[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

The Stereochemistry of the Perbenzoic Acid Oxidation of Optically Active *exo*-Acetylnorbornane[1]

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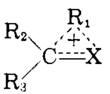
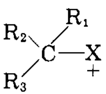
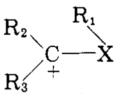
(−)-*exo*-Acetylnorbornane of known optical purity is prepared by the sequence (−)-*exo*-norbornanecarboxylic acid → acid chloride → (−)-ketone. The optical rotation of enantiomerically pure *exo*-norbornyl acid phthalate is established by analysis of a partially resolved sample for enantiomer content by isotope dilution of *exo*-norbornyl acid phthalate-^{14}C. Combination of this result with data of Winstein and Trifan affords rotations of enantiomerically pure *exo*-norborneol and *exo*-norbornyl acetate. Perbenzoic acid oxidation of the active ketone gives *exo*- acetate with 94.2–100% retention of optical purity, indicating less than 2.9% attack at C.1. The implications of the results for an understanding of the type of hybridization in the transition state of 1,2-rearrangements are discussed.

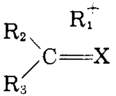
The present paper represents a study of the nature and role of electronic delocalization as reflected in the stereochemistry of the migrating group of 1,2-rearrangements. The experiments are concerned with the stereochemistry of the Baeyer–Villiger oxidation of *exo*-acetylnorbornane, a system that was chosen for scrutiny for reasons given in the introduction.

Introduction.—The kinetics and product distributions associated with the migration of groups (R_1, R_2, R_3) in molecular rearrangements to a cationic electron-deficient terminus X (to which other groups, not shown here, may be attached) are recognized to depend upon a number of steric and electronic influences.[2] Qualitative resonance theory[2c] provides a simple basis for anticipation of the electronic part of the net effects upon rates and products that attend a change in structure. The transition state for the step involving migration of R_1 can be represented as a resonance hybrid (I) made up of the contributing structures Ia-c.

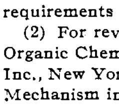

I


Ia


Ib


Ic

In some cases,[3] rearrangement is concerted with the breaking of a bond between X and a departing group Y, in which case the notation II becomes appropriate. The relative importance of the b-structures are expected to increase with increasing ability of the non-migrating groups (R_2,R_3) to support adjacent positive charge, *i.e.*, $H < CH_3 <$ phenyl. For invariant R_2 and R_3, the relative contributions of the c-structures are expected to increase in the order $R_1 = H < R_1 = CH_3 < R_1 =$ higher alkyl. On the basis of electronegativities or ionization potentials, variations in the migration terminus X are expected to increase the relative importance of the a-structures in the order $X = O < X = N < X = C$.[4] Thus, with increasing electron demand at the migration terminus, the relative importance of the c-structures, with the migrating group cationic, increases. Increased importance of the c-structures also is anticipated when $X = O$ on the grounds that the bond energy increment (difference between C═X and C—X) increases in the order $X = C < X = N < X = O$. Much of the literature on the Baeyer–Villiger and Criegee rearrangements, where $X = O$, is suggestive of this effect. Thus, peracid oxidations of alkyl or cycloalkyl methyl ketones usually give the acetates; alkyl or cycloalkyl migration predominates to the virtual exclusion of methyl migration.[5] Rate studies[5e,f] support the concept of a relatively cationic migrating group in the Baeyer–Villiger rearrangement. Greater sensitivity to electronic effects in the migrating group seems to be manifested in the rates of acetolysis of phenyl-substituted cumyl peroxy-*p*-nitrobenzoates III (R = aryl), which show[6] a Hammett ρ-value of -5.1, than in the acetolysis of phenyl-substituted neophyl *p*-bromobenzenesulfonates IV (R = aryl) which show[7] a ρ-value of -3.7.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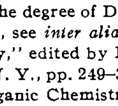
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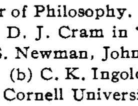
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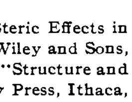
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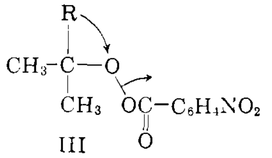
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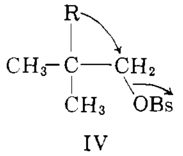
IV

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[1] (a) This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18 (600)-1544. Reproduction in whole or in part is permitted for any purpose of the United States Government. (b) Taken in part from a dissertation submitted by Shigeto Suzuki in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] For reviews, see *inter alia* (a) D. J. Cram in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., pp. 249–304; (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 474–522; (c) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 522–532.

[3] (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, This Journal, **74**, 1113 (1952); (b) F. Brown, E. D. Hughes, C. K. Ingold and J. F. Smith, *Nature*, **168**, 65 (1951); (c) D. J. Cram, This Journal, **74**, 2137 (1952).

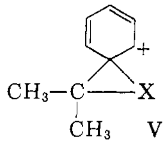
[4] *Cf.* P. Magee, Dissertation, University of California at Los Angeles, 1955, and references therein cited.

[5] (a) S. L. Friess, This Journal, **71**, 14 (1949); (b) S. L. Friess and N. L. Farnham, *ibid.*, **72**, 5518 (1950); (c) W. von E. Doering and L. Speers, *ibid.*, **72**, 5515 (1950), and references therein cited; (d) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955); (e) M. F. Hawthorne, paper at Reaction Mechanisms Conference, Swarthmore, Pa., Sept., 1956; (f) M. F. Hawthorne, W. D. Emmons and K. S. McCallum, This Journal, **80**, 6393 (1958).

[6] S. Winstein and K. Nelson, unpublished work, quoted by S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958).

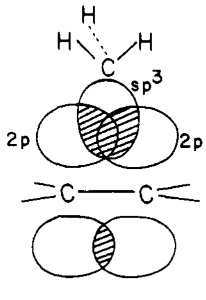
[7] R. Heck and S. Winstein, *ibid.*, **79**, 3432 (1957).

