sodium phosphate buffer (pH 7.6–9.6) in an open container at room temperature. Immediately after the addition, circulation (~140 ml/min) of the straw-colored solution through an esr cell was started and the signals were recorded. The pH was kept at the desired value by the occasional addition of 1 *M* NaOH. In some cases oxygen or nitrogen was bubbled through the reaction mixture. Stable radicals formed in the autoxidation of THB were observed in a similar manner.

Registry No.—Thyroxine, 51-48-9; **2b**, 20224-53-7; **6**, 20224-54-8; **7**, 20224-55-9; **10**, 12349-50-7; **13**, 12349-49-4.

The Kinetics of the Decarboxylative Dehydration of β-Anisyl-β-hydroxy-α-phenylpropionic Acid[1,2]

DONALD S. NOYCE AND ERNEST C. MCGORAN[3]

Department of Chemistry, University of California, Berkeley, California 94720

Received September 25, 1968

The decarboxylative dehydrations of *erythro*- and *threo*-β-anisyl-β-hydroxy-α-phenylpropionic acids proceed at different rates in dilute aqueous sulfuric acid solution. Both stereoisomers give *trans*-4-methoxystilbene. The diastereoisomers are interconverted at a rate which is slower than decarboxylation in dilute sulfuric acid solution, but at a rate more rapid than decarboxylation in more acidic medium. These facts are interpreted in terms of generation of a dipolar ion which loses carbon dioxide more rapidly than it reacts with water.

The behavior of β-hydroxy acids under a variety of circumstances has been studied in these laboratories; in addition to studies of the mechanism of acid-catalyzed dehydration[4,5] many features of the decarboxylative dehydration have been elucidated.[6-8] The reaction shows a particularly modest increase in rate with increasing acidity of the medium;[6] a plot of log *k* *vs.* H_0 typically has a slope of 0.4–0.6. It was shown that there are circumstances in which racemization (*e.g.*, of β-hydroxy-β-arylbutyric acids) is no more rapid than decarboxylation. This situation applies at low acidities. At higher acidities racemization was much more rapid than any other reaction of the β-hydroxy acids. It was also shown[1] that both diastereoisomers of α-methyl-β-hydroxy-β-(*p*-tolyl)propionic acid gives *trans*-*p*-propenyltoluene. In order to examine the kinetic features of decarboxylative dehydration more thoroughly, particularly in relation to the stereochemistry of the process, we have sought a compound which would be more suitable than β-anisyl-β-hydroxybutyric acid. For this purpose we have chosen to examine the kinetic behavior of the two diastereoisomers of β-anisyl-β-hydroxy-α-phenylpropionic acid (**1**). Ultraviolet spectra are distinctive for the four possible products, both *cis*- and *trans*-α-phenyl-*p*-methoxycinnamic acids, which could result from simple acid-catalyzed dehydration, as well as *cis*- and *trans*-4-methoxystilbenes, which could result from decarboxylative dehydration. These differences in spectra thus make it easy to follow the course of the reaction of **1** in detail.

A mixture of the two isomers of **1** was prepared by an Ivanov reaction and separated by chromatography over alumina. The *threo* configuration is assigned to the predominant isomer (mp 151–152°) on the basis of the following arguments. Zimmerman and Traxler[9] have unambiguously determined the configuration of the two diastereoisomers of α,β-diphenyl-β-hydroxypropionic acid (**2**) by a direct chemical method. More recently Canciell, *et al.*,[10] have shown that it is generally true that *threo* isomers of compounds such as **2** show a larger coupling constant between the α and β hydrogens than do the *erythro* isomers. Coupling constants very similar to those reported for *threo* **2** and *erythro* **2** were observed for the two diastereoisomers of **1**.

In fairly dilute sulfuric acid at 65° *threo* **1** and *erythro* **1** separately showed excellent first-order kinetics as followed by the appearance of the spectrum of *trans*-4-methoxystilbene. *threo* **1** reacted more rapidly than *erythro* **1**. These observations show that there is not rapid interconversion of the two diastereoisomers.

