The Synthesis of Hydroxymethylcarbamates

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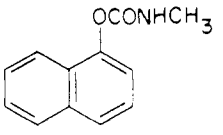
An apparently general method for the synthesis of hydroxymethylcarbamates has been developed and applied to the preparation of 1-naphthyl hydroxy-methylcarbamate, 3,4-dichlorobenzyl hydroxymethyl-carbamate, 2-methyl-2-methylthiopropionaldehyde O-(hydroxymethylcarbamoyl)oxime, and the corresponding sulfone of this latter material. The mass spectra of these materials are also discussed.

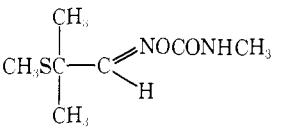
A major mode of metabolism of foreign substances in plants is oxidative. In the case of aryl methylcarbamates, both N-methyl and nuclear hydroxylation are known to occur (Balba *et al.*, 1968; Balba and Casida, 1968; Friedman and Lemin, 1967; Kuhr and Casida, 1967; Wilkinson, 1968). For purposes of identification and toxicological evaluation, authentic and frequently relatively large samples of potential or known metabolites are required. This paper describes an apparently general route for the synthesis of hydroxymethylcarbamates.

Various methods of preparation for this class of compounds have been reported. Dorough and Casida (1964) have described the synthesis of 1-naphthyl hydroxymethylcarbamate (carbaryl metabolite E) by the reaction of 1-naphthyl carbamate with paraformaldehyde in acetic acid. Although the route was attractive in its simplicity, the desired product was a minor constituent of a seven-component mixture. Isolation and purification were accomplished by preparative tlc. More recently a relatively general method for obtaining this type of compound has been reported by Balba *et al.* (1968). This scheme, which involves the preparation of an aryl benzyloxymethylcarbamate with subsequent hydrogenolysis to the desired hydroxymethylcarbamate, has been applied successfully to a wide variety of phenolic substrates but, in the case of 1-naphthyl benzyloxymethylcarbamate, the attempted hydrogenolysis gave mainly 1-(5,6,7,8-tetrahydronaphthyl) hydroxymethylcarbamate, with only about 2% of the desired 1-naphthyl hydroxymethylcarbamate.

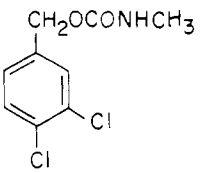
Recent studies of the plant metabolism of the broad spectrum insecticide carbaryl (Sevin), aldicarb pesticide (Temik) (Bartley *et al.*, 1970), and Herbicide UC 22463 (3,4-dichlorobenzyl methylcarbamate) (Andrawes and Herrett, 1969), three carbamates, markedly different in structure, have required the synthesis of the hydroxymethylcarbamates which might arise from these materials. In the case of the carbaryl metabolite material sufficient for toxicological evaluation was required; neither the method of Balba *et al.* (1968) nor that of Dorough and Casida (1964) would satisfy this need. In the case of the aldicarb and UC 22463 derivatives, the Dorough and Casida (1964) technique was abortive and it was anticipated that the catalytic debenzylation route would also be unsuccessful.



Carbaryl Insecticide (SEVIN)

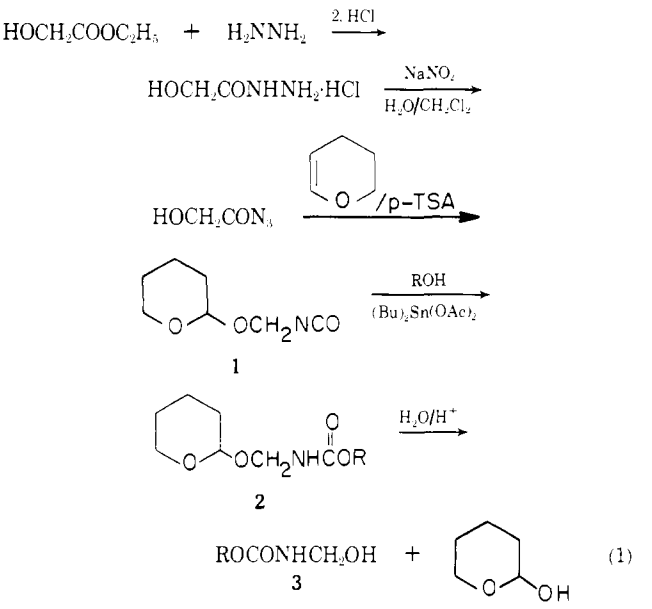


Aldicarb Pesticide (TEMIK)



Herbicide UC 22463

The approach developed to fulfill these needs is outlined in Equation 1.



(1)

The probable utility of this approach was suggested by the fact that Hoover *et al.* (1963) had prepared **1** by an alternate route and had reacted it with 1-naphthol to give **4** (**2**, R = 1—$C_{10}H_7$). Later, Balba (1968) alluded to unpublished work by Slade and Casida (1968) involving the acid cleavage of **4**(**2**, R = 1 —$C_{10}H_7$) to the desired hydroxymethylcarbamate **9**, (**3**, R = 1—$C_{10}H_7$). This method has now been developed and generalized.

The key intermediate in this study is (2-pyranyloxy)methyl isocyanate, **1**. Hoover *et al.* (1963) reported the preparation of this compound by the reaction of monomeric formaldehyde with isocyanic acid at low temperatures. Subsequent reaction of the product of this reaction with dihydropyran produced **1**. In the present work no effort was made to isolate **1**, since it was found that this material could be used as formed, *in situ*, and still give satisfactory yields of the (2-pyranyloxy)methylcarbamate **2** and its hydrolytic product **3**.

