Rearrangement Accompanying the Addition of Acetic Acid to Two Bicyclo[n.1.0]alkanes[1]

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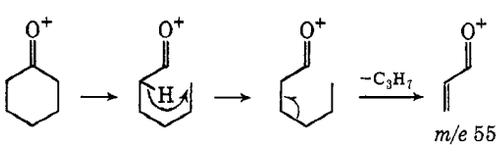
Addition of acetic acid-*O*-*d* to bicyclo[2.1.0]pentane and subsequent cleavage of the resulting acetate by $LiAlH_4$ gave cyclopentanol-d_1. The alcohol was oxidized and the resulting cyclopentanone was treated with base to effect α-deuterium exchange. Mass spectral isotopic distributions were determined for cyclopentanol-d_1 and cyclopentanone-d_1 before and after exchange. No label was lost on oxidation but 33–36% of the label was lost in exchange. Similar experiments were carried out with bicyclo[3.1.0]hexane. Again no oxidation loss was observed. Exchange losses were less than in the bicyclopentane system. That hydride migration occurs chiefly from C_6 was demonstrated from the degree of shift of *m/e* 55, the base peak in the mass spectrum of the labeled cyclohexanone. Neither oxidative nor exchange losses were observed for methylcyclopentyl acetates, produced along with cyclohexyl acetates, in the addition of acetic acid to bicyclo[2.1.0]hexane.

Halogen addition to bicyclo[2.1.0]pentane has been observed to proceed with rearrangement giving principally 1,2-dihalocyclopentanes rather than the 1,3-dihalocyclopentanes,[2] products of direct addition. These results, as well as other demonstrations of rearrangements accompanying ionic addition to simple cyclopropanes,[3] prompted us to examine for rearrangement the acid-promoted acetolysis of two bicyclo[*n*.1.0]alkanes. Bicyclo[2.1.0]pentane (**1**) and bicyclo[3.1.0]hexane (**2**) were chosen for the study because the principal position of bond rupture and addition is different in the two bicycloalkanes. Earlier work in our laboratory[4] showed that bicyclo[2.1.0]pentane gave only the acetate resulting from rupture of the internal $0^{1,4}$ bond. In contrast, bicyclo[3.1.0]hexane gave an acetate–olefin mixture consisting largely of those products formed by rupture of an external $1^{1,6}$ bond. Nevertheless, the latter bicycloalkane also gave 17% cyclohexyl acetate, an acetate resulting from rupture of the $0^{1,5}$ bond.

The two bicycloalkanes were treated with acetic acid-*O*-*d*, 0.08 *N* in deuteriosulfuric acid, for 46–48 hr at 25°. The crude mixtures of cycloalkyl acetates thus obtained were converted by lithium aluminium hydride to the cycloalkanols, which were oxidized with chromic acid in acetone to the corresponding ketones. The ketones in turn were treated with sodium methoxide–methanol at 25° for 8 days to exchange deuterium at the α positions. Isotopic distributions were determined for the cyclopentanols, methylcyclopentanols, and all the ketones, and are summarized in Table I. Also given in Table I are the corresponding percentage losses of deuterium by oxidation and exchange. Reliable isotopic distributions could not be obtained for the cyclohexanols because of the interference of an $M^+ - 1$ peak which was large relative to M^+. Therefore, the isotopic distributions of the cyclohexanol were assumed to be the same as that of the *trans*-2-methylcyclopentanol produced in the same ring-opening experiment.

To ascertain the extent of β deuterium loss in the oxidation of alcohols, the efficiency of deuterium exchange, and the limits of error of the mass spectral analyses of cycloalkanols and cycloalkanones, cyclohexanol-2-d_1 and cyclopentanol-2-d_1 were prepared by treating the appropriate cycloalkene oxide with lithium aluminum deuteride. These labeled cycloalkanols were oxidized and samples of the resulting cyclohexanones were treated under various conditions to establish that methanol–sodium methoxide at 25° for 8 days was sufficient to exchange all of the deuterium in the labeled ketones. These ancillary experiments also showed that no β deuterium was lost in the standard oxidation of cyclopentanol-2-d_1 to cyclopentanone-2-d_1. For reasons already given, the oxidative loss of label from cyclohexanol-2-d_1 could not be determined. Isotopic distributions and limits of error for this series of experiments are given in the Experimental Section.

