The Nitrous Acid Deamination of the Norbornylamines.   Carbon and Nitrogen Rearrangements of Norbornyl Cations[1]

By JEROME A. BERSON[2] AND ALLEN REMANICK
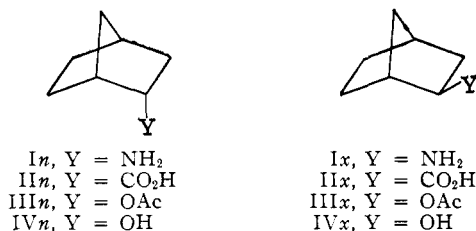
The deaminations of optically active endo- and exo-norbornylamines in glacial acetic acid lead to different amounts of retention of optical purity in the exo-acetate product, in contrast to the report of Corey that the per cent retention was independent of the stereochemistry of the starting material.   The sources of the discrepancies are examined.   The results do not require the postulate of a common carbonium ion precursor of the products from the two amines.   A survey is made of the racemizing processes that occur in norbornyl cations.   The competition between hydride shift and conversion to solvolysis product as a function of solvent is discussed.

Since the earlier investigation[3] of the nitrous acid deamination of endo-norbornylamine in this laboratory, it has become possible to analyze the products with far greater precision than was then accessible to us. Heretofore,[3] detection of endo-norbornyl product in the presence of a large amount of exo- could not be pushed below about 7% of the former.   With capillary gas chromatography, however, it is possible to detect as little as 0.5% or even less of endo-norborneol in the exo isomer.   A re-examination of the product from the deamination of endo-norbornylamine[3] by this technique has now revealed the presence of 4–5% of the endo-alcohol.   Accordingly, we undertook a reinvestigation of this deamination as well as that of exo-nor-bornylamine.

Results

Quantitative Basis for Determination of the Stereochemical Outcome of the Deaminations.—To determine the extent of racemization in a deamination of an optically active amine, it sometimes is convenient or necessary to rely upon indirect correlations of the optical purities of reactant and product.   In the case of endo-norbornylamine (In) we have heretofore assumed that its synthesis[3] from the corresponding acid IIn[4] via the Schmidt reaction does not involve racemization. This assumption, combined with the correlations of endo-acid IIn with exo-acid IIx[4] and of the latter with exo-alcohol IVx and acetate[5] IIIx, provided the basis for a study[3] of the stereochemistry of the deamination

In, Y = NH₂	Ix, Y = NH₂
In, Y = NH₂	Ix, Y = NH₂
IIn, Y = CO₂H	IIx, Y = CO₂H
IIIn, Y = OAc	IIIx, Y = OAc
IVn, Y = OH	IVx, Y = OH

of In.   Although Schmidt reactions generally are found to occur with complete retention of configuration,[6] there could be cause for apprehension in the exo-norbornyl series.   The conditions of the reaction, which involve the use of concentrated sulfuric acid,

are disturbingly reminiscent of those in which clear examples of heterolyses have occurred[7–9] to give carbonium ion intermediates.   The known behavior of the 2-norbornyl cation[10] would then ensure partial or complete racemization.   Accordingly, it seemed prudent to establish an independent correlation of the optical purities of exo-norbornylamine (Ix) and exo-norbornyl acetate (IIIx), our projected reactant and product in the deamination study.   This was effected as shown in Chart I.   The Schmidt reaction with (+)-

CHART I
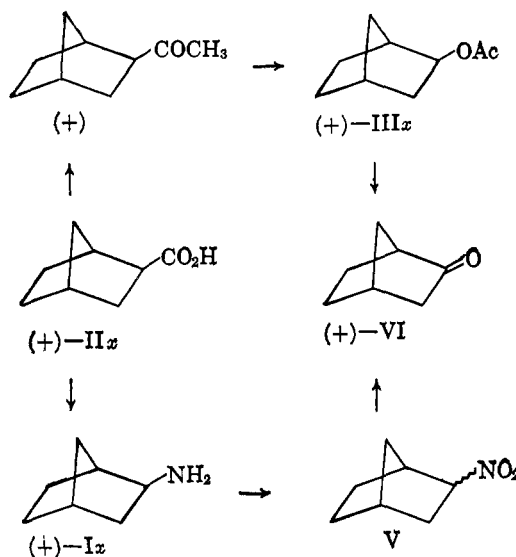
exo-norbornanecarboxylic acid (IIx), 23.0% optically pure,[4] led to (+)-exo-norbornylamine (Ix), oxidation of which with anhydrous peracetic acid[11] gave 2-nitro-norbornane (V).   In a Nef reaction, the crude optically active nitro compound V was converted by aqueous alkali to (+)-2-norbornanone (VI).   The maximum rotation of VI was known by its correlation[12] with exo-norbornyl acetate (IIIx), and those of the reference compounds IIx and IIIx were derived by isotopic dilution analysis.[4,5]   The optical purity of the (+)-norbornanone (VI) derived from 23.0% optically pure

(3) J. A. Berson and D. A. Ben-Efraim, J. Am. Chem. Soc., 81, 4094 (1959).

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

(5) J. A. Berson and S. Suzuki, ibid., 81, 4088 (1959).

(6) Cf. inter alia, A. Campbell and J. Kenyon, J. Chem. Soc., 26 (1946).

(7) R. K. Hill and O. T. Chortyk, J. Am. Chem. Soc., 84, 1064 (1962).

(8) (a) C. Schuerch and E. H. Huntress, ibid., 71, 2223 (1949);   (b) P. A. S. Smith in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Part 1, p. 544–545;   (c) R. F. Brown, N. M. van Gulick, and G. H. Schmid, J. Am. Chem. Soc., 77, 1094 (1955), and references therein cited.

(9) (a) O. Wallach, Ann., 379, 182 (1911);   369, 63 (1909);   (b) L. Bouveault and Levallois, Compt. rend., 146, 180 (1908).

(10) (a) S. Winstein and D. Trifan, J. Am. Chem. Soc., 74, 1147 (1952);   (b) ibid., 74, 1154 (1952).

