Deuterioxide-Catalyzed Exchange Reactions of Methylenecyclopropanecarboxylic Acids with Deuterium Oxide[1]

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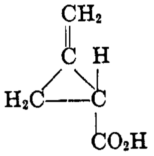
Rates of deuterioxide-catalyzed exchange of deuterium oxide with 2-methylenecyclopropane-1-carboxylic acid (**1**), 3-methylenecyclopropane-*cis*-1,2-dicarboxylic acid (**2**), 3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid (**3**), and the corresponding saturated carboxylic acids, cyclopropanecarboxylic acid (**4**), cyclopropane-*cis*-1,2-dicarboxylic acid (**5**), and cyclopropane-*trans*-1,2-dicarboxylic acid (**6**), were measured by means of n.m.r. spectroscopy. Rates of deuterioxide-catalyzed racemization of **1** and **3** were also determined. At 152°, the extrapolated rate constant for exchange of **1** is $>10^4$ greater than that for **4**. The rate of racemization of **1** was found to be equal to its rate of exchange indicating that the postulated carbanion intermediate is either planar or exists long enough for inversion at carbanionic carbon to occur several times before it abstracts a deuteron from the solvent. The exchange reaction of **2** appears to involve a carbanion intermediate which is converted to **2** and **3** at equal rates. The kinetics of the exchange reactions of **2** and **3**, which are considerably more complicated than those of **1**, could be treated satisfactorily after making several reasonable assumptions. Over the temperature range studied, the estimated rate constant for exchange of one α-hydrogen of the unsaturated *cis*-diacid **2** is ~100 times greater than the corresponding rate constant for the unsaturated *trans*-diacid **3**. At 152°, the extrapolated rate constants for **2** and **3** are $>10^5$ greater than those for the saturated diacids **5** and **6**. Using the derived expressions for the exchange of **3**, which require the assumption that exchange occurs *via* a carbanion that is converted to **2** and **3** at effectively equal rates, the rate constant for exchange of one α-hydrogen is calculated to be identical with that obtained using the derived expressions for the racemization of **3**.

In addition to providing unequivocal evidence that Feist's acid is 3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid (**3**), study of the n.m.r. spectrum of **3** as its disodium salt in deuterium oxide containing sodium deuterioxide revealed that the α-hydrogens undergo exchange with solvent at a moderate rate at room temperature.[2] In order to determine the extent to which this exchange is accelerated by the exocyclic double bond, we have examined in some detail the deuterioxide-catalyzed exchange reactions of the α-hydrogens of the sodium salts of 2-methylenecyclopropane-1-carboxylic acid (**1**), 3-methylenecyclopropane-*cis*-1,2-dicarboxylic acid (**2**), **3**, and the related saturated acids, cyclopropanecarboxylic acid (**4**), cyclopropane-*cis*-1,2-dicarboxylic acid (**5**), and cyclopropane-*trans*-1,2-dicarboxylic acid (**6**). We have also determined the rates of racemization of **1** and **3** under conditions similar to those used to determine the rates of exchange.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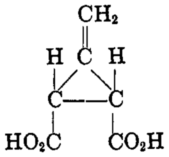
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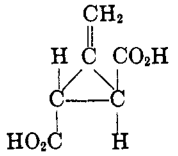
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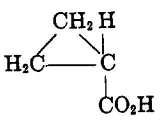
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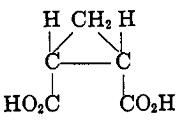
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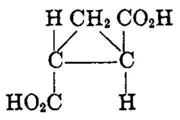
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Experimental Section

Melting points and boiling points are uncorrected. Rotations were determined of samples in 2-dm. tubes, unless stated otherwise, with a Rudolph and Sons polarimeter (no. 251). Gas-liquid partition (g.l.p.) chromatograms were obtained using a 0.25 in. × 10 ft. column that contained a packing of Dimer Acid (Emery Industries, Inc., Los Angeles, Calif.) on firebrick in an Aerograph Model A-700 (Wilkens Instrument and Research, Inc., Walnut Creek, Calif.).

