Mechanism of Deoxymercuration with Hydrochloric Acid

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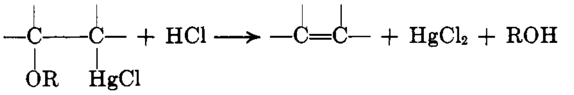
The deoxymercuration rates of oxymercurials derived from various olefins have been determined in 75% ethanol. The relative rates for β-ethoxy-α-chloromercuri compounds obtained from ethylene, propylene, 2-butene, isobutylene, cyclohexene, styrene, and *m*-methyl-, *p*-methyl-, *m*-chloro-, *p*-chloro-, *m*-bromo-, and *p*-bromostyrene are 1.00, 14.4, 86.3, 1560, 106, 72.1, 140, 415, 10.5, 36.6, 7.58, and 30.4, respectively, at 0° with hydrochloric acid. The ρ-value of the Hammett plot is −2.93 for the styrene derivatives. On the basis of these results, the mechanism of deoxymercuration is discussed.

Deoxymercuration is a characteristic reaction of a special type of organomercurial, $>C(OR)-\overset{|}{C}(HgZ)-$ (R = H, alkyl, and acyl; Z = acid radical), which can be prepared easily by the addition of mercuric salts to olefins in the solvent ROH.[1] The mechanism of this reaction is interesting, because it proceeds readily under very mild conditions, and this type of reaction has not been observed in the other organometallics. Moreover, elucidation of deoxymercuration will help to clarify the mechanism of the reverse reaction, oxymercuration, whose mechanism is not yet clear, despite the fact that it is well known and an established experimental method.[2]



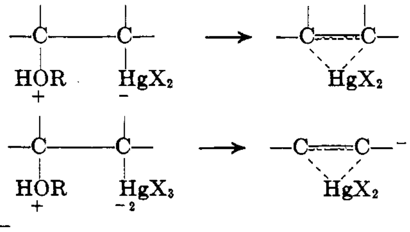
$$-\underset{OR}{\overset{|}{\underset{|}{C}}}-\underset{HgCl}{\overset{|}{\underset{|}{C}}}- + HCl \longrightarrow -\overset{|}{C}=\overset{|}{C}- + HgCl_2 + ROH \qquad (1)$$

In recent years, Kreevoy and co-workers have published extensive studies of deoxymercuration of α-methoxy-β-iodomercuri compounds with perchloric acid. In this system, the rate equation is second order with respect to the mercurials and hydronium ion.[3] With hydrochloric acid, however, the rates are much faster, the reaction is complete even in the presence of a slight excess of the acid, and the rate equation was found to be third order with respect to the mercurials, hydronium ion, and chloride ion.[4]

$$\text{rate} = k_3[\text{S}][\text{H}^+][\text{Cl}^-] \qquad (2)$$

Recently, Kreevoy and co-workers reported that the deoxymercuration rates of 2-methoxyethylmercuric iodide in aqueous perchloric acid containing iodide ion can be expressed by a general equation (3). They concluded that three kinds of reaction proceed concurrently and the rate-determining steps are formation of mercurinium ion from the protonated substrate and of intermediates as shown below.[5]

$$\text{rate} = \{k_2 + k_3[\text{I}^-] + k_4[\text{I}^-]^2\}[\text{H}^+][\text{S}] \qquad (3)$$



Before this publication, we had finished the work presented here and obtained the conclusion that our mechanism proposed previously[4] should be corrected. Although our conclusion is essentially the same as that obtained by Kreevoy, our results on the structural effects on the rates will help to clarify the nature of deoxymercuration more precisely. Also, the comparison of the results in the presence of iodide ion with those in the presence of chloride is desirable.