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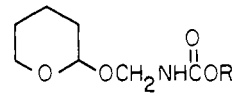
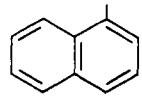
Table I. (2-Pyranyloxymethyl)carbamates

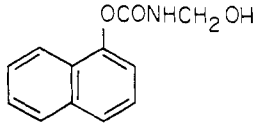


No.	R	M.P. °C	Yield, %	Anal.[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
4		79–81[b]	50	...	...	...	...	...	...
5	$3,4\text{-}Cl_2C_6H_3CH_2$—	residue	50	...	...	...	...	...	...
6	$CH_3SC(CH_3)_2CH{=}N$—	59–61	51.4	49.6	49.7	7.6	7.4	9.7	9.7
7	$CH_3\overset{\overset{O}{\|}}{S}C(CH_3)_2CH{=}N$—	71–74	67	47.1	46.9	7.2	7.2	9.1	9.4
8	$CH_3\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}(CH_3)_2CH{=}N$—	122–124	65	44.7	45.3	6.9	7.1	8.7	8.6

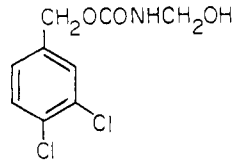
[a] In each case, the infrared spectrum of the compound supports the proposed structure. [b] Hoover *et al.* (1963) report 80–81° C.

The preparation of the compounds **2** was accomplished as described in the Experimental section. In this procedure the critical points appear to be: A good quality of glycolhydrazide hydrochloride must be used; the volume of the water in the azide preparation must be kept small, the temperature low, and the extraction thorough; in the carbamoylation reaction, the mixture should be kept acidic and dibutyltin diacetate should be used as the catalyst, because in instances where 1,4-diazabicyclooctane (DABCO) was employed as a catalyst, severely decreased yields were obtained; the temperature during the base extraction (about 5% sodium hydroxide or bicarbonate) must be kept low, and the reacton mixture must subsequently be washed until neutral. The (2-pyranyloxymethyl)carbamates, compounds **4** through **8** prepared in this work, are summarized in Table I.

The hydrolysis of the pyranyloxy compounds to the hydroxymethylcarbamate was easily accomplished with dilute aqueous mineral acid. In the conversion of **4** and **5** to **9** and **10**, where both the pyranyloxy compound and the hydroxymethylcarbamates are relatively water-insoluble, a cosolvent, such as acetone, was used in the hydrolysis step.

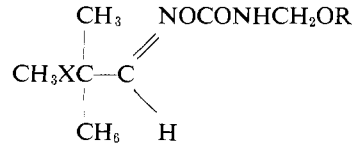


9



10

In the case of the aldicarb-related compounds, it was necessary to consider as potential metabolites not only the hydroxymethylcarbamate **11** derived from the sulfide oxime, but also the corresponding sulfoxide **12** and sulfone **13** since it is known that aldicarb pesticide is rapidly converted to sulfoxide and sulfone *in vivo* (Coppedge *et al.*, 1967; Metcalf *et al.*, 1966). Hence, in addition to **6**, the pyranyloxy compounds **7** and **8** were also prepared and their hydrolysis was studied. In contrast to **9** and **10**, compounds **11**, **12**, and **13** were quite water-soluble. Thus the major problem encountered in the preparation of these materials arose from their water-solubility and the concomitant difficulty in separating them from the hydrolytic byproduct, 2-hydroxypyran.



11, $X{=}S$, $R{=}H$

12, $X{=}\overset{\overset{O}{\|}}{S}$, $R{=}H$

13, $X{=}\overset{\overset{O}{\|}}{S}$, $R{=}H$

14, $X{=}\overset{\overset{O}{\|}}{S}$, $R{=}CH_3$

15, $X{=}\overset{\overset{O}{\|}}{S}$, $R{=}CH_3$

The synthesis of **11** was accomplished through the use of a heterogeneous system (ether/water) containing a trace of hydrochloric acid. The structure of **11** rests on elemental analysis together with nmr, infrared, and mass spectral data. Further support comes from the observed tlc behavior of **11** (R_f = 0.19) relative to **6** ($R_f \sim 0.8$) in 1:1 ethyl acetate:chloroform and the fact that **11** gives a positive test with chromotropic acid, indicative of the release of formaldehyde upon treatment with acid.

The preparation of **13** was accomplished in a similar manner from **8**. This sulfone was also prepared by the oxidation of **11** with excess peracetic acid. As in the case of **11**, the structural assignment for this sulfone rests on elemental analysis and spectral data. The tlc behavior of **13** (R_f = 0.67, 2:1 dioxane:benzene) as compared with that of the sulfoxide **12** (R_f = 0.33) is consistent with the proposed structure. Com-