Carboxylic Acids 1–6.—2-Methylenecyclopropane-1-carboxylic acid (**1**), b.p. 85-5–86.0° (6 mm.), n^{23}_{D} 1.4728, lit.[3] b.p. 94–98° (22 mm.), 3-methylenecyclopropane-*cis*-1,2-dicarboxylic acid (**2**), m.p. 117–120°, lit.[4] m.p. 120.5–121.5°, and Feist's acid (**3**), m.p. 197–200°, lit.[5] m.p. 200°, were prepared following previously described procedures.[3-5] Cyclopropanecarboxylic acid (**4**), n^{24}_{D} 1.4371, was purchased from Aldrich Chemical Co. Cyclopropane-*cis*-1,2-dicarboxylic acid (**5**), m.p. 136–138°, lit.[6] m.p. 139–142°, and cyclopropane-*trans*-1,2-dicarboxylic acid (**6**), m.p. 173–176°, lit.[6] m.p. 177–177.5°, were prepared by the method described by McCoy[6] with the exception that ethyl acrylate was used in the initial ring-closure reaction instead of methyl acrylate.

Resolution of Feist's acid (**3**) was accomplished by fractional crystallization of its brucine salt, as has been described previously.[7] (−)-**3**, m.p. 197–200°, $[\alpha]^{24}_{D}$ −71.1° (0.022 g. in 2 ml. of ethanol), lit.[7] m.p. 200°, was obtained in 25% yield.

Resolution of 1.—2-Methylenecyclopropane-1-carboxylic acid (18.3 g., 0.187 mole) and 73.5 g. (0.185 mole) of carefully purified brucine[8] were dissolved in 175 ml. of water at 65°. The solution was concentrated under reduced pressure at 65° until crystals began to separate. Sufficient water was added to reproduce a clear solution at 65°, and the solution was allowed to cool slowly to room temperature. The crystalline precipitate (56.3 g.) was collected and recrystallized twice from the minimum amount of water necessary to effect solution at 65°. The brucine salt weighed 39.5 g. (43%) and had m.p. 79–85°, $[\alpha]^{23}_{D}$ −31.8° (0.037 g. in 2 ml. of water). The salt was added to 400 ml. of 0.2 *N* sulfuric acid at 65°. The solution that resulted was cooled to room temperature, and 100 ml. of 0.2 *N* sulfuric acid was added. Brucine sulfate, which crystallized from the solution, was collected by suction filtration, and the filtrate was extracted five times with 200-ml. portions of ether. The ether extracts were combined, dried with magnesium sulfate, and distilled to give 6.3 g. (80% from the brucine salt) of (−)-**1**, b.p. 83–86° (5 mm.), $[\alpha]^{25}_{D}$ −1.84 (neat). The mother liquors from the crystallization were combined and concentrated to dryness under reduced pressure with a maximum temperature of 65°. The residual brucine salt was decomposed as described above to give 5.0 g. of (+)-**1**, $[\alpha]^{25}_{D}$ 1.74° (neat). Examination of (+)-**1** and (−)-**1** by g.l.p.c. indicated that the substances were >99% pure.

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(1) This research was supported in part by Grant CA-05528 from the National Cancer Institute of the U. S. Public Health Service.

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(3) E. F. Ullman and W. J. Fanshawe, *J. Am. Chem. Soc.*, **83**, 2379 (1961).

(4) M. G. Ettlinger and F. Kennedy, *Chem. Ind.* (London), 891 (1957).

(5) F. R. Goss, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **123**, 327 (1923).

(6) L. L. McCoy, *J. Am. Chem. Soc.*, **80**, 6568 (1958).

(7) F. Feist, *Ann.*, **436**, 139 (1924).

(8) H. Kacser, *J. Chem. Soc.*, 2908 (1950).

Rates of Exchange.—Concentrated (~4 N) solutions of sodium deuterioxide in deuterium oxide were prepared by adding with cooling carbon dioxide free deuterium oxide (>99.7 atom % deuterium) to *ca.* 0.1-g. portions of freshly cut sodium under a stream of dry, carbon dioxide free nitrogen. Dilution of these solutions gave the 0.95–1.5 N sodium deuterioxide solutions used in the kinetic determinations.