(11) Cf. W. D. Emmons, ibid., 79, 5528 (1957).

(12) K. Mislow and J. G. Berger, ibid., 84, 1956 (1962).

acid $(+)$-IIx via amine Ix and nitro compound V was 22.4%, as calculated from the above-described correlations. In other words, the net retention in the Schmidt reaction could not have been less than about 97%. We therefore felt confident in the optical purity of the exo-amine Ix. With the Schmidt reaction in the exo series now having been shown to be stereochemically safe, we assumed that the conversion of endo-acid IIn to endo-amine In also was free from racemization.

Since $(+)$-endo-norborneol (IVn) having 65% of the highest reported[10a] rotation was oxidized[13] to $(+)$-norbornanone (VI) with 59% of the maximum rotation calculated on the basis of Chart I, it appears that the optical resolution of IVn acid phthalate[10b] was about 91% complete.

Nitrous Acid Deaminations.—In glacial acetic acid, both endo-In and exo-Ix norbornylamines reacted with nitrous acid (generated in situ by addition of sodium nitrite) to give norbornyl acetates as the predominant products. Small quantities of norborneols, norbornyl nitrates, and hydrocarbons also were formed. These minor side products were separated from the norbornyl acetate fraction either by preparative vapor chromatography or by elution chromatography under conditions that were shown in control experiments not to fractionate the acetates epimerically or optically.

The acetate product from both the endo- and exo-amines consisted mainly of exo-norbornyl acetate, but small amounts of endo-acetate also were observed. The data of Table I show that a somewhat greater proportion of endo-acetate seemed to be formed from endo-amine than from exo-amine.

In the optically active series, the acetate products obtained from either amine were optically active, but the observed rotations were those of the mixtures of exo- and endo-acetates, these substances or the corresponding alcohols being essentially inseparable on a preparative scale by the distillation or gas chromatographic techniques at our disposal. In order to interpret the observed rotations in terms of optical purities, it was necessary to know not only the epimeric composition of the acetate mixture but also the specific rotation of one of the components. We determined the latter quantity by taking advantage of the observation[10] that exo-norbornyl acetate can be selectively racemized by p-toluenesulfonic acid under conditions that do not affect the optical purity of endo-norbornyl acetate. The optical rotation due to endo-acetate remaining after such treatment of the reaction product from endo-amine was too small to measure. However, lithium aluminum hydride cleavage of the selectively racemized acetate mixture and then oxidation of the resulting alcohols gave 2-norbornanone (VI). The optical rotatory dispersion curve of this substance had been reported by Mislow and Berger[12] and had shown that observable rotations in the ultraviolet region could be expected even from samples of low optical purity. Conversion to the ketone thus served as a convenient way of amplifying the optical activity. The rotation of the norbornanone sample derived from the deamination of endo-amine and treatment of the acetate product by the above procedure was kindly determined for us by Professor Kurt Mislow at two

wave lengths in the ultraviolet. From these data and the original product composition and rotation, it was possible to calculate the retentions of optical purity in both acetates as exo, $18 \pm 0.6\%$; endo, $85 \pm 12\%$. The experimental error in the latter figure is large enough so that the result cannot confidently be distinguished from complete retention in the formation of endo-acetate. In the deamination of endo-amine, therefore, a total of 21% $(0.953 \times 18 + 0.047 \times 85)$ of the replacement of amino by acetoxy occurs by non-racemizing processes.

The above device used to obtain the optical purity of the endo-acetate product from endo-amine In was not conveniently applicable to the product from exo-amine Ix. Only about half as much (ca. 2%) endo-acetate IIIn was formed from Ix as from In, and it was therefore difficult to determine the composition of the product mixture accurately. This uncertainty introduced such a large error into the determination of optical purity of the IIIn product that the value would not have been reliable to better than a factor of two. Consequently, the optical purity of the exo-acetate formed from exo-amine was calculated from the two extreme assumptions regarding the optical purity of the IIIn present, i.e., no racemization, or racemization equivalent to that of IIIx. On this basis, exo-amine Ix gave exo-acetate IIIx with $11 \pm 2\%$ retention of optical purity.

The major differences in behavior of the two epimeric amines are: (i) The endo-amine gives about twice as much endo-acetate as does the exo-amine. (ii) The retention of optical purity in the exo-acetate is substantially greater in the product from endo-amine than in that from exo-amine. Further, little, if any, racemization is observed in the endo-acetate product from endo-amine. The results are summarized in Table I.

TABLE I

PRODUCTS FROM THE DEAMINATIONS OF THE NORBORNYLAMINES IN ACETIC ACID[a]

Product	From exo		From endo	
	Yield, %	Optical purity, %	Yield, %	Optical purity, %
Total acetate	87[b]	...	80[b]	...
Total alcohol	10[b]	...	16[b]	...
Total nitrate	2 ± 0.5[b]	...	4[b]	...
endo-Acetate	2 ± 0.5[c]	100[f]	4.7 ± 0.5[c]	85 ± 12
exo-Acetate	98[c]	11 ± 2	95.3[c]	18 ± 0.6[e]
endo-Alcohol	~1[d]	...	5.3 ± 0.5[d]	...
exo-Alcohol	~99[d]	...	94.7[d]	...

[a] Unless otherwise indicated, the experimental uncertainty in the figures is estimated to be 0.5–1 unit. [b] % of total recovered product. [c] % of acetate product fraction. [d] % of alcohol product fraction. [e] Calculated as described in text. [f] Assumed.

While this work[14] was in progress, there appeared a paper by Corey and co-workers[15] on the deamination of the norbornylamines. Neither our experimental results nor our theoretical conclusions are in agreement with those of Corey.

It was previously suggested[3] that at least part of the survival of optical activity in the deamination product from endo-amine In is attributable to direct displacement by solvent or lyate ion. Corey, et al., objected on

(13) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, J. Am. Chem. Soc., 83, 3986 (1961).

(14) The major experimental results are cited by J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Part 1, pp. 181–182 and 208–209.