Further, whereas in acetolysis at 75° of *p*-bromobenzenesulfonates IV, some increase in migratory aptitude of alkyl over methyl can be discerned, the relative rates being R = phenyl, 203, R = isopropyl, 5.3, R = methyl, 1.0; the rate sequence is dramatically steepened in acetolysis at 25° of the peroxyesters III, the relative rates for the series being R = phenyl, 2×10^5, R = isopropyl, 3.2×10^3, R = methyl 1.0.[4,8] The phenyl cases are not considered below because of the special stabilization associated with contributions of the type V.[2]

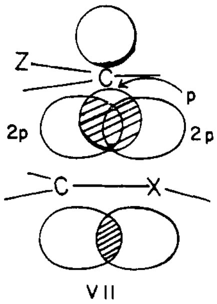


V

There remains the question of a precise formulation of the manner in which positive charge is distributed in the migrating alkyl group. The geometry of the migrating carbon would not be expected to be important for the operation of an inductive effect. Hyperconjugative stabilization also might not put critical geometric requirements on the migrating carbon, *i.e.*, as long as the hyperconjugating C–H bond orbitals are not orthogonal[9–11] to the orbital that binds the migrating carbon to the rest of the system, some stabilization could probably occur if this orbital were sp^3, p or some intermediate type, although the degree of stabilization presumably would be greatest with p. However, there are quantum mechanical grounds[12] for representing the hybridization in methyl migrating from carbon to carbon as sp^3. In this view, the methyl group is held in a molecular orbital formed from a tetrahedral sp^3 orbital of the methyl group and the 2p atomic orbitals that contribute to the π-bond between the migration origin and terminus (VI). That tetrahedral geometry of the migrating carbon is at least permissive—if not required—of rearrangement is indicated by the facile rearrangement of bicyclic bridgehead groups,[13a,5,e,f] in which flattening of the configuration would be prohibitively costly in energy.[13a,b] The possibility that it might be energetically advantageous to re-hybridize the relevant orbitals of the migrating group to sp^2—producing a planar, trigonal configuration—when a system (Z) of easily delocalized electrons is contiguous to the migrating carbon, thus allowing the electron deficiency of the remaining p-orbital to be filled partially from Z and partially from the π-cloud (VII), does not seem to have been treated theoretically. In this connection, it is noteworthy that neighboring benzhydryl in the rearrangement–acetolysis of substituted neopentyl *p*-bromobenzenesulfonates (IV, R = benzhydryl) contributes an extra driving force ($L^{14,3a}$) of about 1.1 kcal./mole to heterolysis (after correction[3a] is made for inductive retardation by the γ-phenyl groups) as compared to migrating methyl (IV, R = CH_3).[4] Nevertheless, conjugative stabilization by the phenyl groups must be relatively inefficient in this case, since migrating isopropyl in IV contributes an extra driving force essentially as great (1.0 kcal./mole) as that of benzhydryl.[4] Comparable data for the more critical case of migration to oxygen, where the migrating group bears a relatively greater burden of charge, are not available. Benzyl has about the same migratory aptitude as isopropyl in the Baeyer–Villiger reaction, despite inductive retardation.[5f] This result, although not unambiguously free of steric implications,[5f] is at least consistent with an electronic distribution in the transition state that leaves the migrating group relatively cationic.



VI



VII

To provide information on whether a migrating alkyl carbon in rearrangement to oxygen departs appreciably from tetrahedral geometry, we have studied the Baeyer–Villiger oxidation of *exo*-acetylnorbornane (VIIIa). Delocalization[15,16] of the C.1–C.6 bonding electrons in the solvolysis of *exo*-norbornyl arenesulfonates (VIIIb) is apparently extensive well before C.2 achieves trigonal geometry. The solvolysis rates of the *exo*-sulfonates are some 350 times faster than those of the corresponding *endo*-derivatives,[15,17] and thus even the onset of departure of the arenesulfonate ion results in interaction of the developing *p*-orbital at C.2 with the C.1–C.6 bonding electrons. In the Baeyer–Villiger oxidation of VIIIa, with norbornyl migrating, flattening and electron deficiency at C.2 might well result in delocalization (IX). Since rotation of the side chain in the intermediate X[18] is essentially free, attack on the migrating group in a number of conformations could occur either at C.2 or at C.1. With optically active

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[8] (a) S. Winstein, P. Magee and K. Nelson, unpublished work; (b) *cf.* S. Winstein and T. G. Traylor, THIS JOURNAL, **77**, 3747 (1955), footnote 18; (c) S. Winstein, Conference on Hyperconjugation, Indiana University, Bloomington, Ind., June 2–4, 1958.

[9] V. J. Shiner, THIS JOURNAL, **78**, 2653 (1956).

[10] W. H. Saunders, Jr., S. Asperger and D. H. Edison, *Chemistry & Industry*, 1417 (1957).

[11] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, THIS JOURNAL, **80**, 2326 (1958).

[12] M. J. S. Dewar, *J. Chem. Soc.*, 2885 (1953).

[13] (a) P. D. Bartlett and L. H. Knox, THIS JOURNAL, **61**, 3184 (1939); (b) W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher and W. P. Whelan, *ibid.*, **75**, 1008 (1953).

[14] (a) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948); (b) S. Winstein, E. Grunwald and L. Ingraham, *ibid.*, **70**, 821 (1948).

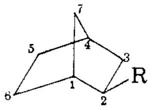
[15] (a) S. Winstein and D. Trifan, *ibid.*, **74**, 1147 (1952); (b) **74**, 1154 (1952).

[16] J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

[17] (a) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *ibid.*, **74**, 1127 (1952); (b) correction for "internal return"[15] gives a rate factor of *ca.* 1000 for the actual ionization process.