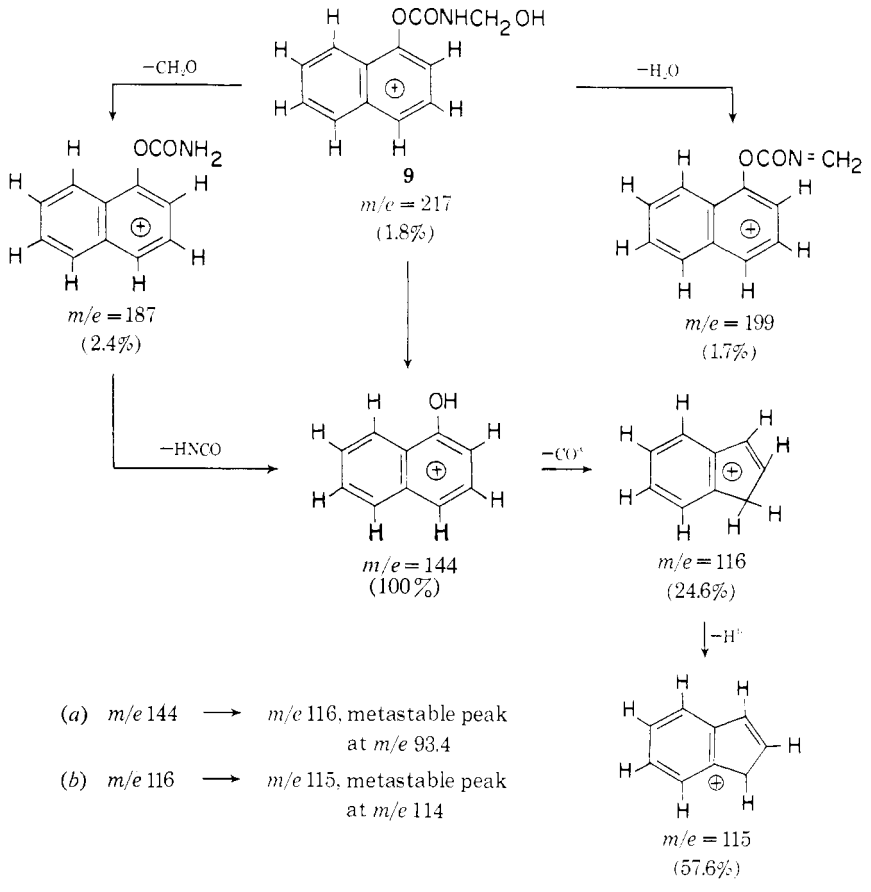


Figure 1. Mass spectral fragmentation of 1-naphthyl hydroxymethylcarbamate (9)

pound **13** also gives a positive test for formaldehyde with chromotropic acid reagent.

An attempt to prepare **12** by an oxidation similar to that employed for **13** gave an oily product whose spectral properties and tlc behavior indicated it to be about 70 mole% **12** and 30 mole% **13**. No attempt to optimize this process was made, although it is likely that control of the temperature at which the oxidation is performed would decrease the formation of sulfone. The hydrolysis of **7** to **12** did not result in isolable product, although the desired material could be detected by tlc analysis (R_f = 0.33, 2:1 dioxane:benzene) where a positive chromotropic acid test for formaldehyde was obtained.

The acid-catalyzed methanolysis of **6** gives the methoxymethylcarbamate **14**, identical with a product obtained from methoxymethyl isocyanate and 2-methyl-2-methylthiopropionaldehyde oxime. When **13** was dissolved in methanol in the absence of acid, no change could be detected after 18 hr. Addition of two drops of 10% hydrochloric acid to this solution resulted in the rapid conversion of **13** to the ether **15**. This product was also formed by the acid-catalyzed methanolysis of **8**. Ether **15** was not isolated as a solid or analyzed; its identification depends upon infrared, nmr, and tlc studies (R_f = 0.79, 2:1 dioxane:methanol). These results indicate that alcohols should probably not be used as cosolvents in the preparation of hydroxymethylcarbamates.

The mass spectra of these hydroxymethylcarbamates have been obtained, and possible major breakdown schemes have been deduced therefrom. The *m/e* values and the intensity relative to the 100% peak are recorded for certain fragments. Metastable peaks are identified where they support a particular pathway.

A portion of the fragmentation of 1-naphthyl hydroxymethylcarbamate **9** is shown in Figure 1 and is similar in many ways to the reported breakdown of carbaryl (Damico and Benson, 1965). The loss of H_2O or CH_2O from the parent ion (*m/e* = 217) results in the *m/e* = 199 (P-18) and *m/e* = 187 (P-30) fragments, but the major pathway involves loss of $HOCH_2NCO$ to give the 1-naphthol peak (*m/e* = 144, P-73). A peak at *m/e* = 72 was also observed and found to be of about 6% intensity. Mass measurement showed it to be composed of two fragments, 2% $C_2H_2NO_2$ (calculated: 72.008512; found: 72.008576) and 98% $C_{10}H_8O/2$ (calculated: 144.0575310; found: 2 × 72.028791 = 144.057582) assignable to a doubly-charged α-naphthol ion. The *m/e* = 116 and 115 peaks are also relatively important in the breakdown of carbaryl and 1-naphthol. This portion of the pathway is strongly supported by appropriate metastable peaks.

The major fragments arising in the mass spectrum of 3,4-dichlorobenzyl hydroxymethylcarbamate **10** are summarized in Table IIa and some of the major pathways are indicated in Figure 2. The masses are based on Cl^{35} but, in each case, the isotopic ratios were in agreement with those predicted. Metastable peaks which support many of the fragmentation routes described in Figure 2 were found and are summarized in Table III.

As in the case of **9** there are P-30 (*m/e* = 219) and P-18 (*m/e* = 231) peaks corresponding, respectively, to loss of CH_2O and H_2O from the parent molecule. The rest of the proposed breakdown is not remarkable, corresponding very closely to that found for UC 22463 and its parent alcohol.

The relative intensities of various fragments seen in the mass spectrum of **13** are summarized in Table IIb and related in Figure 3. The fragmentation pattern is generally similar to

Table II. Relative Intensities of Various Mass Spectral Peaks

(a) Relative Intensities of Certain Peaks in the Mass Spectrum of 10

	m/e													
Relative intensity, %	249	231	219	176	175	159	147	141	133	123	113	111	89	77
	0.9	17.5	5.4	37.8	100	59.4	9.4	30	2.3	27	7.6	20.1	12.1	16.6

(b) Relative Intensities of Certain Peaks in the Mass Spectrum of 13

	m/e																
Relative intensity, %	238	221	208	165	159	130	129	122	87	86	85	81	80	79	69	68	67
	0.04	30	0.06	12	19	0.8	8	8	67	100	97	75	65	26	29	97	97

(c) Relative Intensities of Certain Peaks in the Mass Spectrum of 11

	m/e										
Relative intensity, %	206	176	160	133	130	114	100	89	87	86	85	69
	0.11	0.11	40	40	100	29	31	10	11	35	60	13

Table III. Metastable Peaks in the Mass Spectrum of 10[a]

Transition	Metastable	Transition	Metastable	Transition	Metastable
249 → 231	214.3	176 → 141	113	159 → 123	95.2
251 → 233	216.3	178 → 143	114.9	161 → 125	97.0
249 → 176	124.4	175 → 147	123.5	147 → 111	83.8
251 → 178	126.2	177 → 149	125.4	149 → 113	85.7
219 → 176	141.4	159 → 133	111.3	141 → 113	90.6
221 → 178	143.4	161 → 135	113.2	143 → 115	92.5

[a] For the Cl^{35}, Cl^{35} and Cl^{35}, Cl^{37} species in the case of dichloro compounds and Cl^{35} and Cl^{37} species in the case of monochloro intermediates.

that described for aldicarb sulfone (Benson and Damico, 1968) for which no molecular ion was reported. With **13** a trace of molecular ion is detected. In each case *m/e* 86 is the 100% peak. The loss of CH_3SO_2 from the parent to give *m/e* 159 also occurs with aldicarb sulfone. The structure of the *m/e* 122 fragment has been supported by mass measurement. This fragment is frequently encountered with compounds containing this structural unit (Bartley *et al.*, 1970). The P-30 (*m/e* 208) peak is also present in this mass spectrum but no P-18 peak is observed.

