Preparation and characterization of some α,α-disubstituted-α-hydroxythiolesters

WILMA E. ELIAS
Department of Chemistry, University of Victoria, Victoria, British Columbia

Received December 9, 1969[1]

A series of α,α-disubstituted-α-hydroxythiolesters has been prepared from ketone cyanohydrins by the Pinner reaction. The esters have been characterized both by classical methods and by analysis of their i.r. n.m.r., and u.v. spectra.

Canadian Journal of Chemistry, **48**, 3662 (1970)

Introduction

In view of the widely-known hydrogenolytic and reductive desulfurization reactions which organic thio compounds undergo in the presence of Raney nickel (1, 2) and other reducing agents (3, 4 and, for instance, refs. given in 5*a*), and of the hydrogenolysis reactions of carbonyl compounds with vicinyl oxygen-containing groups (*e.g.* refs. given in 5*b* and 6, but compare with 7), it was considered that an examination of the reactions of α-hydroxythiolesters with a number of reducing agents would be of interest. Since α-hydroxythiolesters are not reported in the literature it was necessary to develop a method for the preparation of these compounds. This paper reports the synthesis and characterization of a number of compounds of structure $RR'C(OH)COSC_2H_5$.

Several methods for the preparation of thiolesters have been developed,[2] among them reaction of an acyl halide or acid anhydride with the appropriate thiol, transesterification, reaction of an acyl halide with the appropriate lead mercaptide, and the Pinner reaction. In view of the presence of the tertiary alcohol hydroxyl in the compounds desired, the latter method suggested itself as the most likely to be of general use. The acid-catalyzed addition of an alcohol across the triple bond of a nitrile, followed by hydrolysis of the imidate salt[3] (eq. 1)

$$[1]\quad RCN + R'OH + \text{anhydrous } HX \rightarrow$$
$$RC({=}NH{\cdot}HX)OR' \xrightarrow{\text{hydrolysis}} RCO_2R' + NH_4^+ + X^-$$

was first reported by Pinner and Klein (9) and has since been used quite extensively but, although some cyanohydrins have been treated with alcohols and some nitriles with thiols, no report of the reaction of cyanohydrins with thiols has been found.[4]

Results and Discussion

The thioimidate hydrochlorides were prepared according to the 'standard' procedure for bringing about the Pinner acid-catalyzed reaction. The necessity for maintaining the reaction temperature close to 0 °C was manifested during one preparation which was allowed, inadvertently, to warm under its own heat of reaction; there was generated an odor far more powerful and obnoxious than that associated with the normal process. The resultant mixture was not analyzed, but it was assumed that this indicated the formation of at least some thionamide (10 and refs. therein, 14). Only a slight excess of thiol was used, since reaction of imidate salts with excess alcohol is a synthetic route to ortho esters (10 and refs. therein).

Crystalline thioimidate hydrochlorides were obtained from only a few of the cyanohydrins (marked with an asterisk in Table 1); large masses of granular, white crystals were obtained in each case. Reaction mixtures which did not deposit crystals became very viscous, frequently set to a glass, and often developed colors ranging from yellow to deep orange.

No attempt was made to isolate the thioimidate hydrochlorides, which were converted directly to the corresponding α-hydroxythiolesters as described in the experimental section, *i.e.*, the thiolesters were purified only by distillation through a short Vigreux column, during which a fore-run and two or three fractions were collected.

---

[1] Revision received July 27, 1970.

[2] A brief review is given in ref. 8.

[3] The nomenclature of compounds RC(=NH)OR′ is confused; they have been called iminoethers, iminoesters, imidic esters, imidoates, imidates, imidoethers, and imidoesters. The convention adopted by Roger and Neilson (10) in naming them imidates, will be followed in this series of papers. Chemical Abstracts lists these compounds as esters of imidic acids.

[4] No recent, comprehensive review of the Pinner reaction is known to the author, but several partial reviews are available (10–13).