In 0.8 *M* sulfuric acid, the exclusive product is *trans*-4-methoxystilbene from both isomers. Control experiments showed that there is essentially none of the substituted cinnamic acid formed by simple dehydration, and that less than 1% of the *cis*-4-methoxystilbene is formed. Thus, the decomposition of both stereoisomers of **1** gives the same *trans* olefin, an observation which is completely in accord with the previous stereochemical results obtained in the study of α-methyl-β-hydroxy-β-(*p*-tolyl)propionic acid.[1]

When the kinetic studies were carried out at 65° in more concentrated sulfuric acid medium (about 1 *M*) the usual first-order plot was no longer linear, but showed some curvature. For *threo* **1** a plot of (log [*threo* **1**]) *vs.* time was slightly concave upward.

The lack of simple first-order behavior shows up more clearly in our kinetic measurements at 44°. Under these conditions and working in more concentrated sulfuric acid media, neither isomer showed simple first-order behavior. For *threo* **1** the plot of (log [*threo* **1**]) *vs.* time is concave upward initially and becomes linear only after about 50% reaction. For *erythro* **1** the corresponding plot is slightly concave downward, again becoming linear after approximately 50% reaction. Moreover, the limiting slope for the later stages of reac-

(1) Previous paper: D. S. Noyce and S. K. Brauman, *J. Amer. Chem. Soc.*, **90**, 5218 (1968).

(2) Supported in part by grants from the National Science Foundation (G 13125, GP 1572, and GP 6133X).

(3) Dow Chemical Co. Graduate Fellow in Chemistry, 1964–1965.

(4) D. S. Noyce, P. A. King, C. A. Lane, and W. L. Reed, *J. Amer. Chem. Soc.*, **84**, 1638 (1962).

(5) D. S. Noyce and R. A. Heller, *ibid.*, **87**, 4325 (1965).

(6) D. S. Noyce, L. Gortler, M. J. Jorgenson, F. B. Kirby, and E. C. McGoran, *ibid.*, **87**, 4329 (1965).

(7) D. S. Noyce, S. K. Brauman, and F. B. Kirby, *ibid.*, **87**, 4335 (1965).

(8) D. S. Noyce, L. M. Gortler, F. B. Kirby, and M. D. Schiavelli, *ibid.*, **89**, 6944 (1967).

(9) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957).

(10) J. Canciell, J. Basselier, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1906 (1963).

tion for both isomers stabilizes at the same value. Further information regarding analysis of these observations is given in the Experimental Section.

Experimental Section[11]

β-Anisyl-β-hydroxy-α-phenylpropionic Acid (1).—A mixture of the *threo* and *erythro* isomers was obtained by an Ivanov reaction.[12] To the Ivanov reagent prepared from 46 g (0.29 mol) of sodium phenylacetate and isopropylmagnesium chloride was added 39.5 g (0.29 mol) of *p*-anisaldehyde in 200 ml of ether. Vigorous stirring and slow addition were helpful in preventing the formation of an awkward, thick, gummy mass. After heating for an additional 8 hr, the reaction mixture was hydrolyzed by pouring onto ice and a 6 *N* HCl aqueous acetone solution. Work-up in the usual fashion afforded a mixture of crude acids. Chromatography on Baker alumina first removed a substantial amount of unreacted phenylacetic acid. Continued elution with 1:1 ether–petroleum ether (bp 30–60°) afforded 6 g (7.7%) of *erythro* acid, followed by 25.4 g (32%) of *threo* acid. The *erythro* acid was purified by three crystallizations from ethyl acetate–petroleum ether (bp 30–60°), mp 169–170°.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92; neut equiv, 272. Found: C, 70.70; H, 6.04; neut equiv, 274.

The *threo* acid was similarly purified, mp 151–152°.

Anal. Found: C, 70.62; H, 5.94; neut equiv, 274.

Ivano and Nicolov[12] reported a single isomer, mp 136.5° dec, while Blicke and Cox[13] reported an acid of mp 168–170° on extensive crystallization of material originally melting at 139–140°.

Methyl *erythro*-β-anisyl-β-hydroxy-α-phenylpropionate was prepared by esterification of the *erythro* acid with diazomethane. Recrystallization from ethyl acetate–petroleum ether (bp 30–60°) and sublimation gave material of mp 88.5–89.5°.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.37; H, 6.46.

Similarly **methyl *threo*-β-anisyl-β-hydroxy-α-phenylpropionate** was prepared, mp 95–96°.

Anal. Found: C, 71.48; H, 6.52.