Information about label location was also gained in one case from the shift of mass spectral fragmentation peaks. In this manner, we learned that addition of DOAc to bicyclo[3.1.0]hexane produced no cyclohexyl acetate labeled at C_4. This result was obtained by determining the percentage shift of the base peak of the exchanged cyclohexanone. Earlier mass spectral studies[5] of deuterium-labeled cyclohexanones have demonstrated that the base peak at *m/e* 55 is generated through the fragmentation depicted below.



According to this fragmentation mechanism, 50% of *m/e* 55 will be shifted to *m/e* 56 if all the label is located at C_3 and all the label has been exchanged from C_2. Any deuterium located at C_4 would necessarily be lost. Therefore, if no label is located at C_4, the percentage *m/e* 55 → 56 shift should be one-half the d_1 content of the ketone after exchange. For both exchanged cyclohexanone samples the determined percentage shifts[6]

(1) (a) Paper XI in a series dealing with carbon–carbon bond fission in cyclopropanes. (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society and the National Science Foundation, for support of this work. Acknowledgment is also made to the National Science Foundation for support in obtaining the mass spectrometer used in this study.

(2) R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965).

(3) (a) A. Aboderin and R. L. Baird, *ibid.*, **86**, 2300 (1964); (b) N. C. Deno, D. LaVietes, J. Mockus, and P. C. Scholl, *ibid.*, **90**, 6457 (1968); (c) N. Deno and D. N. Lincoln, *ibid.*, **88**, 5357 (1966); (d) H. Hart and R. H. Schlosberg, *ibid.*, **90**, 5189 (1968).

(4) R. T. LaLonde and L. S. Forney, *ibid.*, **85**, 3767 (1963).

(5) For references see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 143, 144.

(6) The method of calculating peak shift is that given by J. Karliner and C. Djerassi, *J. Org. Chem.*, **31**, 1945 (1966).

Table I

Percentage Isotopic Composition of Cycloalkanols and Cycloalkanones Originating from the Addition of Acetic Acid and Acetic Acid-*O*-*d* to Bicyclo[*n*.1.0]alkanes, 1 and 2

			Isotopic composition, %			Percentage deuterium loss[a]	
				Cycloalkanone			
Bicycloalkane	Cycloalkyl acetate	Expt no.	Cycloalkanol	Before exchange	After exchange	Oxidation[b]	Exchange[c]
1 [2.1.0]	Pentyl	1	d_0, 24	35	*d*		
			d_1, 73	69			
			d_2, 3	6			
2		2	21	18	47		
			79	80	52		
			0	2	1	0	36
3		3	27	27	49		
			70	70	51		
			3	3	0	0	33
[3.1.0]	Hexyl	1	d_0	19	28		
			d_1	75	68		
			d_2	6	4		10
[3.1.0]	*trans*-	2	22 ± 1[e]	20 ± 1	20 ± 2		
	2-Me		74 ± 1	75 ± 1	75 ± 2		
	Pentyl		4 ± 1	5 ± 1	5 ± 2	0	0
	Hexyl	2	22 ± 1[f]	21 ± 1	30 ± 1		
			74 ± 1	76 ± 1	66 ± 1		
			4 ± 1	3 ± 1	4 ± 3	0	13

[a] Calculated as the percentage loss relative to the total deuterium content of alcohol and the percentage loss relative to the total deuterium content of the ketone prior to exchange. [b] Calculated as $100\% \times (\Sigma\%d_i \times i$, alcohol $- \Sigma\%d_i \times i$, ketone$)/\Sigma\%d_i \times i$, alcohol. [c] Calculated as $100\% \times (\Sigma\%d_i \times i$, ketone $- \Sigma\%d_i \times i$, ketone after exchange$)/\Sigma\%d_i \times i$, ketone. [d] Insufficient material remained for an exchange experiment. [e] Isotopic distributions are the averages of three mass spectra and limits represent the maximum deviation from the average. [f] The isotopic distribution of the deuterated cyclohexanol is assumed to be the same as that of 1-methylcyclopentanol.

