[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Rearrangement of *trans*-9-Decalyl Perbenzoate and Per-*p*-nitrobenzoate in Methanol and Aqueous Methanol

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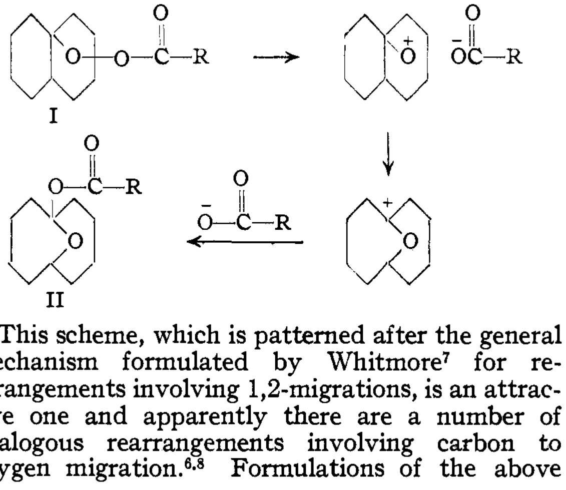
The rearrangement of *trans*-9-decalyl perbenzoate and *trans*-9-decalyl per-*p*-nitrobenzoate has been investigated in methanol and aqueous methanol. When the perbenzoate is rearranged in the presence of a high concentration of lithium *p*-nitrobenzoate the resulting benzoate ester is not contaminated with the *p*-nitrobenzoate ester. Similarly, the rearrangement of the per-*p*-nitrobenzoate into the isomeric ester is not disturbed by a high concentration of benzoate ion. The rearrangement of each of the peresters is accompanied by concurrent solvolysis which results in the formation of the acid from which the perester is derived. Thus the perbenzoate yields rearranged ester together with benzoic acid and other solvolysis products. The per-*p*-nitrobenzoate similarly yields *p*-nitrobenzoic acid as well as the rearranged ester. The ratio of solvolysis to rearrangement has been shown to be temperature dependent and the kinetics of the acid formation is consistent with a mechanism involving a rate-determining formation of an intermediate which undergoes simultaneous conversion into rearranged ester and solvolytic products. The solvolysis which accompanies the rearrangement and the exchange experiments are interpreted in terms of an ion pair intermediate.

The rearrangement of 9-decalyl peresters (I) into isomeric esters (II) was discovered[2] and investigated[3,4] by Criegee. This rearrangement is of interest from a preparative[2,5] as well as a mechanistic[3,6] point of view as it provides an excellent method for preparing cyclodecane derivatives. We have recently used this method for preparing cyclodecane derivatives and wish to report in this paper certain observations and experiments pertaining to the mechanism of the rearrangement of decalyl peresters.

It seems clear that the rearrangement of decalyl peresters involves an ionic mechanism as it has been shown that the rate of rearrangement of the solid perbenzoate, IIIa, increases with the ionizing power of the solvent.[3] Moreover, the rate of rearrangement of the peresters increases with the strength of the acid from which the perester is derived.[3] In view of these findings, together with the observation that the rearrangement appeared analogous to the Wagner–Meerwein and related rearrangements, Criegee suggested[3,4] the mechanism



This scheme, which is patterned after the general mechanism formulated by Whitmore[7] for rearrangements involving 1,2-migrations, is an attractive one and apparently there are a number of analogous rearrangements involving carbon to oxygen migration.[6,8] Formulations of the above type have proved extremely important primarily due to the conspicuous success with which products can be predicted and rationalized for a number of related rearrangements[9]; however, these formulations do not give a detailed description of the mechanism. In the case of the Wagner–Meerwein and related rearrangements several possible variations and interpretations of the general Whitmore formulation have been recognized and discussed[9–12] and much information contributing to our understanding of these rearrangements has resulted from recent investigations.[11–13] It would appear that the various possible mechanisms which need to be considered in connection with the Wagner–Meerwein rearrangement must also be considered in the present case.

In our work we were particularly interested in investigating to what extent, if any, dissociation into free ions might be occurring. Apparently the above formulation was not intended to imply dissociation of this type as Criegee suggested that free ions were not involved.[3] In order to obtain information on this point we have studied the rearrangement in the presence of foreign anions to see if the isomeric rearrangement would be diverted by interchange of anions.

Decalyl perbenzoate (IIIa) was rearranged in methanol and aqueous methanol in the presence of lithium *p*-nitrobenzoate and decalyl per-*p*-nitrobenzoate (IIIb) was rearranged in similar solvents in the presence of benzoate ions. These particular combinations were selected because it had previously been shown that these peresters undergo rearrangement at markedly different rates.[3]

The exchange experiments were carried out by adding the carefully purified perester to the refluxing solvent containing the foreign anion in the form of the lithium salt. After refluxing for a period in excess of 10 half-lives for the rearrange-

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[1] Minnesota Mining and Mfg. Fellow, 1952–1953.

[2] R. Criegee, *Ber.*, **77B**, 722 (1944).

[3] R. Criegee and R. Kaspar, *Ann.*, **560**, 127 (1948).

[4] R. Criegee, *Fortschr. chem. Forsch.*, **1**, 508 (1950).

[5] A. C. Cope and G. Holzman, THIS JOURNAL, **72**, 3062 (1950).

[6] P. D. Bartlett, *Record of Chem. Progr.*, **11**, 47 (1950).

