1, Wiley: New York, N.Y., 1974; p 106.
(32) Kuhlmann, K. F.; Grant, D. M. *J. Am. Chem. Soc.*, **1968**, 90, 7355–7357.
(33) Oldfield, E.; Norton, R. S.; Allerhand, A. *J. Biol. Chem.*, **1975**, 250, 6368–6380.
(34) Pines, A.; Gibby, M. G.; Waugh, J. S. *Chem. Phys. Lett.*, **1972**, 15, 373–376.
(35) Pausak, S.; Pines, A.; Waugh, J. S. *J. Chem. Phys.*, **1973**, 59, 591–595.
(36) Pausak, S.; Tegenfeld, J.; Waugh, J. S. *J. Chem. Phys.*, **1974**, 61, 1338–1344.
(37) Reinhold, D. F. Unpublished results, Merck Sharp and Dohme Research Laboratories.
(38) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.*, **1970**, 92, 1347–1350.
(39) Zehavi, U.; Ben-Ishai, D. *J. Org. Chem.*, **1961**, 26, 1097–1101.
(40) Opella, S. J.; Nelson, D. N.; Jardetzky, O. *J. Chem. Phys.*, **1976**, 64, 2533–2535.
(41) Canet, D. *J. Magn. Reson.*, **1976**, 23 361–364.
(42) Karady, S.; Ly, M. G.; Pines, S. H.; Chemerda, J. M.; Sletzinger, M. *Synthesis*, **1973**, 50–51.
(43) Reference 28, pp 315–316.
(44) Levy, G. C.; Cargioli, J. D.; Anet, F. A. L. *J. Am. Chem. Soc.*, **1973**, 95, 1527–1535.
(45) Wehrli, F. W. *Topics in Carbon-13 NMR Spectroscopy*, Vol. 2, Wiley: New York, N.Y., 1976; pp 343–389.

Stereochemistry of Allylic Rearrangements. 16. Ion-Pair Return Associated with Solvolysis of *exo*- and *endo*-Bicyclo[3.2.1]oct-3-en-2-yl *p*-Nitrobenzoate in Aqueous Acetone

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Abstract: Ion-pair return associated with solvolysis of *exo*- and *endo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (**4**-OPNB and **6**-OPNB) in aqueous acetone results in racemization of optically active ester (reaction 3), equilibration of the carboxyl oxygen atoms (reaction 4), and exo ⇄ endo isomerization (reaction 5). All processes are first order and intramolecular. Rate constants for solvolysis (k_t), loss of optical activity (k_α), racemization corrected for geometric isomerization (k_{rac}), and oxygen equilibration (k_{eq}) have been determined for solvolysis of both isomers in 80 and 90% acetone. In all cases $k_\alpha > k_t$ and the initially formed solvolysis product, >99% exo alcohol (**4**-OH), is racemic. For **6**-OPNB, k_{rac} and k_{eq} are similar if not the same. This indicates that ionization gives an intermediate with equivalent carboxyl oxygen atoms and allylic carbon atoms. However, for **4**-OPNB, k_{eq} is three to five times larger than k_{rac}. In this case there is a path for randomizing the carboxyl oxygen atoms without loss of optical or geometric configuration. This shows that, although the unperturbed cation (**3**) is symmetrical, the initially formed ion-pair intermediate is not, i.e., the enantiomeric allylic *p*-nitrobenzoates give enantiomeric intermediates.

In earlier work we investigated the solvolysis of α,γ-dimethylallyl[1] and *cis*- (**1a**)[2b] and *trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoates (**1b**)[2a] in aqueous acetone (eq 1). These systems are related to symmetrical cations and thus solvolysis of optically active substrates results in loss of optical activity (eq 2). In each case, ion-pair return results in racemization of optically active substrate (eq 3) and randomization of the carboxyl oxygen atoms of ^{18}O-labeled ester (eq 4). These transformations are intramolecular, i.e., no exchange with added *p*-nitrobenzoic acid.[1,2]

$$\mathrm{ROCOAr} \xrightarrow{k_t} \mathrm{ROH} + \mathrm{ArCO_2H} \qquad (1)$$

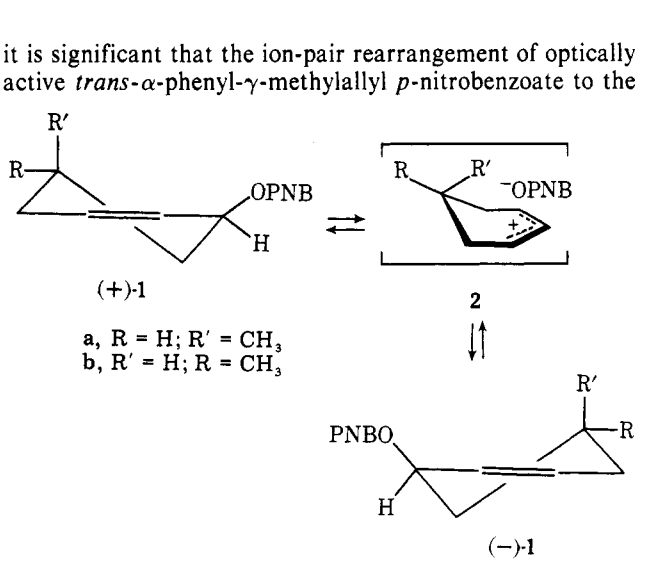
$$(d \text{ or } l)\text{-ROCOAr} \xrightarrow{k_\alpha} \text{inactive products} \qquad (2)$$

$$(d \text{ or } l)\text{-ROCOAr} \xrightarrow{k_{rac}} dl\text{-ROCOAr} \qquad (3)$$

$$\mathrm{R\text{-}OC^{18}OAr} \xrightarrow{k_{eq}} \mathrm{R\text{-}{}^{18}OC^{18}OAr} \qquad (4)$$

$$\textit{exo}\text{-R-OCOAr} \underset{k_t^{en}}{\overset{k_t^{ex}}{\rightleftharpoons}} \textit{endo}\text{-ROCOAr} \qquad (5)$$