(15) E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, J. Am. Chem. Soc., 85, 169 (1963).

the grounds that "this hypothesis is inconsistent with the reasonable expectation that a concerted backside displacement reaction with solvent as nucleophile should be far less likely for amine deamination than for sulfonate solvolysis." By "less likely," the authors[15] presumably meant "competes less efficiently with carbonium ion-formation." It seems to us, however, that the opposite view, namely that the compressed energy scale[16] in deaminations brings the rates of several competing processes closer together, is equally reasonable *a priori*. The authors[15] then stated that in the deamination of *exo*-norbornylamine, "the *exo*-diazonium ion . . . is clearly not subject to concerted backside displacement for steric reasons and consequently, any retention of optical activity in the product must come from an optically active carbonium ion." In our opinion, this objection is insufficient to rule out the displacement mechanism, especially since concerted backside nucleophilic displacement reactions giving configurational inversions *are known for both endo and exo-norbornyl p-bromobenzenesulfonates*.[17]

Finally, Corey, *et al.*,[15] reported that the retentions of skeletal integrity in the deaminations of both *endo*- and *exo*-amines were essentially identical (15–16%) and suggested[15,18] that a classical optically active norbornyl cation was the common intermediate in the formation of the active products in each case. But the reported[15] identity is not in accord with our finding (Table I) that *exo*-acetate from *endo*-amine retains much more optical purity than that from *exo*-amine. In seeking the cause of the discrepancy between our results and those of Corey, *et al.*, we are led to point out that, in our hands, it is difficult to reproduce the results of these nitrous acid deaminations with high accuracy. Our result of 11 ± 2% for the retention of optical purity in the *exo*-acetate from *exo*-amine is the average of three separate runs, the relative reproducibility being only about one part in ten.[19a] It is also significant that the ^{14}C-scrambling pattern in the deamination of *endo*-norbornylamine is reproduced with poorer precision than is that in the solvolysis of the *p*-bromobenzenesulfonate,[19b] as has been pointed out.[3] Since Corey, *et al.*,[15] reported only one run for each amine, we do not know if they experienced the same difficulty. In any case, if the discrepancies between our results and Corey's are due to this cause, it would seem that those[15] whose mechanistic proposal requires identical stereochemical results of the *endo*- and *exo*-amine deaminations should bear the burden of proof.

It seems at least as probable, however, that the sources of the discrepancies lie in factors other than the irreproducibility of the deaminations. The three most likely such factors are: (1) Our results apply only to acetate products, which we separated from the accompanying small amounts of nitrates, alcohols, and hydrocarbons. Corey, *et al.*,[15] reduced the crude reaction mixtures catalytically, thus converting nitrate esters to norborneols, and then acetylated. Their rotations

thus reflect optical purities of acetates of three different origins in the deamination, *i.e.*, that formed as acetate, that formed as nitrate, and that formed as alcohol.

(2) The optical purity reported by Corey, *et al.*,[15] for the product from *exo*-amine was calculated on the assumption that the observed rotation is that of *exo*-acetate. These authors recognized that the optical purity of the *endo*-acetate product (their sample contained 4%) might be much higher, but seemed to feel that this would not affect the results appreciably. To be confident of this position, one would have to know the rotation of optically pure *endo*-acetate. This datum was not available to Corey, *et al.*, who stated that *exo*- and *endo*-acetates have "about the same magnitude of optical rotation." The uncertainty of this relationship has been alluded to previously,[3,6,13] and the matter is settled for the first time in the present paper (see Experimental). For reasons given in the Experimental, we are unable to convert Corey's observed rotation into a proper % retention figure. The reported value[15] is, however, unreliable even on the basis of the ·stated[15] assumption. The observed rotation[15] of $-0.892°$ would then receive a contribution of up to $-0.222°$ due merely to the presence of 4% of unracemized *endo*-acetate. In other words, as much as a quarter of the total rotation used[15] as a basis for the calculation of retention in the *exo* product could be attributable to *endo* product.

(3) In the case of the *endo*-amine, Corey, *et al.*,[15] used the scrambling of a deuterium label originally at C-2 as a measure of loss of skeletal integrity. Thus, *endo*-norbornylamine-2-*d* with 1.00 atom of deuterium per molecule gave norbornyl acetate, which upon ester cleavage and oxidation gave 2-norbornanone with 0.42 atom of deuterium per molecule (42% rearrangement of the label). This result was interpreted[15] as corresponding to 16% retention of optical activity and 84% racemization in a hypothetical stereochemical experiment and thus appeared to be in close agreement with the value of 15% retention found[15] for the *exo*-amine deamination. The conclusion was based on the assumption that the % racemization is measured by twice the % rearrangement, which is true only if deuterium scrambling measures *a single kind* of the two most likely racemization processes (Wagner–Meerwein rearrangement and 6,2-hydride shift). To the extent that deuterium scrambling results from *both* of these, it is an exaggerated measure of the true amount of racemization, for, taken in combination, these
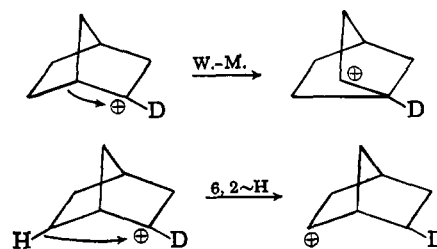
processes will produce skeletal rearrangement that is greater than half the racemization.[19b] That the apparent value[15] of 16% of product formed by non-racemizing processes in the *endo*-amine case (as measured by deuterium scrambling) is not incompatible with our observation of 21% (as measured by actual racemization) is shown by the following calculation.

(16) *Cf.* (a) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); (b) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2893 (1957); (c) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 1 (1956).

(17) S. J. Cristol and G. D. Brindell, *J. Am. Chem. Soc.*, **76**, 5699 (1954).

(18) *Cf.* also E. J. Corey and J. Casanova, Jr., *ibid.*, **85**, 165 (1963).