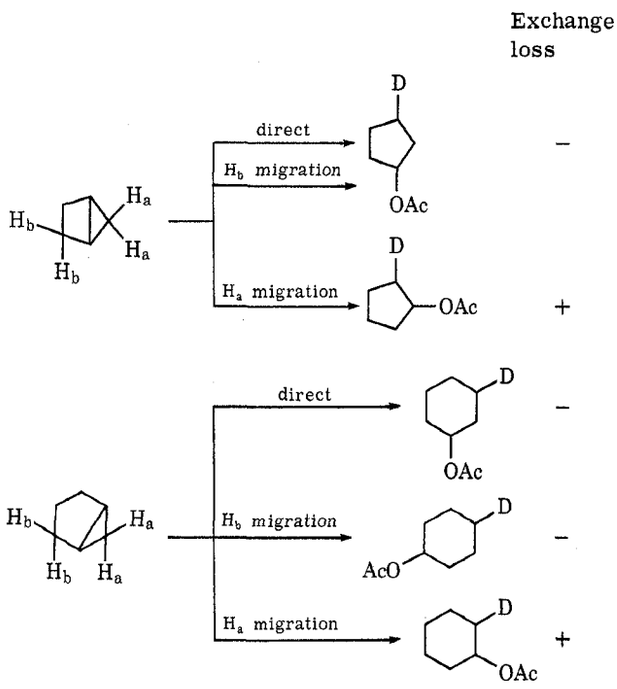
m/e 55 → 56 were 34%. One-half of the observed d_1 content in the cyclohexanone samples after exchange is 34 and 33% (Table I, rows 4 and 6). Since the determined percentage shifts agree well with the calculated values, it is concluded that no deuterium is located at C_4.

Discussion

There are three outstanding aspects of the results pointing to three principal features of the process through which deuterium is introduced. First, the amount of d_2 species in ketones originating from DOAc addition to bicyclo[*n*.1.0]alkanes in no case is greater than 6%. This result indicates that neither deuteron–proton exchange preceding bond fission nor acetate formation through addition to olefins are important competing processes. Second, DOAc addition to an internal bond of unlabeled bicycloalkanes ultimately leads to ketones which lose label on exchange. This result indicates that addition of acetic acid across the bond connecting bridgehead carbons is not a simple 1,3 addition but must involve rearrangement, at least in part. Third, the lack of oxidative and exchange loss from methylcyclopentanol and methylcyclopentanone, coupled with the formation of less than 2% of 1-methylcyclopentyl acetate,[4] indicates a near absence in external addition of the type of rearrangement which accompanies internal addition.

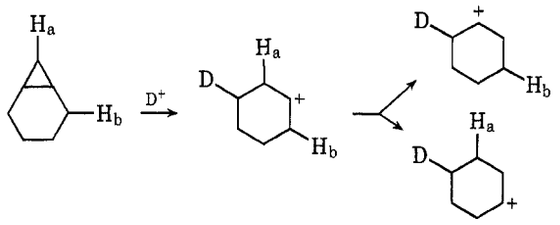
The second of the above three characteristics is interpreted within the framework of Scheme I. The scheme allows for addition across the internal bond of the bicyclo[*n*.1.0]alkanes to proceed by three routes: direct addition, hydride migration from the one-carbon bridge (H_a), and hydride migration from the *n*-carbon bridge (H_b). Acetates formed by direct addition and H_b-migration routes are indistinguishable by exchange loss of label.