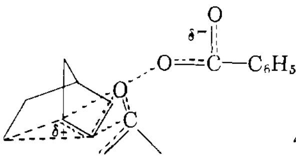
[18] W. von E. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953).

ketone, this would lead to partially or completely racemized acetate VIIIc.[19]

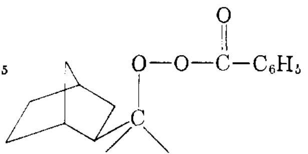


VIIIa, R = $COCH_3$
b, R = OBs
c, R = OAc
d, R = CO_2H
e, R = $OCOC_6H_4CO_2H$
f, R = OH
g, R = COCl

Results.—The rotation of optically pure *exo*-norbornanecarboxylic acid (VIIId) is known.[20] Since the requisite methyl ketone VIIIa was to be prepared from VIIId by methods that could not change the optical purity, it was only necessary to establish the rotation of optically pure acetate VIIIc. Winstein and Trifan[15b] had reported a resolution of *exo*-norbornyl acid phthalate (VIIIe) by recrystallization of the cinchonidine salts of VIIIe (which fractionated only slowly), regeneration of partially resolved VIIIe and fractional crystallization of VIIIe racemate from the excess enantiomer; the racemate unfortunately was less soluble, and the enantiomer accumulated in the mother liquors. Optically active materials having properties invariant with further recrystallizations and having opposite and equal rotations ($[\alpha]_D$ +8.45°, −8.49) finally were obtained.[15b] The acid phthalate VIIIe, $[\alpha]_D$ + 8.45°, gave *exo*-norborneol VIIIf, $[\alpha]_D$ −2.41°. The acetate VIIIc of the latter showed α^{25}_D + 10.39° (neat, 1 dcm.). A repetition[21] of the resolution gave acid phthalate and corresponding derivatives with rotations about 10–12% higher than before, indicating that apparent constancy of properties can be achieved in this system before optical purity is reached. Since the degree of resolution was thus in doubt, and since the phase behavior of racemate–enantiomer mixtures of VIIIe was such as to discourage attempts at establishing optical purity by conventional means, we resorted to the isotope dilution technique.[20,22]



IX



X

Phthalic anhydride-*carbonyl*-^{14}C was prepared by the route[23] *o*-tolylmagnesium bromide + $^{14}CO_2$ → *o*-toluic acid-*carboxyl*-^{14}C → phthalic acid-*carboxyl*-^{14}C → phthalic anhydride-*carbonyl*-^{14}C. Pure racemic *exo*-norborneol[15b] (VIIIf) reacted with this material in pyridine to give the labeled acid phthalate VIIIe. Non-radioactive, partially resolved VIIIe, obtained by following the above described[15,21] resolution procedures, was analyzed for enantiomer content. Admixture of a known quantity of optically active VIIIe, $[\alpha]_D$ + 4.96°, with a known quantity of labeled VIIIe, recovery of the pure racemate by recrystallization and assay of the latter for specific radioactivity relative to starting labeled phthalate indicated that the optically active sample contained 49.4% enantiomer. The enantiomer content could not be greater than this in view of the optical result in the Baeyer–Villiger reaction (*vide infra*), and the statistical uncertainty in the isotope dilution analysis set a lower limit for enantiomer content at 46.7%. Optically pure *exo*-acid phthalate therefore has $[\alpha]_D$ 10.0°, with a possible upper limit of 10.6°, and optically pure *exo*-norborneol VIIIf and *exo*-norbornyl acetate VIIIc thus have rotations within the ranges $[\alpha]_D$ 2.85–3.02° and α_D 12.3–13.0° (neat, 1 dcm.), respectively.

In preliminary experiments with racemic materials, reaction of *exo*-norbornanecarboxylic acid VIIId with thionyl chloride gave the acid chloride VIIIg. The epimeric purity of VIIIg was established by its hydrolysis in 89% yield to the starting acid VIIId and by its ammonolysis in 85% yield to an amide, m.p. 184–185°, which appeared to be epimerically pure since its melting point was unchanged by recrystallization. Application of the same criteria in the *endo* series indicated that the *endo*-acid chloride was also epimerically pure. Water converted it quantitatively to the pure *endo*-acid, and ammonia produced the *endo*-amide, m.p. 210–211°, in 96% yield. Mixtures of the *endo*- and *exo*-amides had sharp melting points that gradually changed upon recrystallization. The phase diagram showed no minimum over the entire composition range. Similar phenomena also were observed with mixtures of the semicarbazones of the epimeric norbornyl methyl ketones which showed only slight depressions of m.p. Reaction of the *exo*-acid chloride with dimethylcadmium produced a liquid ketone VIIIa, which formed a semicarbazone, m.p. 182–183°, in 96% yield. That the ketone was epimerically pure was evidenced by the facts (i) that the m.p. of its semicarbazone was unchanged by recrystallization and (ii) that oxidation with perbenzoic acid in chloroform, a reaction that would be expected to retain[24,25,26] epimeric configuration, produced *exo*-norbornyl acetate uncontaminated with its *endo*

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(19) J. Wilt and A. Danielzadeh, *J. Org. Chem.*, **23**, 920 (1958) have reported that peroxytrifluoroacetic acid oxidation of neopentyl methyl ketone and neophyl methyl ketone gave neopentyl acetate (40% yield) and neophyl acetate (38.5% yield), respectively. Rearranged materials (*t*-amyl acetate and benzyldimethylcarbinyl acetate, respectively) were not observed. On the other hand, a rearrangement within the migrating group, formally analogous to the possibility we are testing here, has been observed by J. Meinwald, M. C. Seidel and B. C. Cadoff, THIS JOURNAL, **80**, 6303 (1958), who have reported that peracetic acid oxidation of norbornenone produced not only the normal product, the δ-lactone of (4-hydroxy-2-cyclopentenyl)-acetic acid, but also the γ-lactone of (2-hydroxy-3-cyclopentenyl)-acetic acid. It has not been established that the latter product is not an artifact resulting from subsequent allylic rearrangement of the normal product independent of the Baeyer–Villiger process itself, although the conditions used (sodium acetate buffer) were unfavorable to allylic rearrangement. For another example of a double rearrangement, see the conversion of *n*-propylbenzene-β-^{14}C to *n*-propylbenzene-α-^{14}C reported by R. M. Roberts and S. G. Brandenberger, *ibid.*, **79**, 5484 (1957).

(20) J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4083 (1959).

(21) E. Clippinger, Dissertation, University of California at Los Angeles, 1954.

(22) S. Graff, D. Rittenberg and G. L. Foster, *J. Biol. Chem.* **133**, 745 (1940).