(19) (a) The variations in results do not seem to be attributable to optical fractionations occurring during the preparation of the *exo*-amine from *exo*-carboxylic acid, the Schmidt reaction being reproducible with high precision (see Experimental); (b) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

Corey, et al.,[15] examined the proton magnetic resonance spectrum of their norbornanone product in a search for 6,2-hydride shift but stated that they would not have detected 5% or less of such a process. Accordingly, we may take 5% as an upper limit of the total amount of 6,2-hydride shift. In terms of a threefold symmetric intermediate for hydride shift,[19b] this corresponds to 15% contribution of this path. For the purposes of this calculation, it is immaterial whether this is formulated as a discrete intermediate, e.g., VII; or the equivalent in terms of isotopic labeling, a 1:1:1 mixture of twofold symmetric nonclassical ions (VIII, IX, and X); or another operationally equivalent set of six classical ions. The total product acetate would then be made up of 21% of nonracemized,

VII   VIII   IX   X
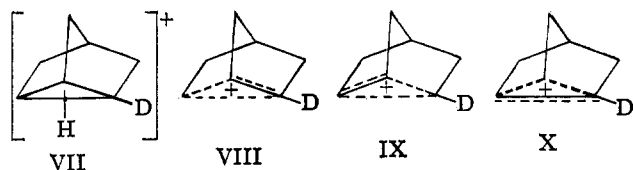
nonrearranged material, 15% of racemized material with 66.7% rearrangement, and 64% of racemized material with 50% rearrangement. The total % rearrangement would then be $0 + 10 + 32 = 42\%$, or just the observed[15] amount. This calculation shows that tracer scrambling, unless it is accompanied by a very accurate determination of the amount of 6,2-shift, is a deceptive measure of racemization in this system. In the experiment reported,[15] the inability to detect what superficially looked like a small amount of hydride shift could have led to a gross error in the estimate from tracer scrambling of % racemization.

Moreover, the assumption[15] of 0% hydride shift, which is necessary if the tracer scrambling result in the endo-amine deamination is to be equated directly with racemization, is incompatible with the proposed[15] mechanism. Since the cation derived from exo-amine deamination is suggested[15] to be the same as that from endo-amine deamination, it follows that if the latter does not suffer hydride shift, then the former also does not. But using Corey's figure of 15% retention for the exo-amine case and the known[19b] over-all 48% rearrangement in a ^{14}C-tracer scrambling experiment carried out under the same conditions, we calculate that the extent of rearrangement in the racemic portion of the product from exo-amine would be $48/0.85 = 56.5\%$. There is no way to achieve this much rearrangement without hydride shift. The calculated figure represents about 13% net 6,2-hydride shift ($3 \times 13 = 39\%$ contribution of the threefold symmetric path) in the racemic portion, and this same amount of hydride shift would have to occur in the case of endo-amine if the Corey mechanism held. A fit to the observed 42% over-all rearrangement figure for endo-amine would then require that the racemic portion of the product be 58% rearranged ($3 \times 0.13 \times 66.7 + 0.61 \times 50$) and that it make up 72% of the total product. The remaining 28% would then represent retention of skeletal integrity and hence of optical purity. This figure is almost twice as large as the 16% retention value deduced[15] from the assumption of 0% hydride shift in the endo-amine reaction. The latter assumption[15] leads, therefore, to an internal inconsistency, since either the value 16% retention, or the

mechanism proposed[15] to fit the value (or both) must be incorrect.[20a]

Although the proposal of complete mechanisms for the deaminations of the norbornylamines on the basis of the present evidence seems unwarranted,[20b] it is clear that the experimental results do not require the assumption[15] that all of the products derive from a carbonium ion.

Racemizing Processes in the Norbornyl Cation.— It is now possible to make a survey of the racemizing processes that occur in norbornyl cations. This involves comparisons of the extent of isotope-position rearrangement in the racemic portion of the product. For these calculations, the over-all ^{14}C-scrambling data of Roberts, Lee, and Saunders[19b] must be dissected in such a way as to omit from consideration that part of the product which involves neither isotopic scrambling nor loss of optical purity. This can be done by means of eq. 1, where R is the % rearrangement in the racemic portion of the product, N is the observed[19b] gross % rearrangement of isotope position, and P is the fraction of skeletal integrity retained. The quantity P is given by eq. 2, where F_x and F_n are the fractions of exo and endo products, and P_x and P_n are the respective optical purities.

$$R = N/(1 - P) \tag{1}$$

$$P = F_x P_x + F_n P_n \tag{2}$$

The experimental quantities required for eq. 1 and 2 are available from the data reported here and elsewhere,[4,5,10,19b,21] and are summarized in Table II, where calculated values for R are also given. It is assumed that racemization results from carbon and hydrogen shifts within cationic intermediates,[10,19b] not from the intervention of optically inactive neutral species such as norbornene or nortricyclene.[22] It is also assumed that the % rearrangement is insensitive to temperature, in agreement with the limited experimental test of the point.[19b]

At first glance, one gets the impression of a striking regularity of behavior of the cations in solvent acetic acid. The R-values for the acetolyses of endo- and exo-p-bromobenzenesulfonates appear to be identical within experimental error. Similarly, the R-values for deamination also are independent of the stereochemistry of the starting material, although the "deaminative" R seems to be different from the "acetolytic" R. Although these correspondences offer some superficially attractive bases for interpretation, the temptingly obvious conclusion that identical R's correspond to identical cation structures does not explain the apparently discordant R-values in aqueous solvent (Table II). From these data it seems that although the acetolytic racemizing processes are inde-

(20) (a) The apparent irreconcilability would be removed if there were a gross error in the ^{14}C-tracer experiment of Roberts, et al.,[19b] and the % rearrangement for the exo-amine product were 42.5% instead of 48%. This would allow 15% retention of skeletal integrity and 0% hydride shift. The discrepancy seems much too large to be ascribed to experimental error. Furthermore, Roberts reports[19b] direct evidence for 6,2-hydride shift in the aqueous fluoroboric acid deamination of a mixed endo-exo amine sample. It seems entirely probable that 6,2-shift also would occur in acetic acid. (b) For a discussion of the intricacies of deamination mechanisms and related processes, see E. H. White and C. A. Aufdermarsh, J. Am. Chem. Soc., **83** 1179 (1961).

