Ethyl Dimethylcarbamate Hydrothiocyanate. Preparation and Properties

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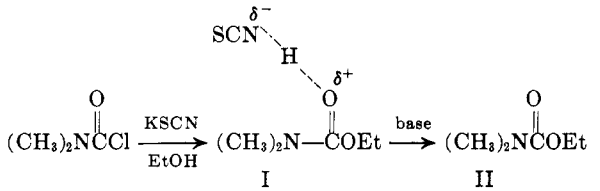
The reactions of carbamoyl halides with thiocyanate ion have received little prior attention. In connection with recent studies of solvent effects on the course of these reactions, we have prepared a novel "salt" to which we have assigned the structure, ethyl dimethylcarbamate hydrothiocyanate (I).

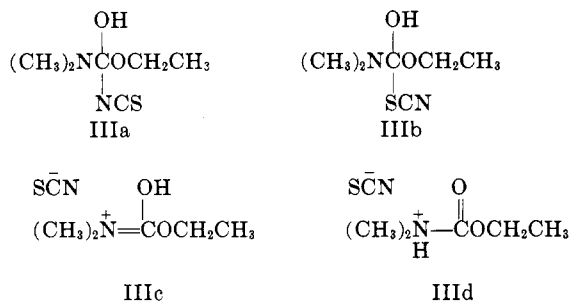
The reaction of dimethylcarbamoyl chloride[1] with potassium thiocyanate in absolute ethanol afforded I in 60% yield, as a reasonably volatile liquid which decomposed slowly at room temperature to an intractable red gum. It could, however, be stored for extended periods of time at −20°.



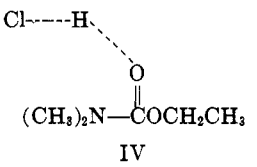
I II

Neutralization of an aqueous solution of I followed by extraction, gave a quantitative yield of free ethyl dimethylcarbamate (II). Treatment of a benzene solution of I with amines resulted in the immediate precipitation of the amine hydrothiocyanate, with ultimate isolation of nearly theoretical amounts of II. Titration of the strongly acidic aqueous solutions of I revealed that this product contained 96% of the calculated amount of hydrothiocyanic acid. Unfortunately, a satisfactory elemental analysis of I could not be obtained owing to its instability at elevated temperatures.

Of the possible structural representations for the hydrothiocyanate, I was considered the most convenient on the basis of infrared and n.m.r. spectral properties. The infrared spectrum was identical with that of the free carbamate II with the exception of broad intense absorption from 3600 to 2400 cm.$^{-1}$ (N–H), and strong bands at 2075 (NCS^-), 1690 (C=O), and 800 cm.$^{-1}$ (C–S). That the carbonyl function interacts with the acid proton is reflected in the shift of its stretching frequency ($\Delta\nu$ = 30 cm.$^{-1}$) from that of the free carbamate II. A shoulder on this band at 1720 cm.$^{-1}$ is usually observed owing to the presence of small amounts of II. The possibilities of the covalent structures IIIa and IIIb were ruled out by the absence of absorptions characteristic of covalent isothiocyanate and thiocyanate.[2] The n.m.r. spectrum[3] (given in p.p.m. from TMS) consisted of a triplet centered at 1.28 (CH_3–C), a singlet at 2.92 (CH_3–N), a quartet at 4.10 (–CH_2–), and a singlet at 8.81 (H–NCS). The integrated peak areas were in the ratio 3:6:2:1. This was identical with the n.m.r. spectrum of II with the exception of the singlet at 8.81 p.p.m. (clearly attributable to the acid proton). The absence of any differences in chemical shifts or splitting patterns between the spectra of the hydrothiocyanate and the free carbamate indicated that the carbamate nitrogen of the hydrothiocyanate was not involved in bonding with the proton or in stabilization of the positively charged carbonyl. The ionic structures IIIc and IIId were therefore eliminated.



It was assumed that the initial product of the reaction in ethanol was the hydrochloride IV which then reacted with dissolved potassium thiocyanate to precipitate potassium chloride and produce I. This was at least partially confirmed by allowing the carbamoyl chloride to react completely with ethanol before adding potassium thiocyanate—a procedure which had little effect on the yield of I. Attempts at isolation of IV failed because of its instability. Similarly, attempts at conversion of IV to the corresponding hydriodide or fluoroborate, with the appropriate potassium salts, resulted in isolation of the free carbamate II with only traces of acidity detectable.