(23) W. H. Stevens and D. A. Holland, *Science*, **112**, 718 (1950).

(24) R. B. Turner, THIS JOURNAL, **72**, 878 (1950).

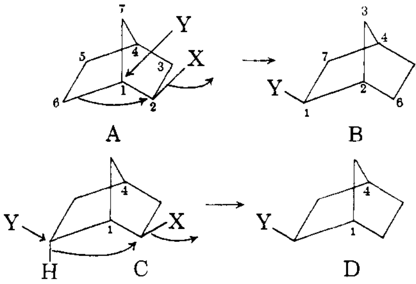
(25) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

(26) T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).

isomer. The ketone prepared from the *endo*-acid chloride was a mixture of epimers with the *endo* isomer apparently predominant. The m.p. of the semicarbazone prepared from this material changed slowly with repeated recrystallizations, and the infrared spectra of fractions from distillation of the ketone suggested contamination with *exo*-ketone. Oxidation of the ketone mixture with perbenzoic acid gave a mixture of *endo*- and *exo*-norbornyl acetates. The causes for the difference in the behavior of the two acid chlorides toward dimethylcadmium are not clear. Either (i) the rates of formation of an enolic intermediate from either species during contact with the organometallic are comparable, but the rate of the enol → *exo* reaction is much faster than that of the enol → *endo* reaction, *i.e.*, the equilibriium favors *exo* material almost exclusively, or (ii) the rate of enolization of *endo* material is faster than that of *exo*, perhaps because of the sterically more exposed position of the C.2 hydrogen in the former.

Optically active *exo*-norbornanecarboxylic acid (VIIId) was prepared by partial resolution of the racemate *via* the quinine salt. A sample of this material, $[\alpha]_D$ $-8.06°$, was converted, as in the racemic series, to the acid chloride and thence to the methyl ketone VIIIa, α^{25}_D $-21.58°$ (neat 1 dcm.). No optical fractionation was possible in this sequence, and therefore the ketone and the starting acid had identical optical purities. Oxidation of the ketone with somewhat less than an equivalent of perbenzoic acid in dry chloroform gave a mixture containing acetate and unreacted ketone. The latter was recovered with unchanged properties *via* the Girard T derivative. The non-ketonic fraction consisted mainly of *exo*-norbornyl acetate contaminated with a trace of hydroxylic impurity—presumably *exo*-norborneol—the presence of which was suggested by a weak band at 2.9 μ in the infrared spectrum. Infrared analysis for the presence of the product of methyl migration, *exo*-methyl norbornanecarboxylate, was inapplicable because of the similarity of the spectrum of the methyl ester to that of the acetate. However, the absence of methyl ester was demonstrated during subsequent saponification of the crude acetate, from which no non-volatile acid was obtained. The rearrangement therefore occurred with exclusive norbornyl migration. Recovered ketone and crude acetate accounted for 84% of the starting material. Purification of the acetate was effected by conversion to the acid phthalate and re-conversion to the acetate. This procedure did not involve any re-crystallizations and therefore could not have affected the optical purity. The recovered pure acetate had α^{25}_D $-3.577° \pm 0.007°$ (neat, 1 dcm.). It was chemically homogeneous as indicated by elemental analysis, and its infrared spectrum and refractive index were in precise agreement with those reported[15] for *exo*-acetate. It therefore could not have contained more than *ca.* 6%[15] of *endo*-acetate. A more sensitive measure of the amount of *endo* isomer was afforded by the observation that the optical activity of the product acetate was destroyed completely by heating in acetic acid containing *p*-toluenesulfonic acid under conditions[15] where the *endo*-acetate is optically stable but the *exo*-acetate is not. The limits of polarimetric error were small enough to have detected 1–2% of *endo*-acetate.

On the basis of $[\alpha]_D$ 27.8° as the rotation of optically pure[20] *exo*-norbornanecarboxylic acid (VIIId), the ketone starting material was 29.0% optically pure. (This is a maximum value since $[\alpha]_D$ 27.8° is a minimum value for VIIId.) Assuming complete retention of optical purity in the Baeyer–Villiger rearrangement and α_D 12.3° (neat, (1 dcm as the rotation of optically pure *exo*-aectate, the product acetate should have had α_D $-3.57°$, in precise agreement with the observed value. More conservatively, the maximum theoretical value for the product acetate is obtained by using 13.0° as the rotation of optically pure acetate. On this basis, the maximum rotation that could have been observed was $-3.80°$. The product acetate therefore had not less than 94.2% of the optical purity of the starting ketone. Consequently, not more than 2.9% of the acetate could have been formed by attack at C.1. The remote possibility of a completely concerted double rearrangement, which would lead to attack *entirely* at C.1 and result in inversion of absolute configuration (*quasi-inversion*[27]), is eliminated by the following argument.



Schmidt degradation[28] of $(-)$-*endo*-norbornanecarboxylic acid produces $(+)$-*endo*-norbornylamine. Retention of the absolute configuration of the norbornane skeleton in this process is hardly questionable. Nitrous acid deamination of the $(+)$-amine gives $(-)$-*exo*-norbornyl acetate with retention of the absolute configuration at C.4.[28] Thus, $(-)$-*exo*-acetate has the same absolute configuration as $(-)$-*endo*-acid. Since the latter has the same absolute configuration as $(-)$-*exo*-acid[20] and $(-)$-*exo*-ketone, $(-)$-*exo*-acetate and $(-)$-*exo*-ketone have the same absolute configuration.

Discussion.—One interpretation of the observed lack of rearrangement to C.1 in the Baeyer–Villiger reaction is that not enough stabilization is achieved by delocalization of the C.1–C.6 bonding electrons to cause a change in hybridization of the transition state from type VI to type VII, and therefore C.2 remains pyramidal. There remains

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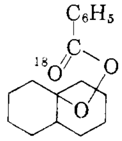
(27) We propose the term *quasi-inversion* to designate a process in which an asymmetric center suffers a formal change of configuration although none of its directly attached bonds is broken. The earliest example is the conversion of (+)-isopropylmalonamidic acid to its enantiomer by multi-step interchange of the carboxamido and carboxyl groups [E. Fischer and F. Brauns, *Ber.*, **47**, 3181 (1914)]. In the hypothetical single-step process A → B, the absolute configuration at C.4 is quasi-inverted. In C → D, both C.1 and C.4 are quasi-inverted.

