[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

CONCERNING THE MECHANISM OF THE ESTER ACID CHLORIDE REARRANGEMENT[1]

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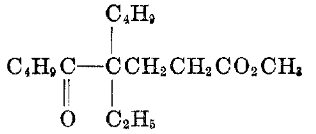
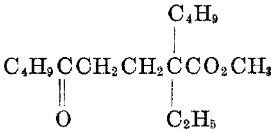
Since the ester acid chlorides of unsymmetrical dibasic acids are of utility in a variety of syntheses, their rearrangement has been the object of considerable interest. The known examples of this rearrangement have been recently reviewed (1). Evidence for the rearrangement has rested entirely on the isolation of two products from reaction of an ester acid chloride prepared from a half ester believed to be homogeneous. Illustrative of the rearrangement is the isolation and characterization (2) of isomers I and II from reaction of di-*n*-butylcadmium with either of the isomeric ester acid chlorides from α-*n*-butyl-α-ethylglutaric acid. Since this acid is severely hindered at one carboxyl and unhindered at the other, it was possible to establish with some certainty the homogeneity of the half esters used as starting materials. It follows that rearrangement occurred during either formation or reaction of the ester acid chlorides. Although data included in this earlier investigation (2) indicated that rearrangement occurred, at least in part, *after* formation of the acid chloride, in subsequent literature it has been assumed either that rearrangement occurs during formation of the acid chloride or that the ester acid chloride represents an equilibrium mixture of the two possible isomers.



$$C_4H_9\underset{\underset{O}{\|}}{C}-\overset{\overset{C_4H_9}{|}}{\underset{\underset{C_2H_5}{|}}{C}}CH_2CH_2CO_2CH_3$$

I



$$C_4H_9\underset{\underset{O}{\|}}{C}CH_2CH_2\overset{\overset{C_4H_9}{|}}{\underset{\underset{C_2H_5}{|}}{C}}CO_2CH_3$$

II

Some investigators have ascribed their success in avoiding rearrangement to formation of the acid chloride with highly purified thionyl chloride (3) or with oxalyl chloride (4). Chase and Hey (1) have ascribed the rearrangement to a "tautomeric equilibrium" proceeding through a lactone as intermediate, as indicated in formulas III–VI.

It was indicated that thermal energy at relatively low temperature would be sufficient to cause the bond ruptures necessary for establishment of this equilibrium. In the present investigation, this possibility has been eliminated by the observation that the ester acid chloride VII is nearly unaffected by distillation at temperatures above 100°, whereas keto esters I and II were formed in nearly equal amounts (2) by reaction of this ester acid chloride at temperatures below 40°.

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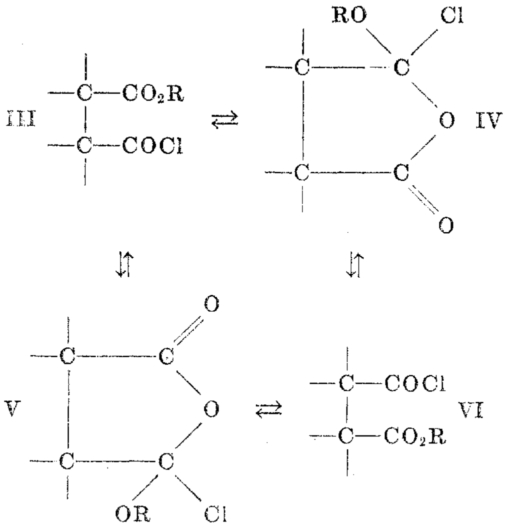
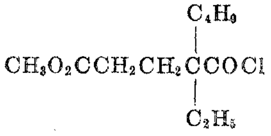
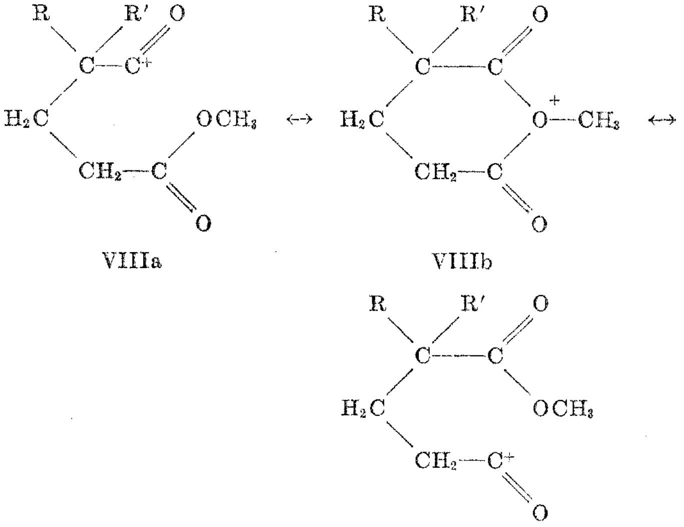