It was reported previously that the third-order constant k_3 in eq. 2 increased in lower concentrations of hydrochloric acid ($<$ *ca.* 0.05 *M*) and this was explained in term of the increase of the activity of the acid.[4] Kreevoy, however, concluded correctly that this is due to an oversimplified rate equation (2) and that the hydronium ion induced term, $k_2[\text{H}^+][\text{S}]$, should be added on the basis of his observation that 2-isopropoxyethylmercuric chloride could be deoxymercurated with perchloric acid. Although this conclusion is correct, the rate due to the $k_2[\text{H}^+][\text{S}]$ term is much smaller than that due to the $k_3[\text{H}^+][\text{S}]$ term. For example, only 1.92% of 2-ethoxypropylmercuric chloride (initial concentration of 0.0286 *M*) in 75% ethanol containing 0.107 *M* perchloric acid decomposed after 20 hr. at 25°, despite the fact that more than 50% of the same compound (initial concentration of 0.0226 *M*) in the same medium containing 0.0425 *M* hydrochloric acid decomposed in 1 hr. at 0°. Therefore, the values of k_3 can be determined by eq. 2 without appreciable effects due to the term $k_2[\text{H}^+][\text{S}]$, so far as the rates are determined in the higher acid concentrations ($>$ *ca.* 0.05 *M*). The third term in eq. 3 does not appear to be important in the case of deoxymercuration with hydrochloric acid, because k_3 values remained constant in the higher acid concentrations than 0.05 *M* as was shown in the previous paper.[4] This is reasonable considering that the complexing power of chloride ion is much weaker than that of iodide ion. The structural effect on k_3, therefore, can be determined by the simplified eq. (2).

By the same method as described in the previous paper,[4] the rates of deoxymercuration have been determined with the organomercurials derived from propylene, 2-butene, isobutylene, cyclohexene, and styrene and its methyl, chloro, and bromo derivatives (*meta* and *para*).

The mercurials were prepared by treating with sodium chloride the oxymercuration products which were obtained by the addition of mercuric acetate to olefins in acetic acid or ethanol. In the cases of *p*-methyl-, *p*-chloro-, and *p*-bromostyrene, solid products were obtained which could be recrystallized from ethanol. In the other cases, there were obtained oily products which

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(1) See, for example, J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(2) K. Ichikawa, *Kogyo Kagaku Zasshi*, **66**, 1037 (1963).

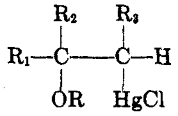
(3) M. M. Kreevoy and B. M. Eisen, *J. Org. Chem.*, **28**, 2104 (1963).

(4) K. Ichikawa, H. Ouchi, and S. Araki, *J. Am. Chem. Soc.*, **82**, 3880 (1960).

(5) M. M. Kreevoy, G. Stokker, R. A. Kretcher, and A. K. Ahmed, *J. Org. Chem.*, **28**, 3184 (1963).

TABLE I

KINETIC RESULTS OF DEOXYMERCURATION OF A WITH HYDROCHLORIC ACID



$$R_1-\overset{R_2}{\underset{OR}{C}}-\overset{R_3}{\underset{HgCl}{C}}-H$$

A

Olefin	R	R_1	R_2	R_3	k_3 at 0°, l.^{2}/mole sec.$^{-1}$	ΔH^*, kcal./mole	S^*, e.u.	Relative rate at 0°
Ethylene[a]	CH_3CO	H	H	H	6.31×10^{-4}	18	−6	1.00
Propylene	CH_3CO	H	CH_3	H	1.00×10^{-2}	16	−9	15.9
Ethylene[a]	C_2H_5	H	H	H	1.53×10^{-3}	20	1	1.00
Propylene	C_2H_5	H	CH_3	H	2.28×10^{-2}	18	0.5	14.4
Butene-2	C_2H_5	H	CH_3	CH_3	1.32×10^{-1}	18	4.5	86.3
Isobutylene	C_2H_5	CH_3	CH_3	H	2.46	15	−3	1560
Cyclohexene	C_2H_5	H	$-(CH_2)_4-$		1.67×10^{-1}	16	−5	106
Styrene	C_2H_5	H	C_6H_5	H	1.14×10^{-1}	17	0	72.1
m-Methyl-	C_2H_5	H	*m*-Me-C_6H_4	H	2.15×10^{-1}			140
p-Methyl-	C_2H_5	H	*p*-Me-C_6H_4	H	6.34×10^{-1}	15	−4	415
m-Chloro-	C_2H_5	H	*m*-Cl-C_6H_4	H	1.61×10^{-2}	18	−1	10.5
p-Chloro-	C_2H_5	H	*p*-Cl-C_6H_4	H	5.60×10^{-2}	18	3	36.6
m-Bromo-	C_2H_5	H	*m*-Br-C_6H_4	H	1.16×10^{-2}	19	4	7.58
p-Bromo-	C_2H_5	H	*p*-Br-C_6H_4	H	4.65×10^{-2}	18	2	30.4