TABLE 1

Preparation, physical properties, and analysis of $RR'C(OH)COSC_2H_5$

Compound No.	Substituents		Reaction time (days)	Yield† thiolester (%)	Boiling points (°C)‡				Molar refractivities		Saponification equivalent		Sulfur content (%)	
	R	R′			Reduced pressure	Atmospheric pressure	η_D§	d_4‖	Calculated¶	Found	Calculated	Found	Calculated	Found
1	CH_3	CH_3	7*	59.2	90–95/19–20	200–203	1.4155 (28)	1.051 (29)	39.258	39.26	148.2	143.5, 145.0	21.60	20.31, 20.91 **††
2	CH_3	C_2H_5	20*	53.3	89–92/20–21	211–214d./710	1.4773 (28)	1.053 (27)	43.905	43.55	162.2	155.0, 157.0	19.73	19.42, 19.22, 19.22**‡‡
3	C_2H_5	C_2H_5	14	25.6	101–103/20	219–223					176.3	166.0, 167.5	18.19	15.31, 15.75**§§
4	CH_3	n-C_3H_7	13	73.2	68–76/1	223–224.5	1.4752 (25)				176.3	167.4, 166.1, 163.3		
5	CH_3	i-C_3H_7	14	59.4	60–63/1	221–224.5	1.4689 (25)	0.9978 (25)	48.552	49.19	176.3	170.9, 174.9, 177.5	18.19	18.08, 18.04
6	CH_3	n-C_6H_{13}	15	79.4	150–158/8	267.5–270	1.4733 (24.5)				218.4	211.3, 211.7, 215.9		
7	C_2H_5	n-C_4H_9	13	64.8	113–116/2.5	250.5–252	1.4732 (24.5)	0.9764 (25)	57.846	58.73	204.3	202.7, 200.7	15.69	15.58, 15.63
8	CH_3	$C_6H_5—CH_2$	15	80.2	176–185/11–20	281.5–288.5	1.5424 (26)	1.0968 (26)	63.693	64.55	224.3	217.7, 218.2, 224.3		
9	Cyclohexyl		3*	65.7	122–125/7	261.5–262.5	1.5092 (26.5)	1.096 (26)	51.143	51.57	188.3	185.9, 182.5	17.03	16.71, 16.65
10	2-Methylcyclohexyl		16	31	110–125/5									
11	3-Methylcyclohexyl		11*	62.8	106–110/3	184.5–185.5	1.5030 (27.5)	1.0608 (27.5)	56.818	56.38	202.3	199.0, 196.5, 202.6	15.85	15.74, 15.75‖‖
12	4-Methylcyclohexyl		11	79.5	107–109/3	267.5–268	1.5030 (27)	1.0627 (27)	56.818	56.28	202.3	198.1, 200.0, 205.1	15.85	15.67, 15.64
13	Cyclopentyl		2*	74.9	103–107/7	240.5–242	1.4984 (27)	1.1025 (26)	46.496	46.36	174.3	176.1, 175.7, 181.1	18.39	18.18

*Crystalline thioimidate hydrochlorides were obtained.
†The sum of the weights of all fractions with reasonably small b.p. ranges was used to calculate the percentage of the theoretical yield. *All* yields are for the conversion of cyanohydrin to the ester.
‡Boiling points are given for the fractions used to determine the physical constants, including spectra and upon which the quantitative analyses are based. The figures to the right of the oblique indicate the pressure (mm of Hg) at which the distillation was conducted.
§Temperatures at which the determinations were made are given in parentheses.
‖The determinations were made in semimicro pycnometers such as described by Schneider (25). Temperatures at which determinations were made are given in parentheses.
¶Calculated, using the atomic parameters reported by Vogel, as summarized by D. J. Pastro and C. R. Johnson (28).
**Analyses denoted by ** were carried out by the author, using the Parr-bomb combustion method, followed by gravimetric determination of the sulfate. Other analyses were carried out by the Alfred Bernhardt Laboratory, Mulheim, Germany.
††Spectroscopic measurements were carried out on a preparation which analyzed for 21.79% S.
‡‡Spectroscopic measurements were carried out on a preparation which analyzed for 19.72 and 19.84% S.
§§Spectroscopic measurements were carried out on a preparation which analyzed for 15.26 and 15.41% S.
‖‖Anal. Calcd.: C, 59.37; H, 8.97. Found: C, 59.59; H, 8.86 (on a sample which had been stored for some months).

