[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY, AND THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Roles of the Potential Anions in the Rearrangements of *trans*-9-Decalyl Hydroperoxide Benzoate and *p*-Methoxy-*p'*-nitrobenzyl Peroxide[1]

BY DONALD B. DENNEY AND DOROTHY G. DENNEY

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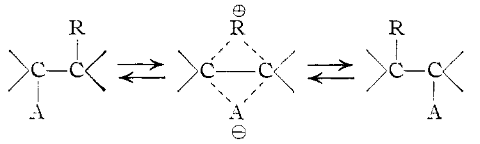
The benzoate of *trans*-9-decalyl hydroperoxide (VI) which was labeled with oxygen-18 in the carbonyl group, was allowed to rearrange in methanol and acetic acid to give labeled 1-benzoyl-1,6-epoxycyclodecane (Xa and b). Xa and b were reduced with lithium aluminum hydride to afford benzyl alcohol and 1,6-dihydroxycyclodecane. The oxygen-18 content of the products showed that during the rearrangement the two oxygens of the benzoate group do not become equivalent and that the carbonyl group remains as such in Xa and b. When *p*-methoxy-*p'*-nitrobenzoyl peroxide (XVI), which was labeled with oxygen-18 in the *p*-nitrobenzoyl carbonyl, was allowed to rearrange in thionyl chloride, labeled *p*-methoxyphenyl-*p*-nitrobenzoyl carbonate (XVII) was isolated. The carbonate XVII was allowed to react with ammonia to give *p*-nitrobenzamide (XVIII). The oxygen-18 content of XVIII shows that during the rearrangement 66% of the excess oxygen-18 is retained as carbonyl oxygen. The implications of these experiments are discussed.

Introduction

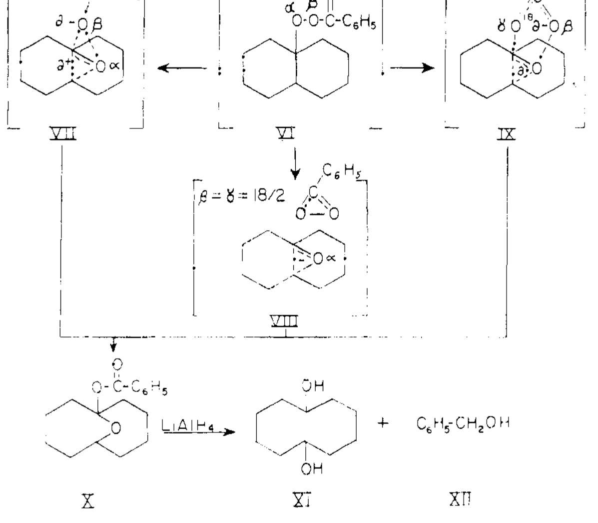
It has come to be recognized that many ionic organic reactions do not necessarily proceed with the formation of completely solvated and separated ions, but rather there may be a minimum separation of the two ions to give ion pairs which then further react to give products. Although this behavior is probably quite general, only a few types of organic reactions have been investigated to the degree required to be able to define the details of ion pair formation. One type of reaction has received considerable attention. These reactions are 1,2-shifts, in which as the C–A bond of I undergoes heterolysis R moves over to stabilize the forming positive charge. These movements give rise to the ion pair II, which may undergo further ionization or may collapse to the rearranged product III. A considerable number of systems which behave in this manner have been studied by Winstein and his co-workers.[2] They have shown that substances like I can give rise to two kinetically distinguishable ion pairs, "internal" or "intimate" ion pairs in which no solvent is interposed between the cation and A^- and "external" or solvent separated ion pairs in which a small number of solvent molecules are between the cation and A^-. One of the problems which is of interest in reactions of this type concerns the role of A; *i.e.*, the distance which A becomes separated from the cation, whether A will exchange with other anions and how the nature of A affects the rate of the reaction. We have attempted to throw some light on the nature of A in two rearrangements which are similar to those shown. In the cases reported here the rearrangement is not taking place along a carbon–carbon bond but rather along a carbon–oxygen bond.