[a] Calculated from the data in the previous paper.[4]

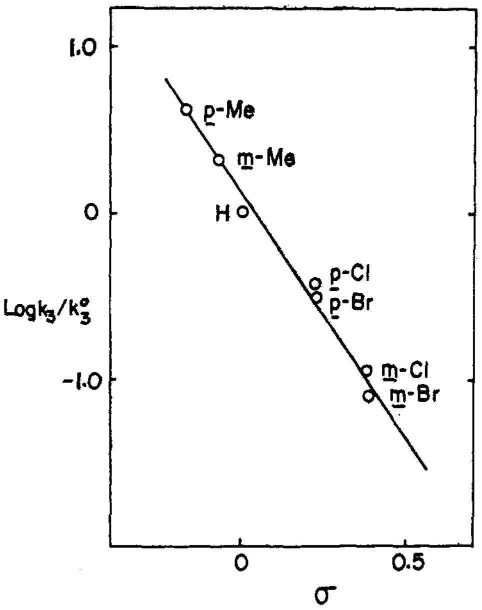


Figure 1.—Hammett plot of deoxymercuration with hydrochloric acid.

could not be further purified. However, it has been shown that these oily products are pure enough for the present purpose by the fact that the total mercury contents (determined by the stannous chloride[6] or zinc–aqueous sodium hydroxide method[4]) agreed with those that were obtained by the determination of mercuric chloride formed by deoxymercuration at infinity points.

The preparation of butene-2, isobutylene, cyclohexene, and styrene derivatives in acetic acid was not successful. Although the addition proceeded, the products gave considerable amounts of mercuric oxide upon treating with aqueous sodium hydroxide, even after removing the inorganic mercury salt by washing the chloroform solutions of the oxymercuration products with water. This indicates the presence of unknown impurities.

The rates were determined in 75% ethanol. For the compounds studied, it has been shown that the rates, to more than 80% reaction, can be expressed by eq. 2. The third-order rate constants decreased slightly when the concentrations of hydrochloric acid were increased from 0.04 to 0.15 *M*, because of the simplified rate equation, approaching constant values. All these results are in good agreement with those which were reported for the case of β-alkoxyethylmercuric chlorides derived from ethylene.

The results of the kinetic measurements are summarized in Table I. The values of k_3 given in the table are those obtained at the higher hydrochloric acid concentration of 0.15 *M*, except for the case of isobutylene (0.045 *M*) where the rates were too fast to measure at this acid concentration. In the case of styrene derivatives, the rates were determined with 0.0425 *M* acid for experimental convenience. The H^* and S^* values have been calculated from the data at three different temperatures between −10 and 25°.

From the data in Table I, it is clear that the alkyl or aryl substitution of the hydrogen of β-acetoxy- or β-ethoxyethylmercuric chloride results in an increase in rate. The effect of the aryl group is larger than that of alkyls. Dialkyl substitution on the same carbon (the case of isobutylene) results in a remarkable rate increase. In the case of styrene derivatives, the Hammett plots, using usual σ-values, give good linear relationship with a ρ-value of −2.93 (Figure 1). These results suggest that there exists a relationship between deoxymercuration and solvolysis of the corresponding halides, $R_1R_2C(Cl)$-CH_2R_3.

In the previous paper, it was concluded that the rate-determining step is the reaction of chloride ion with the mercurinium ion which is formed by the splitting of ROH from the protonated species, $CH_2(^+ORH)CH_2$-HgCl. As was pointed out by Kreevoy, this mechanism is not correct and is excluded by the facts that 2-alkoxyethylmercuric chlorides and 2-acetoxyethylmercuric chloride give rise to unique rates, and that no tendency of the rates to drift towards a common value

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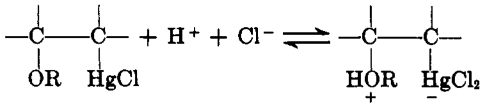
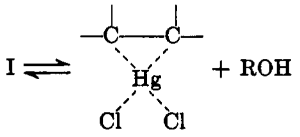
(6) J. N. Bartlett and W. M. McNabb, *Ind. Eng. Chem., Anal. Ed.*, **19**, 484 (1947).

as the reaction proceeds is observed. Therefore, the rate-determining step should be the second step in the mechanism described below.