Scheme I



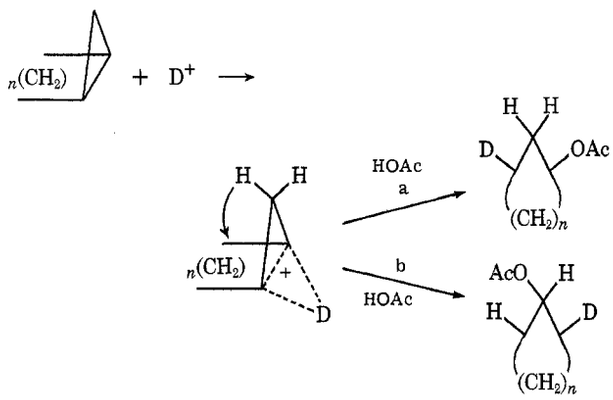
However, in the case of cyclohexyl-*d* acetate, no label could be detected at C_4 in the mass spectral shift value study. On this basis, the total amount of rearrangement is occurring by H_a migration only. In the case of bicyclo[2.1.0]pentane, the results based on exchange experiments indicate only the extent of rearrangement which takes place by H_a migration. Interestingly, H_a migration taking place in the addition to the more highly strained bicyclopentane is occurring more than twice as often as it does in the addition to the bicyclohexane.

Exclusion of H_b migration in the addition to the bicyclohexane means that free carbonium ions, as depicted below, can be eliminated as the major route in rearrangement, since there is no reason why H_a should migrate and H_b should not. The major involvement of a carbonium ion intermediate in the acid-promoted



acetolysis of bicyclo[n.1.0]alkanes has been rejected previously[7] on the basis of stereochemical results. That rearrangement by way of H_a and H_b migration occurs with unequal facility is not unreasonable if the rearrangement should take place through a transition state closely resembling the starting bicycloalkane. In this case H_b is virtually a cyclopentyl proton while H_a is much like a cyclopropyl proton, a proton type already known to display migrating tendencies in the course of addition reactions.[3] However, various corner- and edge-protonated cyclopropane intermediates in equilibrium—the type proposed previously by other workers to explain rearrangement in halogenation, acylation, and acid-promoted solvolysis of simple cyclopropanes[3]—are inappropriate for the acid-promoted acetolysis of the two bicycloalkanes. Such intermediates in equilibrium should lead to labeled acetates which would undergo oxidative loss of label. No oxidative loss was detected in studies of either bicycloalkane.

The simplest possible mechanism consistent with the results of H_a migration consists of deuteration of the internal bridge followed by (a) solvent attack to give the product of direct addition and (b) migration of a hydrogen from the one-carbon bridge and solvent attack at the same carbon center to give rearranged product.



Finally, it is noteworthy that addition of DOAc to the internal bond of *endo*-6-methylbicyclo[3.1.0]hexane was found earlier to give labeled *cis*-2-methylcyclohexyl acetate, which on sequential hydrolysis, oxidation, and exchange lost no deuterium.[7] The reason for the lack of hydride migration remains to be established.

(7) (a) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **86**, 4068 (1964); (b) R. T. LaLonde and A. D. Debboli, Jr., *J. Org. Chem.*, **35**, 2657 (1970).

Experimental Section

Spectra were obtained as follows: nmr, in CCl_4, 2% TMS (10 τ) using a Varian A-60A spectrometer; ir, in CCl_4 using a Perkin-Elmer 621 spectrometer, absorption maxima at 2115 and 2169 cm^{-1} of carbon monoxide were used as calibration standards for measuring C–D stretching frequencies; mass, 20 eV, chamber temperature 165° using a Hitachi Perkin-Elmer RMU-6 spectrometer with an all-glass heated indirect inlet at 25°. Isotopic distributions were calculated by the method of Biemann.[8] Glpc was performed on a Varian Aerograph Model 200 using columns 5 ft × 0.25 in. containing the liquid phase on Chromosorb W.