For each exchange experiment, 1 mequiv. of acid/ml. of solution and sufficient sodium perchlorate to give an ionic strength of 2.26 were added to the sodium deuterioxide solution. A portion of each solution was titrated with standard acid to check the base concentration, and a second portion was sealed in a 0.5-cm.-o.d. soft glass n.m.r. tube that had been washed successively with benzene, concentrated sulfuric acid, water, ammonium hydroxide, and water, and dried at 120° for 12 hr. As soon as practical after preparation of the solution, its n.m.r. spectrum was determined using a Varian Associates HR-60 system equipped with integrator and base-line stabilizer and housed in an air-conditioned room. When it was necessary to delay examination of the n.m.r. spectrum of a solution for more than 1 hr. after its preparation, the sample was stored at −12°. At least 12 determinations of the relative intensities of the various bands in the spectrum of the solution were made by electronic integration. Successive determinations were made by alternately increasing and decreasing the applied field. The extent of exchange of the α-hydrogens was determined by comparison of the integral of the lines due to the α-hydrogens with those due to either the β-hydrogens, where present, or the exocyclic methylene hydrogens. The mean deviation in either the upfield or downfield ratio was less than 0.02 unit, and the upfield and downfield averages differed by less than 0.02 unit. Regular checks of the accuracy of the integrator were made by examination of a standard solution of propionic acid in sodium deuterioxide solution.

For each run at temperatures below 118°, the n.m.r. tube containing the sodium deuterioxide solution of the acid was immersed in a bath of glycerine maintained at constant temperature (±0.1°) with boiling butanol (117°), isobutyl alcohol (108°), the azeotrope of butanol (24.8 mole %) and water (93°), and benzene (80°). Runs at 152 ± 2° were effected by placing the tubes in a small closed air space maintained at temperature with boiling cyclohexanone. At suitable intervals of time, the sample was removed from the bath, cooled rapidly to −12°, allowed to warm to room temperature for examination of its n.m.r. spectrum, and then replaced in the bath. After about five determinations, the last of which was made after at least one half-life for the exchange reaction had passed, the sample was titrated with standard acid to recheck the base concentration.

Standard alkaline solutions were used to estimate the extent of attack by sodium hydroxide on the glass under the conditions of the kinetic runs. Although spectrometric analysis (performed by Mr. J. Voth) indicated that the glass of the n.m.r. tubes contained 6.2% boron, it was found that at 117° the normality of an initially 0.1 N sodium hydroxide solution decreased by only 5% after 70 hr., and that of an initially 0.5 N sodium hydroxide solution decreased by only 10% after 30 hr. For runs carried out below 118°, it was unnecessary to make specific corrections for loss of alkali.

Racemization of (−)-**3**.—Levorotatory Feist's acid [(−)-**3**] was added to a solution of sodium deuterioxide and sodium perchlorate in deuterium oxide to give a solution that was 0.5 M in (−)-**3**, as its disodium salt, *i.e.*, (−)-$\mathbf{3}^{2-}$, 0.5 M in sodium deuterioxide, and 0.26 M in sodium perchlorate. The rotation and alkalinity of the solution were checked, and a portion was sealed in a long-necked, boron-free glass (Corning No. 7280) ampoule and heated rapidly to the reaction temperature by immersion in the glycerine bath. After a suitable time interval, the ampoule was cooled rapidly to 0° and opened, and the rotation of the solution was determined using a 1-dm. tube. The solution was resealed in the same ampoule and returned to the constant-temperature bath. After five determinations, the last of which was made after at least one half-life for racemization had passed, the alkalinity of the solution was rechecked by titration.

