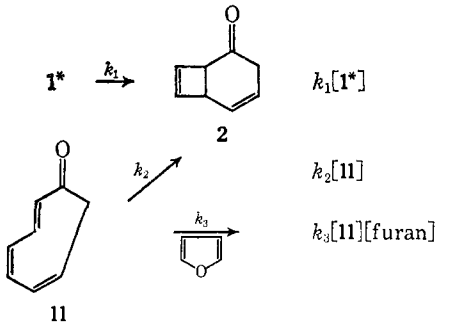
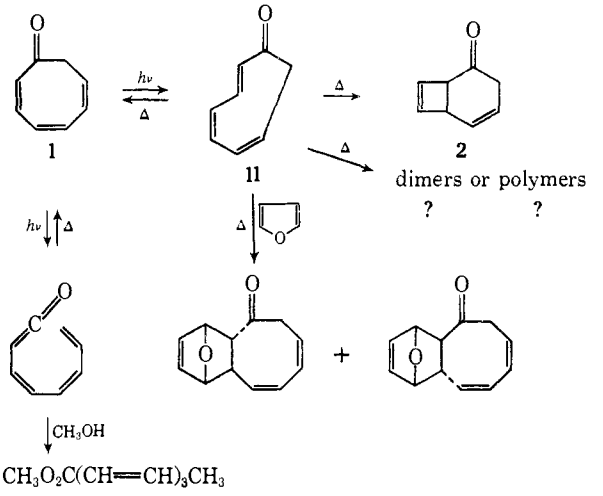
by a thermal electrocyclic reaction of *trans,cis,cis*-2,4,6-cyclooctatrienone (**11**).[9] In the first case, the yield of bicyclic ketone will not depend in any way on the concentration of furan. In the second case, the yield of bicyclic ketone in the presence of furan will be given by the ratio k_2[**11**]/k_3[**11**][furan]; *i.e.*, the yield of



bicyclic ketone **2** will be inversely proportional to furan concentration. Irradiations at room temperature in varying concentrations of furan show that a competition does exist between cycloaddition and the electrocyclic reaction which produces bicyclic ketone **2**. It is clear that furan is not quenching an excited state of 2,4,6-cyclooctatrienone, since the disappearance of starting material is as rapid in the presence as in the absence of furan. The present state of the photochemistry of 2,4,6-cyclooctatrienone may now be summarized as shown in Scheme I.[10a]

Scheme I



Acknowledgment. This investigation was supported by a grant (GM-14305) from the National Institute of General Medical Science, U. S. Public Health Service.

(9) R. S. H. Liu[10] has shown that direct irradiation of *cis,cis*-1,3-cyclooctadiene and thermal isomerization (80°) of *cis,trans*-1,3-cyclooctadiene gives in each case bicyclo[4.2.0]oct-7-ene. Both reactions are orbital symmetry-allowed processes.

(10) R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).

(10a) NOTE ADDED IN PROOF. J. K. Crandall and R. P. Haseltine (*ibid.*, **90**, 6251 (168)) have trapped an intermediate in the photochemistry of 2,7-cyclooctadienone.

(11) National Aeronautics and Space Administration Trainee, 1965–1968.

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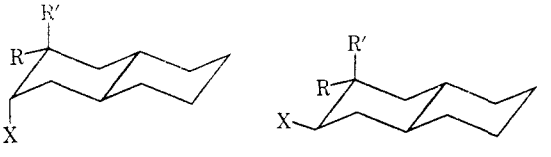
Stereochemistry of Elimination in Deamination of the *trans*-2-Decalylamines[1]

Sir:

Axial cyclohexyl primary amines undergo nitrous acid deamination with extensive elimination, typically 50–80% of the total product, whereas equatorial amines yield only 5–25% of olefin.[2–6] White and Bachelor have reported that a somewhat similar situation obtains in the related decomposition[7] of various N-nitroso amides derived from the epimeric 3-aminocholestanes.[4] We have confirmed this general pattern with respect to decompositions of the N-nitroso carbamates **1a** and **2a** derived respectively from *trans-trans*-2-decalylamine (**1d**) and *trans-cis*-2-decalylamine (**2d**). Decomposition of **1a** in boiling cyclohexane yields a product mixture composed of 80% 1- and 2-octalins and 20% of a mixture of the epimeric ethyl *trans*-2-decalyl carbonates. Under the same conditions, the equatorial epimer **2a** yields a product containing 41% olefin. In acetic acid, the proportions of olefin in the product are 78% from **1a** and 14% from **2a**.