Materials.—Sulfuric acid-d_2, D_2O, and $LiAlD_4$ were purchased from Merck Sharp and Dohme of Canada Limited, Montreal. Acetic acid-*O*-*d* was prepared from excess acetic anhydride and D_2O and contained 25% HOAc according to nmr analysis. Bicyclo[2.1.0]pentane was prepared according to the procedure of Criegee[9] and bicyclo[3.1.0]hexane was prepared by the method of Smith and Simmons.[10] The preparations of cyclopentanol-2-d_1 and cyclohexanol-2-d_1 are described elsewhere in this section under separate headings.

General Procedure for $LiAlH_4$ Hydrogenolysis of Acetates.—The crude acetate obtained from ring opening was dissolved in a small amount of ether and the solution was added dropwise to $LiAlH_4$ in anhydrous ether. The resulting mixture was heated to reflux for 1 hr and then stirred overnight. The excess $LiAlH_4$ was decomposed by careful addition of water and the salts were dissolved by addition of cold, dilute H_2SO_4. The ether layer was dried ($MgSO_4$). Removal of the ether by distillation through a 12-in. Vigreux column gave a residue from which the desired alcohol was separated by glpc. All hydrogenolyses were carried out by the method described above unless otherwise indicated. When only a small sample of the crude mixture of alcohols was available, a portion of the mixture was separated by glpc for purposes of identification and mass spectral analysis and the oxidation step was carried out on the remaining portion of the crude mixture.

General Procedure for the Oxidation of Alcohols to Ketones.—A cooled acetone solution of the alcohol was treated with Jones reagent[11] added in a dropwise manner until a faint yellow color persisted. The mixture was poured into 25–50 ml of water and the resulting mixture was extracted continuously with ether for 48 hr. The ether extract was separated, washed twice with saturated $NaHCO_3$ solution, and dried ($MgSO_4$). Ether was removed by careful distillation to give a residue from which the desired ketone was separated by glpc.

General Procedure for Deuterium–Hydrogen Exchange.—A solution of NaOMe in MeOH, prepared by adding about 30 mg of sodium to 1 ml of MeOH, was added to the ketone in 2 ml of methanol. The resulting solution was stored at room temperature in a sealed glass tube for 8 days. Thereafter, the solution was poured into 50 ml of water and the resulting mixture was extracted continuously with ether for 3 days. The ether layer was separated and dried ($MgSO_4$). Removal of the ether by careful distillation gave a residue from which the exchanged ketone was isolated by glpc. All exchange experiments were carried out by the method described above.

Addition of DOAc to Bicyclo[2.1.0]pentane.—A sealed glass tube containing 2.55 g of bicyclo[2.1.0]pentane, 400 mg of sulfuric acid-d_2, and 100 ml of acetic acid-*O*-*d* was maintained at 25° for 48 hr. Thereafter, the contents of the tube were added to 200 ml of saturated brine and the resulting mixture was extracted continuously with 400 ml of ether for 2 days. The ether extract was neutralized cautiously with solid Na_2CO_3 and dried ($MgSO_4$). Careful distillation of ether left 4.5 g of light yellow oil. Glpc (5 ft, 15% 20M Carbowax, 90°) showed peaks corresponding to cyclopentanol (<3%, 7.5 min), cyclopentyl acetate (6.3 min), and some residual ether. The procedure described here is typical of the three ring-opening experiments carried out with bicyclo[2.1.0]pentane.

A. $LiAlH_4$ Hydrogenolysis.—The crude acetate, 4.5 g, afforded 520 mg of cyclopentanol-d_1 purified by preparative glpc.

(8) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, pp 224–225.

(9) R. Criegee and R. Rimmelin, *Chem. Ber.*, **90**, 414 (1957).