I II III

Rearrangement of *trans*-9-Decalyl Hydroperoxide Benzoate.—Criegee and Kaspar[3] have studied the rearrangement of *trans*-9-decalyl hydroperoxide benzoate (VI) to 1-benzoyl-1,6-epoxycyclodecane (X) and have shown that it has the properties of an ionic reaction. More recent studies by Bartlett and Kice[4] and Goering and Olson[5] have more clearly defined the mechanism of this transformation. They have shown that during this rearrangement there is no exchange between the migrating benzoate ion and benzoate ions in the solution. It has also been demonstrated that *para* substituents on the benzoate group affect the rate of rearrangement in a manner entirely commensurate with its being an ionic reaction.[4] It is possible to envision several reasonable paths for the conversion of VI to X. The kinetic[4,5] evidence indicates that there is most probably an intermediate of very low stability formed from VI, and this intermediate then decomposes to X and other products. We have written the three structures VII, VIII and IX for this intermediate. For convenience the cation has been represented as involving partial bonding to the oxygen and carbon; in actual fact it may more closely resemble the rearranged structure.[4]

Oxygen-18 labeled VI was prepared by allowing benzoyl chloride-$CO^{18}Cl$ to react with *trans*-9-



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[1] A portion of this work has been reported as a communication, D. B. Denney, THIS JOURNAL, **77**, 1706 (1955).

[2] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, *ibid.*, **78**, 328 (1956).

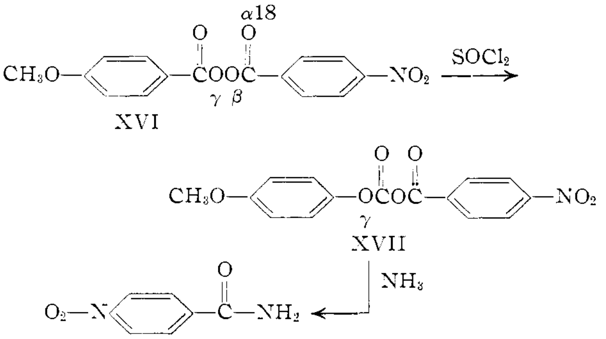
[3] R. Criegee and R. Kaspar, *Ann.*, **560**, 127 (1948).

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

[5] H. L. Goering and A. C. Olson, *ibid.*, **75**, 5853 (1953).

decalin hydroperoxide. This material was allowed to rearrange in methanol and acetic acid to form Xa and b. If intermediate VII is the correct one then the excess oxygen-18 in X should still be incorporated in the carbonyl group. In VIII the two oxygens of the anion become equivalent, and therefore in X half of the excess oxygen-18 will be in the carbonyl group and the remainder will be in the ether oxygen of the carboxylate group. Formation of X *via* IX will provide a product in which all of the excess oxygen-18 is in the ether oxygen of the carboxylate group. The position of the label in Xa and b was determined by reducing them with lithium aluminum hydride to the glycols XIa and b and benzyl alcohols XIIa and b. Inspection of the oxygen-18 analytical values for these compounds (Table I) indicates that XIa and b contain less than 2% of the excess oxygen-18, it all being in the benzyl alcohols XIIa and b. These findings clearly eliminate VIII and IX as possible intermediates in the rearrangement of VI to X. They also point strongly to a path in which the carbonyl oxygen is retained as such during the transformation. These results can be represented by VII. Further discussion of this reaction will be reserved until later in this paper.