Examination of the data presented in Table 1 shows that, although the yields of thiolesters were variable, the synthesis is practicable. (The esters derived from diethyl ketone and 2-methylcyclohexanone were formed in lower yield, and were obtained in a much less pure state, than the other compounds.)

The α-hydroxythiolesters were characterized by classical methods and by their spectroscopic properties.[5] The results of the classical analyses are summarized in Table 1; in addition, three of the esters have been hydrolyzed to the corresponding α-hydroxyacids, as described in the experimental section.

In analyzing the spectra, cognizance of the impurities in **3** and **10** has been made, and information concerning these compounds has been included only where it is non-equivocal and completely in accord with that obtained for the other compounds. This is emphasized by enclosing compound numbers (**3**) and (**10**) in parentheses wherever used.

Nuclear Magnetic Resonance Spectra

Quartets at 2.82–2.92 p.p.m. and triplets at 1.16–1.26 p.p.m. confirmed the presence of the $S—CH_2—CH_3$ group (15*a*, *b*, 16); in some instances, further splitting indicated the magnetic non-equivalence of the methylene protons. The presence of the OH group was confirmed by deuterium oxide exchange.

Ultraviolet Spectra

All solutions were scanned over the region 200–670 mμ. For all compounds there was a single, reasonably sharp peak the base of which tailed off more gradually on the short wavelength side than on the long. As seen from Table 2*a*, absorption was not intense, but occurred at almost identical wavelengths for all but **1** and was in the region expected. The ultraviolet spectra of thiolesters are not widely reported in the literature, but data for three aliphatic esters have been included in Table 2*b*.

Infrared Spectra

The i.r. spectra were examined for bands for OH, C═O, C—S, and C═C groups. No evidence of carbon–carbon unsaturation was detected, indicating the stability of the tertiary hydroxyl group to the experimental conditions employed in the preparation of these compounds. On the other hand, characteristic absorptions for C═O in the range 5.89–5.99 μ (20–22), C—S in the range 7.00–7.05 μ (22) and, except for (**10**) one to three bands not present in the precursors in the range 9.92–10.75 μ (22), were found. Except for **8**, the OH group gave a band or shoulder at 2.73–2.78 μ and a band at 2.80–2.86 μ; **8** showed only a band at 2.8 μ.

TABLE 2

Ultraviolet spectra of thiolesters

Compound	λ_{max} (mμ)	ε_{max} ($\times 10^{-3}$)	Reference
(a) α-Hydroxythiolesters			
1	259	16.6	
4	243	3.16	
5	242.7	2.65	
6	243	3.30	
7	240.5	3.06	
8	243	3.80	
9	242.7	1.74	
11	243	3.37	
12	241.3	5.0	
13	243	3.31	
(b) Thiolesters reported in the literature			
n-Butyl thiolacetate	≃230	4.0	17
2-Methylcyclohexyl thiolacetate	231.5	4.5	18
2-hydroxy-3-chloropropyl thiolacetate	≃230	4.0	19

Thus, both the classical and spectroscopic analyses provide evidence that compounds of the desired structures were obtained, and were obtained in a sufficient state of purity to serve all practical purposes, by the simple purification method described. Furthermore, it can be concluded that the reaction of ethane thiol with ketone cyanohydrins is a reaction of at least reasonable generality, and hence that the work reported here extends the scope of the Pinner reaction. However, it cannot be claimed that the method is general for the production of α,α-disubstituted-α-hydroxythiolesters, since it rests upon the availability of the requisite cyanohydrins and thus will be mainly confined to esters derived from methyl and some ethyl open-chain, and alicyclic ketones.