A small sample of *cis*-α-phenyl-*p*-methoxycinnamic acid was prepared by irradiation of *trans*-α-phenyl-*p*-methoxycinnamic acid. Recrystallization of the crude acid mixture from benzene gave recovered *trans* acid. From the mother liquors the *cis* acid was obtained, and purified by crystallization from benzene, mp 124–125° (lit.[14] mp 123°).

Kinetic Procedures.—The rate of decarboxylation was determined by measuring the increase of absorption at 315 mμ with a Beckman DU spectrophotometer using 10-cm cells. Stock solutions of the hydroxy acid were prepared in dioxane, and diluted with sulfuric acid of the requisite concentration, so that the final solution contained 5% dioxane and was $\sim 5 \times 10^{-7}$ *M* in hydroxy acid. At these very low concentrations, special precautions to avoid photochemical isomerization were taken.

Product Studies.—*cis*-4-Methoxystilbene is relatively stable under the decarboxylation conditions.[15] The rate of isomerization of *cis*-4-methoxystilbene (extrapolated to 64% in 0.8 *M* sulfuric acid) is 6.8×10^{-6} sec^{-1}. Under these same conditions the rate of decarboxylation of the *erythro* acid is 7×10^{-4} sec^{-1}. The ratio of decarboxylation to isomerization rates is therefore 108. Further *cis*-4-methoxystilbene is recovered almost completely unchanged under the conditions of the following experiment.

Separate samples of the *erythro* and *threo* acids were heated at 65° for 45 min in 1.5 *M* sulfuric acid, and the products of the reaction examined carefully. These conditions are sufficient to cause almost complete decarboxylation. The aqueous solutions were extracted with pentane, and the pentane extracts washed carefully with 10% sodium bicarbonate solutions. From the pentane extracts upon evaporation, the residue was taken up in a measured quantity of 95% ethanol, and the uv spectrum then recorded (Cary Model 14 spectrophotometer). In each case the spectrum was superimposable on that of an authentic sample of *trans*-4-methoxystilbene. Thus, the *trans* isomer is the exclusive product of decarboxylative dehydration.

Simple dehydration of the β-anisyl-β-hydroxy-α-phenylpropionic acids was shown to be an insignificant competing reaction, even in relatively concentrated mineral acid solutions as shown by the following experiment. A sample of the *erythro* acid (0.1 g) was heated at 64.7° for 5 hr in 250 ml of 0.8 *M* sulfuric acid (5% dioxane added). The resulting suspension was extracted with chloroform, and the neutral and acidic material separated. The neutral material was *trans*-4-methoxystilbene (as above). The bicarbonate extracts were carefully acidified (cold) to a pH of 2, and extracted with chloroform. The layer was dried, concentrated, and the spectrum determined. From the absorbance at 306 mμ, the maximum amount of α-phenyl-*p*-methoxycinnamic acid formed was determined; less than 0.8% of substituted cinnamic acids was formed.

Analog Computer Simulation of Kinetic Pattern.—The complex behavior of two substances, E and T, which may be interconverted, both of which give a third compound, irreversibly, was simulated by employing a Pace analog computer.[16] The results were registered on an X–Y recorder, and were compared with the experimentally found data. The experimental apparent percentage reaction was plotted against time on a scale such that 95% reaction was presented over the full time scale.

In the scheme (eq 1) the ratio k_3/k_4 was constrained to a value of 2, and k_1 and k_2 were varied over a reasonable range of values.

$$\begin{array}{ccc} & \overset{k_3}{\rightleftharpoons} & \\ \textit{erythro}\ \mathbf{1} & & \textit{threo}\ \mathbf{1} \\ {\scriptstyle k_1}\searrow & & \swarrow{\scriptstyle k_2} \\ & \text{stilbene} + CO_2 + H_2O & \end{array} \qquad (1)$$

The conditions which would give concentration *vs.* time values to match the experimentally observed situations were sought. To be particularly noted is that the observed rate behavior at 44° in 2–4.5 *M* acid could be very satisfactorily reproduced, including initial rates, and also the ultimate, and similar rates for both isomers after 50–70% reaction. As an example of the results obtained, the data in Table I show the range of acceptable values under one set of conditions.