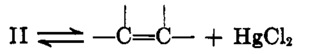
$$-\underset{\text{OR}}{\overset{|}{\underset{|}{C}}}-\underset{\text{HgCl}}{\overset{|}{\underset{|}{C}}}- + H^+ + Cl^- \rightleftharpoons -\underset{\underset{+}{\text{HOR}}}{\overset{|}{\underset{|}{C}}}-\underset{\underset{-}{\text{HgCl}_2}}{\overset{|}{\underset{|}{C}}}- \qquad (4)$$

I



(5)

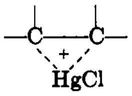
II



$$\text{II} \rightleftharpoons -\overset{|}{C}=\overset{|}{C}- + HgCl_2 \qquad (6)$$

Structural effects on rate would then be similar to those obtained in solvolysis reactions. The results shown in Table I are in good agreement with the mechanism.

Deoxymercuration can be considered as a cleavage reaction of an ether with a chloromercuri group on the β-carbon. Under the mild conditions where deoxymercuration proceeds rapidly, ether cleavage does not take place. The latter requires much more drastic conditions. This shows that the presence of $-HgCl_2^-$ on the β-carbon results in a special type of stabilization of the activated complex or intermediate leading to deoxymercuration. The π-complex II in eq. 5 is the most probable intermediate, in which the positive charge resulting from the splitting of ROH is neutralized by the $-HgCl_2^-$ group. This might be considered as a neutralized form of mercurinium ion B and even more stable. This could be the reason why the deoxymercuration in the presence of halide ions is much faster than that in the absence of the same ions.



B

The mechanism of oxymercuration with mercuric chloride can be explained as the reverse reaction of deoxymercuration mentioned above. Recently, Allen, *et al.*,[7] studied the kinetics of oxymercuration with mercuric chloride and supported the mechanism proposed by Chatt[1] which involves formation of mercurinium ion as the rate-determining step, on the basis of the fact that the oxymercuration rate is much slower in anhydrous solution than in aqueous solution. However, this can be explained by assuming that the reverse reaction of eq. 5 is slow, since it involves the formation of ion I. The retarding effect of the addition of sodium chloride, which was observed by Allen, *et al.*, can be attributed to a decrease in the concentration of free mercuric chloride due to formation of Na_2HgCl_4, etc.

Experimental

Materials.—Commercial cyclohexene and styrene were used after redistillation. Propylene, 2-butene, and isobutylene were prepared by the dehydration of isopropyl alcohol, *sec*-butyl alcohol, and *t*-butyl alcohol by the method described by Kistiakowsky.[8] Substituted styrenes were obtained from the corresponding α-phenylethyl alcohols by potassium acid sulfate method[9] under reduced pressure (*ca.* 100 mm.), and their physical properties are listed in Table II. These alcohols were prepared by sodium borohydride reduction of commercial acetophenones in ethanol. The yields were more than 90%.

TABLE II

PHYSICAL CONSTANTS OF STYRENES AND THE CORRESPONDING ALCOHOLS

Starting ketone, $XC_6H_4COCH_3$ X	Alcohol B.p., °C. (mm.)	Alcohol n_D (°C.)	Styrene B.p., °C. (mm.)	Styrene n_D (°C.)
p-Me	120 (19)	1.5192 (20)	66 (19)	1.5443 (19)
m-Me	95 (6)	1.5252 (25)	62 (15)	1.5403 (18.5)
p-Cl	125 (15)	1.5413 (20)	73 (12)	1.5425 (20)
m-Cl	117 (11)	1.5404 (24)	58 (6)	1.5600 (25)
p-Br	125 (11)	1.5673 (16)	90 (14)	1.5973 (15)
m-Br	128 (11)		75 (6)	1.5884 (24)

The mercurials were prepared by the usual oxymercuration method.[1] The following example for the case of propylene derivative shows a typical experimental procedure.