IV

In an effort to determine the effect of the carbamate moiety on hydrothiocyanic acid, the addition of I to olefins was studied. The reaction with norbornylene proceeded easily, affording a product mixture whose composition was determined as 90% *exo*-2-norbornyl isothiocyanate and 9% *exo*-2-norbornyl thiocyanate, accompanied by very small amounts of the *endo* isomers of both. A comparison was made between this method and the reported method[4] of adding hydrothiocyanic acid to olefins (Table I). With norbornylene, both procedures gave the same product distribution in identical yields of 85%. α-Methylstyrene, by both methods, afforded only α,α-dimethylbenzyl isothiocyanate; however, I gave substantially better yields (87%) than the alternate procedure (66%).

(1) Diethylcarbamoyl chloride and, presumably, other dialkylcarbamoyl chlorides give similar results. Diphenylcarbamoyl chloride, however, gave diphenylcarbamoyl thiocyanate as reported [T. B. Johnson and L. H. Levy, *Am. Chem. J.*, **38**, 456 (1908)].

(2) R. G. R. Bacon in "Organic Sulfur Compounds," Vol. I, N. Kharash, Ed., Pergamon Press Inc., New York, N. Y., 1961, p. 307; K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p. 28; L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(3) Obtained in carbon tetrachloride using a Varian A-60 spectrometer.

(4) L. S. Luskin, G. E. Generet, and W. E. Craig, *J. Am. Chem. Soc.*, **78**, 4965 (1956).

TABLE I
HNCS ADDITIONS TO OLEFINS

Olefin	% yield I	% yield NaSCN/H+
Norbornylene	85[a]	85[a]
α-Methylstyrene	87	66[b]
Ethyl acrylate	25	38[b]
Cyclohexene	0	0

[a] Total addition products. [b] Reported yield; see ref. 4.

With ethyl acrylate, the product of both methods was ethyl β-thiocyanatopropionate in yields of 25% from I, and 38%[4] from the reported method. Both procedures, when applied to cyclohexene, gave an orange resin, with none of the expected addition products isolable. Presumably, the mode of addition of hydrothiocyanic acid to olefins is essentially the same for both methods, further indicating that the acid proton is, at best, only loosely bound to the carbamate moiety. The addition of I to olefins is considered superior to previously available methods, by virtue of its shorter reaction time, simpler procedure, cleaner products, and comparable yields.

The previously mentioned reaction of I with amines provides a simple route to the little-studied hydrothiocyanic acid amine salts, again demonstrating the utility of I as a carrier for hydrothiocyanic acid, and as such, its potential usefulness as a synthetic reagent.

Experimental[5]

Ethyl Dimethylcarbamate Hydrothiocyanate (I).—A suspension of 22.7 g. (0.234 mole) of potassium thiocyanate and 25 g. (0.234 mole) of dimethylcarbamoyl chloride in 100 ml. of absolute ethanol was stirred at room temperature for 72 hr. The precipitate was removed by filtration and the filtrate was concentrated to remove excess ethanol. The residue was triturated with 250 ml. of pentane. Evaporation of this solvent, followed by distillation of the crude material at 40.5–41.5° (5 mm.), afforded 24.4 g. (60%) of ethyl dimethylcarbamate hydrothiocyanate: $n^{25}D$ 1.4547; ν (CCl4) 3025, 2075, 1690, and 800 cm.$^{-1}$; $\lambda_{max}^{CH_3CN}$ 238 mμ (log ε 2.12).

Anal. Calcd.: neut. equiv., 176.2. Found: neut. equiv., 169.2.

A solution of 3.5 g. (0.02 mole) of hydrothiocyanate I in 20 ml. of ether was washed with aqueous sodium carbonate solution until neutral, dried, and concentrated. Distillation of the residue at 47–48° (15 mm.) afforded 2.2 g. (95%) of ethyl dimethylcarbamate, $n^{15}D$ 1.4166 (lit.[6] $n^{15}D$ 1.4171).

Anal. Calcd. for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.09; H, 9.44; N, 11.68.

Reaction of Amines with I. General Procedure.—To a solution of 5.3 g. (0.03 mole) of I in 25 ml. of benzene, was added 2.8 g. (0.03 mole) of aniline dropwise with stirring. When the addition was complete, the precipitate was collected by filtration and recrystallized from methylene chloride–ether affording 4.0 g. (89%) of aniline hydrothiocyanate, m.p. 82.5–83.5° (lit.[7] m.p. 80–81°).

Anal. Calcd. for $C_7H_8N_2S$: C, 55.24; H, 5.30; N, 18.40; S, 21.06. Found: C, 55.40; H, 5.29; N, 18.19; S, 21.12.