Ion-pair return associated with solvolysis of the isomeric 5-methyl-2-cyclohexenyl *p*-nitrobenzoates (**1**) is completely stereospecific, i.e., there is no detectable geometric isomerization.[2] Presumably in this case a conformational factor, rather than inherent structural properties of allylic ion-pair intermediates, controls the stereochemistry.[3] In this connection it is significant that the ion-pair rearrangement of optically active *trans*-α-phenyl-γ-methylallyl *p*-nitrobenzoate to the



trans-γ-phenyl-α-methylallyl isomer involves substantial (~70%) loss of optical configuration.[4]

Evidently, in flexible cyclohexenyl systems such as **1**, the quasi-axial conformation is related to the best transition state for cleavage or formation of the allyl bond.[3] This means that the isomeric 5-methyl-2-cyclohexenyl *p*-nitrobenzoates give symmetrical cations that differ conformationally as illustrated by the **1** → **2** transformation. The anion is generated on the side of the out of plane C-5 carbon atom and this side is also favored for capture of the cation (microscopic reversibility). Thus the

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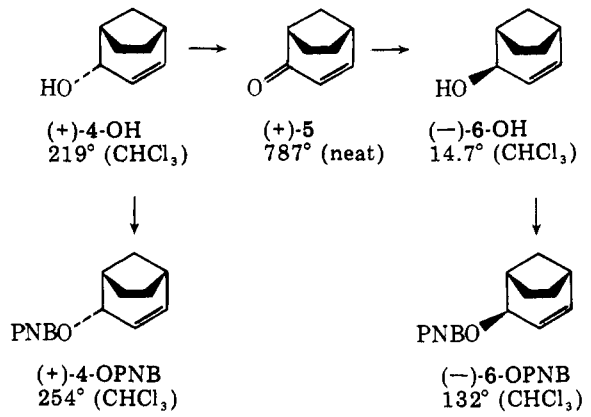
Scheme I



initially formed intermediate is conformationally predisposed for return with preservation of geometric configuration.[3] Or, to put it another way, return with inversion would require a conformational change as well as migration of the anion to the other side of the allyl plane.

We now report the results of a similar investigation of the solvolysis of *exo*- (**4**-OPNB) and *endo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (**6**-OPNB) in aqueous acetone. In this bicyclic system the symmetrical allylic cation (**3**) is rigid and

3

structurally independent of the epimer from which it is derived. Thus the only difference in ion-pair intermediates derived from the two isomers is in the location of the anion.

Results

The preparation of **4**-OH from the *endo*-bicyclo[2.2.2]-oct-5-en-2-yl system was reported earlier.[5] In the present work a superior method for large-scale preparation of **4**-OH was developed which involves allylic bromination of readily available bicyclo[3.2.1]oct-3-ene,[6] followed by hydrolysis of the bicyclic allylic bromide. As would be expected from earlier work, the latter reaction is completely stereoselective and gives **4**-OH without contamination by the endo isomer (**6**-OH).

The endo system (**6**) was derived from **4**-OH as shown in Scheme I. This involved chromic acid oxidation[7] of the exo alcohol to bicyclo[3.2.1]oct-3-en-2-one (**5**) followed by $LiAlH_4$ reduction (inverse addition) of the unsaturated ketone. This reduction gave a mixture consisting of 89% **6**-OH, 2% **4**-OH, 4% bicyclo[3.2.1]octan-2-one, and 5% of a mixture of saturated bicyclo[3.2.1]octan-2-ols.[8] The allylic alcohols were separated from the saturated contaminants by silver nitrate extraction which gave 6-OH containing <2% of **4**-OH. The *p*-nitrobenzoate derivatives (**4**-OPNB and **6**-OPNB) used in the kinetic experiments were shown to be configurationally homogeneous by saponification (methanolic KOH) and examination of the resulting alcohol by GC.

The resolution of the *exo*-bicyclo[3.2.1]oct-3-en-2-yl system (**4**) and determination of absolute rotations for **4**-OH, **4**-OPNB, and **5** have been reported.[5a] The relative rotations observed in the present work were in excellent agreement with the earlier results. Absolute rotations and configurations are shown in Scheme I. Configurations are known from the correlation with the corresponding active saturated bicyclo[3.2.1] compounds of known configuration.[8]

Optically active **6**-OH was derived from active **4**-OH by oxidation to **5** followed by reduction. In this case **4**-OH was oxidized to **5** with manganese dioxide. This reaction does not result in loss of optical purity in the 5-methyl-2-cyclohexenyl system (**1**)[9] and presumably the optical configuration is fully preserved in the **4**-OH → **5** transformation. Silver nitrate extraction of the $LiAlH_4$ reduction product results in partial racemization of active **6**-OH and thus could not be used to separate active **6**-OH from the saturated contaminants. The active **6**-OPNB used in the polarimetric experiments was derived from the reduction product and contained known amounts of saturated contaminants (determined by saponification with methanolic potassium hydroxide and GC analysis of the resulting alcohol mixture). These contaminants are optically stable under the conditions of the kinetic experiments and thus do not complicate determination of k_α for this isomer.