TABLE I

H_2SO_4, *M*	H_0	Starting isomer	k_2/k_1	k_3/k_1	Final rate, sec^{-1}
2.49	−0.93	*threo*	5 ± 1	3.5 ± 1	4.2×10^{-4}

Epimerization Studies.—It was necessary to use an indirect method for determining the ratio of *threo* to *erythro* isomer at equilibrium inasmuch as the acids were unstable in dilute sulfuric acid. It seemed that the methyl esters would provide reasonable models. Approximately 0.10 g of the methyl ester of one pure diastereoisomer or a mixture of esters of known composition was dissolved in 50 ml of dioxane, and diluted to 5 l. with 1 *M* sulfuric acid. After being kept at 44° for 5 hr, the reaction mixture was poured over ice, saturated with salt, and extracted thoroughly with ether. The combined ether extracts were washed with Na_2CO_3, dried over $MgSO_4$, concentrated, and the remaining esters dissolved in pyridine. The nmr spectrum of the pyridine solution was determined and the ratio of the two isomers determined from multiple scans. The ester methyl peaks are well separated in pyridine solution, that for the *erythro* isomer being 6 cycles to higher field than the peak for the *threo* isomer. Approaching the equilibrium from both sides gave an equilibrium value of *threo*/*erythro* of 2.02 ± 0.09.

Activation Parameters.—Values for the activation parameters for the decarboxylative dehydration of both *erythro* **1** and *threo* **1** can be calculated at $H_0 = 0$ from the rates of the two isomers at 64° and the mathematically separated rates at 43.72° (with a short extrapolation needed). Using the value of 8.9×10^{-5} sec^{-1} for the final observed rate at 43.72° ($H_0 = 0$), the activation parameters listed in Table II are obtained. It should be noted that the nature of the separation of the rates in the fashion described here precludes obtaining high precision in the energy

(11) Analyses are by the Microanalytical laboratory, Department of Chemistry, University of California, Berkeley. Melting points are uncorrected; nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer.

(12) D. Ivanov and N. I. Nicolov, *Bull. Soc. Chim. Fr.*, **51**, 1325 (1932).

(13) F. F. Blicke and R. H. Cox, *J. Amer. Chem. Soc.*, **77**, 5401 (1955).

(14) Y. de Schuttenbach, *Ann.*, **6**, 77 (1936).

(15) D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 4633 (1968).

(16) We wish to express our appreciation to Professor E. Grens of the Department of Chemical Engineering, University of California, for counsel in the use of the analog computer, and for making these facilities available to us.

TABLE II

ACTIVATION PARAMETERS FOR THE DECARBOXYLATIVE DEHYDRATION OF β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID

erythro			*threo*		
k_1, sec^{-1} [a]	E_a, kcal	$\Delta S^{\pm}$, eu	k_2, sec^{-1} [a]	E_a, kcal	$\Delta S^{\pm}$, eu
2.97×10^{-5}	34	+26	1.19×10^{-4}	31	+19

[a] At 44°, $H_0 = 0$.

of activation, and particularly in the apparent entropy of activation. Nevertheless, the entropy of activation is strikingly positive.

Results and Discussion

The results of kinetic measurements at two temperatures and in media of varied sulfuric acid concentration are given in Tables III, IV, and V. These kinetic results are best discussed in separate sections dealing with rate behavior of the two diastereoisomers of **1** in various concentrations of mineral acid.

TABLE III

DECARBOXYLATIVE DEHYDRATION OF *threo*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 64.21°

H_2SO_4, M	H_0 [a]	$10^4 k_{initial}$, sec^{-1}	$10^4 k_{final}$, sec^{-1}
0.03076	1.80	1.07	Same
0.050	1.58	1.70	Same
0.05974	1.50	2.00	Same
0.100	1.25	3.73	Same
0.1364	1.09	3.73	Same
0.200	0.89	6.28	Same
0.294	0.67	7.82	Same
0.322	0.62	8.50	Same
0.408	0.49	10.2	Same
0.459	0.42	12.8	
0.7504	0.12	16.9	15.6
0.7734	0.10	17.4	14.1
1.070	−0.11	23.6	19.6
1.614	−0.42	34.0	29.6

[a] H_0 was measured at 64°.