a, X = N(NO)CO_2Et; R = R′ = H
b, X = N(NO)CO_2Et; R = D; R′ = H
c, X = N(NO)CO_2Et; R = H; R′ = D
d, X = NH_2; R = R′ = H
e, X = NH_2; R = D; R′ = H
f, X = NH_2; R = H; R′ = D

This behavior, particularly with regard to nitrous acid deamination, has been widely attributed[2,8] to the occurrence of an E2 *trans*-diaxial elimination of a proton and a nitrogen molecule from the diazonium ion in the case of the axial amine (see **3**). An alternative explanation[3] involves the removal of the *trans*-axial proton from a carbonium ion, the configurational identity of which is maintained by weak association with a counterion (a vibrationally excited ion pair; see **4**). In the case of the equatorial amine or the derived ion

(1) This work was supported by Grant AM 06419-05 from the National Institutes of Health.

(2) J. A. Mills, *J. Chem. Soc.*, 260 (1953); C. W. Shoppee, R. E. Lack, and P. Ram, *ibid.*, *C*, 1018 (1966).

(3) E. H. White and D. J. Woodcock, "The Chemistry of the Amino Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1968, p 440.

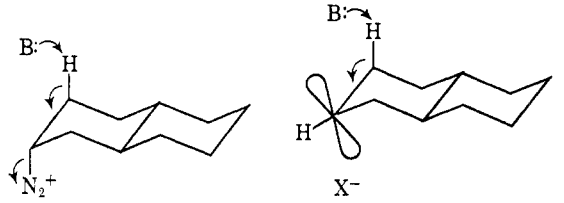
(4) E. H. White and F. W. Bachelor, *Tetrahedron Letters*, 77 (1965).

(5) E. J. Jankowski, Ph.D. Thesis, University of Pittsburgh, 1966.

(6) W. Hückel and K. D. Thomas, *Ann.*, **645**, 177 (1961); W. Hückel and K. Heyder, *Chem. Ber.*, **96**, 220 (1963); K. Schreiber and H. Ripperger, *Ann.*, **655**, 136 (1962); G. Drefahl and S. Huneck, *Chem. Ber.*, **93**, 1961 (1960); A. K. Bose, *Experientia*, **9**, 256 (1953).

(7) (a) E. H. White and J. E. Stuber, *J. Am. Chem. Soc.*, **85**, 2168 (1963); (b) E. H. White and C. A. Aufdermarsh, Jr., *ibid.*, **83**, 1179 (1961); (c) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 1 (1956).

(8) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954); A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **79**, 2888 (1957); A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, pp 104–105; H. Christol and J. M. Bessière, *Bull. Soc. Chim. France*, 2141 (1968); P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, p 40; D. V. Banthorpe, "Elimination Reactions," Elsevier Publishing Co., New York, N. Y., 1963, p 164.



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pair no such favorable stereoelectronic arrangement is available.

We now wish to report that the 2-octalin formed in the decomposition of the N-nitroso carbamates **1a** and **2a** in boiling cyclohexane is actually the product of a predominantly *cis* elimination. Furthermore, the nitrous acid deamination in acetic acid of the epimeric *trans*-2-decalylamines **1d** and **2d** also results in predominantly *cis* elimination, although the *axial* epimer undergoes substantial *trans* elimination as well.