To correlate rotations of **6**-OH and **6**-OPNB with **5**, a homogeneous sample of active **6**-OH was obtained from the reduction product by chromatography on silica gel—chromatography of the *p*-nitrobenzoate (**6**-OPNB) results in racemization. Control experiments showed that chromatography of **6**-OH, conversion to **6**-OPNB, and regeneration of **6**-OH by saponification with methanolic potassium hydroxide does not result in loss of optical configuration.

Solvolysis of *exo*- (**4**-OPNB) and *endo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (**6**-OPNB) in aqueous acetone is accompanied by ion-pair return which results in racemization of optically active substrate (randomization of the allylic carbon atoms). Thus the polarimetric rate constant (k_α, eq 2) exceeds the titrimetric rate constant (k_t, eq 1). Titrimetric (k_t) and polarimetric (k_α) rate constants for solvolysis of **4**-OPNB and **6**-OPNB in 80 and 90% aqueous acetone (v/v) are presented in Table I. These rate constants were determined by methods described earlier.[1,2]

In the titrimetric experiments reactions were followed to ~80% completion and infinity titers were in good agreement with calculated values. Rate constants were steady in all cases except for solvolysis of the endo ester (**6**-OPNB) in 90% acetone in which case an upward drift of about 5% at 75% reaction was observed. This results from isomerization to the more reactive exo isomer. At 75% reaction the unsolvolyzed ester contains 18% **4**-OPNB. Isomerization is also involved in the other cases; however, the amount of epimer that accumulates is low (~5% at 75% reaction) and does not cause a detectable drift in the integrated first-order constants.

Both **4**-OPNB and **6**-OPNB give **4**-OH containing less than 1% of the endo isomer (**6**-OH) as the initial product. Under the conditions of the kinetic experiments, **4**-OH isomerizes slowly and eventually gives an equilibrium mixture of 72% exo (**4**-OH) and 28% endo (**4**-OH) isomer. For solvolysis of **4**-OPNB, the product contains 0.6% of the endo alcohol (**6**-OH) at 10% reaction and this increases to 2% at 50% solvolysis. Similarly, at 10% solvolysis, the product derived from the less reactive

Table I. Titrimetric (k_t) and Polarimetric (k_α) Rate Constants for Solvolysis of *exo*- (**4**-OPNB) and *endo*-Bicyclo[3.2.1]-oct-3-en-2-yl *p*-Nitrobenzoate (**6**-OPNB) in Aqueous Acetone at 99.6 °C.

isomer[a]	k_t,[b] 10^4 min^{-1}	k_α,[b] 10^4 min^{-1}
	A. 80% Acetone (v/v)	
4-OPNB	10.2 ± 0.1[c]	14.4 ± 0.1[d]
6-OPNB	2.80 ± 0.03	3.20 ± 0.06
	B. 90% Acetone (v/v)	
4-OPNB	0.775 ± 0.007	1.12 ± 0.01
6-OPNB	0.338 ± 0.006	0.615 ± 0.015

[a] Substrate concentration 0.04 M except as indicated. [b] Values are average and average deviation of five to seven points; reactions followed to 75–80% completion. [c] Average and average deviation of four independent experiments in which substrate concentration was varied from 0.02 to 0.04 M. [d] Average of two independent experiments with substrate concentrations of 0.02 and 0.04 M.

6-OPNB contains 1.3% 6-OH and this increases to 9% at 80% reaction. Control experiments with pure 4-OH showed that not all of the endo alcohol detected at early stages of the reaction results from isomerization of 4-OH. However, from these experiments it is clear that the initial product contains <1% of the endo isomer. The stereoselective exo capture of the bicyclic carbonium ion (3) is consistent with our earlier observations.[5]

Solvolysis of optically active 4-OPNB and 6-OPNB results in first-order loss of optical activity. Polarimetric reactions were followed to 80% completion and in all cases k_α was steady. Observed changes in rotations were about 5° for 4-OPNB and 1° for 6-OPNB and rotations were determined with a precision of ±0.005°. Thus k_α as well as k_t can be determined with good precision.

The optically active 4-OPNB used in the polarimetric experiments was homogeneous and solvolysis resulted in complete loss of optical activity. In the polarimetric experiments with active 6-OPNB the final rotation was of opposite sign and about 4% as large as the original value. This residual rotation resulted from the presence of unreactive optically active contaminants in the active 6-OPNB. The final rotation was stable and no change was observed on heating for an additional 16 half-lives.

Evidently, solvolysis of active 4-OPNB and 6-OPNB gives completely racemic products. The exo alcohol (4-OH) is not optically stable under the conditions for solvolysis. However, the rate of racemization is slow relative to solvolysis. In a control experiment, racemic 4-OPNB was solvolyzed in 80% acetone containing active 4-OH. At 65% solvolysis ~50% of the original activity remained. In a product study, the 4-OH isolated at 45% reaction for solvolysis of active 4-OPNB had no detectable rotation. Because of high rotations in the exo series, as little as 1% retention of optical configuration could have been detected.

The formation of completely racemic products indicates that the symmetrical allylic cation (3) is the product-forming intermediate. This result is similar to our earlier observation that the isomeric 5-methyl-2-cyclohexenyl *p*-nitrobenzoates give completely racemic products.[2,10] However, our results are in contrast to the recent report[11] that solvolysis of cyclohex-2-enyl 3,5-dinitrobenzoate in 60% aqueous acetone involves 64% retention of optical configuration. We have no explanation for the difference in behavior of the cyclohexenyl systems except for the possiblity that acyl–oxygen cleavage may be involved in the latter case.