(21) S. Winstein and E. Clippinger, unpublished; E. Clippinger, Dissertation, University of California at Los Angeles, 1955.

(22) The evidence on this point is incomplete. For a review, see ref. 23.

TABLE II

ISOTOPE POSITION REARRANGEMENTS IN RACEMIZING PROCESSES OF NORBORNYL DERIVATIVES

Reactant	Solvent	Gross % rearr., N	F_x	F_n	P_x	P_n	$R,^a$ %
exo-ROBs	HOAc	60.6	1.00	0.00	0.00	..	60.6
exo-ROBs	75% acetone	54.5	1.00	.00	.00	..	54.5
endo-ROBs	HOAc	56.0	1.00	.00	.07	..	60.4
endo-ROBs	75% acetone	44.5	1.00	.00	.13	..	51.2
exo-RNH₂, HONO	HOAc	48.0^b	0.98	.02	.11	1.00	54.0 ± 2
endo-RNH₂, HONO	HOAc	43.2^b	0.95	.05	.18	0.85	54.6 ± 4

^{a} Calculated from eq. 1; estimated uncertainty in R is about 0.5-1 unit unless otherwise indicated.　^{b} Value reported[19b] for the total product alcohol after lithium aluminum hydride reduction.　This presumably is derived from acetate, alcohol, and nitrate (see Table I). We assume that the gross N is the same as the N for acetate.　The resulting R is relatively insensitive to whether or not this assumption is strictly correct.

pendent of the geometry of the starting material, the hydrolytic ones are not.

To rationalize the results, the effects of ion-pair return must be taken into account. That solvolyses of norbornyl derivatives pass through ion-pair intermediates is clear from extensive previous studies by Winstein and his co-workers.[10,21,23a] The behavior of endo and exo derivatives differ, however. The intimate ion-pair from the exo compound returns to the covalent condition and is re-formed several times before actual solvolysis. This process results in rearrangement (or in the unsubstituted norbornyl case, racemization) of the starting substrate. The polarimetric vs. titrimetric rate ratio (k_α/k_t) shows that for every event leading to solvolysis product, exo-norbornyl p-bromobenzenesulfonate (exo-ROBs) is exposed to racemizing ion-pair formation about six times in acetic acid and about twice in 75% acetone. In the case of endo-ROBs, $k_\alpha = k_t$, so that if there is ion-pair return, it is without stereochemical consequences. If 6,2-hydride shift can occur in the ion-pair, the recycling in the exo derivative provides an opportunity for extra shuffling of the isotopic label that is denied to the endo. Although direct evidence on the question of hydride shift in ion-pairs derived from the parent norbornyl cation has not been available, these processes are facile in substituted norbornyl systems.[21,24,25] It therefore seems likely that the simple norbornyl system also experiences them, and that this is the most likely cause of the discrepancy between the exo and endo R-values in aqueous acetone. In principle, it is possible to dissect the over-all isotopic scrambling results in such a way as to reveal the extent of scrambling that occurs in each pass of exo-ROBs through the ion-pair condition, but it is doubtful that the accuracy[26] of the available data justify the calculation. Qualitatively, however, it is necessary to assume that the total contribution of 6,2-shift within the ion-pair to the over-all isotopic scrambling result is greater in aqueous acetone than in acetic acid if the results of Table II are to be explained in this way.

A quantitatively more significant comparison is that between the R-values for endo-ROBs in the two solvents. Here ion-pair return is not a factor, and the R-values measure scrambling processes that presumably occur at the solvated cation stage. The greater R-

value in acetic acid is in accord with the suggestion[10,19b,23b] that 6,2-shift follows Wagner–Meerwein rearrangement in the norbornyl cation and that the more highly nucleophilic aqueous solvent captures the cations more rapidly.

The R-values of Table II also bear on the question of the mechanism of solvolysis of endo-norbornyl p-bromobenzenesulfonate. It has been stated,[15] for example, that the possibility has not been excluded that the reaction may proceed by way of preliminary rearrangement of endo-sulfonate to the exo isomer. This would require identical R-values from endo and exo starting materials and thus appears to be in conflict with the 75% acetone results (Table II), where the discrepancy seems to be greater than experimental error.

The above analysis now permits a more meaningful examination of the R-values (Table II) for the deaminations in acetic acid of the norbornylamines. In these cases, R is essentially independent of the geometry of the starting amine. In the amine deaminations, there is no evidence that return to RN_2^+ can occur once carbon–nitrogen heterolysis is achieved. Although such a process is not inconceivable,[27] until it has been demonstrated in this system, there seems to be no advantage in invoking it. The correspondence in R-values for the two amine systems is then most simply taken to mean that both systems get only one chance to racemize and shuffle isotopic label, and that the intermediates for the racemic portions of the products are the same in both cases. (Note that this is not the conclusion reached by Corey,[15] who proposed that the intermediates for the total products were the same.) This intermediate presumably is merely the solvated norbornyl cation. It may be significant that the extent of 6,2-hydride shift in this species in acetic acid solvent seems to be somewhat greater in the cation from exo- or endo-ROBs than in that from exo- or endo-RNH₂. The experimental error in the "deaminative" R, however, is large enough (see Table II) to suggest that, for the present, the apparent gap between it and the "acetolytic" R be interpreted with diffidence.

Experimental[28]

Optical Rotation of endo-Norbornyl Acetate in Solvent Acetic Acid.—To a sample of 0.2401 g. of endo-norborneol,[13] $[\alpha]_D$

(23) (a) For a review, see J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Part 1, p. 168; (b) for discussion, see ibid., p. 145 ff.

(24) S. Winstein and A. Colter, unpublished; A. Colter, Dissertation, University of California at Los Angeles, 1956.