[7] F. C. Whitmore, THIS JOURNAL, **54**, 3274 (1932).

[8] P. D. Bartlett and J. D. Cotman, *ibid.*, **72**, 3095 (1950); S. L. Friess and N. Farnham, *ibid.*, **72**, 5518 (1950); W. von E. Doering and L. Speers, *ibid.*, **72**, 5515 (1950).

[9] G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., p. 475.

[10] F. Brown, E. D. Hughes, C. K. Ingold and J. F. Smith, *Nature*, **168**, 65 (1951).

[11] (a) S. Winstein, *et al.*, THIS JOURNAL, **74**, 1113 (1952); (b) **74**, 1133 (1952).

[12] S. Winstein and R. Heck, *ibid.*, **74**, 5584 (1952), and preceding papers in this series.

[13] D. J. Cram, *et al.*, *ibid.*, **74**, 339 (1953), and preceding papers in this series. See also D. Y. Curtin, *et al.*, *ibid.*, **74**, 5905 (1952), and preceding papers.

ment the solution was cooled and the neutral fraction containing the rearranged ester was isolated in such a way as to avoid fractionation and analyzed spectrophotometrically. The rearranged benzoate (IVa) and the rearranged *p*-nitrobenzoate (IVb) absorb at the same frequencies in the ultraviolet; however, the intensities are sufficiently different so that mixtures can be analyzed by a method[14] which involves setting up simultaneous equations in two unknowns. The experimental measurements required for this method are the optical densities of the unknown and of synthetic solutions of known concentration at two wave lengths. In order to test the analytical method synthetic mixtures of IVa and IVb were prepared and analyzed. These results, which are tabulated in the Experimental section, show that 1% of one component in the other could be detected with certainty.

Tables I and II show typical results of rearrangements carried out in the presence of foreign anions. The first table shows that the rearranged ester, IVb, which was obtained from the rearrangement of decalyl per-*p*-nitrobenzoate in the presence of lithium benzoate, did not contain detectable amounts of IVa which would result from exchange of anions. Similarly, the data recorded in Table II show that the rearrangement of decalyl perbenzoate is not disturbed by the presence of *p*-nitrobenzoate ion as the rearranged ester was not contaminated by IVb.

TABLE I

REARRANGEMENT OF DECALYL PER-*p*-NITROBENZOATE IN THE PRESENCE OF LITHIUM BENZOATE AT REFLUX TEMPERATURE

Expt.	Perester, 10^2 *M*	Solvent	Li benzoate, 10^2 *M*	Analysis of rearranged ester, % IVa in IVb	Analysis of recovered acid, % *p*-nitrobenzoic in benzoic acid
1	2.5	Methanol	2.7	0	19
2	2.5	75% MeOH	2.7	0	25
3	2.4	85% MeOH	155.0	0	..

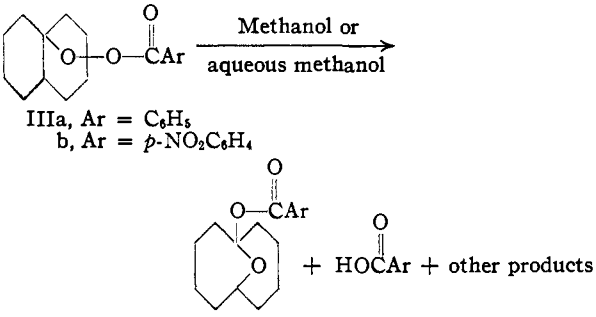
TABLE II

REARRANGEMENT OF DECALYL PERBENZOATE IN THE PRESENCE OF LITHIUM *p*-NITROBENZOATE AT REFLUX TEMPERATURE

Expt.	Perester, 10^2 *M*	Solvent	Li *p*-nitrobenzoate, 10^2 *M*	Analysis of rearranged ester, % IVb and IVa	Analysis of recovered acid, % benzoic in *p*-nitrobenzoic acid
4	2.5	Methanol	2.4	<1	25
5	2.5	75% MeOH	2.4	<1	22
6	2.1	Methanol	58.3	<1	..
7	2.8	90% MeOH	150.0	<1	..

It seems clear that formation of the crossed rearranged ester by exchange would depend on and probably be first order in the foreign anion concentration and therefore the results of experiments three and seven are especially significant. The concentrations of lithium salts used in these experiments are nearly as high as possible due to the solubility limits of the salt, and the absence of detectable exchange products indicates that the rearrangement does not involve free ions and is intramolecular.

Tables I and II also include the analyses of the acids recovered from the exchange experiments. These samples were obtained by acidifying the reaction mixture after removal of the neutral fraction. The composition of the acids obtained in this way corresponds to the composition of the lithium salt remaining after the rearrangement. The acid samples were analyzed spectrophotometrically by the method used for analyzing the rearranged esters, and by comparison of melting points to a phase diagram. At first it was thought that these analyses as well as the analyses of the rearranged ester should provide a sensitive measure of anion exchange provided that the lithium salt concentration was not too high. This was, however, found not to be the case as the isolated acid contained appreciable amounts of the acid from which the perester was derived even though the analysis of the rearranged ester clearly showed that exchange had not occurred. This was found to be due to the simultaneous formation of rearranged ester and acid when the perester is rearranged in methanol or aqueous methanol:



IIIa, Ar = C_6H_5
b, Ar = p-$NO_2C_6H_4$

IVa, Ar = C_6H_5
b, Ar = p-$NO_2C_6H_4$

Thus the rearrangement of IIIa produces some benzoic acid together with the rearranged ester IVa and the rearrangement of IIIb similarly results in the simultaneous formation of IVb and *p*-nitrobenzoic acid. The products indicated by the above equation for the rearrangement of IIIa have been isolated in amounts which account for 95% of the perester. The data for a typical material balance study are shown in Table III. These data are in accord with the kinetic experiments described later and with the reported[5] yield of 70% for the conversion of IIIa to IVa in refluxing methanol.

