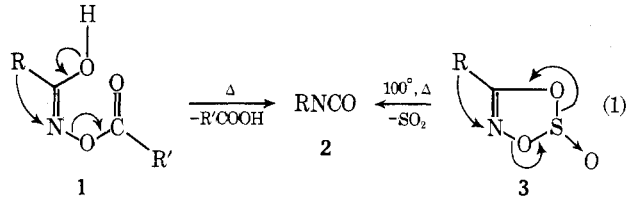
Thermolysis of 1,3,2,4-Dioxathiazole 2-Oxides. Nitrile Oxide Intermediates

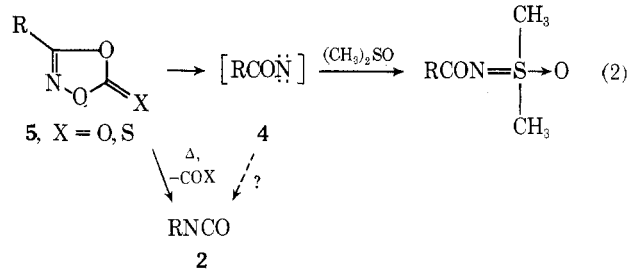
Summary. Nitrile oxide intermediates were trapped during the thermolysis of 5-substituted 1,3,2,4-dioxathiazole 2-oxides using dimethyl acetylenedicarboxylate, ethyl propiolate, and norbornene as dipolarophiles.

Sir: The thermal rearrangement of hydroxamic acid esters **1** to isocyanates **2** (Lossen rearrangement)[1,2] has been studied for many years and is currently considered to be a concerted process similar to the Hoffman and Curtius rearrangements.[3] The cyclic sulfite esters **3** also yield isocyanates in excellent yields[4-7] and have been postulated[7] to decompose by a similar (concerted) mechanism (eq 1).



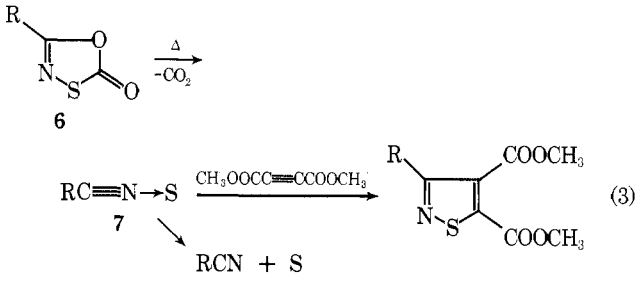
(1)

Attempts to trap intermediates during the course of this type of decomposition have been uniformly unsuccessful. Acyl nitrenes **4** were considered as potential intermediates by early investigators but precursors of this type are reported[3] to be formed only under photolytic conditions and not to rearrange readily to isocyanates. By contrast, however, the cyclic hydroxamate esters **5** also yield isocyanates in high yields on thermal decomposition[4,5] but in the presence of certain trapping agents (dimethyl sulfoxide,[6] triphenylarsine[8]) are reported to produce derivatives indicative of acyl nitrene intermediates (eq 2).



(2)

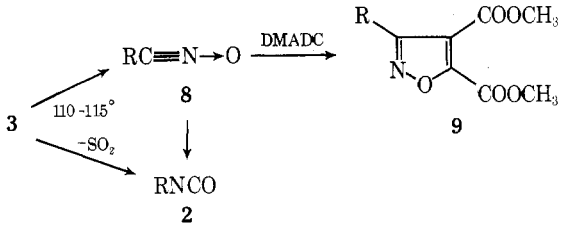
Similar attempts[6] to trap intermediates during decomposition of **3**, however, were not successful. Cyclic thiohydroxamate esters of type **6** do not undergo the Lossen rearrangement to yield isothiocyanates. Instead, nitrile sulfides **7** are produced which have been trapped with suitable dipolarophiles[9-11] (eq 3).



