EXPERIMENTAL

Ir spectra were taken on a Perkin-Elmer 377 spectrophotometer. Nmr spectra were recorded on a Varian HA-100 instrument with TMS as an internal standard. Melting points were determined on a Büchi apparatus and are uncorrected.

Compounds **5c** (19) and **6a-c** (20) were prepared as previously described.

General Procedure for the Preparation of 1-Chlorooximes **3** and **4**.

Isoamyl nitrite (30 mmoles) was added dropwise to a stirred solution of ester **5** or **6** (25 mmoles) in diethyl ether previously saturated with hydrogen chloride (50 ml.). After 8 hours standing at room temperature, the solvent and volatile compounds were removed first under reduced pressure, then *in vacuo* by warming up to 70-80°. The oily residue was crude **3** or **4** in ca. 90% purity (nmr analysis). In the case of **3c** and **4a**, treatment of the oily product with pentane and cooling at -15° gave crystals of analytical purity. See Table I.

General Procedure for the Preparation of Isoxazole Derivatives **7** and **8**.

A solution of triethylamine (20 mmoles) in dry benzene (100 ml.) was added during 2 hours to a boiling solution of 1-chloro-oxime **3** or **4** (10 mmoles) in dry benzene (900 ml.). The mixture was then refluxed for 2 hours, washed with aqueous hydrochloric acid, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column (100 g.) with benzene-ethyl acetate (9:1) as eluent gave pure **7** or **8**; see Table II.

Alkaline Hydrolysis of Lactone **8b**.

A solution of lactone **8b** (0.14 g.) and sodium hydroxide (0.48 g.) in 95% ethanol (20 ml.) was allowed to stand overnight at room temperature. After acidification with hydrochloric acid, the solvent was removed under reduced pressure, the residue was taken up with water and extracted several times with ether. The organic solution was dried over sodium sulfate and evaporated. Treatment of the residue with a small amount of diisopropyl ether gave **9** (0.12 g.), m.p. 140° (from benzene); ir (Nujol): 3330, 2900-2600, 1710 and 1600 cm⁻¹; nmr (perdeu-

terioacetone): δ 3.5-3.7 (1H, m), 3.8-4.2 (2H, m), 5.78 (1H, d, $J = 7.3$ Hz), 6.45 (2H, broad s), 7.42 (5H, s).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.95; H, 4.97; N, 6.19.

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