Rearrangement of *p*-Nitro-*p*′-methoxybenzoyl Peroxide.—Leffler[6] has shown that *p*-nitro-*p*′-methoxybenzoyl peroxide (XVI) will rearrange to *p*-nitrobenzoyl-*p*-methoxyphenyl carbonate (XVII) when heated in thionyl chloride. He also has shown that this rearrangement is an ionic reaction. In an earlier paper,[7] it was shown that the *p*-methoxyphenyl group migrates exclusively to the γ-oxygen in XVI. We have prepared XVI in which the α-oxygen is labeled with oxygen-18. This material was allowed to rearrange to give labeled XVII which was then treated with ammonia to afford XVIII. Table II contains the oxygen-18 analytical values for these compounds. Inspection of the data reveals that this rearrangement does not have the specificity exhibited by VI; 66% of the excess oxygen-18 is retained as carbonyl oxygen; the rest presumably resides in the ether oxygen of the *p*-nitrocarboxylate group.[8] If one considers intermediates for this rearrangement similar to those for the rearrangement of VI, one finds that none of these can adequately explain the results. Combinations of reaction paths like VII and VIII or VII and IX can lead to the observed results, as can an ion pair in which the two oxygens of the anion are not the same distance from the positive charge on the carbonyl carbon. Such an ion pair would of necessity need to be extremely short-lived, since it should lose its asymmetry very rapidly. It is interesting to compare the results in these two rearrangements. In the case of VI the extreme specificity can be ascribed tentatively to two factors. It would seem that the cation should be relatively unstable because it requires the formation of a positive charge at the bridgehead of a 4,4,1-bicyclic system. This instability will lead to rapid collapse of the ion pair. An inspection of models of VI indicates quite clearly that the β-oxygen is much closer to the bridgehead carbon than is the γ-oxygen and can therefore bond with it much more easily than the γ-oxygen. In the case of the substituted benzoyl peroxide XVI the rearranged cation will be considerably more stable than that derived from VI, giving therefore the possibility of a relatively more stable ion pair. An inspection of a model indicates, as would be expected, that there are no pronounced steric effects in the peroxide except that in most conformations the β-oxygen is closer to the anisoyl carbonyl carbon atom than is the α-oxygen. This difference is un-



XVI

XVII

XVIII

TABLE I

Compound	Atom % excess oxygen-18[a]
Benzoic acid (IV)	1.35; 1.38
trans-9-Decalyl perbenzoate (VI)	1.37; 1.37
Benzoate (Xa)	1.29; 1.30
Benzoate (Xb)	1.23; 1.20
1,6-Dihydroxycyclodecane (XIa)	0.02; 0.02
1,6-Dihydroxycyclodecane (XIb)	0.01; 0.01
Benzyl alcohol (XXIa)	1.16; 1.17[b]
Benzyl alcohol (XIIb)	1.19; 1.20
Phenylurethan of XIIa	1.25

[a] There is a decrease in total oxygen-18 content of these molecules as one progresses through the series of reactions, in particular in going from VI to Xa and Xb. These losses most probably occur by exchange during the reaction and the subsequent purification of the products. [b] This material must be contaminated with some other oxygen-containing substance since the phenylurethan gives an analysis which is in reasonably close agreement with the precursor Xa.

TABLE II

Compound	Atom % oxygen-18
p-Nitrobenzoic acid (XIII)	1.12; 1.10
p-Nitrobenzamide (XV)	1.12; 1.11
p-Nitrobenzoyl-*p*-methoxyphenyl carbonate (XVII)	1.31; 1.31 1.31; 1.28[a]
p-Nitrobenzamide (XVIII)	0.81; 0.80 0.80; 0.79

[a] This compound was analyzed by two different investigators using two different trains and three different mass-spectrometers. As it can be seen the reproducibility of the results is good; however, the explanation for the high values obtained eludes us.

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[6] J. E. Leffler, THIS JOURNAL, **72**, 67 (1950).

[7] D. B. Denney, *ibid.*, **78**, 590 (1956).