In the present case it is clear from the product studies that solvolysis involves exclusive alkyl–oxygen cleavage—the initial product from both isomers is completely racemic alcohol consisting of >99% of the exo isomer (4-OH). Alkyl–oxygen cleavage is also indicated by the high solvolytic reactivity—4-OPNB and 6-OPNB are more reactive than cyclohexyl *p*-nitrobenzoate in 80% acetone at 100 °C[9] by factors of 1200 and 330. Presumably the secondary cyclohexyl *p*-nitrobenzoate undergoes acyl–oxygen cleavage. It should also be noted that the initial product derived from ether-^{18}O labeled 4-OPNB and 6-OPNB contains no excess ^{18}O.

The titrimetric constants (k_t) in Table I were determined in the usual manner from the rate of formation of acid. This does not correspond to the total rate of disappearance because of the accumulation of the epimer in the unsolvolyzed ester. The reactions involved in solvolysis are summarized in Scheme II. The integrated rate equation for this process is complex;[12] however, a simplifying approximation can be made because isomerization is relatively slow.

Rate constants for total disappearance of starting ester ($k_t + k_i$) were determined using eq 6. This equation differs from

$$(k_t + k_i)t = \ln [RX]_0/[RX]_t F \qquad (6)$$

that used to determine k_t only by the last term, F, which is the mole fraction of the remaining ester with the original configuration. Or, to put it another way, the integrated rate equation has been modified to account for accumulation of the geometric isomer. To determine F, unsolvolyzed ester was isolated at six appropriate time intervals and compositions were determined by $LiAlH_4$ reduction followed by GC analysis of the diastereomeric bicyclic alcohols.

This treatment ignores the reverse reaction of the isomerization in Scheme II and eq 6 applies only during early stages of the isomerization. However, because of the high k_t/k_i ratio, isomerization is in the early stages during the period that reactions were followed (to ~80% solvolysis). Thus the simplifying approximation appears justified.

Values of ($k_t + k_i$) are presented in Table II. Except for solvolysis of 6-OPNB in 90% acetone, this composite constant was steady as would be expected since k_t was steady and F varied only from about 0.98 to 0.92 during the reactions. For solvolysis of 6-OPNB in 90% acetone, ($k_t + k_i$) showed a slight downward trend and the value in the table was obtained by extrapolation to zero time. In this case isomerization is more important than in the other cases—F varies from 0.95 at 18% reaction to 0.80 at 75% reaction—and there is a detectable upward drift in k_t because of the accumulation of the more reactive exo isomer. Presumably the downward drift in ($k_t + k_i$) results from the back reaction of the isomerization. The rate constants for isomerization (k_i) shown in Table II were obtained by difference from ($k_t + k_i$) and k_t.

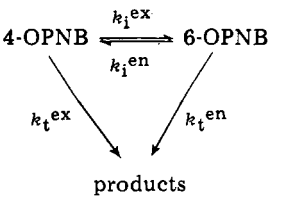
The gap between the polarimetric constant (k_α) and the constant for disappearance of the substrate ($k_t + k_i$) results from ion-pair return to racemic substrate. Rate constants for racemization of remaining ester with the original configuration (k_{rac}) are included in Table II. These were determined by difference (eq 7). This relationship involves the implicit as-

Table II. Rate Constants for Solvolysis of 4-OPNB and 6-OPNB in Aqueous Acetone at 99.6 °C.

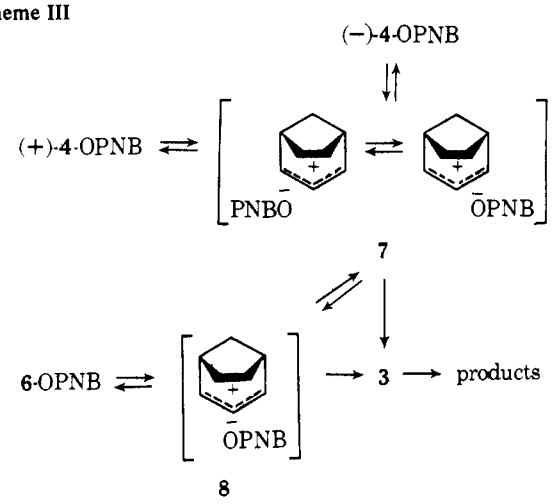
isomer	$(k_t + k_i)$,[a] 10^4 min^{-1}	k_i,[b,c] 10^4 min^{-1}	k_{rac},[c,d] 10^4 min^{-1}	k_{eq}, 10^4 min^{-1}
	A. 80% Acetone (v/v)			
4-OPNB	10.7 ± 0.1	0.5 ± 0.2	3.7 ± 0.2	10.4 ± 0.1[e]
6-OPNB	2.96 ± 0.01	0.17 ± 0.06	0.24 ± 0.09	0.363 ± 0.02[f]
	B. 90% Acetone (v/v)			
4-OPNB	0.85 ± 0.1	0.07 ± 0.02	0.28 ± 0.02	1.39 ± 0.05[e]
6-OPNB	0.47[g]	0.13 ± 0.03	0.15 ± 0.03	0.116 ± 0.01[h]
			0.12 ± 0.02[i]	

[a] Average and average deviation of five appropriately spaced points covering 75% reaction. [b] Determined from preceding column and k_t from Table I. [c] Uncertainties determined from limiting values of rate constants. [d] Determined from k_α (Table I) and $k_t + k_i$, i.e., $k_{rac} = k_\alpha - (k_t + k_i)$. [e] Average of three points (each in triplicate) for about 25, 50, and 75% oxygen equilibration. [f] Reaction could only be followed to 16% completion because of unfavorable k_t/k_{eq} ratio. [g] Value obtained by extrapolation to zero time. [h] Reaction could only be followed to 34% completion because of unfavorable k_t/k_{eq} ratio. [i] Determined directly from rotations of isolated samples of unsolvolyzed ester.