$CH_3O_2CCH_2CH_2\overset{C_4H_9}{\underset{C_2H_5}{C}}COCl$

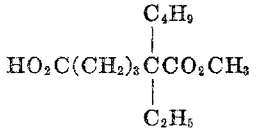
VII

Additional reactions of compound VII and similar compounds have shown that rearrangement occurs only in those reactions in which a Lewis acid extracts the halogen from the acid chloride to leave a positive ion, which may be regarded as the resonance hybrid, VIII. This view is consistent with the previously



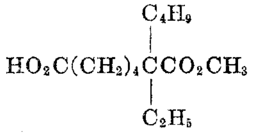
reported (2) evidence that a cadmium reagent makes its initial attack on the halogen of an acid chloride or the oxygen of an anhydride. It would also follow that the Friedel and Crafts reaction should give rearrangement, and, indeed, this reaction was the principal one used by Chase and Hey (1) to yield rearranged products. Reaction of the acid chloride with an alcohol or mercaptan would not be expected to give the ion VIII as an intermediate, and no rearrangement was encountered by von Seemann and Grant (4) in such a reaction. Displacement of the halogen by an enolate ion should not give rearrangement, and numerous illustrations (3, 5) of this reaction fulfill this expectation. Attack on the acid chloride by the highly polar diazomethane, which is the initial step in the Arndt-Eistert homologation, also should not lead to rearrangement. Although Chase and Hey (1) stated, "In none of the many examples [of this reaction] recorded has any evidence of rearrangement been reported", they ascribed this to the methods used for preparation of the acid chlorides.

We have applied the Arndt-Eistert homologation to the ester acid chloride isomeric with VII, and obtained the half ester IX, with no detectable rearrangement to the isomeric half ester. The acid chloride of IX does give rearrangement



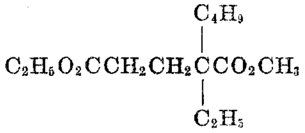
$HO_2C(CH_2)_3\underset{C_2H_5}{\overset{C_4H_9}{C}}CO_2CH_3$

IX



$HO_2C(CH_2)_4\underset{C_2H_5}{\overset{C_4H_9}{C}}CO_2CH_3$

X



$C_2H_5O_2CCH_2CH_2\underset{C_2H_5}{\overset{C_4H_9}{C}}CO_2CH_3$

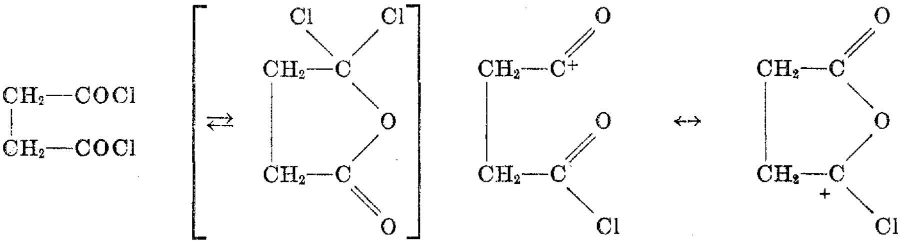
XI

when treated with ferric chloride, and this appears to be the first such rearrangement observed in the adipic acid series. It indicates that resonance stabilization of an ion such as VIII is sufficient to stabilize the ion in the conformation of a seven-membered ring. When the chain was extended an additional carbon to give half ester X, whose ion could resonate only as an eight-membered ring, no rearrangement of the acid chloride occurred in the presence of ferric chloride.

If the ester acid chloride VII is treated with a Lewis acid in diethyl ether, our interpretation of the rearrangement indicates that the diester obtained from this procedure should be that represented by formula XI, in which ethoxyl is attached to the carbonyl occupied by methoxyl in the ester acid chloride. This follows from the fact that steric hindrance adjacent to one carbonyl is so severe that attack by ether should be much more rapid on the carbonyl carrying the charge in formula VIIIc. This experiment actually gave 77–86% yield of diester XI containing no more than a few per cent of the isomeric diester, and this constitutes an excellent method for esterification of the hindered carboxyl. It has been previously reported (2) that heating the diacid under reflux with 15 mole-equivalents of methanol in presence of sulfuric acid for 140 hours yielded only 59% of diester.