[8] It has been shown by D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957), that anhydrides, labeled with oxygen-18 in their carbonyl groups, can be converted to amides in liquid ammonia without any loss of oxygen-18. These results indicate strongly that the conversion of XVII to XVIII should proceed without loss of oxygen-18 from the carbonyl group. It is therefore felt that the oxygen-18 content of XVIII is the same as that of the carbonyl position in XVII. There seems to be no reason to suspect that any oxygen-18 is lost in the conversion of XVI to XVII.

doubtedly reflected in the transition state leading away from XVI and will also be evident at least initially in an ion pair derived from XVI. The results of the above experiments and other unpublished studies indicate that in rearrangements of substances like I, the role of A varies and this depends to a large degree on the nature of the cation, the solvent, etc. It appears that it will not be possible to write a general structure for these intermediates but rather that each case will have to be investigated in its own right.

Experimental

Benzoic Acid-CO^{18}O^{18}H (IV).—A mixture of 74.0 g. (0.379 mole) of benzotrichloride and 25 ml. of H_2O^{18} (*ca.* 1.5 atom % oxygen-18) was heated with stirring on a steam-bath for 24 hr. The resulting solid was filtered and dried to afford 43.0 g. (93%) of benzoic acid, m.p. 118–119°. The acid was recrystallized from benzene–hexane to yield 40.3 g. of material, m.p. 123–124°.

Benzoyl Chloride-CO^{18}Cl (V).—A mixture of 13.0 g. (0.1075 mole) of I and 20 ml. of thionyl chloride was allowed to stand at room temperature for 24 hr. The thionyl chloride was removed *in vacuo* and the product was distilled to yield 13.9 g. (93%) of II, b.p. 88–89° (20 mm.).

***trans*-9-Decalyl Perbenzoate-carbonyl-O^{18} (VI).**—VI was prepared in 72% yield, m.p. 66–66.8° (lit.[9] 67–68°), by the method of Cope and Holtzman.[9]

Labeled 1-Benzoyloxy-1,6-epoxycyclodecane (Xa).—VI was allowed to rearrange in methanol according to the procedure of Bartlett and Kice.[4] An 85% yield of IV was obtained, m.p. 96.7–97° (lit.[9] 96.5–97.5°), after crystallization from methanol–water.

Labeled 1-Benzoyloxy-1,6-epoxycyclodecane (Xb).—VI was allowed to rearrange in glacial acetic acid for 22 hr. at 21°. An 80% yield of Xb, m.p. 94.5–95.5°, was obtained after crystallization from methanol–water.

Reduction of Xa and Xb.—To a stirred suspension of 2.0 g. (0.0526 mole) of lithium aluminum hydride in 50 ml. of ether was added 4.34 g. (0.0158 mole) of Xb in 100 ml. of dry ether. The mixture was stirred and refluxed for 24 hr. After cooling to 0°, water was added and the ether layer was separated from the solid and water. The dried solid was extracted in a Soxhlet with chloroform. The chloroform extract was evaporated to give a solid which was recrystallized from acetone to yield 1.92 g. (71%) of XIb, m.p. 140.6–142.6°.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.04; H, 11.60.

The original ether extracts were dried over magnesium sulfate. The ether was evaporated and the residue was distilled in a molecular still, block temperature 100–110° (20 mm.). One main fraction, 0.70 g. (41%), n^{25}D 1.5378, was obtained. The infrared spectrum of this sample agreed with that of a known sample of benzyl alcohol.

In a similar manner Xa was reduced to XIa and XIIa. The phenylurethans of XIIa and b were prepared by standard methods, m.p.'s 77–78°.

***p*-Nitrobenzoic Acid-CO^{18}O^{18}H (XIII).**—To a solution of 60.0 g. of H_2O^{18} (1.5 atom % oxygen-18) in 500 ml. of dry tetrahydrofuran there was added 185 g. (1.00 mole) of *p*-nitrobenzoyl chloride. The solution was refluxed for two days. The solvent was evaporated and the crude acid was crystallized from methanol, m.p. 240–242°.