Certain fragments from the mass spectrum of **11** are recorded in Table IIc and related in Figure 4. The P-30 peak (*m/e* = 176) is present, although the major decomposition route appears to be via loss of $CH_2{=}S$ to *m/e* = 160 which has been identified by mass measurement (Found, 160.085064; Calcd. for $C_6H_{12}N_2O_3$, 160.084786). This loses CH_2O to give the carbamoyloxime of isobutyraldehyde (*m/e* = 130) which is the most intense peak in the spectrum. In the mass spectrum of aldicarb (Benson and Damico, 1968) the methylcarbamoyloxime of isobutyraldehyde was the most intense peak. Hence, the breakdown of aldicarb and **11** are comparable in this regard. The *m/e* = 85, 86, and 87 entities shown in Figure 4 were also detected in the aldicarb spectrum. The structures postulated for the *m/e* = 133 and 115 ions are quite logical on the basis of our experience with this class

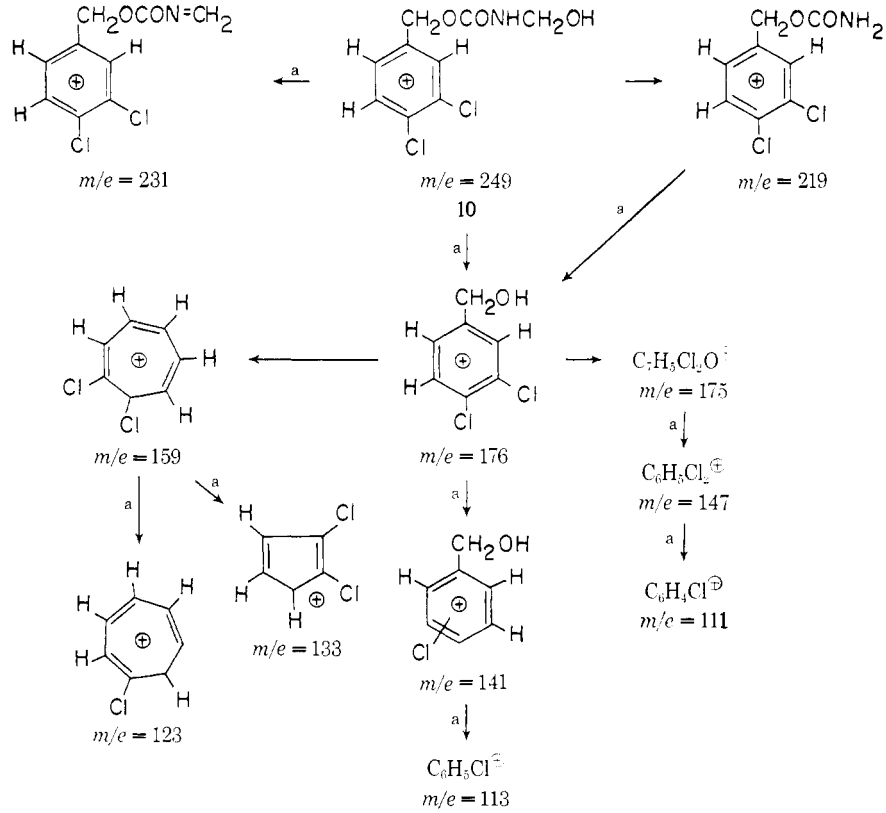


Figure 2. Mass spectral fragmentation of 3,4-dichlorobenzyl hydroxymethylcarbamate (10)