An explanation has been sought for the authentic report (3) that rearrangement occurred on forming an acid chloride from a half ester with impure thionyl chloride. In this instance, rearrangement was assayed by hydrolyzing the acid chloride to a mixture of half esters, and we have found this to be a reliable method of analysis. We have not been able to obtain rearrangement by use of technical thionyl chloride, nor by addition of ten mole-per cent of sulfuryl chloride to the thionyl chloride. It seems most probable that the thionyl chloride giving rearrangement contained a metallic salt, for a preparation to which was added four mole-per cent of ferric chloride gave extensive rearrangement.

A cyclic oxonium ion[2] was first suggested by Prelog and Heimbach-Juhasz (6) to explain the rearrangement of alkoxyacid chlorides to chloro esters. In this instance, the rearrangement occurred at 100° without a catalyst when the oxonium ion contained a five- or six-membered ring; so the alkoxyl group appears able to displace the halogen without help from a Lewis acid when the oxonium ion is one of the less-strained rings. It appears unlikely, however, in view of the thermal stability of ester acid chlorides, that diacid chlorides such as succinyl dichloride, could exist as an equilibrium mixture (formulas XIIa and XIIb) of the sort commonly described (1) to explain the two types of products obtained from these compounds. It seems more probable that succinyl dichloride is properly represented by formula XIIa and that cyclic products result from those reactions in which an intermediate ion such as XIII is formed. An intermediate radical might function similarly.



XIIa XIIb XIIIa XIIIb

EXPERIMENTAL[3]

Materials. α-n-Butyl-α-ethyl-γ-carbomethoxybutyric acid (half ester corresponding to acid chloride VII) was prepared as previously reported (2) and converted to VII at temperatures below 40° (ref. 2, p. 234). *Thionyl chloride* was the technical grade supplied by Hooker Electrochemical Co.; except where use of technical material is specified, it was purified by distillation from quinoline and raw linseed oil (ref. 7, p. 357). *Anhydrous ferric chloride* and *sulfuryl chloride* were practical grades supplied by Distillation Products Industries. *Zinc chloride* was a technical grade dried by fusion. *Triethylamine* (for Arndt-Eistert reactions) was purified according to Sauer (8).

Experiments on rearrangement of ester acid chloride VII. The ester acid chloride was hydrolyzed to half ester(s) either immediately after preparation or after such treatments as recorded in Table I. For this purpose, the ester acid chloride was stirred at room temperature for 20–24 hours with 200 ml. of water containing 2 moles of sodium carbonate per mole of ester acid chloride. At the end of this period, the trace of insoluble oil (non-volatile; presumably dimeric anhydride) was extracted with 20 ml. of benzene. The benzene extract was extracted with 20 ml. of water which was added to the main aqueous phase. Half esters were recovered by acidification with sulfuric acid and extraction with four 30-ml. portions of ether. The extracts were washed with water until the wash gave a negative test for sulfate ion with barium chloride. Distillation of the half esters gave the data summarized in columns 2 and 3 of Table I.

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[2] The oxonium ion proposed by Prelog and Heimbach-Juhasz was analogous to that represented by formula VIIIb, not as incorrectly quoted by Chase and Hey (1).

[3] All boiling points are uncorrected. All distillations were through a 60-cm. column of the simple Podbielniak type which has been described in detail (7). Microanalyses were by the Microanalytical Division of the Department of Chemistry, Univ. of Calif.