Racemization of (−)-**1**.—Four portions of a standard solution of ( )-**1** as its sodium salt, *i.e.*, (−)-$\mathbf{1}^-$, in deuterium oxide containing sodium deuterioxide and sodium perchlorate were sealed in boron-free glass ampoules and maintained at constant temperature. At suitable time intervals up to one half-life for racemization, an ampoule was cooled to 0° and opened. The solution was made acidic to pH 1 with 1 N sulfuric acid and extracted into ether. The ether solution was dried with magnesium sulfate, and the ether was removed by distillation. The residue (*ca.* 0.8 g.) was maintained at 100° (25 mm.) for 1 hr. and then treated with magnesium sulfate and Norit. The mixture was centrifuged, and the rotation of the neat centrifugate was determined using a 0.5-dm. micropolarimeter tube. A control experiment showed that within the experimental error of 0.005° the optical activity of the sample was not affected by the extraction procedure.

Results

2-Methylenecyclopropane-1-carboxylic Acid (1).—The sodium deuterioxide catalyzed exchange of the α-hydrogen of **1**, as its conjugate base, *i.e.*, $\mathbf{1}^-$, with deuterium oxide was followed by measuring the decrease with time of (α-H)/(β-H), where (α-H) and (β-H) are the intensities of the lines due, respectively, to the α- and β-hydrogens of $\mathbf{1}^-$. For each run, a plot of ln [(α-H)/(β-H)] against time was linear to at least 50% exchange. The ratio of the intensities of the lines due to the β- and the exocyclic hydrogens remained constant at 1.00 ± 0.02 during the kinetic measurements, and exchange was not accompanied by the appearance of new lines in the n.m.r. spectrum.

For the exchange reaction of $\mathbf{1}^-$, it can be shown that the observed specific rate constant, k_s, is related to the specific rate constant, k_1, by eq. 1, wherein N_H is the

$$k_s = \frac{(1 - N_H)k_1}{1 + N_H(J - 1)} \qquad (1)$$

mole fraction of protons in the solvent and J is the kinetic isotope effect, k_H/k_D, for the reaction of the carbanionic intermediate with water. Over the course of one half-life for exchange, N_H varied from 0.020 to 0.025. As J may be reasonably assumed to be near unity and certainly less than 4,[9] the variation in k_s is negligible over one half-life, and the observed value of the specific rate constant is about 2% (and no more than 8%) lower than the actual value.

Kinetic runs were carried out at several temperatures from 80.8 to 117°. Variation of the deuterioxide concentration in runs conducted at 107.4 and 116.5° confirmed that the exchange reaction was first-order in deuterioxide ion concentration. Data obtained from two typical runs are given in Table I, and the observed specific rate constants for $\mathbf{1}^-$ and the conjugated bases of the other carboxylic acids are summarized in Table II. In order to obtain reasonable estimates of the ΔH^* and ΔS^* for the exchange reaction, the logarithm of the observed specific rate constant was plotted against $1/T$. The thermodynamic constants for the exchange reactions of $\mathbf{1}^-$ and the other conjugate bases are given in Table III.

The specific rate constant for the deuterioxide-catalyzed racemization of $\mathbf{1}^-$ was determined at 106.0° from the linear plot of the logarithm of the specific rotation *vs.* time. Given in Table IV are the specific rate constants for racemization of $\mathbf{1}^-$ and $\mathbf{3}^{2-}$ together with the respective rate constants for exchange at the same temperature. At 106.0°, the rate constants for deuterioxide-catalyzed exchange and racemization of $\mathbf{1}^-$ are 3.31 × 10^{-4} and 3.22 × 10^{-4} sec.$^{-1}$ M^{-1}, respectively. Thus, within the limits of experimental error, the rate constants are the same.

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[9] See K. Wiberg, *Chem. Rev.*, **55**, 723 (1955).