Reaction of Olefins with I. General Procedure.—A solution of 3.0 g. (0.25 mole) of α-methylstyrene and 4.75 g. (0.027 mole) of I in 10 ml. of benzene was heated under reflux for 2 hr. After cooling, the solution was washed with aqueous sodium bicarbonate, dried, and concentrated. Distillation of the residue afforded 2.3 g. of ethyl dimethylcarbamate, b.p. 31–34° (5 mm.), and 3.8 g. (87%) of α,α-dimethylbenzyl isothiocyanate, b.p. 67–68° (3.5 mm.), $n^{25}D$ 1.5674 (lit.[4] $n^{25}D$ 1.5678).

(5) Melting points are corrected and boiling points are uncorrected. The ultraviolet spectrum was measured on a Cary 14 recording spectrophotometer.

(6) C. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2089 (1952).

(7) H. Krall and R. D. Gupta, *J. Indian Chem. Soc.*, **12**, 629 (1935).

Reactivity and Geometry in Allylic Systems. V. Oxygenation of Cholest-5-en-3-one[1]

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Photosensitized oxygenation of Δ^5 steroids produces the corresponding 5α-hydroperoxides with accompanying shift of the double bond to the Δ^6 position.[2] Studies with deuterium-labeled cholesterol established that the α-hydrogen at C-7 is selectively abstracted, and this result along with other considerations led to postulation of a cyclic "*cis*" mechanism for the sensitized pathway.[3] Recent work with a variety of steroid olefins has shown that the photooxygenation can be substantially blocked when the C–O bond has to develop into a 1,3-diaxial relationship to an alkyl substituent, or when the allylic hydrogen is rigidly equatorial or quasi-equatorial.[1b,4,5] The selective behavior of Δ^5 steroids is thus understandable because oxygenation at C-6 from the α or β side, or at C-5 from the β side, would encounter one or the other of these adverse features. Consequently the report[6] that cholest-5-en-3-one (part structure **1**) gave 6β-hydroperoxycholest-4-en-3-one (**2b**) by the photosensitized pathway is of special interest. This last transformation, unlike those of other Δ^5 steroids, utilized a C-4 hydrogen and suggests either that the carbonyl group profoundly alters the stereochemical requirements for the sensitized process or that the product is derived by some other mechanism.[7,8] To get information on this point we photooxygenated **1** in pyridine with and without added sensitizer.

In a 42-hr. run without sensitizer the crude hydroperoxidic product showed ultraviolet absorption at 242 ± 2 mμ, typical of an α,β-unsaturated ketone system. After reduction with sodium iodide, the ab-

(1) (a) This work was supported by the National Institutes of Health (Grant No. GM 09693) to whom we express our appreciation. (b) Part IV in this series: A. Nickon, N. Schwarz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

(2) (a) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); (b) G. O. Schenck and O. A. Neumuller, *Ann.*, **618**, 194 (1958); (c) G. O. Schenck, O. A. Neumuller, and W. Eisfeld, *ibid.*, **618**, 202 (1958).

(3) (a) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **81**, 6330 (1959); (b) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

(4) (a) A. Nickon and W. L. Mendelson, *Can. J. Chem.*, in press; (b) J. B. DiGiorgio, Ph.D. Dissertation, The Johns Hopkins University, 1960, and unpublished results of Dr. P. J. L. Daniels.

(5) The photooxygenation behavior of monocyclic olefins appears to be governed by similar factors: R. L. Kenney and G. S. Fisher, *J. Org. Chem.*, **28**, 3509 (1963); G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).

(6) G. O. Schenck, K. Gollnick, and O. A. Neumuller, *ibid.*, **603**, 46 (1957).

(7) Fieser, *et al.*, have shown that **1** in cyclohexane readily gives a mixture of the 6β- and 6α-hydroperoxides **2a** and **3a** on treatment with oxygen in the presence of dibenzoyl peroxide and that the isomers are singularly stable to the work-up conditions. We are grateful to Professor Fieser for unpublished experimental details developed by Dr. A. J. Cox [L. F. Fieser, T. W. Greene, F. Bischoff, G. Lopez, and J. J. Rupp, *J. Am. Chem. Soc.*, **77**, 3928 (1955); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 235].

(8) The unusual susceptibility of β,γ-unsaturated ketones to oxygenation has been emphasized by the recent work of E. L. Shapiro, T. Legatt, and E. P. Oliver [*Tetrahedron Letters*, 663 (1964)], who examined $\Delta^{5(10)}$-3-keto steroids and who noted the biological activity of the derived hydroperoxides (see also ref. 6). An example of a nonsteroid β,γ-unsaturated ketone readily oxygenated has recently been described by K. Crowshaw, R. C. Newstead, and N. A. J. Rogers [*ibid.*, 2307 (1964)].