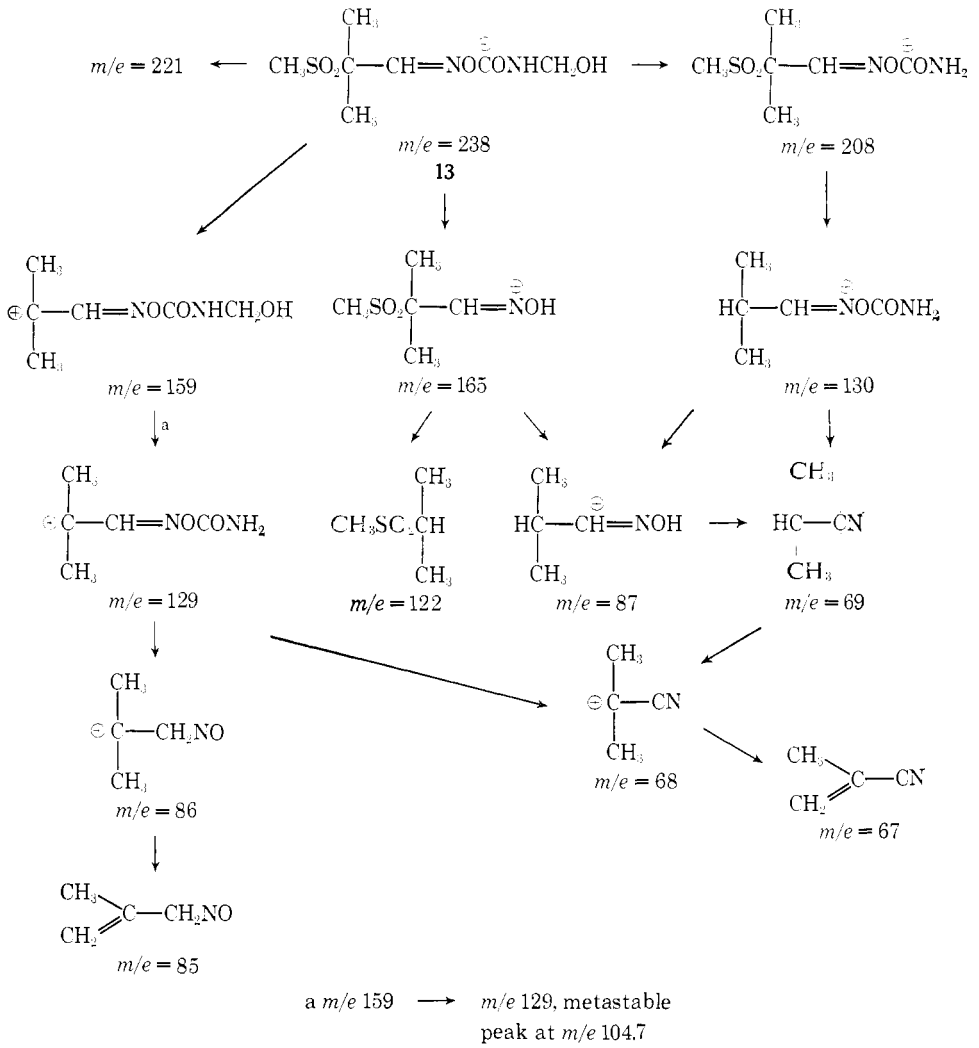


Figure 3. Mass spectral fragmentation of 2-methyl-2-methyl-sulfonylpropionaldehyde O-(hydroxymethylcarbamoyloxime) (13)

of compounds, and the ylide m/e = 89 has been identified by Benson and Damico (1968). The m/e = 100 peak was examined by mass measurement (Found, 100.02221; Calcd. for C_4H_6NH, 100.02209) and is assigned the indicated structure on the basis of the probable stability of the ylide-type configuration.

The mass spectra were determined at the following temperatures: **9**, 90° C; **10**, 90° C; **11**, 90° C; **13**, 200° C.

EXPERIMENTAL

The nmr spectra were obtained on a Varian 60 or 100 megacycle instrument, and infrared spectra were determined on a Baird Atomic 4-55 recording infrared spectrophotometer. The mass spectra were determined on an A.E.I. MS902b High Resolution Mass Spectrometer. The elemental analyses were performed at the Union Carbide Corporation Technical Center. The melting points are uncorrected. The tlc examinations were carried out on E. Merck Silica Gel-F fluorescent plates.

Glycolhydrazide Hydrochloride. Reaction of ethyl glycolate and hydrazine after the method of Curtius and Schwann (1894) produced glycolhydrazide, m.p. 93° C (Heilbron, 1965, reports 93° C). To a solution of 90 g (1 mole) of glycolhydrazide in 500 ml of methanol was added, slowly with stirring, a solution of 36.5 g (1 mole) of hydrogen chloride in 300 ml of methanol. When addition was complete, the solution was allowed to stand for a few minutes and then about 400 ml of methanol was removed *in vacuo*. Solid began to separate. Further chilling and filtration produced a crystalline solid, which upon air-drying weighed 107 g (85%) m.p. 155° C (Heilbron, 1965, reports 155° C). Additional product can be recovered from the filtrate so that an essentially quantitative yield may be obtained. This material is of satisfactory purity for use in the following reactions.

1-Naphthyl (2-Pyranyloxy)methylcarbamate, 4. To a solution of 12.6 g (0.1 mole) of glycolhydrazide hydrochloride in 15 ml of water and 250 ml of methylene chloride was added, portionwise, with vigorous stirring, 7 g (0.1 mole) of solid sodium nitrite at −5° to 0° C over a period of 3 min. The reaction was exothermic. When addition was complete the mixture was stirred at 0° C for 10 min. The methylene chloride layer was then separated and the aqueous layer was thoroughly extracted with methylene chloride. To the combined methylene chloride layers, after drying over magnesium sulfate, was added 24 g (0.15 mole) of dihydropyran and 0.02 g of *para*-toluenesulfonic acid. The mixture was allowed to warm to room temperature over 2 hr and to stand overnight when an infrared spectrum indicated that both pyranyloxy and isocyanate formation were virtually complete. To this solution was added 14 g (0.1 mole) of 1-naphthol and five drops of dibutyltin diacetate after which the mixture was stirred at room temperature. After 12 hr the mixture