TABLE I

EXPERIMENTAL DATA FROM TWO TYPICAL DEUTERIOXIDE-CATALYZED EXCHANGE REACTIONS OF **1** WITH DEUTERIUM OXIDE[a]

Run 1: Temp. = 80.8°, (OD^-) = 0.455 *N*

Time, hr.	$(\alpha\text{-H})/(\beta\text{-H})$[b]	k_s,[c] M^{-1} sec.$^{-1}$ × 10^5
0	0.48	...
0.54	0.47	$(2.{}_3)$
1.57	0.45	$(2.{}_5)$
4.59	0.41	2.1_1
9.58	0.35	2.0_1
21.82	0.23	2.0_6
	Av.	2.0_6
	Graphical	2.0_2

Run 2: Temp. = 116.5°, (OD^-) = 0.09_0 *N*

Time, min.	$(\alpha\text{-H})/(\alpha\text{-H})$[b]	k_s,[c] M^{-1} sec.$^{-1}$ × 10^3
0	0.48	...
34	0.39	1.13
79	0.31	1.03
111	0.25[d]	1.09
148	0.21[d]	1.04
	Av.	1.07
	Graphical	1.04

[a] Solutions were 1.0 *N* in 1^-, and the ionic strength was adjusted to 2.26 with sodium perchlorate. [b] Average deviation from the average (a.d.a.) of at least 12 determinations was ±0.01 unless indicated otherwise. [c] k_s is the observed second-order rate constant. [d] A.d.a. = 0.02.

TABLE II

RATE CONSTANTS FOR DEUTERIOXIDE-CATALYZED EXCHANGE OF CARBOXYLIC ACIDS **1–6** WITH DEUTERIUM OXIDE[a]

Acid	Temp., °C.[b]	$(OD^-)_0$[c]	k_n,[d] M^{-1} sec.$^{-1}$ × 10^4
2	51.0	0.10	21
2	51.0	0.15	20
1	80.8	0.46	0.20
2	80.8	0.10	170
3	80.8	0.48	1.3
1	93.0	0.12	0.88
3	93.0	0.13	3.5
3	93.0	0.46	3.7
1	107.4	0.10	3.4
1	107.4	0.47	3.8
3	107.4	0.12	13
1	116.5	0.09	10
1	116.5	0.50	8.7
3	116.5	0.14	29
3	117.8	0.04	27
4	152	0.34[e]	<0.013
5	152	0.29[e]	<0.003
6	152	0.21[e]	<0.005

[a] Solutions were 1.0 *N* in carboxylate, and the ionic strength was adjusted to 2.26 with sodium perchlorate. [b] ±2° at 152°; otherwise, ±0.1°. [c] Initial deuterioxide concentration; final deuterioxide concentration did not differ by more than ±0.005 unless stated otherwise. [d] The observed specific rate constant for exchange of one α-hydrogen, *i.e.*, for **2**, **3**, **5**, and **6**, $k_n = k_s/2$. [e] Final deuterioxide concentration.

3-Methylenecyclopropane-*cis*-1,2-dicarboxylic Acid (2).—The rate of exchange was followed by measuring the decrease with time of (α-H)/(*exo*-H), where (α-H) and (*exo*-H) are the intensities of the lines due, respectively, to the α- and exocyclic hydrogens of the dianion of **2**, *i.e.*, 2^{2-}. The sequence of reactions postulated for treatment of the kinetics of exchange of 2^{2-} is shown as Scheme I. In this sequence, k_2 is the specific rate constant for the deuterioxide-catalyzed removal of one α-hydrogen from 2^{2-}, k and k' are the rate constants for neutralization of the carbanionic intermediate with retention and inversion of configuration, respectively, and E is the kinetic isotope effect (k_H/k_D) for the deuterioxide-catalyzed removal of one α-hydrogen. Because the kinetics for exchange for the di-

TABLE III

THERMODYNAMIC QUANTITIES FOR DEUTERIOXIDE-CATALYZED EXCHANGE OF CARBOXYLIC ACIDS **1–6** WITH DEUTERIUM OXIDE

Acid	ΔH^*_{90},[a] kcal./mole	ΔS^*_{90},[a] e.u.	k_n at 152°, M^{-1} sec.$^{-1}$ × 10^3	ΔF^*_{152},[b] kcal./mole
1	28.4[c]	0	2.2[d]	28.4
2	15.7[e]	−22[e]	87[d]	25.3
3	22.8[f]	−12[f]	3.3[d]	28.1
4	...	...	$<1.3 \times 10^{-4}$[g]	>36.7
5	...	...	$<3 \times 10^{-5}$[g]	>37.9
6	...	...	$<5 \times 10^{-5}$[g]	>37.4