2-Acetoxypropylmercuric Chloride.—Propylene was introduced into the mixture of mercuric acetate (64 g.) and acetic acid (100 ml.) with good stirring, until no mercuric salt could be detected by the formation of yellow mercuric oxide with aqueous sodium hydroxide. From the resulting clear solution, about half of the acetic acid was removed under vacuum below 65°. The residue was dissolved in chloroform (200 ml.) and washed with water (80 ml.) three times to remove inorganic mercury compounds. To this solution was added, with stirring, 100 ml. of 10% aqueous

TABLE III

MERCURIALS USED FOR DEOXYMERCURATION

Olefin used	Mercuric chloride	M.p., °C.	Hg, % Calcd.	Hg, % Found	Purity of oxymercurial, %[a]
Propylene	2-Acetoxypropyl	54.5–55.5	59.5	58.5[b]	99.0
Propylene	2-Ethoxypropyl	22.1–23	62.0	6.15[b]	99.9
2-Butene	2-Ethoxy-1-methylpropyl	Oil	59.5	58.6[c]	98.5
Isobutylene	2-Ethoxy-2-methylpropyl	Oil	59.5	59.0[c]	98.7
Cyclohexene	2-Ethoxycyclohexyl	57.8–59.0	55.2	55.0[c]	99.1
Styrene	2-Ethoxy-2-phenylethyl	43.0–45.3	52.1	51.5[c]	98.8
m-Methyl-	2-Ethoxy-2-(*m*-methylphenyl)ethyl	Oil	50.1	49.3[c]	98.5
p-Methyl-	2-Ethoxy-2-(*p*-methylphenyl)ethyl	54.8–56.8	50.1	49.5[c]	99.0
m-Chloro-	2-Ethoxy-2-(*m*-chlorophenyl)ethyl	Oil	47.7	47.5[c]	99.8
p-Chloro-	2-Ethoxy-2-(*p*-chlorophenyl)ethyl	58.8–59.8	47.7	47.0[c]	98.8
m-Bromo-	2-Ethoxy-2-(*m*-bromophenyl)ethyl	Oil	43.1	42.8[c]	98.0
p-Bromo-	2-Ethoxy-2-(*p*-bromophenyl)ethyl	58.0–59.0	43.1	42.7[c]	98.5

[a] Calculated from the amounts of the mercuric chloride formed at infinity points. [b] Zinc dust–aqueous sodium hydroxide method.[4] [c] Stannous chloride method.[6]

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[7] E. R. Allen, J. Cartlidge, M. M. Taylor, and C. F. H. Tipper, *J. Chem. Soc.*, 1437 (1959).

[8] G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **57**, 376 (1935).

[9] C. G. Overberger and J. H. Saunders, *Org. Syn.*, **28**, 31 (1948).

sodium chloride over a period of about 1 hr. The chloroform was removed under reduced pressure leaving a residue of 2-acetoxypropylmercuric chloride which crystallized on standing overnight, m.p. 54.4–55.5°.

The other mercurials listed in Table III were prepared by a similar method.

Kinetic Measurement.—The same method as was described in the previous paper[4] was used without any change.

Organotin Esters of Amino Acids and Their Use In Peptide Syntheses

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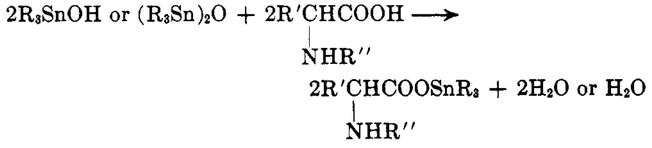
Trialkyltin esters of amino and N-acylamino acids were prepared and their chemical properties were investigated. The use of the trialkyltin group as a protective group in the syntheses of peptides is described.

While organotin esters of aliphatic and aromatic carboxylic acids have been synthesized[1-3] and biologically tested, especially as fungicides,[4] those of amino acids have received little attention. The preparation of the tributyl- and triphenyltin esters of N-acetylglycine was reported.[5] A more recent work claims the preparation of the trimethyltin ester of α-alanine and the triethyltin ester of β-alanine.[6]

In the present work the synthesis and chemical properties of organotin esters of both amino and N-acylamino acids were investigated. They were found also to be suitable for use as intermediates in the syntheses of peptides.