(25) W. G. Woods, R. A. Carboni, and J. D. Roberts, J. Am. Chem. Soc., 78, 5653 (1956).

(26) We are indebted to Professor J. D. Roberts for a discussion of this point.

(27) (a) For an example of internal return of a neutral species to a cation, see H. L. Goering and R. R. Josephson, J. Am. Chem. Soc., 83, 2588 (1961); (b) for an example of a reversible step in a diazonium salt decomposition, see J. M. Insole and E. S. Lewis, ibid., 85, 122 (1963); E. S. Lewis and J. E. Cooper, ibid., 84, 3847 (1962).

(28) Rotations at the sodium D line were measured at 25° in jacketed polarimeter tubes cooled with thermostated circulating water. The instrument was a Rudolph Model 80 high precision polarimeter reading directly to 0.001°. Capillary vapor chromatography was carried out with the Barber–Colman Model 20 instrument using argon carrier and a radium ionization detector with the operating variables specified. Packed column

+1.226° (CHCl₃), in a 2.00-ml. volumetric tube was added 0.3483 g. of acetic anhydride and 1.0 ml. of acetic acid. After 5 days at room temperature, the mixture was diluted to the mark with acetic acid and the rotation determined. On the assumption of complete reaction,[10] the sample showed $[\alpha]$D +10.5° (c 16.5 in acetic acid, l 1). Since the sample of endo-norborneol used had 65% of the rotation reported[10b] for the most highly resolved sample ($[\alpha]$D 1.89°, obtained from resolution of the acid phthalate) and gave 2-norbornanone with 59% of the rotation of optically pure (see below) material, the resolution of the acid phthalate[10b] was about 91% complete. The maximum rotation of endo-norborneol is thus $[\alpha]$D 2.08° (CHCl₃) and that of endo-norbornyl acetate $[\alpha]$D 17.8° (HOAc). Winstein and Trifan[10b] report $[\alpha]$D 14.00° (HOAc) for a sample of endo-norbornyl acetate of unspecified optical purity. However, since their most highly resolved sample was about 91% optically pure, the value 14.00° leads to a value of at least 15.4° for optically pure material. We have no information on the optical rotation of neat endo-norbornyl acetate or of endo-norbornyl acetate in solvent exo-norbornyl acetate. Since the rotation reported by Corey[15] is that of the undiluted liquid sample, we have no way of calculating % retention from his data.

Optically Active exo-Norbornylamine (Ix) by the Schmidt Reaction.—A solution of hydrazoic acid in chloroform, prepared from 10.5 g. of sodium azide, 10.5 ml. of water, 14.8 g. of concentrated sulfuric acid, and 100 ml. of chloroform, was dried over calcium sulfate and added to a solution of 10.5 g. of (+)-exo-norbornanecarboxylic acid,[4] $[\alpha]$D +6.40° (95% ethanol), 23% optically pure, in 50 ml. of chloroform. The mixture was cooled to 0°, stirred, and treated dropwise with 31 ml. of concentrated sulfuric acid. The ice bath was removed and the mixture allowed to come to room temperature, whereupon gas evolution began, followed by spontaneous boiling. After 15 min., the mixture was heated at reflux for 90 min., cooled to room temperature, and poured onto ice, the layers were separated, and the aqueous phase was washed with fresh chloroform. The aqueous layer was then made basic with dilute sodium hydroxide solution, the amine extracted with ether, and the ether layer dried over potassium hydroxide pellets. The ether layer was decanted and evaporated to dryness, and the residue was distilled in vacuo directly into tared 2.00-ml. volumetric tubes. The vacuum was broken by letting in dry nitrogen, and one of the tubes was removed, stoppered immediately, weighed, and made up to the mark with 5.58 N hydrochloric acid. The sample, 0.4384 g., showed α +1.077°, whence $[\alpha]$D +4.95° (in 5.58 N HCl). The procedure avoided handling of the exceedingly sensitive free amine, which rapidly forms a carbonate and therefore can be weighed in a conventional manner only with difficulty.

In a second run with the same batch of acid, there was obtained amine of $[\alpha]$D +4.72° (in 5.58 N HCl).

In a third run with acid of $[\alpha]$D +19.3°, 47.4 g. of acid gave 23.0 g. of amine, b.p. 77° (50 mm.). This material was assumed to have the same optical purity as the starting acid (69.5%). Another sample of amine was prepared from (−)-exo-acid of $[\alpha]$D −13.0°, 48% optically pure.

Correlation of exo-Norbornylamine (Ix) with 2-Norbornanone (VI).—To a magnetically stirred, ice-cooled solution of 3.3 ml. of 90% hydrogen peroxide in 15 ml. of ethylene chloride was added dropwise during 90 min. 14.7 g. of acetic anhydride. After completion of the addition, stirring was continued for 30 min. at 0° and 30 min. at room temperature. An additional 9 ml. of ethylene chloride was added, the mixture was heated to reflux, and 3.0 g. of exo-norbornylamine, $[\alpha]$D +4.72°, 23% optically pure, in 3 ml. of ethylene chloride was cautiously added dropwise during 30 min. There was a vigorous reaction, and a pale blue color remained at the end of the addition. After having been heated at reflux for another 15 min., the reaction mixture became yellow. Heating was continued for another 45 min., the mixture was cooled to 0°, washed with dilute ammonia and with water, dried over calcium sulfate, evaporated, and distilled. The product, a pale blue liquid, was collected as two arbitrary fractions, both with b.p. 72° (5 mm.). Fraction 1 weighed 0.87 g.; fraction 2 weighed 0.77 g.