***p*-Nitrobenzoyl Chloride-CO^{18}Cl (XIV).**—A mixture of 300 ml. of thionyl chloride and 80.0 g. (0.431 mole) of XIII was refluxed for 8 hr. The thionyl chloride was removed *in vacuo* and the acid chloride was recrystallized from hexane to yield 56.5 g. (63%) of XIV, m.p. 71.5–72°.

The amide was prepared by standard procedures, m.p. 200–201°.

***p*-Nitro-*p*'-methoxybenzoyl Peroxide-*p*-nitrobenzoylcarbonyl-O^{18} (XVI).**—The procedure of Leffler[6] was followed exactly. The yield was 13% of material, m.p. 114° dec. (lit.[6] 108°).

Labeled *p*-Nitrobenzoyl-*p*-methoxyphenyl Carbonate (XVII).—The peroxide XVI was rearranged as reported by Leffler.[6] The yield was 40% of material, m.p. 123–124° (lit.[6] 126–129°).

Labeled *p*-Nitrobenzamide (XVIII).—The carbonate XVII, 0.80 g. (0.00252 mole), was added to 20 ml. of liquid ammonia at −33°. The mixture was stirred and the ammonia was allowed to evaporate. The solid residue was washed with 5% sodium hydroxide solution. The amide was recrystallized from methanol to yield 0.20 g. (48%) of XVIII, *m*.p. 200–201°, no depression with an authentic sample.

NEW BRUNSWICK, N. J.

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

COMMUNICATIONS TO THE EDITOR

STEROIDAL LACTONES

Sir:

We wish to report the preparation of two steroids, III and V, which significantly reverse the electrolyte effects of mineralocorticoids.

Treatment of 17α-ethynyl-5-androstene-3β,17β-diol[1] with ethylmagnesium bromide in tetrahydrofuran, followed by carbonation with gaseous carbon dioxide yielded, upon hydrolysis, 3β,17β-dihydroxy-5-androsten-17α-ylpropiolic acid (I)[2], m.p. 234–235° (dec.), [α]D −132.5° (diox.); *Anal.* Calcd. for $C_{22}H_{30}O_4 \cdot H_2O$: C, 70.18; H, 8.57. Found: C, 70.19; H, 8.46. Saturation of the triple bond by hydrogenation in ethanol with palladium on carbon catalyst afforded 3-(3β,17β-dihydroxy-5-androsten-17α-yl)-propionic acid γ-lactone (II),[2] m.p. 190-191°, [α]D −91.5° ($CHCl_3$); *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.40; H, 9.90. Oppenauer oxidation of II yielded 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)-propionic acid γ-lactone (III),[2] m.p. 148–150° (163–165°), [α]D +76.5° ($CHCl_3$); *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.31; H, 8.94.

The 19-nor analog of III was prepared. The Grignard reagent of 3-methoxy-17α-ethynyl-1,3,5-(10)-estratrien-17β-ol[3] was prepared in tetrahydrofuran and carbonated with gaseous carbon dioxide. There was obtained upon hydrolysis 3-methoxy-17β - hydroxy - 1,3,5(10) - estratrien - 17α - ylpropiolic acid monohydrate (IV), m.p. 204–207° dec. ($-H_2O$ 120–140°), [α]D −17.7° (diox.) *Anal.* Calcd. for $C_{22}H_{26}O_4 \cdot H_2O$: C, 70.94; H, 7.58. Found: C, 70.74; H, 7.93. The acid hydrate IV was suspended in ammonia and ethanol and treated

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(1) H. E. Stavely, THIS JOURNAL, **61**, 79–80 (1939).

(2) J. A. Cella, U. S. Patent 2,705,712, April 5, 1955.

(3) F. B. Colton, U. S. Patent 2,666,769, Jan. 19, 1954.