[a] The maximum errors calculated using the appropriate least-squares equations and assuming ±10% errors in k_n at the extreme temperature were ±1.5 kcal./mole for ΔH^* and ±4 e.u. in ΔS^*. [b] From $k_n = (kT/h)e^{-\Delta F^*/RT}$, where k and h are the Boltzmann constant and the Planck constant. [c] The least-squares equation of the data in Table II gave E_A, the Arrhenius activation energy, = 29.2 kcal./mole, and A, the pre-exponential factor, = 2.14×10^{13}. The root-mean-square deviation (r.m.s. dev.) for the least-squares equation was 0.033. [d] Extrapolated value using the appropriate least-squares equation. [e] E_A = 16.5 kcal./mole and A = 2.53×10^8. [f] The least-squares equation, r.m.s. dev. = 0.024, gave E_A = 23.6 kcal./mole and A = 4.26×10^{10}. [g] Calculated maximum values.

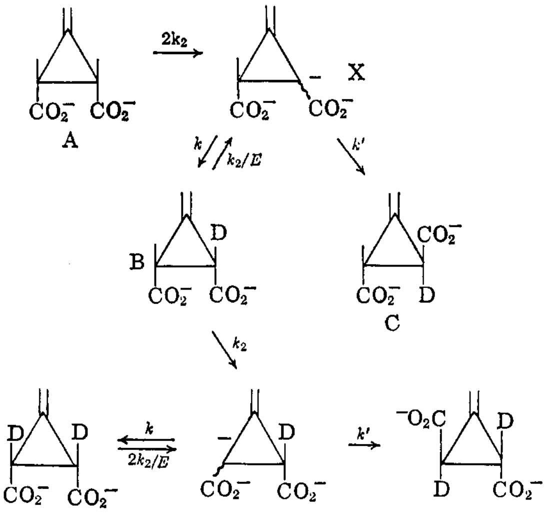
TABLE IV

COMPARISON OF EXCHANGE AND RACEMIZATION RATES OF **1** AND **3**[a]

Acid	Reaction	Temp., °C.[b]	$(OD^-)_0$[c]	k_n, M^{-1} sec.$^{-1}$ × 10^4
1	Racemization	106.0	0.50	3.2_2
1	Exchange	106.0	...	3.3_1[d]
3	Racemization	80.7	0.41	1.2_6
3	Exchange	80.7	...	1.2_0[d]
3	Racemization	107.0	0.12	$11._9$
3	Exchange	107.0	...	$12._3$[d]
3	Racemization	107.0	0.12	$12._0$[e]

[a] Solutions were 1.0 *N* in carboxylate unless stated otherwise; the ionic strength was adjusted to 2.26 with sodium perchlorate. [b] ±0.1°. [c] Initial concentration of sodium deuterioxide. [d] Calculated using the appropriate least-squares equation of data given in Table II. [e] Concentration of **3** was 0.14 *M*.

SCHEME I



carboxylic acids are complex, certain reasonable assumptions were made in order to simplify treatment of the data. It was assumed that secondary isotope effects and those effects arising from the presence of protons in the solvent could be neglected. Further, Feist's acid (**3**), which is formed quantitatively from the reaction of **2** with hydroxide,[4] is assumed not to undergo further observable exchange during examination of the exchange reaction of $\mathbf{2}^{2-}$. This last assumption is certainly reasonable because at the temperatures used, $\mathbf{2}^{2-}$ undergoes exchange at more than 100 times the rate of $\mathbf{3}^{2-}$.

Examination of the kinetic scheme shows that, when all the **2** has exchanged, the limiting value for (α-*H*)/(*exo*-H), arising from monodeuterated **3**, is given by eq. 2. It was found experimentally that this limiting

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{1}{2}\sum_{n=0}^{n=\infty}\frac{(k/k')^n}{(E+1)^n[(k/k')+1]^{n+1}} \qquad (2)$$

value, which was assumed to be that at which the plots of (α-H)/(*exo*-H) begin to level off, was approximately 0.27. If E is taken to be approximately 5,[9] it must be concluded that $k \approx k'$.