(10) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

The mass spectrum showed M^+, m/e 87, and the isotopic composition given under the appropriate heading of Table I, row 3. Isotopic compositions of cyclopentanol-d_1 obtained in experiments 1 and 2 are given in rows 1 and 2, respectively.

B. Oxidation.—The 520-mg sample of cyclopentanol-d_1 was oxidized to 350 mg of cyclopentanone-d_1 purified by preparative glpc (5 ft, 15% Carbowax 20M, 100°). The mass spectrum showed M^+, m/e 85, and the isotopic composition given under the appropriate heading of Table I, row 3. Isotopic compositions of cyclopentanone-d_1 obtained in runs 1 and 2 are given in rows 1 and 2, respectively.

C. Exchange.—Cyclopentanone-d_1, 350 mg, gave after purification by glpc 40 mg of cyclopentanone, whose isotopic distribution is given in row 3.

Addition of DOAc to Bicyclo[3.1.0]hexane.—In the first experiment, a sealed glass tube containing 3.52 g of bicyclohexane, 400 mg of sulfuric acid-d_2, and 100 ml of acetic acid-*O*-*d* was maintained at 25° for 47 hr. Thereafter the contents of the tube were poured into 800 ml of water and the resulting mixture was extracted continuously with ether for 8 days. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and reduced in volume to 50 ml by careful distillation of the ether. The concentrated extract was treated immediately with $LiAlH_4$. In the second experiment, 3.32 g of bicyclo[3.1.0]hexane was treated with 400 mg of D_2SO_4 and 100 ml of acetic acid-*O*-*d*; processing as described for the first sample gave 4.14 g of yellow oil after removal of most of the ether by distillation.

A. $LiAlH_4$ Hydrogenolysis.—The ethereal solution of acetates from the first experiment afforded, after purification by glpc (5 ft, 15% Carbowax 20 M, 125°), 250 mg of cyclohexanol-d_1: mass spectrum m/e (rel intensity) 101 (10), 100 (20), 99 (10), 98 (9), 84 (62), 83 (84), 82 (35), 67 (48), 66 (43), 59 (36), 58 (100), 57 (70). In the second experiment, the sample of crude acetates gave a mixture of alcohols from which was isolated by glpc 530 mg of *trans*-2-methylcyclopentanol-d_1, mass spectrum m/e (rel intensity) 101 (20), 100 (3), 83 (38), 82 (12), 68 (20), 67 (26), 58 (23), 57 (100); nmr τ 6.32 (m, 1 H, CHOH), 9.03 (br d, J = 6.5 Hz, 2.3 H, $CHCH_3$), and cyclohexanol-d_1, mass spectrum identical with that of the first sample. The isotopic composition of the cyclohexanol (row 6) was taken to be the same as that of the methylcyclopentanol-d_1 which is given in Table I, row 5.

B. Oxidation.—A sample of the cyclohexanol-d_1 (250 mg) obtained from the first experiment gave after purification by glpc (5 ft, 15% Carbowax 20 M, 100°) 99 mg of cyclohexanone-d_1: mass spectrum m/e (rel intensity) 99 (80), 70 (47), 69 (50), 57 (28), 56 (78). The isotopic composition is given in Table I, row 4. A 100-mg sample of the cyclohexanol-d_1 from the second experiment was oxidized and gave, after purification by glpc, 55 mg of cyclohexanone-d_1 whose isotopic composition is given in Table I, row 6. A 327-mg sample of *trans*-2-methylcyclopentanol-d_1 on oxidation gave, after purification by glpc, 110 mg of 2-methylcyclopentanone-d_1, mass spectrum m/e 99 (M^+), whose isotopic composition is given in Table I, nmr τ 8.96 (d, $CH_3/CH_2 + CH = 0.32$).

C. Exchange.—Samples of cyclohexanone-d_1 originating from first and second experiments, and 2-methylcyclopentanone-d_1, afforded samples of the corresponding exchanged ketones whose isotopic compositions are given in Table I, rows 4, 6, and 5, respectively.