TABLE III

PRODUCTS ISOLATED FROM THE REARRANGEMENT OF 0.212 MOLE OF DECALYL PERBENZOATE IN REFLUXING METHANOL

Product	Amount isolated	Yield, %
IVa	0.160 mole	76
Benzoic acid	0.040 mole	19
"Other products"[15]	8.0 grams	

It is clear that the acid which accompanies the rearranged esters is formed during and not subsequent to the rearrangement as neither IVa nor IVb produces measurable amounts of acid under

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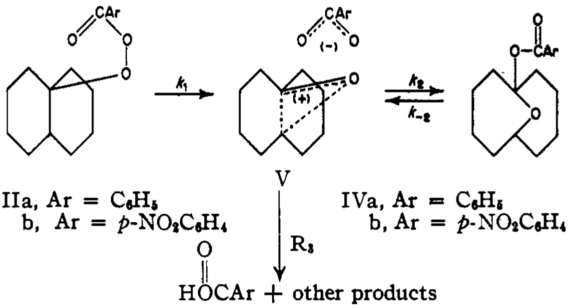
[14] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 29.

the conditions of the rearrangement. Due to these side products of the rearrangement, the analyses of the acids recorded in Tables I and II are not a measure of exchange but instead indicate the extent of the accompanying solvolysis of the perester which results in the formation of the acid. The ratio of solvolysis to rearrangement can, however, be more accurately determined by titrating the acid which is produced during the rearrangement. The solvolysis product designated "other products" in the above equation has been isolated in substantial amounts from large preparative experiments; however, they have not been identified. It is clear from the boiling point behavior that a mixture of products is formed.[15]

The intramolecular nature of the rearrangement together with the simultaneous solvolytic reaction suggests that the rearrangement of decalyl peresters in methanol falls into the class designated "internal rearrangements" by Winstein and co-workers.[12] Indeed, there appears to be very close parallelism between the present case and certain allylic,[16] homoallylic[12] and Wagner–Meerwein[12,17] rearrangements which similarly are internal and accompanied by solvolysis. In view of the extensive work which has been carried out on these similar rearrangements it appears that our present results can best be formulated as shown in Chart I which involves a common intermediate for the rearrangement and solvolysis.

CHART I



IIIa, Ar = C_6H_5
b, Ar = $p\text{-}NO_2C_6H_4$

IVa, Ar = C_6H_5
b, Ar = $p\text{-}NO_2C_6H_4$

$HO\overset{O}{\overset{\|}{C}}Ar$ + other products

As far as the rearrangement is concerned the present formulation is similar to the one proposed by Criegee with the exception that it is now clear that the intermediate does not involve free ions and can probably best be described as an ion pair.

There is very little information available concerning the nature of the intermediate cation or cations. As in the case of many rearrangements of this general type, it is not clear whether migration accompanies or succeeds the ionic fission of the O–O bond. Bartlett[6] has previously discussed the meager evidence bearing on this point and concluded that migration might be simultaneous with ionization. The above formulation for the cation in V, which suggests participation by the C_9–C_{10} bonding electrons in the ionization, has been used for brevity and because of recent evidence[12] indicating "non-classical" cations of this type in rearrangements which we believe to be very similar to the present one.

In the present rearrangement the probability of an intermediate or transitory bicyclo[4.4.1] bridgehead carbonium ion is of interest in connection with the observation[18,19] that bicyclo[2.2.1] and -[2.2.2] bridgehead carbonium ions appear to be relatively unstable tertiary cations. Apparently a bicyclo[4.4.1] system is large enough to tolerate a trigonal hybridized[20] positive carbon atom at the bridgehead without appreciable strain.

Decalyl perbenzoate (IIIa) rearranges and solvolyzes in methanol at a rate which can be conveniently followed by periodic titrations of aliquots with standard methanolic sodium methoxide. From this rate of appearance of the solvolysis product (benzoic acid) it can be shown that the perester is reacting by a first order process as required by the above scheme and k_1 can be evaluated as follows.

If k_2 is negligibly small, a condition which indeed applies as demonstrated by separate measurement, then the rate of acid formation (A) is related to the perester concentration (PE) and specific rate constants as shown by equation 1.

$$dA/dt = \frac{k_1k_3}{k_2 + k_3}PE \qquad (1)$$

The perester concentration at any time is expressed by equation 2, where PE_0 is the initial perester concentration and the last term represents the amount of material which has been converted to acid and rearranged ester.

$$PE = PE_0 - A(1 + k_2/k_3) \qquad (2)$$

From equations 1 and 2 the relationship shown by equation 3 is obtained.

$$dA/dt = \frac{k_1k_3}{k_2 + k_3}PE_0 - k_1A \qquad (3)$$

From the latter, equation 5 can be obtained by knowledge of the fact that the constant PE_0 can be expressed in terms of the final acid concentration A_∞ (measured by the "infinity" titer) as shown in equation 4.