Scheme II



Scheme III



sumption that isomerization gives completely racemic epimer.

$$k_\alpha - (k_t + k_i) = k_{rac} \quad (7)$$

The rate constant for racemization of **6**-OPNB in 90% acetone at 99.6 °C was also determined by isolating samples of unsolvolyzed substrate at appropriate times and determining k_{rac} directly from the optical purity of the unsolvolyzed **6**-OPNB. This is the case where the indirect determination of k_{rac} was judged to be least reliable because of the drift in $(k_t + k_i)$. Unsolvolyzed ester was isolated at times corresponding to 30 and 58% solvolysis. Pure **6**-OPNB could not be separated from the endo isomer without racemization and thus the isolated ester was saponified and pure **6**-OH was isolated by chromatography on silica gel. All operations were shown to preserve optical configuration. A sample of **6**-OH was also derived from the original active **6**-OPNB and k_{rac} was determined from the two rotations. As shown in Table II, k_{rac} determined directly agrees, within the combined uncertainties, with the value obtained indirectly with eq 7.

In systems such as the present, k_α corresponds to total ionization provided that the ion pair, as well as the unperturbed cation, is symmetrical.[1,2] In the present case $k_\alpha - k_t$ corresponds to total return to racemic ester including return to the epimer, and k_{rac} is the constant for return to racemic ester with the original configuration.

An independent method for measuring return is determining the rate of equilibration of the carboxyl oxygen atoms in the unsolvolyzed ester (reaction 4).[1,2] In this work we have determined k_{eq} (randomization of carboxyl oxygen atoms) for comparison with k_{rac} (randomization of allylic carbon atoms) for both isomers.

The rate constants for oxygen equilibration (k_{eq}) in Table II were determined by a method described earlier.[1,2] Carbonyl-^{18}O labeled **4**-OPNB and **6**-OPNB containing about 5% excess ^{18}O were solvolyzed and samples of unsolvolyzed ester were isolated at times corresponding to about 25, 50, and 75% solvolysis. In all cases the total ^{18}O content remained constant. Thus in this system there is no enrichment due to an isotope effect.[2b]

To determine the ^{18}O distribution, the ester was reduced with $LiAlH_4$ to the corresponding alcohol which contains the ether oxygen atom of the isolated ester. The alcohol was purified by chromatography on silica gel which removes the epimer. Chromatography of the ester results in oxygen equilibration and thus the epimer could not be removed at that stage. The homogeneous alcohol was reconverted to the *p*-nitrobenzoate derivative for determination of the ^{18}O content. In earlier work it was found that for consistency it is necessary to use the same derivative for determination of relative ^{18}O contents.[1b]

Control experiments showed that $LiAlH_4$ reduction of carbonyl-^{18}O ester gives ^{18}O free alcohol and that reduction of ether-^{18}O ester gives alcohol which after chromatography on silica gel gives a *p*-nitrobenzoate derivative with the original ^{18}O content. These experiments show that the starting ester was discretely labeled and that the method used to determine the ^{18}O distribution in the unsolvolyzed ester does not mix the carboxyl oxygen atoms.

For **4**-OPNB, k_{eq} is about as large as k_t and equilibration could be followed to about 80% completion. Good first-order behavior was observed in both solvents. In the case of **6**-OPNB, solvolysis is faster than equilibration and the reaction could only be followed to 34% completion in 90% acetone and 16% completion in 80% acetone (76% solvolysis in each case). Here again k_{eq} was steady over the range that reactions could be followed.

From the kinetic behavior it is apparent that oxygen equilibration (eq 4) and racemization (eq 3) are intramolecular. This was confirmed by exchange experiments in which **4**-OPNB and **6**-OPNB were solvolyzed in the presence of ^{14}C-labeled *p*-nitrobenzoic acid. Second-order exchange constants (k_{exc}) were determined as described earlier.[13]

Exchange constants (k_{exc}) for solvolysis in 80% acetone (99.6 °C) are 0.0283 L mol^{-1} h^{-1} for **4**-OPNB and 0.040 L mol^{-1} h^{-1} for **6**-OPNB. For **6**-OPNB, k_{exc} = 0.0030 L mol^{-1} h^{-1} in 90% acetone at 99.6 °C. The amount of exchange between unsolvolyzed ester and acid produced by solvolysis can be determined for any stage of solvolysis with these second-order exchange constants.[13] For solvolysis of 0.04 M **4**-OPNB, <2% of the remaining ester has undergone exchange at 76% solvolysis in 80% acetone. At this point the unsolvolyzed ester contains ~5% of the epimer and racemization and equilibration are 39 and 77% complete. For **6**-OPNB in 80% acetone, there is <1% exchange at 76% solvolysis, 12% racemization, and 17% equilibration. At this point the remaining ester contains ~8% of the epimer. For **6**-OPNB in 90% acetone there is <4% exchange at 74% solvolysis, 41% racemization, and 37% equilibration. At this point there is ~18% of the epimer in the unsolvolyzed ester. These exchange experiments clearly show that racemization and oxygen equilibration are intramolecular and that geometric isomerization is also largely intramolecular.