By heating equivalent amounts of the amino or N-acylamino acids with trialkyltin hydroxide or oxide in benzene or toluene, the respective organotin esters were obtained (Table I). The water formed in the reaction was removed by azeotropic distillation.



$$2R_3SnOH \text{ or } (R_3Sn)_2O + 2R'\underset{NHR''}{CHCOOH} \longrightarrow 2R'\underset{NHR''}{CHCOOSnR_3} + 2H_2O \text{ or } H_2O$$

$R = C_2H_5, C_4H_9$
$R'' = H, CH_3CO, C_6H_5CO, C_6H_5CH_2OCO$

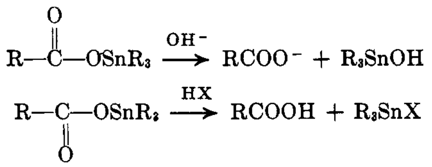
In the case of glycine, alanine, tyrosine, and tryptophan the addition of dimethylformamide was necessary for completing the reaction.

The investigated monoacidic amino acids required 1 equiv. of organotin oxide or hydroxide for complete reaction and dissolution, while aspartic acid and tyrosine required 2 equiv.

The tri-*n*-butyltin esters of α-alanine, α-aminobutyric acid, valine, and leucine were isolated by distillation under high vacuum. They had relatively high melting points and were soluble in organic solvents.

The organotin esters of the N-acylamino acids were soluble in alcohol, benzene, or toluene and insoluble in cold petroleum ether. They were stable to water and alcohol. The triethyltin esters had generally higher melting points than the corresponding tributyltin compounds.

Owing to the high electropositivity of the tin atom, the trialkyltin esters were attacked readily by strong electrophilic and nucleophilic reagents as follows.



$$R-\overset{O}{\overset{\|}{C}}-OSnR_3 \xrightarrow{OH^-} RCOO^- + R_3SnOH$$

$$R-\underset{O}{\underset{\|}{C}}-OSnR_3 \xrightarrow{HX} RCOOH + R_3SnX$$

These reactions are very fast, and we found that they can be used also for the rapid quantitative volumetric determination of organotin esters. Thus organotin esters can be titrated quantitatively with sodium methoxide in benzene–methanol or with perchloric acid in dioxane, and with aqueous sodium hydroxide or hydrochloric acid, using thymol blue as indicator.

Heating the N-acylaminotin esters with benzylamine or ammonia under anhydrous conditions in nonhydroxylic solvents such as toluene did not lead to cleavage of the ester group or to amidation, while in the presence of water or alcohol these esters were readily split to give the ammonium salt of the N-acylamino acids. This inability for amide formation is in contrast to the behavior of ordinary alkyl esters which give amides under such conditions. This behavior prevents the use of the organotin esters as acylating agents, indicating the weak electrophilic character of their carbonyl group. Further evidence for this is obtained from the infrared spectra of the organotin esters, which did not show the characteristic absorption of the carbonyl group of alkyl esters[7] at 1740–1750 cm.$^{-1}$. Strong absorptions were found in the region 1550–1600 cm.$^{-1}$ (COO$^-$, amide).[8] The spectra also showed absorptions at about 870 (Sn–O) and about 1050–1070 cm.$^{-1}$ (Sn–C).[9]

The organotin esters of the N-acylamino acids were stable to electrophilic reagents such as ethyl chloroformate and 2,4-dinitrofluorobenzene, even on heating in toluene solution. The inertness to the last reagent was especially interesting in view of the extreme insolubility of trialkyltin fluorides.[2]

Acetic acid was found to cleave the organotin esters immediately, giving the trialkyltin acetate besides the free N-acylamino acids.

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[1] J. G. A. Luijten and J. G. M. Van der Kerk, "Investigations in the Field of Organotin Chemistry," Tin Research Institute, Greenford, Middlesex, England, 1958, p. 92.

[2] R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

[3] R. A. Cummins and P. Dunn, *Australian J. Chem.*, **17**, 185 (1964).

[4] Ref. 1, p. 54; *Tin Its Uses*, **No. 63**, 13 (1964); **No. 64**, 5 (1964).

[5] N. V. Philips' Gloeilampenfabrieken, Dutch Patent 96,805 (Jan. 16, 1961); *Chem. Abstr.*, **55**, 27756 (1961).

[6] D. A. Kochkin and S. G. Verenikina, *Tr. Nauchn. Issled. Vitamin Inst.*, **8**, 39 (1961).

[7] M. S. C. Flett, "Characteristic Frequencies of Chemical Groups in the Infrared," Elsevier Publishing Co., London, 1963, p. 39.

[8] See ref. 7, pp. 35, 23.

[9] V. S. Griffiths and G. A. W. Dervish, *J. Mol. Spectry.*, **11**, 81 (1963).