$$PE_0 = A_\infty(1 + k_2/k_3) \qquad (4)$$

$$dA/dt = k_1(A_\infty - A) \qquad (5)$$

Integration of 5 gives equation 6 which conveniently enables the evaluation of k_1 as the slope of a plot of $\ln A_\infty/(A_\infty - A)$ against time.

$$\ln A_\infty/(A_\infty - A) = k_1t \qquad (6)$$

The necessary data required for this treatment are the benzoic acid concentrations A during a run and the final acid concentration A_∞. It should be noted that the kinetic method involves measuring the rate of formation of a product resulting from one of two simultaneous processes. Inasmuch as the ratio of rearrangement to solvolysis (k_2/k_3 in the above scheme) would be expected to vary with

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[15] Although we have not been able to separate pure components from the mixture by fractionation, it appears from unsaturation tests and infrared spectra that a major component is 11-oxabicyclo[4.4.1]-hendecene-1. Presumably the ester VI, for which there is also kinetic evidence, and methyl 1-(11-oxabicyclo[4.4.1]hendecyl) ether are also present.

[16] W. G. Young, S. Winstein and H. L. Goering, THIS JOURNAL, 73, 1958 (1951).

[17] D. J. Cram, *ibid.*, 74, 2129, 2137 (1952).

[18] P. D. Bartlett and E. S. Lewis, *ibid.*, 72, 1005 (1950), and prior papers in this series.

[19] W. von E. Doering, *et al.*, *ibid.*, 75, 1008 (1953).

[20] See J. W. Linnett and A. J. Poe, *Trans. Faraday Soc.*, 47, 1033 (1951), for theoretical considerations concerning the electronic configuration of positive carbon.

temperature and indeed does, the infinity titer A_∞ must be obtained by permitting the reaction to reach completion at constant temperature.

The specific first order rate constant k_1 has been determined at several temperatures for decalyl perbenzoate by fitting the kinetic data to equation 6 by application of the method of least squares. Typical plots, which illustrate how well the data fit this equation, are shown in Fig. 1. The reactions were followed from 50–94% completion and in all cases a satisfactory least square fit was obtained over the entire range.

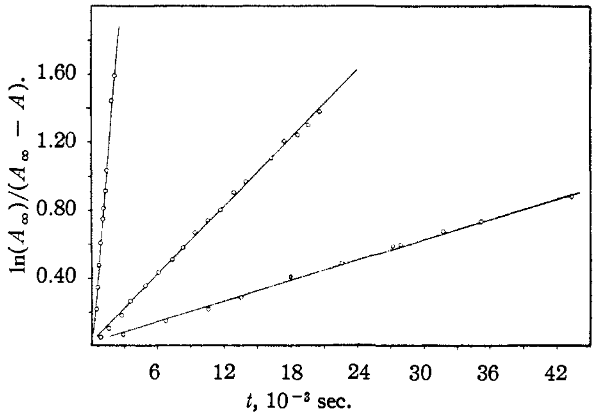

Fig. 1.—Rate of acid formation during the rearrangement of decalyl perbenzoate in methanol at 50° (upper line, expt. 14), 30° (middle line, expt. 13) and 20° (lower line, expt. 10).

The results of the kinetic experiments on the rearrangement of decalyl perbenzoate are summarized in Table IV. The probable error of the slope (p),[21a] and the probable error involved in evaluating the dependent variable (r)[21b] are included as an indication of how consistently and how well the data are fit by equation 6. The temperature dependence of the specific rate constants in this table is such as to give a straight line when log k_1 is plotted against the reciprocal of the absolute temperature. The least square fit (experiments 8 through 15) corresponds to the following activation parameters[22]: $\Delta H^{\ddagger} = 23.1 \pm 0.5$ kcal./mole, $\Delta S^{\ddagger} = -0.9 \pm 1.7$ e.u.

It is significant that the interpolated rate constant of 4.1×10^{-5} sec.$^{-1}$ at 24.6° is in excellent agreement with the value of 4.9×10^{-5} sec.$^{-1}$ observed by Bartlett and Kice.[23] These workers measured the rate of disappearance of decalyl perbenzoate in methanol by a method which involves direct analysis for perester.

The rearrangement of decalyl per-p-nitrobenzoate (IIIb) in methanol and aqueous methanol is also accompanied by solvolysis. Due to the limited solubility of IIIb at temperatures where the rate is slow enough to measure we have been unable to use the above method for studying the kinetics of rearrangement and solvolysis for this compound. At 20°, for example, a 0.03 molar solution represents the maximum concentration, and as only a fraction of perester is converted to acid this concentration is too low for reproducible measurements. The specific rate constant k_1 for IIIb in methanol at 20° has been estimated as $2.7 \pm 1 \times 10^{-4}$ sec.$^{-1}$ which is about ten times greater than the constant for IIIa.