Except for the geometric isomerization, ion-pair return in this bicyclic system is similar to that observed for the 5-methyl-2-cyclohexenyl system (**1**).[2] The return to solvolysis ratios is similar for the two systems and in each case, $k_{rac} = k_{eq}$ for one of the isomers (**1a**[2b] and **6**-OPNB) and $k_{eq} > k_{rac}$ for the other (**1b**[2c] and **4**-OPNB). Evidently, ionization of the endo ester (**6**-OPNB) leads to an ion-pair intermediate (**8**) in which the carboxyl oxygen atoms and allylic carbon atoms are equivalent as illustrated in Scheme III. Thus return results in randomization of the allylic carbon atoms and carboxyl oxygen atoms and $k_{rac} = k_{eq}$. However, for the exo isomer (**4**-OPNB), $k_{eq} > k_{rac}$, which means that enantiomeric exo ion-pair intermediates (**7**) are involved. Presumably the dissociated cation (**3**) is the product-forming intermediate as indicate in the scheme.

The geometric isomerization (**7** ⇄ **8**) associated with ion-pair return in the rigid bicyclic system is in contrast to the preservation of geometric configuration in the 5-methyl-2-cyclohexenyl system (**1**).[2] This is additional evidence that conformational factors are involved in the completely stereospecific ion-pair return in the flexible 5-methyl-2-cyclohexenyl system.[2-4]

The return to solvolysis ratios is larger in 90% than in 80% acetone as would be expected. For solvolysis of **6**-OPNB, k_α corresponds to most, if not all, of the ionization and the k_α/k_t ratio increases from 1.14 for 80% acetone to 1.82 for 90% ac-

etone. A similar dependence of k_α/k_t ratios on solvent composition was observed earlier for solvolysis of symmetrical allylic *p*-nitrobenzoates in aqueous acetone.[1b,2a] For **4**-OPNB the k_α/k_t ratios are similar for the two solvents. However, in this case k_α does not correspond to total ionization because of return (detected by carboxyl-oxygen equilibration) without loss of optical configuration. In this case the rate constant for detectable ionization is $(k_t + k_i + k_{eq})$ and the ratio of this quantity to k_t increases from 2.1 for 80% acetone to 2.9 for 90% acetone.

Experimental Section

Purities of bicyclic alcohols and ketones and compositions of mixtures were determined by capillary GC, 200-ft column coated with TCEP or 150-ft column coated with Ucon Polyglycol LB-550-X.

Materials. Racemic *exo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (**4**-OPNB), mp 85.4–86.4 °C (lit.[5b] 86.2–86.6 °C), and (+)-**4**-OPNB, $[\alpha]^{25}_D$ 229° ($CHCl_3$), were prepared as described earlier.[5] Carbonyl-^{18}O **4**-OPNB and **6**-OPNB (4.94 or 5.16% excess ^{18}O) were prepared from the corresponding alcohols and *p*-nitrobenzoyl chloride-^{18}O.[1] *p*-Nitrobenzoic acid-7-^{14}C for the exchange experiments,[13] and aqueous acetone solvents,[1] were also prepared as described previously.

***exo*-Bicyclo[3.2.1]oct-3-en-2-ol (4-OH).** Most of the **4**-OH used in this work was prepared from bicyclo[3.2.1]oct-2-ene, bp 131–134 °C,[6] as described by the following typical preparation. A solution of 100 g (0.93 mol) of bicyclo[3.2.1]oct-2-ene, 165 g (0.93 mol) of *n*-bromosuccinimide, and 0.1 g of benzoyl peroxide in 500 mL of carbon tetrachloride was warmed to initiate the reaction and then refluxed for 30 min. After filtration, the mixture was concentrated with a rotary evaporator and the residual 2-bromobicyclo[3.2.1]oct-3-ene was added slowly to a stirred suspension of 100 g (1 mol) of calcium carbonate in 1 L of 65% aqueous acetone. After the mixture was stirred for 12 h, the acetone was removed by distillation and the alcohol was separated from the basic mixture by steam distillation. Saturation of the distillate with sodium chloride followed by extraction with ether gave 67 g of crude **4**-OH. Analysis by GC showed the product to be 94% pure **4**-OH and free of the endo isomer (**6**-OH). The crude **4**-OH was converted to **4**-OPNB which was recrystallized to a constant melting point of 85.6–86.0 °C. Saponification gave **4**-OH, mp 82.2–83.2 °C (lit.[5a] 82.7–83.7 °C).

***(dl)-endo*-Bicyclo[3.2.1]oct-3-en-2-yl *p*-Nitrobenzoate (6-OPNB).** In a typical experiment 13 ml of 1 M lithium aluminum hydride ($LiAlH_4$) was added dropwise to 4.18 g (34.2 mmol) of bicyclo[3.2.1]oct-3-en-2-one (**5**)[5] in 100 mL of ether at −80 °C. The solution was stirred at −80 °C for 4 h after which 3 mL of 5% aqueous sodium hydroxide was added. Filtration, drying the organic layer, and solvent removal gave 3.85 g of 89% pure **6**-OH. The contaminants were 2% **4**-OH, 4% *exo*-bicyclo[3.2.1]octan-2-ol, 1% *endo*-bicyclo[3.2.1]octan-2-ol, and 4% bicyclo[3.2.1]octan-2-one. Reduction with insufficient $LiAlH_4$ did not prevent formation of the saturated compounds. The conditions reported[5b] to convert **5** to a binary mixture of **6**-OH and **4**-OH also gave the saturated bicyclic alcohols in the amounts indicated above. Evidently these contaminants could not be detected by methods available in the earlier work.[5b]

To 100 mL of ice-cold 10% aqueous silver nitrate was added 3.8 g of the crude **6**-OH from the $LiAlH_4$ reduction. The cold solution was extracted with four 50-mL portions of hexane and then mixed with 250 mL of concentrated ammonium hydroxide. The resulting solution was extracted with ether. After drying, the ether was removed and the residual product was 98% pure **6**-OH. The contaminant was 2% **4**-OH. This product was purified by sublimation, mp 68.2–69.5 °C. Anal. ($C_8H_{12}O$) C, H.