Cyclopentanone-2-d_1 from Cyclopentene Oxide.—Cyclopentene oxide, 4.693 g, was treated with $LiAlD_4$ in ether solution and gave 4.5 g of cyclopentanol-2-d_1 after distillation. A sample was purified further by glpc for mass spectral analysis. The isotopic distribution was d_0, 16 ± 1%; d_1, 80 ± 1%; d_2, 5 ± 2%. Jones oxidation and processing in the usual manner gave 2.7 g of cyclopentanone-2-d_1 whose isotopic distribution was d_0, 18 ± 1%; d_1, 77 ± 1%; d_2, 5 ± 1%. A 1.07-g sample which had been treated with NaOMe–MeOH (~5 *M*) for 8 days at 25° and processed in the usual manner had the following isotopic distribution: d_0, 99 ± 1%; d_1, 2 ± 1%; d_2, 2 ± 1%.

Cyclohexanone-2-d_1 from Cyclohexene Oxide.—Following the procedure used in the preparation of cyclopentanone-2-d_1, cyclohexene oxide (6.34 g) was treated with $LiAlD_4$ and a 986-mg portion of the resulting alcohol (3.03 g) was oxidized by the Jones procedure to give 460 mg of cyclohexanone-2-d_1 whose isotopic distribution was d_0, 20 ± 2%; d_1, 79 ± 2%; d_2, 1 ± 1%. A sample treated with NaOMe–HOMe (~5 *M*) for 8 days at 25° gave cyclohexanone: d_0, 98 ± 2%; d_1, 2 ± 1%; d_2, 0.

Registry No.—**1**, 185-94-4; **2**, 285-58-5; acetic acid, 64-19-7; *trans*-2-methylcyclopentanol, 25144-04-1.

Intramolecular Cyclizations Leading to N-Bridgehead Bicyclics. 5,5-Diphenylhydantoin Derivatives

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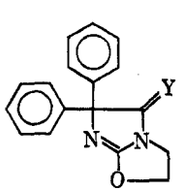
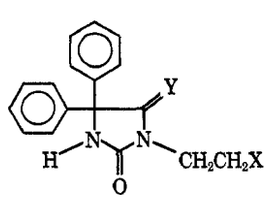
The synthesis and study of the intramolecular cyclizations of 3-(2-hydroxyethyl)-5,5-diphenylhydantoin mesylate (**2a**) and 1-(2-hydroxyethyl)-4,4-diphenyl-2-imidazolidinone mesylate (**2b**) are described. Although both N- and O-alkylation reactions are possible, only the products resulting from intramolecular O-alkylations were obtained.

The reported high concentrations of 5,5-diphenylhydantoin (DPH) in brain tissue and its preferred localization in primary brain tumors[1,2] suggested the synthesis of highly reactive DPH analogs as potential brain antitumor agents.[3] The nitrogen bridgehead bicyclic compounds **1a** and **1b** are part of the results of this work, and, in addition to their behavior as powerful alkylating agents, these compounds have clarified the course of intramolecular cyclization in the 3-substituted hydantoin and the 1-substituted imidazolidinone ring systems.



1a, Y = O
b, Y = H_2



2a, Y = O; X = OSO_2CH_3
b, Y = H_2; X = OSO_2CH_3
c, Y = O; X = OH

The synthesis of **2a** and **2b** and the determination of the structures of their cyclized products helped to resolve the question of whether intramolecular N-

(1) H. Firemark, C. G. Barlow, and L. J. Roth, *Int. J. Neuropharmacol.*, **2**, 25 (1963).
(2) I. Rosenblum and A. A. Stein, *Biochem. Pharmacol.*, **12**, 1453 (1963).
(3) V. E. Marquez, L.-M. Twanmoh, H. B. Wood, Jr., and J. S. Driscoll, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971, Division of Medicinal Chemistry, paper no. 36.