(28) J. A. Berson and D. A. Ben-Efraim, THIS JOURNAL, **81**, 4094 (1959).

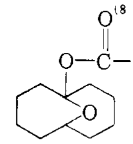
the question whether this interpretation is also a necessary one, *i.e.*, whether the transition state resonance hybrid could involve contributing structures with C.1 cationic and still afford a product resulting exclusively from attack at C.2.

It is doubtful that such high selectivity would originate in purely steric factors. The ground state conformation shown in X (O, C, C.2, and C.1 planar) for the intermediate peroxy ester is not appreciably strained, nor is the transition state derived from it obviously less favorable sterically than those derived from other conformations. Further, in X, C.1 is actually slightly closer to the migration terminus oxygen than is C.2, as is shown by calculations[1b] based on normal bond angles and distances; this favorable geometry is maintained for a considerable portion of a reasonable hypothetical migration path.

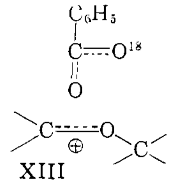
A reaction that has some analogy to the one at hand is the rearrangement of 9-decalyl perbenzoate (XI) to the hemiketal benzoate XII.[29] The rearrangement has been discussed in terms of an ion-pair mechanism,[30,31] and electronic delocalization in the benzoate part of the ion-pair XIII has been postulated.[32] Yet XI-*carbonyl*-^{18}O gives[33] exclusively XII-*carbonyl*-^{18}O, indicating complete selectivity for one of the two oxygens. Explanations for the preference have invoked steric[33] and electrostatic[32] factors, but a detailed understanding of the differences between this case and those where partial or complete equilibration of ^{18}O between potentially equivalent oxygen atoms does occur[34] is still lacking. In the Baeyer–Villiger rearrangement we have studied, migrating norbornyl is presumably bound even more tightly to the rest of the reacting system than is migrating benzoate ion in the ion pair intermediate of the decalyl perbenzoate rearrangement. It is conceivable, therefore, that even if delocalization as in IX were important, the product might still be formed by exclusive reaction at C.2. For test systems of this type, involving migrating groups that are in principle plausibly subject to electronic delocalization, loss of structural individuality of potentially identical atoms (racemization in our case) is clearly interpretable. However, the complete *absence* of structural "scrambling" (complete retention in our case), although suggestive of the absence of extensive electronic delocalization, cannot yet be used as an unambiguous criterion.



XI



XII



XIII

Experimental[35]

Partial Resolution of *exo*-Norbornanecarboxylic Acid (VIIId).—A mixture of 102.5 g. of VIIId[20] and 237 g. of quinine trihydrate was dissolved in 5 l. of boiling acetone. The solution was allowed to cool to room temperature. After 24 hours, the precipitated salt (284 g., 84%) was filtered off and recrystallized twice more from acetone to give 149 g. of salt. This material was taken up in 400 ml. of chloroform, treated with 150 ml. of 5 *N* sulfuric acid, the aqueous layer separated and the chloroform layer washed with 90 ml. of 5 *N* sulfuric acid and then with three portions of water. After having been dried over calcium sulfate, the chloroform was evaporated and the residue was recrystallized from aqueous methanol to give 38.5 g. of (−)-VIIId, $[\alpha]^{25}D$ −7.73° (*c* 12.4 in 95% ethanol, *l* 1), $[\alpha]^{25}D$ −8.06° (*c* 2.57, in 95% ethanol, *l* 4), m.p. 56–58°. Apparently, $[\alpha]D$ of this material has a slight concentration dependence. The higher value of $[\alpha]D$ was used for subsequent calculations since it was determined at almost the same concentration as that used[20] (*c* 2.4) for the sample in the correlation scheme.

Anal. Calcd. for $C_8H_{10}O_2$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.67.

Racemic *exo*-norbornane carbonyl chloride was prepared by treating 30 g. of the racemic acid with 40 g. of thionyl chloride. Gas was evolved vigorously. After 11 hours at room temperature, the excess thionyl chloride was evaporated *in vacuo* and the residue was distilled to give 31.8 g. (94%) of a colorless liquid with a penetrating unpleasant odor, b.p. 81.7–81.9° (12 mm.), reported[36] b.p. 83–84° (12 mm.). When 1.06 g. of this material and 8 ml. of water were shaken for 10 minutes, a precipitate formed which was filtered, washed with water and dried to give 0.83 g. (89%) of the *exo*-acid, m.p. 56–57°.

Racemic *exo*-norbornanecarboxamide was formed by dissolving 4.5 g. of the acid chloride in 100 ml. of dry ether and passing dry ammonia gas into the solution. The white precipitate was filtered, washed with water, dried, and recrystallized from methanol to give 3.3 g. (85%) of amide, m.p. 184–184.5°, reported[36] m.p. 187–188°, reported[37] m.p. 182°. Recrystallization did not change the m.p.

Anal. Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.80; H, 9.54; N, 10.33.

Racemic *endo*-norbornane carbonyl chloride, prepared in 96% yield from the racemic acid by the same procedure as was used in the *exo*-series, was a colorless liquid, b.p. 76–77° (7 mm.), reported[38] b.p. 80–81° (8 mm.). A sample was treated with water to give the *endo*-acid, m.p. 64–65°, in quantitative yield. With ammonia in ether, the acid chloride gave a 96% yield of *endo*-norbornanecarboxamide, m.p. 210–211°, reported m.p. 206°,[36] m.p. 205–206°,[38] m.p. 210–211°.[39] Mixtures of the *endo*- and *exo*-amides over the entire composition range were prepared. These melted sharply at temperatures between those of the pure components. No minimum was observed.