The ratio of rearrangement to solvolysis (k_2/k_3) can readily be determined from the infinity titer A_∞ and initial perester concentration by the relationship expressed by equation 7. Table V shows

$$(PE_0 - A_\infty)/A_\infty = k_2/k_3 \qquad (7)$$

how this ratio varies with temperature and solvent changes. In these experiments the rearrangements were carried out at constant temperature by adding the perester to the thermostated solvent. The values in the table were found to be reproducible to within about 5%. The k_2/k_3 values show a consistent downward trend with increase in temperature and comparisons of experiments 15 with 19 and 11 with 16 indicate a similar response to increase in ionizing power of the solvent. It is of interest to note in this connection that 2-phenyl-1-propyl p-bromobenzenesulfonate, which undergoes simultaneous rearrangement and solvolysis shows similar behavior, the ratio of internal rearrangement to acetolysis decreasing with increase in temperature and ionic strength.[24]

TABLE IV

THE REARRANGEMENT AND SOLVOLYSIS OF DECALYL PERBENZOATE IN ABSOLUTE METHANOL

Expt.	Temp., °C.	PE_0, 10^2 M	10^5k_1, sec.$^{-1}$	p^a	r,^{b} % of range	n^c	Distance followed, %
8	0.00	4.25	0.10	0.003	2	9	83
9	0.00	3.90	0.11	.003	2	7	84
10	20.11	14.80	2.4	.02	1	12	85
11	20.11	9.68	2.5	.05	2	14	47
12	30.12	3.82	7.8	.2	2	5	60
13	30.12	7.86	8.3	.1	1	18	75
14	50.03	11.62	98	.7	1	13	94
15	50.03	11.32	90	1.5	2	13	78
16^d	20.11	1.34	16	0.2	0.5	4	61
17^d	20.11	1.17	19	0.2	0.7	4	77

^{a} Probable error in k_1. ^{b} Probable error in the dependent variable, $\ln A_\infty/(A_\infty - A)$, expressed as percentage of the total range of the variable. ^{c} Number of observations during a run. ^{d} Solvent 75% methanol.

TABLE V

RATIO OF REARRANGEMENT TO SOLVOLYSIS OF DECALYL PERBENZOATE

Run	Temp., °C.	PE_0, 10^2M	Solvent	k_2/k_3
8	0	4.25	Methanol	6.0
11	20	9.68	Methanol	5.4
13	30	7.86	Methanol	4.8
15	50	11.32	Methanol	4.3
18	Reflux	1.00	Methanol	3.6
19	50	1.30	67% methanol	3.0
20	Reflux	0.80	56% methanol	2.9
21	Reflux	1.10	67% methanol	2.3
16	20	1.34	75% methanol	5.0

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(21) (a) H. Margenau and G. M. Murphy, "Mathematics of Physics and Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1943, p. 502; (b) T. B. Crumpler and J. H. Yoe, "Chemical Computation and Errors," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 228.

(22) K. J. Laidler, "Chemical Kinetics," McGraw–Hill Book Co., Inc., New York, N. Y., 1950, p. 76.

(23) P. D. Bartlett and J. L. Kice, THIS JOURNAL, **75**, 5591 (1953).

(24) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2171 (1952).

During the kinetic experiments it was observed that the infinity titer did not reach a constant value after ten half-periods, but instead showed a slow but measurable increase. This clearly indicates that a slow acid producing reaction is superimposed on the reaction being measured. The superimposed reaction is comparatively slow as indicated by the fact that the infinity titer shows only about 5% increase during 40 half-periods and consequently does not interfere with the kinetic measurements over the range that the reactions were followed. Due to this disturbance it was, however, necessary to adopt a standard procedure of measuring the infinity titer before a significant amount of acid was produced by this secondary process and therefore the infinity titer was determined at or near ten half-periods. Although the superimposed reaction was too slow to accurately determine the total amount of acid that would be produced by this process it appears that at 50° the amount is about 20% as much as that produced by the primary process.

In order to investigate the possibility that the increase in infinity titer might be due to the methanolysis of the rearranged ester, IVa, the rate of this reaction was measured. At 100°, rate constants showing a serious upward trend as summarized in Table VI were obtained from equation 8, the expression for a first order reaction.

$$k' = \frac{1}{t} \ln \frac{a}{a - x} \qquad (8)$$

TABLE VI

METHANOLYSIS OF 0.122 *M* REARRANGED ESTER, IVa, AT 100°

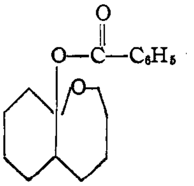
Time, 10^{-5} sec.	Concn. of rearranged ester, 10^2 *M*	k' 10^7 sec.$^{-1}$
3.3	9.0	8.8
4.9	7.1	10.8
6.8	5.2	12.7
8.6	3.9	13.1
10.4	2.4	16.2
11.9	2.0	15.2

The apparent specific rate constant k' measured in this way is related to the rate constants in Chart I as illustrated by equation 9.

$$k' = k_{-2}k_3/(k_2 + k_3) \qquad (9)$$

Presumably the autocatalytic nature of the methanolysis of IVa is due to catalysis by benzoic acid.

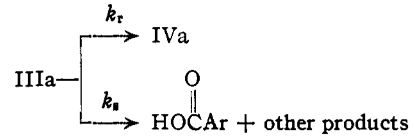
From the above studies or more obviously from the fact that the methanolysis is immeasurably slow below 50° it is clear that the increasing infinity titer is only partly due to the methanolysis of IVa. It appears that some other ester, possibly VI, which would result from migration of C_1 instead of C_{10} is formed in small amounts and solvolyzes slowly. From the k_2/k_3 ratio at 50° it can be estimated that a 5% yield of VI could provide sufficient acid to be responsible for the observed 20% increase in the infinity titer.



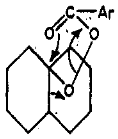
VI

It should be pointed out that other mechanisms besides the one shown in Chart I can accommodate the known facts. For example, it is possible that the simultaneous reactions, solvolysis and rearrangement, are completely independent as illustrated in Chart II and do not involve a common intermediate.