The data from the deuterium labeling experiments are summarized in Table I. The degree of deuteration of the 1-octalin formed provides an estimate of the degree of deuteration in the reactants. The figures in the last column are approximations of the proportion of 2-octalin which is formed by *cis* elimination: they are obtained by correcting the raw data for incomplete deuteration and for isotope effects which can be estimated by the changes in the ratio of 1- to 2-octalin produced.[9] It can be concluded that the proportion of *cis* elimination in the nitrosocarbamate decomposition is *ca.* 92–93% in the case of the axial epimer and 76–81% in the case of the equatorial epimer. In the nitrous acid deamination of the amines in acetic acid the proportion of *cis* elimination is 56–61% for the axial and 78% for the equatorial epimer.[10]

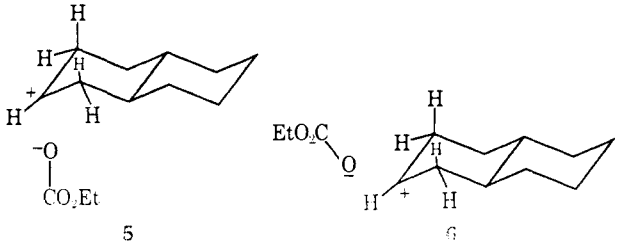
Since the E2 hypothesis has had a considerable influence in the development of some of the mechanistic theories concerning the decomposition of nonaromatic diazonium ions, it is clear that some reevaluation is necessary. We shall contribute to this effort in a subsequent publication. For now, it is sufficient to point out that the hypothesis[3,5,12,13] that ion pairs are involved in diazonium ion formation and decomposition is eminently suited to an explanation of the *cis* eliminations observed here. It has been noted that the partitioning of the carbonium ion in solvolysis reactions conducted in solvents of low polarity (such as acetic acid) is significantly affected by the nature of the leaving group.[14] In the 2-butyl tosylate system, eliminations in such solvents have been shown to be *cis* in character.[15] These observations have been interpreted on the basis that the counterion removes the β proton.

Table I. Decompositions of Labeled N-Nitroso Carbamates in Boiling Cyclohexane and Nitrous Acid Deamination of Labeled *trans*-2-Decalylamines in Acetic Acid

Substrate[a]	% monodeuterated 1-octalin[b]	% monodeuterated 2-octalin[b]	Ratio of 1- to 2-octalin	Isotope effect	Corrected[c] % *cis* elim
1a			1.0		
1b	95	9.5	1.2	1.3	92
1c	95	90	1.0	1.3[d]	93
2a			0.70		
2b	95	83	0.75	1.58	81
2c	95	27	0.81	1.26	76
1d			0.70		
1e	95	54	0.91	1.71	56
1f	94	67	0.90	1.61	61
2f	93	30	*e*	1.66[e]	78

[a] The β-deuterated amines were prepared by a literature method[11] except that tosylate ammonolysis (J. L. Pinkus, G. Pinkus, and T. Cohen, *J. Org. Chem.*, **27**, 4356 (1962)) was used for the *axial* epimers instead of azide displacement. [b] Determined by mass spectrometry at 20 eV. [c] See text. [d] The extent of deuteron loss is too low to establish an isotope effect. The assumed value is the same as that for the related compounds **1b** and **2c**. [e] The octalin yield was too low to allow determination of the ratio. The assumed isotope effect is an average of those for the related compounds **1e** and **1f**.

This concept can readily be applied to the data reported here. Rearrangement of the N-nitroso carbamates **1a** and **2a** must produce the *trans* diazotic esters[7] which by two consecutive or simultaneous bond cleavages[16] yield the ion pairs **5** and **6**.[17] In the case of **5**, the counterion can only remove a β-equatorial hydrogen because the *trans*-axial hydrogen atoms are on the other side of the molecule. In the case of **6**,



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however, the anion is between the neighboring axial and equatorial protons, and either can be removed; the preference for removal of the axial proton might be stereoelectronic in nature. The fact that the degree of stereoselectivity is greater for the axial than for the equatorial N-nitroso carbamate is thus readily understood. Nitrous acid deamination in acetic acid also

(9) Both primary and secondary isotope effects are involved, and they cannot be sorted out from the data. However, in view of the fact that secondary isotope effects are usually much smaller than primary effects, the former can probably be ignored without introducing serious error. This procedure leads to quite reasonable internal consistency; compare the calculated proportions of *cis* elimination for the pairs **1b** and **1c**, **2b** and **2c**, **1e** and **1f**. In any case, the isotope effects are small enough so that our conclusions can hardly be affected by errors from this source.