Fraction 1 above was heated with 50 ml. of 10% sodium hydroxide on the steam bath for 1 hr. The mixture was cooled, poured into 3 N hydrochloric acid, and stirred for 3 hr. Extraction with ether gave a pale blue solution which, after having

been washed with water and dried over magnesium sulfate, was evaporated carefully under a Vigreux column. Two sublimations of the residue at aspirator pressure gave a crystalline solid which still retained a trace of blue color. Most of this was removed by treatment of a pentane solution of the material with charcoal, filtering, evaporating, and resubliming the residue. In this way there was obtained 0.107 g. of 2-norbornanone, vapor chromatographically homogeneous on a 40-m. tri-(β-cyanoethoxy)-propane (TCEP) capillary column at 107° and 10 p.s.i. The retention time and infrared spectrum were identical with those of authentic 2-norbornanone. The material had $[\alpha]$D +6.51° (c 5.3 in CHCl₃). The maximum rotation of 2-norbornanone calculated on the assumption that the Schmidt reaction involves complete retention is 28.3°. From the correlation[12] with exo-norbornyl acetate, it is 29.2°.

Acetolysis of Racemic endo-2-Norbornyl p-Bromobenzenesulfonate.—A sample of the racemic p-bromobenzenesulfonate[10a] was carefully recrystallized thrice from ether–pentane to constant m.p. 62°. This sample was free of hydroxyl impurity as judged by the infrared spectrum measured under conditions where 1% of norborneol could have been detected. A boiling solution of 0.227 g. of potassium acetate in 14.9 ml. of glacial acetic acid was treated in one portion with a solution of 0.625 g. of the sulfonate ester in 3.7 ml. of acetic acid. The mixture was boiled for 17.25 hr., diluted with water, and extracted with hexane. The hexane solution, after having been washed with bicarbonate and water, was dried over magnesium sulfate, and the hexane evaporated with a Vigreux column. The residue was distilled bulb-to-bulb, and the distillate was examined vapor chromatographically on the TCEP capillary column at 122° and 7 p.s.i. It was better than 99.9% homogeneous. The acetate was reduced with lithium aluminum hydride in ether, and the resulting alcohol was isolated by addition of sodium sulfate solution, washing the ether layer with water, drying with magnesium sulfate, and evaporating. Sublimation of the crystalline residue and examination on a 30-m. Ucon HB-550 capillary column at 70° and 80 p.s.i. showed it to be at least 99.5% exo-norborneol. No endo-norborneol could be detected. Under these conditions, the exo-alcohol emerged at 30.75 min. and the endo at 35 min. retention times. Contamination of exo by as little as 0.5% of endo would have been detected without difficulty, as was established by controls.

Amine Deaminations. A. endo-Norbornylamine (In).—The crude product obtained previously[3] from deamination of In in acetic acid contained[3] 5.8% of nitrate ester as indicated by elemental analysis for nitrogen. This material was re-examined on the TCEP capillary at 123° and 7 p.s.i. and showed peaks for acetate (80%), alcohol (16%), and a third peak emerging last (4%) which we assume was nitrate. The acetate was isolated by preparative vapor chromatography on a 6-m. × 4-cm. TCEP column (20% on Chromosorb P) at 115–120° and a flow rate of 700 ml./min. The order of retention times was different on this column, the alcohol emerging after the acetate and nitrate. Sample sizes were 0.4–0.5 ml. The alcohol was collected as a crystalline solid, which was shown to consist of 5.3% endo- and 94.7% exo-norborneols by capillary v.p.c. on the Ucon column. The acetate was collected as a colorless liquid, homogeneous on the TCEP capillary column, α_{obsd} −1.059° (neat, 1 dm.). After repassage through the preparative column, the acetate was distilled bulb-to-bulb. It had α_{obsd} −1.082° (neat, 1 dm.), $[\alpha]$D −1.24° (c 25 HOAc). Reduction of a sample with lithium aluminum hydride–ether gave a norborneol mixture which capillary v.p.c. on the Ucon column showed to be 95.3% exo and 4.7% endo. The experimental error in the absolute magnitude of these figures is about ±0.5%.

Optical Purity of endo-Acetate Product.—Another portion of the same reaction product was chromatographed on alumina under the conditions described in B. The acetate fraction, 3.05 g., homogeneous by v.p.c. (TCEP capillary), and 7.7 g. of p-toluenesulfonic acid monohydrate were made up to 53.5-ml. volume with glacial acetic acid, producing a solution 0.37 M in norbornyl acetate and 0.76 M in sulfonic acid. The solution was heated at 75–80° for 3.5 hr., poured onto ice, extracted with pentane, dried over magnesium sulfate, evaporated under a Vigreux column, and the residue distilled bulb-to-bulb to give 2.45 g. of a partially racemized acetate mixture. This material was converted to alcohols with lithium aluminum hydride in the manner described above, and the crystalline product sublimed to give 1.35 g. of material.

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vapor chromatography was carried out with the Perkin–Elmer Model 154 instrument.

The mixture of alcohols, 2.03 g. of p-benzoquinone, 8.1 g. of aluminum t-butoxide, and 95 ml. of dry benzene were heated at reflux for 21 hr., cooled, allowed to stand overnight, and filtered from insoluble material, the filter cake was washed with ether, and the combined filtrate and washings were washed successively with ice-cold 10% sulfuric acid, 10% potassium hydroxide, and water. After having been dried over magnesium sulfate, the solution was evaporated under a Vigreux column and the residue sublimed to give 0.50 g. of 2-norbornanone. This material was completely free of norborneols (<0.1%) under conditions (2 m. × 0.5 cm., 20% Ucon LB-550-X on Chromosorb P, at 127° and 10 p.s.i. helium) where the ketone and alcohols were well separated (retention times of 12.9 and 18.9 min., respectively). This material was examined in duplicate solutions in the laboratory of Professor Kurt Mislow with an automatic recording Rudolph spectropolarimeter. The following data were recorded at 23°:

Solution 1, 1.435% in isooctane, showed observed rotations of +0.024° at 320 mµ and of +0.016° at 325 mµ in a 0.1-dm. tube. The specific rotations are thus $[\alpha]_{320}$ +17.6° and $[\alpha]_{325}$ +12.2°. From the respective values for the maximum rotations at these wave lengths[12] (1234 and 983°), the optical purity is calculated to be 1.3%.