TABLE I

Experimental Data on Rearrangement of Ester Acid Chloride VII

Half ester used, g.	Fractionation of recovered half esters: Forerun[a] Half esters Residue[b]		Fractionation[c] after esterification: Diester Intermediate[a] Half ester		Rearrangement[d], %	Treatment of ester acid chloride
	Wt., g.	B.p., °C. (mm.)	Wt., g.	B.p., °C. (mm.)		
11.50	0.39	132-146 (1.5)	0.23	119-120.5 (3)	0	Below 40°
	8.62	146-148 (1.5)	1.16	120.5-164 (3)		
	nil		6.74	164-166 (3)		
11.52	0.21	126-136 (0.5)	0.47	119.5-121(3)	1.9	Below 40°
	9.49	136-138 (0.5)	0.74	121-159 (2.5)		
	nil		7.84	159-160 (2.5)		
11.74	1.29	142-162 (3)	0.34	118.5-119 (3.5)	0.9	Stored 6 months in stoppered bottle
	8.61	162-163 (3)	0.85	119-163 (3.5)		
	0.3		7.06	163-163.5 (3.5)		
13.59	2.68	141-159(3)	0.53	116-119 (2.5)	3.4	Heated under reflux 2 hrs. with $SOCl_2$
	7.91	159-162 (3)	0.82	119-160 (2.5)		
	nil		5.94	160-161 (2.5)		
15.99	0.26	136-164 (3)	0.78	123-124 (3.5)	3.8	Distilled in Claisen flask, b.p. 128-130° (4 mm.)
	11.12	167-167.5 (3.5)	1.00	124-167.5 (3.5)		
	1.23		8.75	167.5-168 (3.5)		
14.80	0.79	146-160 (2.5)	0.85	118-119 (3)	4.8	Fractionated in column, b.p. 96-100° (0.5 mm.)
	10.50	160-161.5 (2.5)	0.78	119-163 (3)		
	0.3		8.53	163-164 (3)		
12.93	2.74	149-167 (4)	0.25	119.5-120.5 (3.5)	0.1	Prepared with technical $SOCl_2$[e]
	8.17	167-168 (4)	1.31	120.5-164.5 (3.5)		
	0.1		6.03	164.5-165 (3.5)		
12.04	1.31	149-166.5 (3.5)	0.40	123.5-125 (3.5)	1.5	0.016 mole of SO_2Cl_2 added to preparation
	8.55	166.5-168 (3.5)	1.08	125-167.5 (4)		
	0.2		6.59	167.5-169 (4)		
12.94	2.55	153-164 (4)	2.82	117.5-119.5 (3)	38.8	0.0056 mole of $FeCl_3$ added to preparation
	6.39	164-166 (4)	0.64	119.5-162.5 (3)		
	0.5		2.81	162.5-163 (3)		

[a] A principal constituent of the forerun (col. 2) and the intermediate (col. 4) is α-*n*-butyl-α-ethylglutaric anhydride, usually formed in very small amount during the distillation of half ester. If mineral acid is not carefully removed before distillation, much larger amounts of anhydride are formed. [b] The distillation residue, recorded in col. 2, probably represents diacid formed by complete hydrolysis of ester acid chloride. If such occurs, it will not lower the apparent yield of rearranged product, for in the isomer formed by rearrangement the ester group is hindered. [c] The residue from this fractionation was, in all cases, 0.1 g. or less. [d] $\%$ rearrangement $= \frac{\text{(moles of diester, corrected)(100)}}{\text{moles of half esters esterified}}$. "Correction" of the diester consists of subtracting 0.03 g. of diester per g. of half ester esterified (*Cf.* experimental). [e] When a sample of this thionyl chloride was added to water and the solution made slightly basic, no metallic impurities were precipitated by addition of hydrogen sulfide.

The half esters were heated under reflux for one hour with 2.2 g. (2.8 ml., 15 equivs.) of methanol and 0.35 g. (0.176 ml.) of concentrated sulfuric acid per gram of half esters. The cooled solution was poured into 8.5 ml. of water per gram of half esters, and the products were recovered by the same extraction procedure described above. Data are assembled in columns 4 and 5 of Table I.

In order to determine the amount of unrearranged half ester (corresponding to ester acid chloride VII) esterified by this procedure, 17.7 g. of pure half ester was esterified and worked up as described above. Distillation yielded, after 0.08 g. of fore-run, 0.53 g. of diester, b.p. 128–130° (6 mm.). Thus, the esterification procedure yields 0.03 g. of diester for each gram of unrearranged half ester esterified. This value was subtracted before calculating percentage rearrangement as recorded in column 6 of Table I. It is estimated that this procedure for determining rearrangement is subject to an error of two percentage units or less.

Methyl α-n-butyl-α-ethyl-γ-carbethoxybutyrate (XI). Acid chloride VII was prepared from 54.4 g. of half ester in a yield of 54.5 g. (93%), b.p. 115.5–116.5° (2.5 mm.). This acid chloride, dissolved in 110 ml. of anhydrous ether, was added to a solution of 30 g. of freshly fused zinc chloride in 220 ml. of anhydrous ether. A dense liquid phase separated rapidly from solution. After the mixture had stood at room temperature for 15 hours and been heated under reflux for 4 hours, it was washed with two 100-ml. portions of 1 *N* sulfuric acid followed by four 100-ml. washes with water. Distillation of the product yielded 48.75 g. (86%) of ester XI, b.p. 128.3–128.7° (3.5 mm.). Of this yield, 35.4 g. was collected at 128.3°, n_D^{25} 1.4412. In two smaller runs, yields were 77% and 80.5%.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.15.
Found: C, 65.01; H, 10.21.