Experimental

Preparation of the Cyanohydrins

The cyanohydrins were prepared either by the method of Cox and Stormont (23) or of Bucherer and Grolee (24). In instances where the cyanohydrin was not isolated in a

---

[5] Details of the mass spectra of these compounds will be presented in a subsequent paper.

TABLE 3

Ketone cyanohydrins

Ketone	Boiling point of cyanohydrin (°C/mm of Hg)
Ethyl *n*-butyl	82–84/4
Methyl benzyl	141–144/8
2-Methylcyclohexanone	103–104/5
3-Methylcyclohexanone	106–110/4.5
4-Methylcyclohexanone	118–121/7
Cyclopentanone	81–83/3

pure state, a mixture of the washed extracts and benzene was rendered anhydrous by removal of the benzene–water azeotrope under the vacuum created by a water aspirator. Boiling points not given in Beilstein are listed in Table 3.

Preparation of the α-Hydroxythioimidate Hydrochlorides

Either a mixture of cyanohydrin (1 *M* quantity) and ethyl mercaptan (1.1 *M* quantity) in anhydrous ether or benzene was prepared, or the mercaptan was added to the anhydrous benzene solution of cyanohydrin prepared from 1 *M* quantity of ketone. This mixture was then cooled in an ice bath and hydrogen chloride was passed in to saturation; the weight of hydrogen chloride taken up by the solution was not measured. The anhydrous mixture was then allowed to stand in the refrigerator either until a good crop of glistening white crystals was obtained, or for some days or weeks; typical reaction times are given in Table 1.

Preparation of the α-Hydroxythiolesters

Water was added to the crystalline thioimidate hydrochlorides after removal of the supernatant liquid by decantation; water was added directly to the whole syrup or glass. In either case, steam was passed through the aqueous mixture until the distillate was free from water-insoluble material. The thiolesters, which separated from the cooled distillates as colorless oils, were extracted into ether or benzene and these extracts were worked-up in the usual manner. Final purification consisted of distillation at reduced pressure through a small Vigreux column; boiling points and other physical properties are shown in Table 1.

All esters prepared were clear, colorless liquids of unpleasant odor, an odor which lingered on the skin for several hours after contact. During storage in the refrigerator, the esters from 2- and 3-methylcyclohexanone formed some crystals, which disappeared as soon as the flasks were removed from the refrigerator. All esters were insoluble in water but soluble in methanol, ethanol, ether, benzene, carbon tetrachloride, and chloroform.

Hydrolysis of α-Hydroxythiolesters

Three of the esters were converted to the corresponding α-hydroxyacids (I, $RR'C(OH)CO_2H$). The melting points are uncorrected. Required for I, $R = R' = CH_3$, m.p. 79°; found, m.p. 78.5–79°. Required for $R = CH_3$, $R' = C_2H_5$, m.p. 68–73° (lit. 27*a*); found, m.p. 67.5–68°. Required for I, $R = R' = C_2H_5$, m.p. 79–80° (lit. 27*b*); found, m.p. 78–79°.

Nuclear Magnetic Resonance Spectra

The n.m.r. spectra were determined at 60 MHz on a Varian HA60 spectrometer at room temperature. Deuterochloroform was used as solvent, the solutions being approximately 10% (v/v) in concentration. All chemical shifts are reported as δ values with respect to tetramethylsilane used as an internal standard.

Ultraviolet Spectra

The u.v. spectra were recorded on a Unicam SP700 spectrophotometer. Chloroform was used as solvent, and solutions were approximately 10^{-4} *M*.

Infrared Spectra

The i.r. spectra were recorded either on a Perkin–Elmer 337 or Beckmann IR-4 spectrophotometer, using chloroform as solvent.