Reaction of *endo*-Norbornane Carbonyl Chloride with Dimethylcadmium.—A solution of dimethylcadmium in benzene was prepared by adding 73 g. of dry, powdered cadmium chloride to a cold ethereal solution of methylmagnesium bromide (from 10 g. of magnesium) and displacing the ether with benzene. This suspension (about 150 ml.) was stirred and treated during 3 minutes with 14.5 g. of the *endo*-acid chloride in 75 ml. of dry benzene. After 15 minutes, the mixture was allowed to warm to room temperature, stirred for 2 hours, and poured onto 500 g. of cracked ice. Enough hydrochloric acid was added to make the aqueous layer acidic, the benzene layer was separated, the aqueous layer was washed with fresh benzene, the combined benzene layers were thoroughly washed with water, bicarbonate solution, again with water, and finally with saturated brine. After having been dried over sodium sulfate, the benzene was distilled off and the residue was fractionated to give 8.5 g. of product (70%), b.p. 85–87.2° (18 mm.). Redistillation gave material with a pleasant camphoraceous odor, b.p. 87° (18 mm.), $n^{25}D$ 1.4723.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.11; H, 10.14.

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(29) R. Criegee and R. Kaspar, *Ann.*, **560**, 127 (1948).

(30) P. D. Bartlett and J. L. Kice, This Journal, **75**, 5591 (1953).

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

(32) S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958).

(33) D. B. Denney and D. G. Denney, *ibid.*, **79**, 4806 (1957).

(34) D. B. Denney and B. Goldstein, *ibid.*, **79**, 4948 (1957).

(35) Melting points and boiling points are corrected. Analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

(36) K. Alder, G. Stein, E. Rolland and G. Schulze, *Ann.*, **514**, 211 (1934).

(37) K. Alder, K. Heimbach and R. Reubke, *Ber.*, **91**, 1516 (1958).

(38) G. Komppa and S. Beckmann, *Ann.*, **512**, 17 (1934).

(39) W. R. Boehme, This Journal, **80**, 4740 (1958).

A second preparation made with no deliberate change of conditions had b.p. 82.5–83.5° (16 mm.), n^{25}D 1.4721. Infrared spectra of an early fraction of the distillate showed greater intensity of the peaks at 9.3 and 11.3 μ than in late fractions. This is presumably due to contamination with *exo*-ketone, which absorbs strongly in these regions.

The first preparation of *endo*-ketone gave 60% of a **semicarbazone**, m.p. 179–180° (crude), which after recrystallization from ethanol and 90% ethanol had m.p. 179–180°.

Anal. Calcd. for $C_{10}H_{17}ON_3$: C, 61.50; H, 8.77; N, 21.52. Found: C, 61.55; H, 8.71; N, 21.56.

The second ketone preparation gave 99% of a crude semicarbazone, m.p. 174–175°. The m.p. gradually rose through four recrystallizations from 90% ethanol to 178–179°.

Perbenzoic acid oxidation of the first preparation by the method described for the *exo* series (see below) gave an acetate that contained some *exo*-acetate, as was evidenced by extraneous infrared bands at 8.67, 9.29 and 11.27 μ.

***exo*-Acetylnorbornane (VIIIa)** was prepared from the *exo*-acid chloride and dimethylcadmium by the method already described for the *endo* series. The ketone was obtained in 91% yield as a colorless liquid, b.p. 87° (19 mm.), n^{25}D 1.4710.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.03; H, 10.36.

The semicarbazone was obtained in 99% yield, m.p. 181–182°. Recrystallization from 50% ethanol gave 96% yield of material melting at 182–183°. Further recrystallization did not change the m.p. Admixture with *endo*-semicarbazone caused a small m.p. depression. The 1:1 mixture had m.p. 168–173°.

Anal. Calcd. for $C_{10}H_{17}ON_3$: C, 61.50; H, 8.77. Found: C, 61.69; H, 8.70.

Perbenzoic Acid Oxidation of Racemic *exo*-Acetylnorbornane.—A solution of 14.89 g. (0.108 mole) of perbenzoic acid in 184 ml. of chloroform, which had been carefully freed of mineral acid by washing with water and drying over sodium sulfate, was treated with a solution of 15.4 g. (0.111 mole) of *exo*-acetylnorbornane in 15 ml. of chloroform. The reaction mixture was allowed to stand in the dark at room temperature for 163 hours, after which time it contained no "active" oxygen. The chloroform was removed *in vacuo*, the residue was taken up in 250 ml. of ether, the ether was washed once with ice-cold *N* sodium hydroxide, thrice with ice-water and once with saturated brine. After having been dried over calcium sulfate, the ether was evaporated, and the residue, a pale yellow oil, was treated with a solution of 6.7 g. of Girard reagent T in 108 g. of absolute ethanol and 12 g. of acetic acid. The mixture was kept at 50° for an hour, diluted with a solution of 7.2 g. of sodium hydroxide in 900 ml. of water, and extracted with 450 ml. of ether (in six portions). The combined ether layers (non-ketonic fraction) were washed successively with bicarbonate, water, and saturated brine, and dried over calcium sulfate. The aqueous layer (ketonic fraction) was brought to an acidity of about *N* by addition of 90 ml. of concentrated hydrochloric acid, kept at room temperature for an hour, and extracted with ether (five 60-ml. portions). The ketonic ether layer was washed successively with bicarbonate, water, and saturated brine, and then was dried over calcium sulfate.

The ketonic ether solution was evaporated and the residue distilled to give 2.90 g. of colorless liquid, b.p. 89° (19 mm.), n^{25}D 1.4710, infrared spectrum identical with that of the starting ketone.

The non-ketonic ether solution was evaporated and the residue distilled to give 11.90 g. (85% based on recovered ketone) of material b.p. 105–107° (45 mm.), n^{25}D 1.4575. The infrared spectrum was virtually identical with that of authentic[15] *exo*-norbornyl acetate, although the refractive index (reported[15] n^{25}D 1.4565, in agreement with that, n^{25}D 1.4565, of a sample prepared in our laboratory by Winstein and Trifan's procedure[15]) showed the presence of an impurity. That the impurity was non-ketonic was demonstrated by the absence of absorption at 5.88 μ and by the fact that re-cycling of the acetate through the Girard separation and re-distillation did not change the refractive index.