In order to determine the structure of ester XI, the unhindered ester grouping was hydrolyzed selectively, for each of the three runs. For this purpose, the diester was heated at 35° ± 1° with 1.3 molar equivalents of 0.7 *M* potassium hydroxide in 95% ethanol. Hydrolysis was followed by titration of 1-ml. aliquots of the solution. After consumption of one equivalent of alkali (about 2 hours), the mixture was added to five times its volume of water, and the half ester was isolated as described above for the isomeric half ester. Distillation gave γ-carbomethoxy-γ-ethylcaprylic acid, b.p. 160–162° (3 mm.). For the three runs, yields were 87.5%, 87.9%, and 96%; values for n_D^{25} were 1.4516, 1.4510, and 1.4511. The previously reported (2) value for n_D^{28} was 1.4502, thus n_D^{25} 1.4514. For further confirmation of absence of significant quantities of ethoxyl in this ester, two samples were titrated and gave equivalent weights of 234, 233 (calc'd for methyl ester, 230.3; for ethyl ester, 244.3).

5-Carbomethoxy-5-ethylnonanoic acid (IX). A solution of 23.9 g. (0.09 mole) of γ-carbomethoxy-γ-ethylcaprylyl chloride [b.p. 117–120° (3 mm.), prepared in 96% yield from the half ester] in 50 ml. of dry ether was added at 0° to a stirred solution of 3 mole-equivs. (titrated) of diazomethane (9, 10) in 800 ml. of dry ether. After the resultant solution had stood for 15 hours, ether and excess diazomethane were removed at reduced pressure. The residual diazoketone, which was an oil, was dissolved in 300 ml. of *tert*-butyl alcohol (dried by distillation from sodium), and a trace of white solid was removed by filtration. The solution of diazoketone was arranged for stirring under reflux, and to it was added, during 2 hours, a solution of 2 g. of dried silver benzoate (11) in 20 ml. of purified (8) triethylamine. Nitrogen evolution began after initial gentle warming and continued with mild evolution of heat, but no cooling was required. By the end of the addition, nitrogen evolution had ceased and 91% of the theoretical amount of gas had been collected. The mixture was next heated under reflux for one hour, then allowed to stand for 15 hours. After the warmed solution had been treated with 25 ml. of water and filtered with Super Cel, solvent and triethylamine were removed at reduced pressure. For removal of the last traces of *tert*-butyl alcohol, 100 ml. of benzene was added and distilled at reduced pressure. The residue was treated with 500 ml. of water and extracted with four 50-ml. portions of benzene. The extract was washed with 10% hydrochloric acid, 10% sodium carbonate solution, and water, and then the crude *tert*-butyl methyl ester was distilled from a Claisen flask for the separation of considerable tar. In one run, there was obtained by fractional distillation a pure sample of *tert-butyl 5-carbomethoxy-5-ethylnonanoate*, b.p. 110° (1 mm.), n_D^{25} 1.4403.

Anal. Calc'd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74.

Found: C, 67.49; H, 10.52.

For preparation of the half ester IX, the crude diester was cracked by heating under reflux for 2 hours with 0.5 g. of technical anhydrous toluenesulfonic acid in 100 ml. of dry benzene. The benzene solution was washed with five 50-ml. portions of water for removal of toluenesulfonic acid, then the product was obtained by distillation, wt. 10.28 g. (44% over-all), b.p. 166–168° (3 mm.), n_D^{25} 1.4519. In two other runs, yields were 44.5%, 45%.

Anal. Calc'd for $C_{13}H_{24}O_4$: Eq. wt., 244.3. Found: Eq. wt., 248.

The tribromoanilide of this half ester could not be obtained in a crystalline condition.

Homogeneity of half ester IX. In order to test for rearrangement during the Arndt-Eistert reaction, 10.28 g. of the half ester was esterified with 15 mole-equivs. of methanol by the procedure described previously. Distillation at 3 mm. yielded (a) 8.83 g. of *dimethyl α-n-butyl-α-ethyladipate*, b.p. 128.5–130°; (b) 0.45 g., b.p. 130–155°; and (c) 0.1 g. of residue. Absence of half ester after esterification indicates no rearrangement in the Arndt-Eistert reaction. For analysis, there was used a center cut of Fraction (a), n_D^{25} 1.4430.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.15

Found: C, 65.29; H, 10.04.