TABLE IV

DECARBOXYLATIVE DEHYDRATION OF *erythro*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 64.21°

H_2SO_4, M	H_0 [a]	$10^4 k_{initial}$, sec^{-1}	$10^4 k_{final}$, sec^{-1}
0.03148	1.79	0.302	Same
0.07985	1.36	0.765	Same
0.100	1.25	0.910	Same
0.100	1.25	0.955	Same
0.200	0.89	1.72	Same
0.2652	0.73	2.11	Same
0.3288	0.61	2.50	Same
0.4673	0.41	3.82	Same
0.550	0.31	5.05	
0.5875	0.27	5.16	5.37
0.6998	0.17	5.75	6.43
0.8316	0.06	7.00	7.36
1.538	−0.37	13.8	19.0

[a] H_0 was measured at 64°.

At *low* concentration of mineral acid (<0.5 M) both the *threo* isomer and the *erythro* isomer give excellent pseudo-first-order kinetics. Moreover, the rates for the two isomers are distinctly different, with the *threo* isomer

TABLE V

DECARBOXYLATIVE DEHYDRATION OF *erythro*- AND *threo*-β-ANISYL-β-HYDROXY-α-PHENYLPROPIONIC ACID IN 5% AQUEOUS DIOXANE–H_2SO_4, T = 43.72°

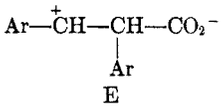
H_2SO_4, M	H_0 [a]	Isomer [b]	$10^4 k_{final}$, sec^{-1} [c]
1.097	−0.30	T	1.84
1.994	−0.69	E	2.78
2.49	−0.93	E	4.36
2.49	−0.93	T	4.20
3.29	−1.31	T	8.63
3.29	−1.31	T	8.82
3.49	−1.41	E	10.2
4.39	−1.85	E	20.6
4.39	−1.85	T	18.9
4.39	−1.85	T	20.1
4.58	−1.95	T	22.9
4.58	−1.95	T	23.6

[a] H^0 was measured at 44°. [b] T, *threo* isomer; E, *erythro* isomer. [c] The error in the rate constant is about ±5%.

reacting about four times more rapidly than the *erythro* isomer. These detailed kinetic observations supplement and substantiate the stereochemical observations of Noyce and Brauman[1] which showed that there was no interconversion of the two epimers of α-methyl-β-hydroxy-β-*p*-tolylpropionic acid in weakly acidic solution.

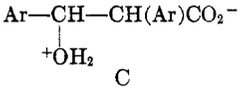
Concurrently, however, both stereoisomers of **1** give *trans*-4-methoxystilbene as the nearly exclusive product. The product-forming step thus takes place from a common intermediate, but this product-forming step cannot be the rate-limiting process. Acceptable species for the product forming intermediate are severely limited. A β-lactone is excluded.[17] The carbonium ion formed by acid-catalyzed loss of water from the hydroxy acid is excluded by the manner on which the reaction rate varies with mineral acid concentration.

An attractive and acceptable intermediate is the dipolar ion E, recognizing that the stereochemical differ-



E

ence between the two epimers is removed as soon as the dipolar ion is symmetrically solvated. A further restriction is that the dipolar ion E loses carbon dioxide more rapidly than it reacts with water to generate the zwitterion C, else equilibration would precede decar-



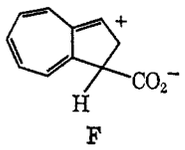
C

boxylation. Equilibration prior to decarboxylation is excluded by the kinetic behavior at low concentrations of mineral acid.

The pH rate profile for a reaction proceeding through the zwitterion C and dipolar ion E should be independent of pH in the region where we have made measurements, except for salt effects. At this juncture the recent observations of Longridge and Long[18] are partic-

(17) D. S. Noyce and E. G. Banitt, *J. Org. Chem.*, **31**, 4043 (1966).
(18) J. L. Longridge and F. A. Long, *J. Amer. Chem. Soc.*, **90**, 3092 (1968).

ularly germane. They showed that the decarboxylation of azulene-1-carboxylic acid proceeds through a zwitterion F, analogous to E. Further they demon-