(3)

As a result of our studies of hydroxamate ester decompositions, we have obtained evidence which is consistent with the formation of nitrile oxides **8** as intermediates in some cases. Thus, the thermolysis of 5-substituted 1,3,2,4-dioxathiazole 2-oxides **3** in the presence of dimethyl acetylenedicarboxylate (DMADC) as a trapping agent produced mixtures of the corresponding isocyanates **2** and dimethyl 3-substituted isoxazole-4,5-dicarboxylates **9** (Scheme I).

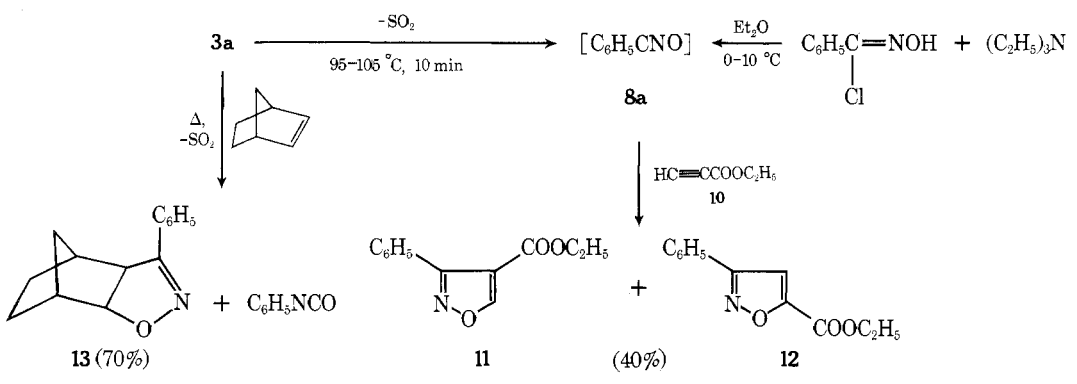
Scheme I



Compd	R	Yield, %[a] 2	9
a	C_6H_5–	55.5	39.3
b	4-$CH_3OC_6H_4$–	32	8
c	4-$O_2NC_6H_4$–		51.5
d	3,4-$Cl_2C_6H_3$–	36.2	57.5
e	*n*-C_9H_{19}–	(75)[b]	(25)[b]

[a] GC, C_6H_5Cl standard. [b] Relative weights by integration.

Scheme II



Products **2** and **9** were readily identified in the reaction mixtures by their GC–mass spectra. The isolated isoxazoles **9a–d** were identical in all respects with the authentic products (Table I) prepared from DMADC and the corresponding α-chloro oximes and triethylamine in ether.

Table I

6	R	Yield, % 9[a]	Mp, °C
a	C_6H_5–	46	52–54 (lit.[12] 62–63)
b	4-$CH_3OC_6H_4$–	73	72.5–73.5
c	4-$O_2NC_6H_4$–	45	103–105
d	3,4-$Cl_2C_6H_3$–	45	112.5–114
f	2,4,6-$(CH_3)_3C_6H_2$–	82	65.5–67

[a] Isolated yields of pure products from α-chloro oximes. All products gave satisfactory combustion analyses (C, H, N) and ir, NMR, and mass spectra.

Thermolysis of **3a** in excess ethyl propiolate **10** produced phenyl isocyanate and a mixture of the isomeric esters **11** and **12** (40% yield) in a mole ratio of 25:75 (Scheme II). The preponderant formation of isomer **12** is difficult to explain by ionic mechanisms and is strong evidence in support of the intermediate formation of benzonitrile oxide in this reaction. Treatment of excess **10** with benzonitrile oxide generated from α-chlorobenzaldoxime produced **11** and **12** in a mole ratio of 30:70, whereas the ratio of the corresponding methyl esters obtained from methyl propiolate is reported[13] to be 28:72. Esters **11** and **12** were easily separated by gas chromatography and identified by comparison of their spectra (ir, NMR, mass) with authentic materials.[14,15] Finally, the decomposition of **3a** in the presence of the more active dipolarophile norbornene produced adduct **13**[16] (mp 97–100 °C, mmp 98–100°) in good yield (Scheme II).