Rearrangement of 5-carbomethoxy-5-ethylnonanoyl chloride. A 7.74-g. sample of half ester IX was converted to the acid chloride in presence of ferric chloride as in the last experiment summarized in Table I. There was obtained 4.45 g. of half esters, b.p. 167–169° (3 mm.). After esterification, distillation at 3.5 mm. yielded (a) 3.25 g. of diester, b.p. 128–129°, (b) 0.11 g. of intermediate, b.p. 129–170°, (c) 1.43 g. of half ester, b.p. 170–171°, n_D^{25} 1.4521, eq. wt. 261, (d) residue, nil. Since, in this instance, rearrangement leads to the half ester with hindered carboxyl, rearrangement amounted to 32%. In order to verify the hindered nature of the carboxyl in the recovered half ester, it was again esterified with 15 mole-equivs. of methanol, and distilled at 3.5 mm. to yield (a) 0.06 g., b.p. 129–170°, (b) 1.13 g., b.p. 170–170.5°. A second run, carried out similarly, gave 29% rearrangement.

6-Carbomethoxy-6-ethyldecanoic acid (X) was prepared by chain extension of IX by the Arndt-Eistert reaction, according to the same procedure described for preparation of IX. The ester acid chloride from IX was obtained in 91% yield, b.p. 127–128° (3 mm.); nitrogen evolution during the Wolff rearrangement was 93% of theory; and the half ester X was obtained in 47.6% over-all yield, b.p. 171–172° (3 mm.). For analysis, there was used a center cut, b.p. 172° (3 mm.), n_D^{25} 1.4530.

Anal. Calc'd for $C_{14}H_{26}O_4$: Eq. wt., 258.3. Found: Eq. wt., 258.

Attempted rearrangement of the acid chloride of X was carried out by making the acid chloride from 9.5 g. of X in the presence of ferric chloride. Following the previously-described procedures, there was obtained 6.61 g. of recovered half esters, b.p. 172–172.5° (3 mm.). After esterification there was obtained (a) 6.59 g. of *dimethyl α-n-butyl-α-ethylpimelate*, b.p. 136–136.5° (3 mm.), n_D^{25} 1.4442; (b) 0.06 g., b.p. 136.5–150° (3 mm.); (c) residue, nil. A homogenized sample of Frac. (a) was analyzed.

Anal. Calc'd for $C_{15}H_{28}O_4$: C, 66.13; H, 10.36.

Found: C, 65.57; H, 10.47.

Absence of half ester containing a hindered carboxyl indicates no rearrangement in this instance.

SUMMARY

Evidence is presented that the ester acid chloride rearrangement of α-n-butyl-α-ethyl-γ-carbomethoxybutyryl chloride (VII) proceeds by way of an intermediate cyclic oxonium ion regarded as a resonance hybrid. The rearrangement also occurs when the ring of the resonating ion contains seven atoms, but does not occur in a case where a ring containing eight atoms would be necessary.

Rearrangement does not occur during formation of the ester acid chloride from the half ester, and the ester acid chloride is relatively stable to storage or heating above 100°. Rearrangement occurs only in those reactions where a Lewis acid removes the halogen to leave the resonating ion.

It is suggested that these data indicate that diacid chlorides such as succinyl dichloride have the normal open-chain structure, and cyclic products are obtained from those reactions proceeding by way of intermediates which may exist as cyclic resonance hybrids.

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REFERENCES

(1) CHASE AND HEY, *J. Chem. Soc.*, 553 (1952).
(2) CASON, *J. Org. Chem.*, **13**, 227 (1948).
(3) STÄLLBERG-STENHAGEN, *J. Am. Chem. Soc.*, **69**, 2568 (1947).
(4) VON SEEMANN AND GRANT, *J. Am. Chem. Soc.*, **72**, 4073 (1950).
(5) STÄLLBERG-STENHAGEN, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 12 (1948), and numerous subsequent papers.
(6) PRELOG AND HEIMBACH-JUHÁSZ, *Ber.*, **74**, 1702 (1941).
(7) CASON AND RAPOPORT, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 238.
(8) SAUER, *J. Am. Chem. Soc.*, **69**, 2444 (1947).
(9) ARNDT, *Org. Syntheses*, Coll. Vol. II, 461 (1943).
(10) BACHMANN, *Org. Reactions*, **1**, 50 (1942).
(11) NEWMAN AND BEAL, *J. Am. Chem. Soc.*, **72**, 5163 (1950).