CHART II



The quantity which we have measured and expressed as k_1 in Chart I would be $(k_r + k_s)$ for this scheme. A conceivable independent intramolecular rearrangement is the S_Ni' type[11a] cyclic process illustrated by VII. Although there is no direct evidence ruling out a process of the type formulated by Chart II and formula VII the same arguments which have previously[25] been used against an S_Ni' type mechanism under similar circumstances, can be presented for the present case. Thus the extreme sensitivity of the rate of rearrangement with change in ionizing power of solvent would indicate a greater polarity in the transition state than would be expected for a reaction proceeding by a cyclic mechanism. From the data of Criegee[8] the following sequence for the relative rates of rearrangement of IIIa can be estimated: AcOH, 10^5; MeOH, 2×10^4; MeCN, 200; benzene, 1. It is also of importance that changing solvent has approximately the same effect on the rate of rearrangement and the rate of solvolysis. Thus addition of water to the methanol, which increases the total rate by a factor of seven does not show a large effect on the ratio of rearrangement to solvolysis and this suggests the rate-determining formation of a common intermediate which is subsequently partitioned.



VII

Another pertinent argument in favor of the mechanism represented by Chart I concerns the solvolysis. It is clear that the methanolysis of III or IV to produce acid involves O–O or alkyl oxygen, rather than acyl–oxygen cleavage. Or in other words, methanolysis likely involves an intermediate of type V and it would thus seem that this same intermediate would be involved in the rearrangement.

Experimental[26]

Materials.—*trans*-9-Decalyl hydroperoxide, m.p. 95–96° (lit.[27] m.p. 95–96°), was prepared according to the method of Criegee[27] from Eastman "practical grade" decalin. The

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(25) S. Winstein and K. C. Schreiber, THIS JOURNAL, **74**, 2165 (1952).

(26) All melting points are corrected.

(27) R. Criegee, *Ber.*, **77B**, 22 (1944).

yields varied from 2–4%. Several attempts to prepare the hydroperoxide by the method of Cope and Holzman[5] were unsuccessful.

trans-9-Decalyl perbenzoate (IIIa) was prepared from decalyl hydroperoxide in 71% yield according to a modification of the method of Criegee.[27] In a typical run 34 g. (0.20 mole) of *trans*-9-decalyl hydroperoxide (m.p. 86–92°) was dissolved in 80 ml. of dry pyridine and the solution chilled to 0°. Maintaining this temperature, 30 ml. (0.25 mole) of benzoyl chloride was added dropwise with stirring. The addition required 45 minutes after which the reaction mixture was kept at 0° for an additional 2 hours and then warmed to room temperature. The product was separated from the reaction mixture in the following manner. The pyridine solution was mixed with ether and the ether solution extracted successively with cold water, dilute hydrochloric acid, water and dilute sodium bicarbonate solution. After drying over magnesium sulfate the ether was removed and the solid residue recrystallized from petroleum ether. Thirty-nine grams (0.142 mole) of perbenzoate, m.p. 62.8–65.4°, was obtained. One recrystallization from petroleum ether gave material, m.p. 66.4–67.8° (lit.[27] m.p. 67–68°). This material, which sometimes rearranged on standing for long periods of time, was stored in a refrigerator and the m.p. checked before use.[28]

trans-9-Decalyl per-*p*-nitrobenzoate (IIIb) was prepared by the method described above for the perbenzoate. It is very difficult to obtain this perester in a pure state due to the ease with which it undergoes rearrangement. The crude solid ester was purified as follows: Eighty grams of perester was pulverized and rapidly washed with 500 ml. of cold methanol, dried and dissolved in 500 ml. of cold benzene. This solution was shaken with cold 5% sodium carbonate solution followed by washings with small portions of cold water until the extracts were neutral to litmus. After drying over magnesium sulfate and filtering, 500 ml. of petroleum ether, b.p. 65–70°, was added and 29 g. of pure IIIb separated as the solution was chilled in an ice-bath. A reproducible capillary melting point could not be obtained in the usual way due to the decomposition (presumably rearrangement into IVb) of the sample on heating. The material gave a clear melt when placed in a bath at 100° or over. This perester was always prepared just before use as it deteriorated on storage.[28]

The rearranged esters, IVa and IVb, were prepared by refluxing the corresponding peresters in methanol.[3] The rearranged benzoate IVa, m.p. 97.3–97.8° (lit.[2] 97–98°), was obtained in 69% yield and the rearranged *p*-nitrobenzoate, IVb, m.p. 128–129° (lit.[3] 127–128°), was obtained in 69% yield from decalyl hydroperoxide.

Lithium benzoate and *p*-nitrobenzoate were prepared by neutralizing the corresponding acids with lithium methoxide which was prepared by dissolving lithium wire in methanol. The salts were isolated by concentration of the methanol solution and purified by dissolving in methanol and concentrating until the solid separated. Aqueous solutions of the salts were neutral to litmus.