Solution 2, 1.695% in isooctane, showed $[\alpha]_{320}$ +18.6° and $[\alpha]_{325}$ +13.0°, whence the optical purity is calculated to be 1.4%.

Control.—As a control experiment on the accuracy of the method at these low rotations and on the possibility of fractionation during oxidation and isolation, the following experiment was performed. A mixture of 0.522 g. of endo-norbornyl acid phthalate, $[\alpha]$D +2.554° (51.0% optically pure[13]) and 8.588 g. of racemic exo-norbornyl acid phthalate was converted to alcohols by steam distillation from 30% sodium hydroxide solution. The crude alcohols were oxidized to ketone by the Oppenauer procedure described above, and the resulting product (which was homogeneous by v.p.c.) was examined in the spectropolarimeter. It showed $[\alpha]_{320}$ +34.3°, $[\alpha]_{325}$ +30.0°, 2.9% optically pure. The optical purity anticipated from the gravimetric composition of the acid phthalate mixture was 2.92%.

B. exo-Norbornylamine (Ix).—The conditions were those used[3] in the deamination of endo-amine. To a solution of 11.5 g. of (+)-exo-norbornylamine, 69.5% optically pure (see above), in 77 ml. of glacial acetic acid was added 11.5 g. of sodium nitrite

over a 2-hr. period. After standing overnight, the mixture was treated with 3 g. more of sodium nitrite and stirred an additional 2 hr. Then 30 ml. of water was added, and the mixture was stirred for an hour, cooled, and poured into 320 ml. of cold 20% sodium hydroxide solution while the temperature was kept below 25°. The mixture was extracted with pentane, the extract was washed with water, cold 10% hydrochloric acid, and water, dried over magnesium sulfate, evaporated with a Vigreux column, and the residue was distilled to give three fractions: (1) 0.92 g., b.p. 31–80° (23 mm.); (2) 0.88 g., b.p. 80–84° (23 mm.); (3) 5.36 g., b.p. 84–87° (23 mm.). Fraction 3 was chromatographed on Merck acid-washed alumina. The acetate fraction was cleanly eluted with 20% ether in pentane; the alcohol fraction was eluted with pure ether. The acetate fraction was distilled bulb-to-bulb. It was free of alcohol or nitrate contaminant and contained less than 1% of adhering solvent. Early chromatographic fractions of acetate had $[\alpha]$D +1.56° (c 20 in HOAc) and later ones had essentially the same rotation, $[\alpha]$D +1.61° (c 20 in HOAc). Lithium aluminum hydride reduction and analysis of the resulting alcohol mixture with the Ucon capillary column showed the acetate fraction to consist of 97.9% exo and 2.1% endo material. The alcohol fraction contained approximately 99% exo and 1% endo material. In a separate run, the composition of the reaction mixture before chromatography was determined by v.p.c. with the TCEP capillary column. This is the source of the figures for % acetate, % alcohol, and % nitrate given in Table I. Three runs under the same conditions followed by examination of the chromatographed acetate fraction gave the following results. Run 1: Amine from (−)-acid of 48% optical purity gave acetate of $[\alpha]$D −0.795° (c 21 in HOAc). The acetate had the composition 97% exo, 3% endo. Run 2: Amine from (+)-acid of 69.5% optical purity gave acetate of $[\alpha]$D +1.58° (HOAc) containing 98% exo, 2% endo. Run 3: Amine of the same origin as in run 2 gave acetate of $[\alpha]$D +1.46° (HOAc) containing 98% exo, 2% endo. Control experiments showed that chromatography by the above procedure caused neither fractionation of endo- and exo-acetates nor racemization of exo-acetate.

[Contribution from the Department of Chemistry of Stanford University, Stanford, Calif.]

Optical Rotatory Dispersion Studies. XCV.[1] Effect of Ring Size in Some Bicyclic Ketones[2]

By Carl Djerassi and J. E. Gurst

A series of bicyclic ketones of known absolute configuration was synthesized, in which the carbonyl-containing ring was five- and six-membered, while the adjacent ring possessed six, seven, or eight carbon atoms. Optical rotatory dispersion measurements demonstrated that the sign of the Cotton effect is not affected by the size of the adjacent ring in saturated bicyclic ketones, but that such a generalization was not warranted in α,β-unsaturated ones. The implications of these results for absolute configurational assignments by means of optical rotatory dispersion are emphasized.

Introduction

The guaianolides and other perhydroazulenes represent an important class of naturally occurring sesquiterpenes,[3] which are being investigated actively in a number of laboratories. Absolute configurational assignments of such sesquiterpenes by chemical correlations have proved to be quite laborious,[4] and frequently

recourse has been taken to optical rotatory dispersion measurements.[5,6]

In order to apply the standard rotatory dispersion method[7] to the determination of absolute configuration of such sesquiterpenic ketones, reference compounds of known configuration are required. Since the sesquiterpenes under consideration are based on the bicyclo[5.3.0]decane system (I) with the carbonyl group in the five-membered ring, no direct models were avail-

(1) Paper XCIV: A. Moscowitz, K. M. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci. U. S.*, **50**, 799 (1963).

(2) Supported by grants No. GM-06840 and CA-07195 from the National Institutes of Health of the U. S. Public Health Service.

(3) For leading references see (a) T. Nozoe and S. Itô in (L. Zechmeister, Ed.) "Progress in the Chemistry of Organic Natural Products," Vol. 19, Springer, Vienna, 1961, pp. 32–119; (b) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(4) *Inter alia*, E. J. Eisenbraun, T. George, B. Riniker, and C. Djerassi, *ibid.*, **82**, 3648 (1960); L. Dolejš, A. Mironov, and F. Šorm, *Collection Czech.*

Chem. Commun., **26**, 1015 (1961); H. Minato, *Tetrahedron*, **18**, 365 (1962), and earlier references cited therein.

(5) C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).

(6) For recent examples see W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963); J. B. Hendrickson, *Tetrahedron*, **19**, 1387 (1963).

(7) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 10.