F

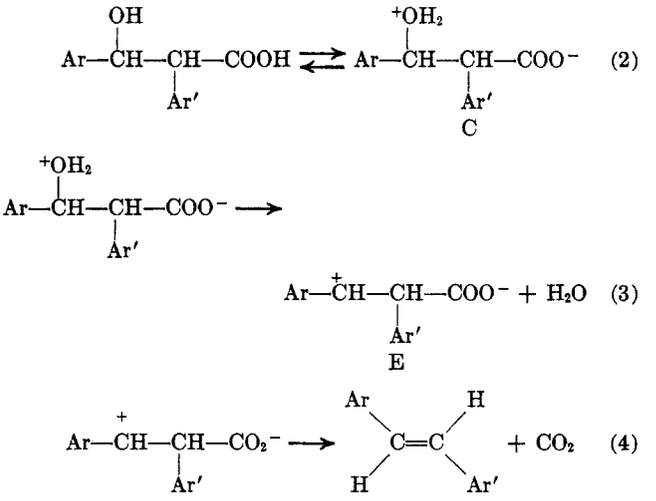
strated that the decarboxylation rate of F is subject to a very pronounced positive salt effect, with rates in 5 *M* salt which are nearly ten times the rates in 0.5 *M* salt. In sulfuric acid they noted that the rate increase in more concentrated acid closely paralleled these salt effects, and that, therefore, the increasing rates in more concentrated mineral acid are the result of a salt effect, not an additional acid-catalyzed reaction pathway.

Returning to a consideration of our data, we therefore conclude that the mechanistic scheme proposed earlier[1] is completely satisfactory to explain the kinetic data obtained in the investigation. Decarboxylation proceeds from a zwitterion C by rate-limiting loss of water to give E irreversibly, followed by very rapid loss of CO_2 to give *trans*-4-methoxystilbene.

In *higher* concentrations of sulfuric acid (0.5–4.0 *M*) the total rate of decarboxylation shows a modest increase in rate due to the salt effect, but not due to an acid-catalyzed reaction. Concomitantly, the acid-catalyzed interconversion of the *threo* and *erythro* isomers become relatively more rapid and more important. This leads to some difficulties in the kinetic measurements as decarboxylation is now proceeding from a variable mixture of the two stereoisomers. For example, in 4.39 *M* sulfuric acid at 44° (Table V), the measured rate constant near the end of a run is the same starting with either isomer, indicating that equilibration was almost complete.

Detailed analysis shows that this interpretation will fit the data. By assuming reasonable values for the rate of acid-catalyzed epimerization, and for the composition of an equilibrium mixture of the two epimers, it was possible to reproduce the observed rates of decarboxylation for the runs in more concentrated sulfuric acid solutions with compounds curves generated by an analog computer.

Thus the decarboxylative–dehydration reaction proceeds by the following mechanism (eq 2–4).



The close relationship between this mechanism and other similar situations should be pointed out. Shiner and Martin[19] have shown that the decomposition of glycidic esters proceeds by way of a zwitterion analogous to C and the parallel with the steps in the present mechanism can be essentially complete, by including a dipolar ion analogous to E. The similarity to the results of Longridge and Long[18] on the decarboxylation of azulene-1-carboxylic acid, has already been mentioned. In addition a parallelism may be noted to the decarboxylative debromination studied by Cristol and Norris[20] and by Grovenstein and Lee.[21] Recently several studies of the decarboxylation of substituted anthranilic and of salicylic acids have been carried out and the mechanistic parallelism is evident.[22–24]

Registry No.—1 (*erythro*), 20445-40-3; 1 (*threo*), 20414-13-5; 1 (*erythro*-methyl ester), 20414-14-6; 1 (*threo*-methyl ester), 20445-41-4.

(19) V. J. Shiner, Jr. and B. Martin, *J. Amer. Chem. Soc.*, **84**, 4824 (1962).
(20) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632, 2645 (1953).
(21) E. Grovenstein and D. E. Lee, *ibid.*, **75**, 2639 (1953).
(22) A. V. Willi, C. M. Won, and P. Vilk, *J. Phys. Chem.*, **72**, 3142 (1968); A. V. Willi, *Helv. Chim. Acta*, **43**, 644 (1960); A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959).
(23) G. E. Dunn, P. Leggate, and I. E. Scheffler, *Can. J. Chem.*, **43**, 3080 (1965).
(24) J. M. Los, R. F. Rekker, and C. H. T. Tonsbeek, *Rec. Trav. Chim. Pays-Bas*, **86**, 622 (1967).