Spectrophotometric Analyses.—The solvent used in all of the spectra determinations was 95% ethanol. The rearranged benzoate, IVa, shows a peak in the ultraviolet spectrum at 230 mμ and the rearranged *p*-nitrobenzoate, IVb, shows a peak at 260 mμ. Both compounds absorb to some extent at each of these frequencies; however, the optical densities are sufficiently different so that mixtures of the two compounds can be analyzed by evaluating the bracketed parameters in equations 10 and 11.[14] In these equations A' is the optical density for a synthetic solution of a single component of concentration C'. The A'/C' values for IVa and IVb are measured at 230 mμ for eq. 10 and at 260 mμ for eq. 11.

$$[A'/C']_{\text{IVa}}C_{\text{IVa}} + [A'/C']_{\text{IVb}}C_{\text{IVb}} = A_{230\text{m}\mu} \qquad (10)$$

$$[A'/C']_{\text{IVa}}C_{\text{IVa}} + [A'/C']_{\text{IVb}}C_{\text{IVb}} = A_{260\text{m}\mu} \qquad (11)$$

When these values are known a mixture of IVa and IVb in solution can be analyzed as follows. The optical density (A) of the unknown is determined at 230 and 260 mμ and the concentration of IVa (C_{IVa}) and IVb (C_{IVb}) can be determined by solving the simultaneous equations.

The same method was used for analyzing mixtures of benzoic acid and *p*-nitrobenzoic acid. In this case the optical densities of synthetic solutions (for A'/C' values) and unknowns were measured at 227.5 mμ (peak for benzoic acid) and 260 mμ (peak for *p*-nitrobenzoic acid). The A'/C' values varied slightly for different batches of solvent and for different spectrophotometers (Beckman, model DU, and Cary recording, spectrophotometers were used) and thus were periodically redetermined. In order to test the method synthetic mixtures of benzoic and *p*-nitrobenzoic acids and of IVa and IVb were analyzed.

TYPICAL "CONTROL" ANALYSES

Mixture	Composition, %	Analysis, %
Benzoic + *p*-nitrobenzoic acids	3.5 (benzoic)	3.3
Benzoic + *p*-nitrobenzoic acids	4.3 (*p*-nitrobenzoic)	3.3
IVa and IVb	3.3 (IVa)	3.7
IVa and IVb	4.4 (IVb)	4.0

Mixtures of benzoic and *p*-nitrobenzoic acids obtained from the exchange experiments were also analyzed by comparison of melting points to a melting point diagram which was prepared from the following data.

p-Nitrobenzoic acid in benzoic acid, %	M.p., °C.	*p*-Nitrobenzoic acid in benzoic acid, %	M.p., °C.
3.2	121	31.0	176
6.2	137	45.0	193
10.0	154	75.0	225
14.0	171	89.0	237
23.0	177		

The indicated melting point corresponds to the temperature at which the last trace of solid disappeared. Analysis by this method gave values within 5–8% of the spectrophotometric analysis. The cryoscopic method was not as reproducible as the spectrophotometric method.

Rearrangement of Decalyl Peresters in the Presence of Foreign Anions.—The general procedure used is illustrated by the following description of experiment 7. To a refluxing solution of 26.0 g. (0.150 mole) of lithium *p*-nitrobenzoate in 100 ml. of 90% methanol was added 0.77 g. (2.8 millimoles) of decalyl perbenzoate (IIIa). After four hours of refluxing, the solution was cooled and transferred into a separatory funnel with 80 ml. of 2% sodium bicarbonate. The solution was extracted with three 80-ml. portions of ether and the combined ether extracts were washed with 5% sodium bicarbonate and water and dried over magnesium sulfate. After removal of the last traces of solvent under reduced pressure 0.58 g. (75% yield assuming IVa) of rearranged ester was obtained which was analyzed spectrophotometrically. A solution of about 3 mg. of the above residue in 100 ml. of 95% ethanol had optical densities of 1.56 and 0.10 at 230.0 and 260.0 mμ, respectively. From the A'/C' values tabulated below, which were determined from synthetic solutions of known concentrations, the relative concentration of IVa and IVb in the rearranged esters can be determined by use of equations 10 and 11.

	230 mμ	260 mμ
$[A'/C']_{\text{IVa}}$	10.95	0.63
$[A'/C']_{\text{IVb}}$	3.28	11.0

Using these parameters the value of 0.147 millimole/kg. is obtained for the concentration of IIIa and the concentration of IIIb is 0.001 or negligible as compared to IIIa.

Rate Measurements.—The rate of benzoic acid formation during the rearrangement of decalyl perbenzoate was followed by periodic analysis of aliquots. Analyses for benzoic acid were performed by titrating an aliquot of the methanolic reaction mixture with a 0.02–0.05 N standard solution of sodium methoxide in absolute methanol. These solutions, which were frequently restandardized against resublimed benzoic acid, were found to be stable over a period of several months.

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(28) The infrared spectra of IIIa, IIIb, IVa and IVb indicate that the peresters prepared by this method are not contaminated with the corresponding rearranged esters.

Brom thymol blue was found to be a suitable indicator for the titrations in methanol. From the high autoprotolysis constant[29] of methanol it is clear that precise acid–base titrations should in principle be possible in this solvent. This indeed was found to be the case in the standardizations; however, in the kinetic experiments high precision was not obtained due to the dilute solutions (the infinite concentrations were about 0.02 *M*) and a rapidly fading end-piont.