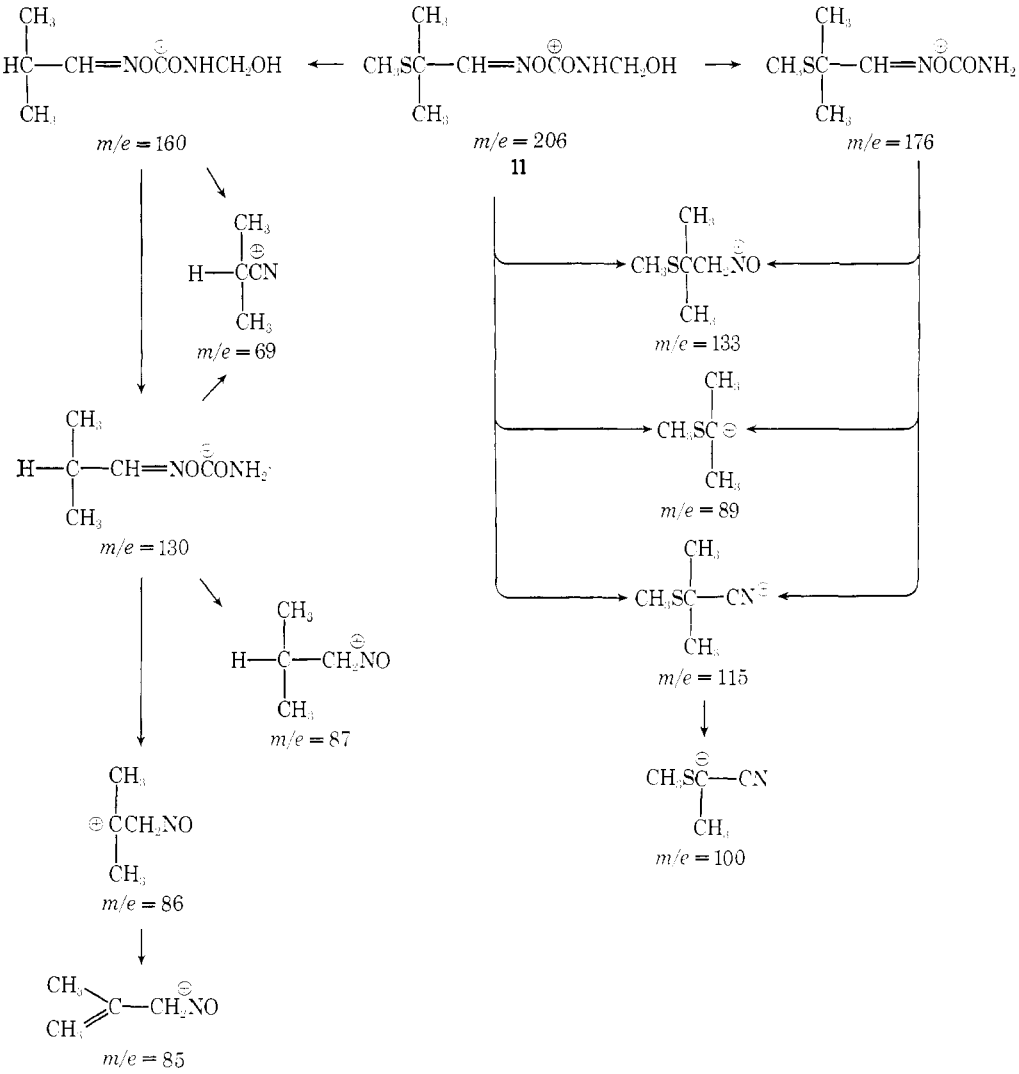


Figure 4. Mass spectral fragmentation of 2-methyl-2-methylthiopropionaldehyde O-(hydroxymethylcarbamoyloxime) (11)

was chilled and washed thoroughly with 2 × 100 ml portions of cold 5% sodium hydroxide, followed by water until the organic layer was neutral. After drying over magnesium sulfate, the methylene chloride solution was concentrated *in vacuo* to a waxy residue. This residue was washed with methylcyclohexane to produce the product described in Table I. The infrared spectrum (1% KBr) supports the proposed structure: 3.0, 3.06, 6.46, 6.52 (NH); 3.26 (arom. CH); 3.4, 3.5 (CH_2/CH_3); 5.7, 5.75 (carbamate C=O); 6.25, 6.65 (arom. C=C); 7.2 (O—CH_2), 8.23 (carbamate C—O); 8.9, 9.35, 9.67, 9.9 (O—C—O); 12.45, 12.95 μ (1-substit. naphthyl ring).

3,4-Dichlorobenzyl (2-Pyranyloxy)methylcarbamate, 5. Employing the same procedure as described for **4**, but involving 22 g (0.17 mole) of glycolhydrazide hydrochloride, 300 ml of methylene chloride, 20 ml of water, 12 g (0.17 mole) of sodium nitrite and 40 g (0.25 mole) of dihydropyran, 21 g (0.12 mole) of 3,4-dichlorobenzyl alcohol was reacted to produce the liquid residue product described in Table I. The infrared spectrum (film) was in agreement with the proposed structure being, in many respects, quite similar to that of **4**.

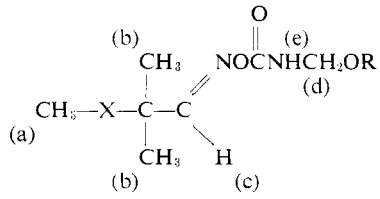
2-Methyl-2-methylthiopropionaldehyde O-[(2-Pyranyloxy)-methylcarbamoyl]oxime, 6. The procedure described for **4** was employed, but using 25 g (0.2 mole) of glycolhydrazide hydrochloride, 15 ml of water, 400 ml of methylene chloride, 14 g (0.2 mole) of sodium nitrite, 40 g (0.25 mole) of dihydropyran, and cold 5% sodium bicarbonate solution (in place of the sodium hydroxide solution), to produce from 26 g (0.2 mole) of 2-methyl-2-methylthiopropionaldehyde oxime [Payne *et al.* (1966)] the product described in Table I. The infrared spectrum (1% KBr) of this material was in agreement with the proposed structure: 3.0, 6.7 (NH); 3.4 (CH_2/CH_3); 5.75 (C=O); 6.18 (C=N); 7.23, 7.33 ($(CH_3)_2C$); 9.0, 9.83 (O—C—O); 10.75 (=N—O); 7.57 μ (SCH_3).

2-Methyl-2-methylsulfinylpropionaldehyde O-(2-Pyranyloxy)methylcarbamoyl Oxime, 7. Using the procedure for **6** but one-half the amount of chemicals, 15 g (0.1 mole) of 2-methyl-2-methylsulfinylpropionaldehyde oxime (Durden *et al.*, 1970) yielded the product described in Table I. The infrared spectrum (1% KBr) of this material agreed with the proposed structure and was quite similar to that of **6** except for the sulfoxide band at 9.55 μ.

2-Methyl-2-methylsulfonylpropionaldehyde O-(2-Pyranyloxy)-methylcarbamoyl Oxime, 8. Using the procedure and amounts of reactants employed for **6**, 25 g (0.15 mole) of 2-methyl-2-methylsulfonylpropionaldehyde oxime (Durden *et al.*, 1970) was reacted to produce the product described in Table I. The infrared spectrum (1% KBr) was similar to that of **6** except for the sulfone bands at 7.75 and 8.95 μ and agreed with the proposed structure.