A solution of 7.0 g. of the acetate and 3.0 g. of sodium hydroxide in 32 ml. of 50% methanol was kept at 60° for 8 hours and then steam distilled. The non-volatile portion was acidified and worked up for organic acids by extraction with ether. The ether extract, after drying and evaporation, left no residue. There was also no suggestion of the powerful, repulsive odor of the norbornanecarboxylic acids. The steam distillate was saturated with sodium chloride and extracted with five portions of ether (total 400 ml.). After having been dried over calcium sulfate and concentrated to a small volume, the solution was treated with 15 ml. of dry pyridine. The remaining ether and part of the pyridine were removed carefully under an efficient Vigreux column and the residue was treated with 7.0 g. of phthalic anhydride. The mixture was heated on the steam-bath for 4 hours, cooled, acidified with ice-cold 4 *N* sulfuric acid, and extracted with benzene. The benzene layer, after having been thoroughly washed with water, was extracted with sodium bicarbonate solution. The bicarbonate layer, after having been washed with benzene and with ether, was acidified with cold 4 *N* sulfuric acid and the liberated phthalate was extracted with ether. After having been dried over calcium sulfate, the ether was evaporated *in vacuo*, the residual oil was dissolved in a solution of 13 g. of sodium hydroxide in 50 ml. of water and the mixture was steam distilled. The steam distillate was saturated with sodium chloride and extracted with several portions of ether. Drying of the ether over calcium sulfate and evaporation gave pure *exo*-norborneol, m.p. 126–127.2°, reported[11] m.p. 127.8–128.5°, reported[15] for *endo*-norborneol, m.p. 152–153°.

The crude alcohol was heated at 80° for 24 hours with 15 ml. of acetic anhydride and 60 ml. of acetic acid, the mixture was diluted with water, extracted with ether, the ether layer was exhaustively extracted with water, bicarbonate, water, and saturated brine, and dried over calcium sulfate. Evaporation of the ether and distillation of the residue gave pure *exo*-norbornyl acetate, b.p. 91–92° (23 mm.), n^{25}D 1.4565, infrared spectrum identical with that of an authentic sample.

Preparation and Perbenzoic Acid Oxidation of (−)-*exo*-Acetylnorbornane.—Twenty-five grams of (−)-*exo*-norbornanecarboxylic acid (*vide supra*), $[\alpha]^{25}$D −8.06° (*c* 2.57 in 95% ethanol, *l* 4) was converted to the acid chloride in 93% yield with thionyl chloride by the same procedure used in the racemic series. Conversion to the active ketone was accomplished in 84% yield with dimethylcadmium by the same procedure used in the racemic series. The ketone, 19.3 g., had b.p. 88–88.4° (19.5 mm.), n^{25}D 1.4710, infrared spectrum identical with that of the racemate, α^{25}D −21.68° (neat, 1 dcm.).

A solution of 16.8 g. (0.122 mole) of perbenzoic acid in 210 ml. of chloroform was treated with 18.1 (0.131 mole) of the above active ketone. After 160 hours in the dark at room temperature, the solution gave a negative test for "active" oxygen. It was worked up exactly as for the racemic series. From the Girard separation, 3.2 g. of starting *exo*-ketone was recovered, n^{25}D 1.4711, α^{25}D −21.58° (neat, 1 dcm.).

The crude acetate (before conversion to acid phthalate for purification) weighed 13.45 g. (81% based on recovered ketone) and had n^{25}D 1.4576, infrared spectrum identical with that of authentic *exo*-acetate. Purification *via* the acid phthalate, regeneration of *exo*-norborneol (m.p. 125–126.5°) and reconversion to the acetate were carried out exactly as in the racemic series. Careful distillation gave: (1) 2.15 g. of acetate, b.p. 90–91.5° (22 mm.), whose infrared spectrum revealed a trace of acetic anhydride; and (2) 6.15 g. of pure *exo*-acetate, b.p. 91.5–91.8° (22 mm.), n^{25}D 1.4565, infrared spectrum identical with that of an authentic sample, α^{25}D −3.577 ± 0.007° (neat, 1 dcm.). Fraction 2 was analyzed.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 70.12; H, 9.25.

A sample of the above acetate showed $[\alpha]^{32}$D −4.89° (*c* 10.01 in acetic acid, *l* 4). The polarimetry solution was used to make up to 10.00 ml. a sample of 1.441 g. of *p*-toluenesulfonic acid monohydrate (0.759 *M*). After 3.7 hours at 79°, the solution was inactive α^{32}D −0.003 ± 0.007°.

***exo*-Norbornyl acid phthalate**, prepared by the procedure of Winstein and Trifan[15] and recrystallized from warm aqueous acetic acid, had m.p. 99–100.5°, reported m.p. 98.6–99.7°,[15] m.p. 102–103°.[38] Steam distillation of a 10-g. sample from 50 ml. of 25% sodium hydroxide gave 4.3 g. (99%) of *exo*-norborneol, m.p. 127.4–128.2°, reported[15] m.p. 127.8–128.5°. Reaction of the latter with acetic anhydride in acetic acid gave *exo*-norbornyl acetate, $n^{25}D$ 1.4565, infrared spectrum identical with that reported.[15]

Partial resolution of the acid phthalate was effected, according to the reported[15] procedure, by recrystallization of the cinchonidine salt from acetone. The salt (40% of the starting salt) obtained after two recrystallizations was converted to the free acid, fractional crystallization of which from dilute acetic acid and from ethyl acetate–pentane finally afforded material of m.p. 73–76°, $[\alpha]^{25}D$ +4.96° (*c* 9.94 in chloroform, *l* 2). The infrared spectrum (in chloroform) was identical with that of the racemate.