Another source of error, for which corrections cannot be made at present, is the small degree of rearrangement that accompanies deamination of the *axial* amine only, by either method. This is revealed by the isolation of some 1-decalyl substitution product (about 1% of the total substitution product) and the occurrence of some intramolecular deuterium migration (presumably indicating rearrangement to the 3 position) in the 2-decalyl esters and alcohols from the α-deuterio analogs of **1a** and **1d**. In view of the apparent unimportance of the rearrangement and the internal consistency of the results, the error from this source must be minor.

(10) The nitrous acid deamination in aqueous solution of labeled *cis*-4-*t*-butylcyclohexylamine was inconclusive, and the authors concluded that the elimination was neither purely *cis* nor purely *trans*.[11]

(11) G. Lamaty, C. Tapiero, and R. Wylde, *Bull. Soc. Chim. France*, 2039 (1968).

(12) T. Cohen and E. Jankowski, *J. Am. Chem. Soc.*, 86, 4217 (1964).

(13) R. A. More O'Ferrall, *Advan. Phys. Org. Chem.*, 5, 331 (1967).

(14) (a) M. Cocivera and S. Winstein, *J. Am. Chem. Soc.*, 85, 1702 (1963); (b) D. J. Cram and M. R. V. Sahyun, *ibid.*, 85, 1257 (1963).

(15) P. S. Skell and W. L. Hall, *ibid.*, 85, 2851 (1963).

(16) M. C. Whiting, *Chem. Brit.*, 2, 482 (1966).

(17) Evidence will be presented in a subsequent publication that these are not tight ion pairs but may correspond to the vibrationally excited ion pairs of White and Woodcock[3] or to an ion pair separated by a nitrogen molecule.[18]

(18) E. H. White, H. P. Tiwari, and M. J. Todd, *J. Am. Chem. Soc.*, 90, 4734 (1968).

produces ion pairs similar to **5** and **6** except that the counterion is $CH_3COO^-\cdots HOH$.[4,5,7a,12] In the case of the axial amine **1d** the decreased stereoselectivity might indicate that, although over one-half of the proton removal is executed by the counterion,[19,20] a substantial proportion of the axial protons are removed by solvent either in E2 fashion or, more likely, after the C–N bond cleavage.[21]

Acknowledgment. We wish to thank the National Institutes of Health for providing the LKB 9000 combined gas chromatograph–mass spectrometer which was used for the deuterium analysis. We also thank Mr. John Naworal for recording the mass spectra.

(19) Cram and Sahyun suggested that nitrous acid deamination in acetic acid could be included in their over-all elimination scheme in which the leaving group removes the proton provided that the leaving group is considered to be NH_2NO.[14b]

(20) White and Woodcock[3] mentioned the possibility that the elimination in this type of reaction is executed by the counterion, but the stereochemical consequences were not discussed.

(21) The explanation of the greater elimination/substitution ratio from **5** must await further experiments, but it may be that the ease of substitution is greater in **6** than in **5** due to steric repulsions that come into play in the latter as the anion approaches the covalent bonding distance.

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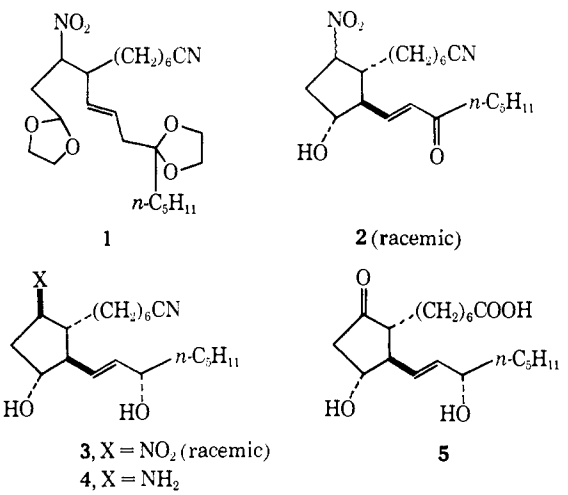
Total Synthesis of Natural (Levo) and Enantiomeric (Dextro) Forms of Prostaglandin E_1

Sir:

In recent communications the total synthesis of racemic prostaglandin E_1 by a number of different routes has been described.[1,2] The readily available nitro ketal **1**, an intermediate in one of the previously described approaches,[1b,3] has recently been found to undergo cyclization using stannic chloride in acetone to give the oily prostanoic acid derivative **2**, essentially free of the undesired 11β-hydroxy epimer[4] and readily purified by column chromatography using silica gel with chloroform as eluent. The intermediate **2** was obtained earlier along with the C-11 epimer using a different cyclization procedure.[1b] Reduction of the enone **2** with zinc borohydride in dimethoxyethane followed by mild base treatment to place the 9-nitro substituent in the more stable β orientation gave a mixture of two nitro diols epimeric at C_{15} (**3** and its C-15 epimer).[1b] These are easily separated chromatographically on silica gel (using CH_2Cl_2–Et_2O–THF, 5:4:1, as solvent), and further, the undesired 15β-hydroxy epimer is reconverted to the intermediate 15-ketone **2** in high yield by selective oxidation with 2,3-dicyano-5,6-dichloro-*p*-benzoquinone, as indicated earlier.[1b] This recycling procedure allows stereoselective channeling of the synthesis to the desired nitro diol **3**, reduction of which with aluminum amalgam affords the corresponding amine **4**. The racemic amine **4** is readily purified *via* the nicely crystalline salt with *p*-nitrobenzenesulfonic acid, mp 134.5–136°.

Treatment of the racemic amine **4** with (−)-α-bromocamphor-π-sulfonic acid[5] in ethyl acetate produced a crystalline salt, $[\alpha]_{578}$ −54° (*c* 1, methanol) in *ca.* 115% of the theoretical amount calculated for a single diastereomer. One recrystallization from methanol (a very small amount) and ethyl acetate afforded in high yield a single diastereomeric salt, mp 157–159°, $[\alpha]_{578}$ −59.6° (*c* 1, methanol). Further recrystallization led to only a slight change in the rotation of this salt (maximum observed, $[\alpha]_{578}$ −59.65°). The free resolved amine **4**, generated from this levo salt using potassium carbonate in aqueous methanol as base, was obtained after extraction as a solid, $[\alpha]_{578}$ −21° (*c* 1.7, methanol). This levo amine **4** was converted to prostaglandin E_1 by the reaction sequence previously described.[1] Recrystallization of



the synthetic product afforded material identical in all respects with natural prostaglandin E_1 (**5**) (including nmr and ir spectra); found: mp 114–116.5°, $[\alpha]_{578}$ −61.6° (*c* 0.56, tetrahydrofuran).

By a similar process the racemic amine **4** was resolved *via* the salt with (+)-α-bromocamphor-π-sulfonic acid[5] to give dextro **4**, $[\alpha]_{578}$ +21° (*c* 1, methanol). The procedure for the conversion of *dl*-**4** to *dl*-prostaglandin E_1[1] when applied to dextro **4** yielded the enantiomer of natural prostaglandin E_1, mp 114–117°, $[\alpha]_{578}$ *ca.* +57° (*c* 0.5, tetrahydrofuran), showing the same infrared spectrum and chromatographic R_f values as racemic and natural forms of prostaglandin E_1. The biological activity of the synthetic preparation of the enantiomer of prostaglandin E_1 was found to be 0.1% of that of the natural hormone in the stimulation of smooth muscle contraction.[6]

(1) For a description of three synthetic routes developed at Harvard, see (a) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968), and (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968).

(2) The most recent synthesis of racemic prostaglandin E_1 has been described by a group at the Upjohn Co.; see W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, **90**, 5895 (1968).

(3) See also E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 5947 (1968).

(4) The orientations of hydroxyl in prostaglandin $F_{1\alpha}$ at carbons 9, 11, and 15 are taken as α in this nomenclature. See B. Samuelsson, *Angew. Chem. Intern. Ed. Engl.*, **4**, 410 (1965).

(5) Obtained from the Aldrich Chemical Co.

(6) We are indebted to Drs. Peter Ramwell and Jane Shaw of the Worcester Foundation for Experimental Biology for the biological measurements. The measured activity may be explained by assuming that this sample contained *ca.* 0.1% of natural (levo) prostaglandin E_1. The slope of the log (dose)–response plot was found to be the same as for natural prostaglandin E_1, which argues against the alternative explanation based on slight bioactivity for the enantiomer of prostaglandin E_1.