1-Naphthyl Hydroxymethylcarbamate, 9. A solution of

Table IV. Nmr Spectral Data of Temik-Related Compounds



No.	Compound X	Compound R	Solvent	Chemical Shifts (δ), Peak Type[a], No. of H (a)	(b)	(c)	(d)	(e)	R
11	S	H	$CDCl_3$	1.98,S,3	1.47,S,6	7.58,S,1	4.86,S,2[b]	~7.0,S,1	~4.8,S,1[b]
14	S	CH_3	$CDCl_3$	1.98,S,3	1.47,S,6	7.55,S,1	4.73,D,2[b]	~7.0,S,1	3.38,S,3
13	SO_2	H	d_6-acetone	2.98,S,3	1.63,S,6	7.91,S,1	4.82,S,2[b]	...	...
15	SO_2	CH_3	$CDCl_3$	3.12,S[c]	1.8,S[c]	7.88,S[c]	4.62,S[c]	...	3.43,D[c]
12	SO	H	d_6-acetone	2.52,S,3	1.52,S,3 1.47,S,3	7.86,S,1	4.76,D[b]	...	...

[a] S, singlet; D, doublet. [b] The hydrogens NH—CH_2—O occurred as a doublet which was sometimes resolved and sometimes was apparently a broad singlet because of the —OH which appeared in this region. [c] Unable to obtain a precise integration because of purity.

15 g (0.05 mole) of **4** in 300 ml of acetone and 120 g of 1% hydrochloric acid was heated rapidly to boiling (60° C) and held there for 30 min when tlc examination indicated completion (4:1 ethyl ether:hexane). After cooling, the acetone was removed *in vacuo* and the residue was extracted twice with ethyl ether to remove the product. After drying over magnesium sulfate, the ether was evaporated *in vacuo* to give a light tan solid. Recrystallization of this from benzene gave **9**, 7 g (65%), m.p. 136–37° C [Dorough and Casida (1964) report 137–39° C]. The following spectral data are recorded: nmr, (d-acetone, tetramethylsilane as the zero reference) δ 4.79 (2H doublet, J = 7Hz, O-CH_2NH—), δ 7.1–8.1 (7H complex multiplet, arom. H); infrared (1% KBr) 3.02 (OH, NH), 3.38 (CH_2), 5.83 (C=O); 6.25 (arom. C=C); 6.55 (NH); 8.03, 8.15 (C—O, aryl-O); 9.9 (CH_2OH) 12.5 (3 adj. arom. H), 12.96 μ (4 adj. arom. H).

Anal. calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.1; N, 6.45. Found: C, 66.45; H, 5.0; N, 6.45.

3,4-Dichlorobenzyl Hydroxymethylcarbamate, 10. Using the same procedure as that described for **9**, but involving 23 g (0.07 mole) of **5** in 300 ml of acetone and 250 ml of 1% hydrochloric acid, there was obtained 8 g (46%) of **10**, m.p. 104–0.5° C (benzene). The following spectral data are recorded: nmr (d-acetone, tetramethylsilane as the zero reference) δ 4.65 (2H multiplet, NCH_2O), δ 5.07 (2H singlet, OCH_2), δ 7.32, 7.48, 7.55 (3H multiplets, arom. H); infrared (1% KBr) 2.85, 3.04 (NH, OH), 3.25 (arom. H); 3.35 (CH_2), 5.9 (C=O), 6.75 (NH), 7.76 (C—O), 9.7 (C—OH), 11.27 (isolated arom. H), 12.35 μ (2 adj. arom. H).

Anal. calcd. for $C_9H_9Cl_2NO_3$: C, 43.2; H, 3.6; N, 5.6. Found: C, 43.2; H, 3.5; N, 5.6.

2-Methyl-2-methylthiopropionaldehyde O-(Hydroxymethylcarbamoyl)oxime, 11. To a well-stirred mixture of 50 ml of water and 50 ml of ethyl ether containing one drop of concentrated hydrochloric acid was added, portionwise, 5 g (0.017 mole) of 2-methyl-2-methylthiopropionaldehyde O-[(2-pyranyloxy)methylcarbamoyl]oxime. Vigorous stirring was continued for several hours, during which time a major portion of the ether evaporated and only a small amount of water-insoluble material remained. The reaction was followed by tlc. The mixture was extracted with 3 × 50 ml portions of methylene chloride and again with 4 × 20 ml portions of ethyl ether. The total extracts were dried over sodium sulfate, which was subsequently removed by filtration, and the resulting filtrate was evaporated *in vacuo* to give a gummy residue. This was dissolved in 75 ml of boiling carbon tetrachloride, the hot solution treated with charcoal, filtered, and the filtrate diluted with hexane until cloudy. Chilling produced a solid which was collected and air dried to give 1.5 g (42%) of product, m.p. 83–84° C (R_f = 0.19, 1:1 ethyl acetate:chloroform). The infrared spectrum (1% KBr) showed the following maxima: 3.05 (NH, OH); 3.33, 3.37, 3.42 (CH_2/CH_3); 5.77 (C=O); 6.65 (NH); 8.17 (C—O); 9.77 (C—OH); 10.8 μ (N—O). The nmr spectrum is recorded in Table IV.

Anal. calcd. for $C_7H_{14}N_2O_3S$: C, 41.03; H, 6.57; N, 13.08. Found: C, 40.76; H, 6.84; N, 13.58.

Methoxymethyl Isocyanate. After several abortive attempts to prepare this material by the reaction of methyl chloromethylether with sodium cyanate (Zenner *et al.*, 1965) the preparation was accomplished as follows. To a suspension of 52 g (0.8 mole) of sodium azide in 250 ml of dry xylene was added slowly with stirring at 40° C over a 30-min period 54 g (0.5 mole) of methoxyacetyl chloride. Cooling was necessary to maintain the reaction at 40° C during the addition period. The mixture was stirred at 60 to 65° C for 6 hr, then cooled to 20° C and filtered. Distillation of the filtrate through a 24-in. Nester-Faust spinning band column gave 28 g (64%) of product, b.p. 89–90° C (Zenner *et al.*, 1965, report b.p. 89–90° C).