In contrast to **3a** and **3c** the dibenzohydroxamates **1a** and **1c** and excess DMADC did not yield 1,3-dipolar adducts when heated at the reflux temperature in chlorobenzene. The primary product in each case was the corresponding isocyanate.

References and Notes

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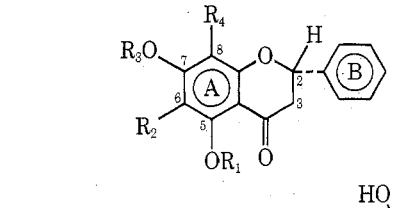
Uvaretin and Isouvaretin. Two Novel Cytotoxic *C*-Benzylflavanones from *Uvaria chamae* L.

Summary: Two cytotoxic principles, uvaretin (**1**) and isouvaretin (**2**), have been isolated from the stem bark of *Uvaria chamae* L. (Annonaceae) and their structures have been established as novel *C*-benzylflavanones.

Sir: An ethanolic extract of the stem bark of *Uvaria chamae* L. (Annonaceae) was found to show activity in vivo against P-388 leukemia in the mouse and in vitro against cells derived from human carcinoma of the nasopharynx (KB).[1] Fractionation of the ethanol extract was guided by assay against KB. The activity was concentrated in the ethyl acetate soluble fraction of an ethyl acetate–water partition. Chromatography of the ethyl acetate fraction over silicic acid afforded uvaretin and isouvaretin.

Uvaretin, $C_{22}H_{18}O_5$,[2] mp 210–211 °C, $[\alpha]^{25}D$ −52° (*c* 0.122, MeOH), gave a positive test (red) with magnesium–hydrochloric acid and formed a trimethyl ether upon treatment with excess ethereal CH_2N_2 for 4 days at room temperature. The uv spectrum of uvaretin showed λ_{max} (MeOH) 324 nm (ϵ 15 400) and 289 (10 500) and showed considerable bathochromic shifts with aluminum chloride (24 nm) sodium acetate[3] (36 nm) which are consistent with a flavanone nucleus with hydroxyl groups present at positions 5 and 7. The ir spectrum (KBr) showed broad hydroxyl bands at 3100 cm^{-1} and a carbonyl absorption at 1630 cm^{-1} which are in accord with the presence of a hydroxyl group at C-5 in a flavanone. The mass spectrum showed a parent peak at *m/e* 362 (100%) and fragment ions at *m/e* 285 (M^+ − 77, 16%), 258 (M^+ − 104, 37%), and 104 (9%) which indicated an unsubstituted B ring.[4,5]

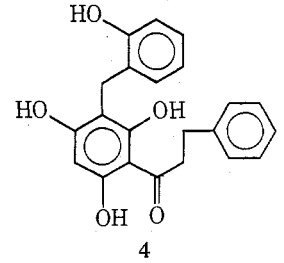


1 and 2, $R_1 = R_2 = R_3 = H$; $R_4 =$ —CH_2—(HO-phenyl)

(or $R_1 = R_3 = R_4 = H$; $R_2 =$ —CH_2—(HO-phenyl))

3, $R_1 = R_2 = R_3 = R_4 = H$

5, $R_1 = R_3 = H$; $R_2 = R_4 =$ —CH_2—(HO-phenyl)



4

The NMR spectrum (60 MHz, acetone-d_6) clearly showed an ABX pattern characteristic of the protons at H-3 (AB) and H-2 (X) of a flavanone nucleus,[3] a 1 H singlet for H-6 (or H-8) at δ 6.10, a 5 H broad singlet for the five protons of ring B at δ 7.5, and a 1 H singlet at δ 12.60