The above **6**-OH was converted to **6**-OPNB, mp 76.5–78 °C (hexane). Anal. ($C_{15}H_{15}NO_4$) C, H. Pure **6**-OH was obtained by chromatography of 98% **6**-OH, 2% **4**-OH on neutral alumina (eluent, pentane containing 0.35% ether). The **6**-OH was shown to be homogeneous by GC and was converted to **6**-OPNB, mp 78.5–80.0 °C.

(−)-*endo*-Bicyclo[3.2.1]oct-3-en-2-yl *p*-Nitrobenzoate. (+)-**4**-OH, $[\alpha]^{24}_D$ 167° ($CHCl_3$), 38% optically pure,[5] was oxidized to (−)-**5** with manganese dioxide[5a] and the resulting ketone was reduced with $LiAlH_4$ at −80 °C as described above. The reduction product was converted to (−)-**6**-OPNB, $[\alpha]^{25}_D$ −100° ($CHCl_3$). Anal. ($C_{15}H_{15}NO_4$) C, H.

Reconversion of the above (−)-**6**-OPNB to alcohol by $LiAlH_4$ reduction gave a product consisting of 92.6% **6**-OH, 1.4% *endo*-bicyclo[3.2.1]octan-2-ol, 4.6% *exo*-bicyclo[3.2.1]octan-2-ol, and 1.4% **4**-OH. The above (−)-**6**-OPNB was used for the polarimetric experiments and product studies.

Kinetic Experiments. Polarimetric and titrimetric rate constants were determined by methods described earlier.[1,2] Reactions were followed to about 80% completion. In the polarimetric experiments, the total change in rotation was about 5° for active **4**-OPNB and 1° for active **6**-OPNB. Independent determinations were reproducible to ±0.005°. For the titrimetric experiments, reactions were followed by titration of 5-mL aliquots with 0.04 M sodium hydroxide to the bromthymol blue end point. For the kinetic experiments ampules were flushed with nitrogen before filling and samples were sealed under nitrogen. Data for the polarimetric and titrimetric experiments are summarized in Table I.

Rates of carboxyl oxygen equilibration were also measured as reported earlier.[1,2] Solutions (0.04 M) of **4**-OPNB-*carbonyl*-^{18}O and **6**-OPNB-*carbonyl*-^{18}O were sealed in heavy-wall ampules with a capacity of about 200 mL. The amount of solution used for each experiment was such that about 0.5–1 g of unreacted ester remained when solvolysis was terminated. Each point was treated as follows. The reaction was quenched by chilling the ampule and acetone was removed with a rotary evaporator. The solution was made basic with aqueous sodium bicarbonate and the resulting solution was extracted with ether. The organic extract was washed with brine, dried (Na_2SO_4), and concentrated to remove the ether. The residual mixture of unsolvolyzed *p*-nitrobenzoate and bicyclic alcohol (solvolysis product) was heated to 60 °C at 0.2 mm for 24 h to remove the alcohol. The residual ester was recrystallized from hexane. The purified recovered ester was shown to be homogeneous by IR and TLC.

The ester was reduced with $LiAlH_4$ and the pentane-soluble reduction products were chromatographed on Woelm activity III neutral alumina (elution with pentane followed by 1, 2, and 3% ether in pentane). Compositions of fractions were determined by GC and fractions of isomerically pure **4**-OH or **6**-OH were reconverted to *p*-nitrobenzoate derivatives for ^{18}O analysis. Control experiments showed that carboxyl oxygen equilibration does not occur during isolation of the unsolvolyzed ester.

Solvolysis Product Studies. Compositions of solvolysis products were determined for various degrees of solvolysis. Samples were quenched by chilling at appropriate times and concentrated with a rotary evaporator. The solutions were made basic with aqueous sodium bicarbonate and extracted with ether. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated with a fractionation column. The alcohol was separated from the unsolvolyzed ester by sublimation and compositions were determined by GC. Control experiments with mixtures of known compositions gave good results (within 1% of known values). Also, direct determination of alcohol compositions, without isolation and sublimation of the alcohol fraction, gave the same result as when the alcohol was isolated. The initial product from both **4**-OPNB and **6**-OPNB is >99% **4**-OH.

The rate of racemization of (+)-**4**-OH under conditions of solvolysis was determined as follows. To a 0.056 M solution of (*dl*)-**4**-OPNB in 80% acetone was added (+)-**4**-OH. The resulting solution, α^{25}_D 0.624°, was heated for 17.5 h (66% reaction) after which the rotation was α^{25}_D 0.280°. Thus, under these conditions there is about 55% racemization of the active alcohol.

The alcohol isolated after solvolysis of (−)-**4**-OPNB, $[\alpha]^{25}_D$ −90° ($CHCl_3$), in 80% acetone for 10.7 h (48% solvolysis) had no detectable activity. Under these conditions racemization of the alcohol would be <50% and <0.5% retention of configuration would have been detected. Thus the initially formed product from active **4**-OPNB is >99% racemic alcohol.

Compositions of unsolvolyzed ester were determined for various stages of solvolysis by isolation of unsolvolyzed ester by the method outlined for the ^{18}O equilibration experiments. To avoid fractionation, the ester was not recrystallized. The residual alcohol-free ester fraction was reduced with $LiAlH_4$ and compositions of the resulting alcohol fractions were determined by GC. Control experiments with mixtures of known compositions gave good results (within 1% of known values).