2-Methyl-2-methylthiopropionaldehyde O-(Methoxymethylcarbamoyl)oxime, 14. FROM METHOXYMETHYL ISOCYANATE AND 2-METHYL-2-METHYLTHIOPROPIONALDEHYDE OXIME. To a solution of 8.7 g (0.1 mole) of methoxymethyl isocyanate and 12 g (0.1 mole) of the title oxime in 100 ml of dry benzene was added 0.05 g of 1,4-diazabicyclo[2.2.2] octane (DABCO) and the mixture was stirred at 60° C for 20 hr. The mixture was then cooled and filtered, and the filtrate was concentrated *in vacuo* to an oily residue which was dissolved in ethyl ether. This solution was washed with water until neutral and, after drying over magnesium sulfate, was concentrated *in vacuo* to an oil which crystallized on standing. Recrystallization from a hexane-xylene mixture produced 12 g (55%) of product, m.p. 46–47° C. The infrared spectrum (1% KBr) showed the following: 3.0, 6.66 (NH); 3.35, 3.41 (CH_2, CH_3); 5.76 (C=O); 6.17 (C=N); 7.2, 7.35 [$(CH_3)_2C$]; 8.2 (ester C—O); 8.88, 9.35 (C—O—C); 10.6, 10.75 μ (N—O). The nmr spectrum is recorded in Table IV.

Anal. calcd. for $C_8H_{16}N_2O_3S$: C, 43.6; H, 7.3; N, 12.7. Found: C, 43.6; H, 7.1; N, 12.5.

By Methanolysis of 9. To a solution of 3 g (0.01 mole) of **9** in 30 ml of methanol was added one drop of 6N hydrochloric acid, and the mixture was allowed to stir at room temperature for 2 days. The mixture was then concentrated *in vacuo* at room temperature to give a residual oil which was taken up in methylene chloride, and this solution, after being washed with a minimum of saturated sodium bicarbonate solution, was dried over sodium sulfate. Filtration and concentration of the filtrate *in vacuo* gave 1 g of residual oil (ca. 45%). Comparison of the infrared and nmr (Table IV) spectra of this material with those of a pure material indicated that the present product was **14**, containing some impurities.

2-Methyl-2-methylsulfonylpropionaldehyde O-(Hydroxymethylcarbamoyl)oxime, 13. By Hydrolysis of **8.** To a mixture of 50 ml of water and 50 ml of ethyl ether containing 10 g (0.031 mole) of **8** was added 1 ml of 5% hydrochloric acid, and the mixture was stirred at ambient temperature until the reaction was complete, as evidenced by tlc (1:1 dioxane:benzene). The mixture was extracted as in the case of the sulfide **11** but the organic extracts contained very little **13**. The aqueous layer was neutralized with sodium bicarbonate and concentrated *in vacuo* at room temperature to a residual gum, which was taken up in 1:1 methylene chloride:ether, filtered, dried over sodium sulfate, and finally concentrated to give a residue. This residue was washed several times with hexane and finally dissolved in 50 ml of ethyl acetate, and the resulting solution was filtered through charcoal. This filtrate was treated with hexane to the cloud-point, and then chilled and seeded to give a gummy solid which was stirred with isopropyl ether until it was no longer sticky. Crystallization from ethyl acetate gave 2 g (27%) of **13** m.p. 85–87° C (bubbling). The infrared spectrum showed the following maxima (KBr): 2.93, 2.99 (OH, NH); 3.33, 3.41 (CH_3/CH_2); 5.82 (C=O); 6.15 (C=N); 6.66 (NH); 7.76, 8.97 (SO_2); 9.65 (C—OH); 10.45, 10.72 μ (=N—O). The nmr spectrum agreed with the proposed structure (Table IV).

By Oxidation of 11. To a solution of 0.7 g (0.0034 mole) of **11** in 15 ml of ethyl acetate was added 4 g of 23% peracetic acid in ethyl acetate dropwise with stirring. A temperature increase to 37° C was observed. After stirring 2 hr at room temperature, the mixture was diluted with hexane until milky and then chilled and scratched with a glass rod to induce crystallization. The solid was collected and recrystallized from ethyl acetate to give 0.6 g (74%) of **13** m.p. 85–87° C (bubbling). The infrared and nmr spectra were the same as those of the previous product and the materials were indistinguishable by tlc (1:1 dioxane:benzene).

Anal. calcd. for $C_7H_{14}N_2O_5S$: C, 35.30; H, 5.93; N, 11.77. Found: C, 35.04; H, 6.13; N, 11.03.

2-Methyl-2-methylsulfonylpropionaldehyde O-(methoxymethylcarbamoyl)oxime, 15. Using a procedure similar to that employed for **14**, 3 g (ca 0.01 mole) of **8** was solvolyzed in 30 ml of methanol containing 1 ml of methanolic hydrogen chloride to give the title product as a residual oil. The tlc (2:1 dioxane:methanol) showed two spots. The major one at R_f 0.79 gave a positive test with chromotropic acid and is **15**, and the other is most likely 2-methoxytetrahydropyran. The infrared and nmr (Table IV) spectra are consistent with the proposed compound plus some impurity.

2-Methoxy-2-methylsulfinylpropionaldehyde O-(Hydroxymethylcarbamoyl)oxime, 12. A solution of 1 g (0.0049 mole) of **11** in 10 ml of ethyl acetate was treated at ambient temperature with 0.38 g (0.0049 mole) of 23% peracetic acid in ethyl acetate (a temperature increase to 31° C was noted) and the mixture was worked up after the manner of **13** to give a residual oil which would not crystallize and which was shown by tlc (2:1 dioxane:benzene) to contain two materials, the title compound (R_f 0.33) and **13** (R_f 0.67) both of which gave a positive test with chromotropic acid. The R_f 0.67 spot was identified by cochromatography with known **13**. The nmr spectrum was consistent with the product being a mixture of 70–74 mole% **12** and 30–25 mole% **13**; those portions of the spectrum attributable to **12** are recorded in Table IV.

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