Preparation of *exo*-Norbornyl Acid Phthalate Carbonyl-^{14}C.—Phthalic anhydride-*carbonyl*-^{14}C was prepared by a procedure similar to that of Stevens and Holland.[23] Carbon dioxide-^{14}C was collected in liquid nitrogen traps on a vacuum line after having been generated by the action of concentrated sulfuric acid on barium carbonate-^{14}C. The gas was used to carbonate *o*-tolylmagnesium bromide at −20°, affording toluic acid-*carboxyl*-^{14}C, m.p. 101–103°, in 91% yield. Oxidation of this acid with aqueous potassium permanganate gave phthalic acid-*carboxyl*-^{14}C, m.p. 200° dec. in 90% yield. With thionyl chloride, phthalic anhydride-*carbonyl*-^{14}C, m.p. 130–131°, was obtained in 89% yield. It was diluted 47-fold with inactive phthalic anhydride and the whole recrystallized from chloroform to give material of m.p. 131°.

The radioactive acid phthalate was prepared from the above anhydride and pure *exo*-norborneol in pyridine, according to the procedure of Winstein and Trifan,[15] recrystallized from 50% acetic acid, and dried *in vacuo* over potassium hydroxide pellets to give material of m.p. 98.5–100°, infrared spectrum identical with that of an authentic sample. The apparent activity of an "infinitely thick" sample, determined by the method previously described,[40] was 2985 ± 11 c./min., and the m.p. and activity were unchanged by recrystallization. Independent mountings of this material gave apparent activities that agreed to within the reproducibility of counting a single mounting (less than 0.5% average deviation). Coincidence loss was negligible at this level of activity with the equipment used.[40] Reproducibility of the "*Q*"-gas flow rate was simplified by interposing an oil manometer flow-meter between the storage tank and the detector.

Isotope Dilution Analysis of (+)-*exo*-Norbornyl Acid Phthalate.—A mixture of 1.611 g. of optically active acid phthalate, $[\alpha]D$ +4.96°, and 2.0030 g. of radioactive acid phthalate was recrystallized twice from ethyl acetate–pentane to give 2.10 g. of racemic acid phthalate, m.p. 99–100.5°, $\alpha^{27}D$ −0.003 ± 0.007° (*c* 9.99 in chloroform, *l* 2), apparent radioactivity 1739 ± 7 cc./min. Recrystallization from ethyl acetate–pentane gave 0.70 g. of material of m.p. 99–100°, apparent radioactivity 1734 ± 6 c./min. The enantiomer content (49.4%) in the starting optically active phthalate was calculated from equation 3 of reference 20. The statistical error was calculated as in reference 20, using 0.5% as the error in an observed activity corrected for background. The sample to background activity ratios and counting times were such as to conform to this error, and reproducibilities of mountings and of activities of a given mounting were always better than 0.5%. The uncertainty in the absolute value of the % enantiomer was 2.7%, *i.e.*, the starting phthalate was 46.7–49.4% optically pure. This gives the values 10.0–10.6° for $[\alpha]D$ of optically pure phthalate. Since phthalate of $[\alpha]D$ 8.45° is of the same optical purity as acetate of α_D 10.39° (neat, 1 dcm.),[15] optically pure acetate has α_D 12.26–13.03° (neat, 1 dcm.).

Acknowledgment.—We are indebted to Professor S. Winstein for permission to quote data in advance of publication, and to the Air Force Office of Scientific Research and the Alfred P. Sloan Foundation for financial support.

LOS ANGELES 7, CALIF.

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[40] J. A. Berson and W. M. Jones, THIS JOURNAL, **78**, 6045 (1956); J. A. Berson, R. D. Reynolds and W. M. Jones, *ibid.*, **78**, 6049 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

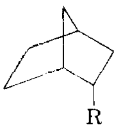
The Reaction of (+)-*endo*-Norbornylamine with Nitrous Acid[1]

BY JEROME A. BERSON AND DAVID A. BEN-EFRAIM

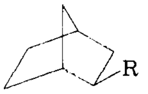
RECEIVED DECEMBER 20, 1958

(−)-*endo*-Norbornanecarboxylic acid, 34–35% optically pure, reacts with hydrazoic acid to give (+)-*endo*-norbornylamine of the same optical purity. In acetic acid, the (+)-amine reacts with sodium nitrite to give *exo*-norbornyl acetate with 23–24% retention of optical purity. The enantiomeric configurations of the amine and product acetate are related on the basis of the stereochemical result and known data on isotope-position rearrangement in this reaction. The optical result is virtually identical with the % retention of skeletal integrity observed in the nitrous acid deamination of *endo*-2-amino-5-norbornene-3-^{14}C. The results suggest that the excess unrearranged portion of the product acetate is derived by direct displacement of solvent on the diazonium ion.

As an adjunct to stereochemical studies in the norbornane series,[2,3] we have prepared optically active *endo*-norbornylamine (Ib) and have examined its reaction with nitrous acid in acetic acid. In addition to its anticipated practical value in providing circumstantial confirmation of the configurational relationship between *exo*-norbornanecarboxylic acid (IIa) and *exo*-norbornyl acetate (IIc), the reaction was of some theoretical interest.



Ia, R = CO_2H; c, R = OBs
b, R = NH_2; d, R = OAc



IIa, R = CO_2H; d, R = OH
b, R = NH_2; e, R = $COCH_3$
c, R = OAc

Diazotization of racemic Ib in aqueous acetic acid[4,5] or in glacial acetic acid[6] occurs with qualitatively predominant inversion of configuration giving *exo*-norborneol and *exo*-norbornyl acetate, respectively. These results are similar to those observed in the acetolysis (and other solvolyses) of *endo*-norbornyl *p*-bromobenzenesulfonate Ic to *exo*-norbornyl derivatives.[7] That the product-determining mechanisms in the amine–nitrous acid

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[1] This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18(600)-1544. Reproduction in whole or in part is permitted for any purpose of the United States Government.

[2] J. A. Berson and D. A. Ben-Efraim, THIS JOURNAL, **81**, 4083 (1959).

[3] J. A. Berson and S. Suzuki, *ibid.*, **81**, 4088 (1959).

[4] G. Komppa and S. Beckmann, *Ann.*, **512**, 172 (1934).

[5] K. Alder, G. Stein, E. Rolland and G. Schulze, *ibid.*, **514**, 211 (1934).

[6] J. D. Roberts, C. C. Lee and W. H. Saunders, THIS JOURNAL, **76**, 4501 (1954).

[7] S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952).