ADDENDUM: Since the original writing of this manuscript the synthesis of *S*-methyl thiomandelate ($C_6H_5CH(OH)COSCH_3$) from tri(methylmercapto)acetophenone has been reported (26).

The author gratefully acknowledges the aid of Dr. R. U. Lemieux, University of Alberta, Edmonton, Alberta, with whom the problem was discussed during the early stages of work, and of Miss P. A. Cockrill, Miss H. L. Dougan, and Mrs. P. J. Hoibak, who rendered invaluable assistance in the laboratory.

Gratitude is also expressed to the University of Victoria and to the National Research Council of Canada for financial assistance.

1. E. MOSSETIG. Org. React. **8**, 218 (1954).
2. H. HAUPTMANN and W. F. WALTER. Chem. Rev. **62**, 348 (1962).
3. J. D. DUTCHER, J. R. JOHNSON, and W. F. BRUCE. J. Amer. Chem. Soc. **67**, 1736 (1945).
4. J. R. JOHNSON and J. B. BUCHANAN. J. Amer. Chem. Soc. **75**, 2103 (1953).
5. J. MARCH. Advanced organic chemistry. McGraw-Hill Book Co., New York, 1968. (*a*) p. 556; (*b*) p. 893.
6. H. O. HOUSE. Modern synthetic reactions. W. A. Benjamin, Inc., New York, 1965. pp. 56, 57.
7. H. ADKINS. Org. React. **8**, 1 (1954).
8. E. M. REID. Organic chemistry of bivalent sulfur. Vol. IV. Chemical Publishing Co. Inc., New York, 1962. pages 24 ff and 63 ff.
9. A. PINNER and F. KLEIN. Ber. **10**, 1889 (1877).
10. R. ROGER and D. G. NEILSON. Chem. Rev. **61**, 179 (1961).
11. R. H. SHRINER and F. W. NEUMANN. Chem. Rev. **35**, 351 (1944).
12. E. N. ZIL'BERMAN and A. E. KULIKOVA. Zh. Obshch. Khim. **30**, 3999 (1960); Chem. Abstr. **55**, 22126 (1961).
13. E. N. ZIL'BERMAN. Russ. Chem. Rev. (English translation), **31**, 620 (1962).
14. R. H. HARTIGAN and J. B. CLOKE. J. Amer. Chem. Soc. **67**, 709 (1945).
15. A. SCHONBERG and K. PRAEFCKE. (*a*) Chem. Ber., **99**, 237 (1966); (*b*) Chem. Ber. **99**, 2433 (1966).
16. A. SCHONBERG and K. PRAEFCKE. Chem. Ber. **100**, 778 (1967).
17. L. H. NODA, S. A. KUBY, and H. A. LARDY. J. Amer. Chem. Soc. **75**, 913 (1953).
18. J. I. CUNNEEN. J. Chem. Soc. 134 (1947).
19. B. SJOBERG. Z. Phys. Chem. **52B**, 209 (1942).

20. K. IGARASHI and T. HONMA. J. Org. Chem. **32**, 2521 (1967).
21. A. W. BAKER and G. H. HARRIS. J. Amer. Chem. Soc. **82**, 1923 (1960).
22. R. A. NYQUIST and W. J. POTTS. Spectrochim. Acta, 7, 514 (1959).
23. R. F. B. COX and R. T. STORMONT. Org. Syn. **15**, 1 (1935).
24. H. BUCHERER and A. GROLEE. Ber. **39**, 1224 (1906).
25. F. SCHNEIDER. Qualitative organic microanalysis. John Wiley and Sons, Inc., New York, 1946. p. 98.
26. G. A. RUSSELL and L. A. OCHRYMOWYCZ. J. Org. Chem. **34**, 3618 (1969).
27. BEILSTEIN. III, (*a*) 324, (*b*) 338.
28. D. J. PASTRO and C. R. JOHNSON. Organic structure determination. Prentice-Hall, Inc., Englewood Cliffs, N.J., 1969. p. 71.