The concentration of decalyl perbenzoate was determined from the weight of material (previously dried to constant weight and checked by melting point) made up to volume with absolute methanol. In runs conducted at 0, 20 and 30° the weighed sample of perester was placed in a volumetric flask and made up to volume with thermostated solvent. After rapid mixing an aliquot was withdrawn, and time was counted from the time of delivery of this first aliquot into a chilled flask. The standard procedure of analyzing aliquots as rapidly as possible after delivery was adopted and an attempt was made to treat all samples uniformly. Samples were titrated to the first blue color of a rapidly fading end-point. Except for the runs at 50° the reactions were carried out in the volumetric flask in which the solution was made up. In the runs at 50° solutions were prepared at room temperature, distributed in ampules containing a little over 5 ml. and placed in the thermostat. After a brief period for equilibration (about four minutes with constant agitation) an ampule was placed in ice-water and time was counted from this point. The aliquot was subsequently taken from the ampule and analyzed. In the runs at 0° the titrations were carried out at this same temperature and time was recorded at the end-point. In all cases aliquots were measured at the same temperature at which the solutions were made up or concentrations were corrected for thermal expansion of the solvent.

Figure 1 shows the number of points taken during a typical run and in a number of cases as many as 15 additional points were taken after 10 half-periods to study the increase in the infinity titer. The value of the infinity titer (A_∞) was determined directly from a point taken near 10 half-periods. If a point was not taken near 10 half-periods the value of (A_∞) was read from a smooth curve of a plot of *A* against time. From the rate of upward drift of the infinity titer it is clear that the amount of acid formed from the superimposed reaction is less than 1% of that formed by the primary process at 10 half-periods.

In a typical kinetic experiment (expt. 10) 4.069 g. (0.0148 mole) of perbenzoate was rapidly dissolved in methanol in a 100-ml. volumetric flask. The solution was made up to 100 ml. and thermostated at 20.11°. Five-ml. aliquots were delivered into a chilled flask at the time intervals indicated in Fig. 1 and analyzed. After obtaining a tentative value for A_∞, the specific rate constant k_1 was obtained from a plot of the type illustrated by Fig. 1. If the tentative A_∞ value corresponded to a time considerably different from 10 half-periods the A_∞ value was adjusted to correspond to 10 half-periods and the data recalculated.

Determination of the Ratio of Rearrangement to Solvolysis (k_2/k_3) for Decalyl Perbenzoate.—Each kinetic experiment provided the necessary data for calculating k_2/k_3 ratios by use of equation 7. The A_∞ values were taken at 10 half-periods. Additional experiments designed to determine this ratio are illustrated by the following example. *trans*-Decalyl perbenzoate (0.3669 g., 0.0132 mole) was added to 100 ml. of refluxing methanol. After 0.5 hour of reflux (estimated as 10 half-periods by extrapolation) the solution was cooled and analyzed for acid by titration. The total of 0.2956 millimole of acid produced corresponds to a k_2/k_3 ratio of 3.5.

Product Balance in the Rearrangement of Decalyl Perbenzoate in Methanol.—Refluxing 58.1 g. (0.212 mole) of pure decalyl perbenzoate (IIIa) in 600 ml. of methanol gave, after adding 200 ml. of water and cooling, 43.7 g. (0.160 mole) of rearranged benzoate (IVa). The mother liquors obtained after the crystalline ester had been collected were concentrated under reduced pressure to 400 ml. and then diluted with 200 ml. of cold water. This solution was extracted with ether several times and the combined ether extracts extracted with 200 ml. of 10% sodium hydroxide followed by water. After drying over magnesium sulfate and removing the ether 8.0 g. of a neutral oily material was obtained.

The basic extract above was acidified with concentrated hydrochloric acid and extracted with ether. Drying and removing the ether gave 4.8 g. (0.040 mole) of benzoic acid. Thus 95% of the starting material has been accounted for, 75.5% as rearranged ester and 18.9% as acid and solvolysis product based on the acid recovered.

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[29] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., p. 256.

[CONTRIBUTION FROM THE DIVISION OF LABORATORIES, MICHIGAN DEPARTMENT OF HEALTH]

The Preparation and Properties of Human Serum Albumin Separated from Placental Extracts

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A procedure is described for the separation and purification of albumin from human placental extracts. Frozen placentas are thawed, chopped and extracted with isotonic saline. After the initial separation of a fraction containing γ-globulin, hemoglobin is separated from the albumin fraction by the addition of zinc and bicarbonate ions. Hematin, resulting from the breakdown of hemoglobin, is removed by filtration at *p*H 4.7 in the presence of sodium caprylate. The residual zinc concentration is reduced by an ion exchange resin and the placental albumin is concentrated and purified by the use of ethanol–water systems in the cold. The albumin is 95–97% pure by electrophoretic analysis and is low in salts and heme pigments.

Introduction

Placentas are a convenient, inexpensive and relatively unrecognized source for many human blood and tissue products, either as therapeutic biologicals or for investigative purposes. There is a mounting demand for immune serum globulin for prophylaxis against measles and poliomyelitis, and for albumin as a plasma substitute; placental sources for these products are large (3.6 million U. S. births annually) and merit consideration.

Placental plasma is approximately the equivalent of normal human plasma[1] in composition and placental extracts are essentially diluted placental plasma containing hemoglobin and tissue globulins. Placental extracts have been shown to contain diphtheria and scarlet fever antitoxins as well as poliomyelitis antibodies, and globulin from placental plasma can modify or prevent measles in the human.[2] Placental enzymes and hormones have

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[1] R. M. Curtis and R. W. Worthington, Jr., *Am. J. Obstet. Gynecol.*, **42**, 428 (1941).

[2] Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **111**, 1764 (1938).