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References and Notes

(1) (a) Goering, H. L.; Pombo, M. M. *J. Am. Chem. Soc.*, 1960, 82, 2515. (b) Goering, H. L.; Pombo, M. M.; McMichael, K. D. *Ibid.*, **1963**, 85, 965.
(2) (a) Goering, H. L.; Doi, J. T. *J. Am. Chem. Soc.*, **1960**, 82, 5850. (b) Goering, H. L.; Doi, J. T.; McMichael, K. D. *Ibid.*, **1964**, 86, 1951.
(3) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.*, **1962**, 84, 2779.
(4) Goering, H. L.; Koermer, G. S.; Linsay, E. C. *J. Am. Chem. Soc.*, **1971**, 93, 1230.
(5) (a) Goering, H. L.; Towns, D. L. *J. Am. Chem. Soc.*, **1963**, 85, 2295. (b) Goering, H. L.; Greiner, R. W.; Sloan, M. F. *Ibid.*, **1961**, 83, 1391. (c) Goering, H. L.; Mayer, U. *Ibid.*, **1964**, 86, 3753.
(6) Alder, K.; Frieger, M.; Weiss, H. *Chem. Ber.*, **1955**, 88, 144.
(7) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.*, **1961**, 83, 2952.
(8) Goering, H. L.; Fickes, G. N. *J. Am. Chem. Soc.*, **1968**, 90, 2862.
(9) Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.*, **1955**, 77, 5172.
(10) Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.*, **1955**, 77, 6249.
(11) Wiberg, K. B.; Nakahira, T. *Tetrahedron Lett.*, **1974**, 1769.
(12) Alberty, R. A.; Miller, W. G. *J. Chem. Phys.*, **1957**, 26, 1231.
(13) Goering, H. L.; Levy, J. F. *J. Am. Chem. Soc.*, **1962**, 84, 3853.

Antiallergenic 8-Azapurines. Structural Characterization of 9-Diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine

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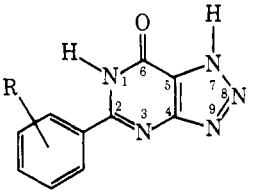
Abstract: The crystal and molecular structure of 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine, $C_{18}H_{22}N_6O_3$, a derivative of the arylazahypoxanthine series of antiallergenic drugs, has been determined from three-dimensional counter X-ray data obtained using Cu Kα radiation. The azapurine crystallizes in the monoclinic space group $P2_1/c$ with four formula units in a cell of dimensions a = 7.448 (2) Å, b = 14.818 (8) Å, c = 17.435 (7) Å, and β = 100.43 (3)°. The observed and calculated densities are 1.29 (1) and 1.300 g cm^{-3}, respectively. The structure has been refined by full-matrix least-squares techniques to a final value of the conventional R factor (on F) of 0.046 using 2355 independent intensities. The 8-azapurine ring is planar, with no atom deviating from the least-squares plane by more than 0.005 Å; this plane is inclined at an angle of only 10.1° to the plane of the phenyl ring, so that the entire 2-aryl-8-azahypoxanthine ring system is nearly planar. This near coplanarity of the two ring systems apparently stems in part from the presence of a strong intramolecular hydrogen bond between N(1)–H of the azapurine and the extracyclic oxygen atom of the propoxyphenyl moiety, the N(1)···OP distance and N(1)–H···OP angle being 2.594 (2) Å and 134°, respectively. A CNDO/2 molecular orbital calculation shows that this propoxy oxygen atom is very electron rich, with a residual charge of −0.22 e; this value is exceeded only by those of the carbonyl oxygen atoms and that of N(3), −0.28 e, while the triazole nitrogen atoms N(7), N(8), and N(9) have only small residual charges of −0.06, −0.06, and −0.10 e, respectively. Hence, the present study again suggests that N(3) in 8-azapurines is relatively much more basic than in the natural purines. The molecules stack in the crystal so that the polar propoxy oxygen atom OP sits directly above the phenyl ring of the next molecule.

Introduction

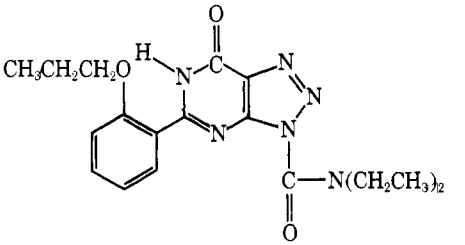
8-Azahypoxanthines have been under recent investigation as antiallergins.[1-4] In a study of a series of 2-phenyl-8-azahypoxanthines, I, the antiallergenic activity was shown to be



I

correlated with the size and hydrogen-bonding capacity of the ortho substituent, R, on the phenyl ring.[2] As a consequence of this observation, it has been suggested that potent antiallergenic activity in this series is associated with coplanarity of the phenyl ring with the azapurin-6-one portion of the molecule;[2] such planarity would be favored by strong intramolecular hydrogen bonding between the proton on N-1 and the ortho substituent on the phenyl ring. This idea has guided further work seeking increased potency and reduced side effects in the antiallergenic field within the 2-phenyl-8-azahypoxanthine series.

We have recently examined the molecular structures of several of these compounds to test this planarity hypothesis and to determine whether there might be other structural features that correlate with antiallergenic activity. In this paper we report the crystal and molecular structure of 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine (II), which is one of a series of derivatives prepared in order to improve oral absorption in the antiallergenic azahypoxanthine series. Besides the question of the coplanarity of the phenyl group with the azapurin-6-one, we were interested in the site of attachment of the diethylcarbamoyl group. Prior to the present study, this aspect of the structure was uncertain.



II

As part of our studies on 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine, we have also performed molecular orbital calculations aimed to assess the importance of the electronic environment on the chemical behavior of compounds within this series.

Experimental Section

X-ray Data Collection. A sample of the title compound was gen-

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