By making the above assumptions, it was possible to solve the differential equations for the concentrations of the various species present in the reaction mixture and to express (α-H)/(*exo*-H) in terms of A/A_0, where A_0 is the initial concentration of **2** and A is its concentration at any subsequent time (see the Appendix). The result is eq. 3. Taking $E = 5$,

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{E+1}{2(2E+1)} + \frac{E-1}{2(2E-1)}(A/A_0) + \frac{2E^2}{(2E-1)(2E+1)}(A/A_0)^{\frac{2E+1}{4E}} \qquad (3)$$

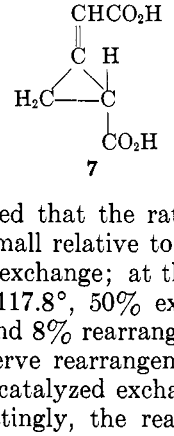
eq. 3 reduces to eq. 3a, and the reduced form was used to obtain (A/A_0) for the various experimental values

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{3}{11} + \frac{2}{9}(A/A_0) + \frac{50}{99}(A/A_0)^{11/20} \qquad (3a)$$

of (α-H)/(*exo*-H). For each deuterioxide-catalyzed reaction of $\mathbf{2}^{2-}$, the plot of ln (A/A_0) against time was linear, and from this linear relationship was obtained the value of the observed specific rate constant, k_s, which is equal to $2k_2$. It can be shown that variation of E between 5 and 1 has a negligible effect on the values of k_s. As k_s was determined at only two temperatures (see Table II), the derived values of ΔH^* and ΔS^* and the extrapolated value of k_s at 152° given in Table III are of somewhat less reliability than similar values for **1** and **3**.

At the temperatures used to study the deuterioxide-catalyzed exchange reactions, the *cis*-diacid was alone among the acids used in the present work in its ability to undergo measurable exchange in the absence of an excess of sodium deuterioxide, *i.e.*, with the acid between 95 and 100% neutralized. The exchange reaction observed appears to be a carboxylate-catalyzed reaction rather than a deuterioxide-catalyzed reaction. 3-Methylenecyclopropane-*cis*-1,2-dicarboxylic acid (**2**) has a second dissociation constant of 6.1 × 10^{-7} at 25° in water.[10] Therefore, when **2** is 97 ± 2% neutralized, the hydroxide ion concentration is approximately 2 × 10^{-7} M. By dividing 2 × 10^{-7} M into the pseudo-first-order rate constant, $k_2{}^1$, obtained for the "self-catalyzed" reaction at 93.0 and 117.8° (1.4 × 10^{-6} and 1.2 × 10^{-5} sec.$^{-1}$, respectively), quotients are obtained that are more than 180 times greater than the values of the specific rate constants for the deuterioxide-catalyzed reaction, *i.e.*, k_2, at 93 and 117.8°, obtained by extrapolation. As the "self-catalyzed" reaction was slower than the deuterioxide-catalyzed reaction by a factor greater than 10^4, it was possible to neglect it during study of the deuterioxide-catalyzed exchange reactions of $\mathbf{2}^{2-}$.

We observed that, as the exchange reaction of $\mathbf{2}^{2-}$ proceeded in the absence of excess deuterioxide, two new bands appeared in the n.m.r. spectrum, one each at lower and higher field than the bands due to $\mathbf{2}^{2-}$ (and $\mathbf{3}^{2-}$). We emphasize that this reaction was the only one of those studied that gave such evidence of a side reaction. The new bands can be rationalized as due to 2-carboxycyclopropylideneacetic acid (**7**), formed by slow rearrangement of **2**,[11] the new low- and high-field bands resulting, respectively, from the vinyl and methylene hydrogens of **7**. It was assumed that the band due to the α-hydrogen of **7** was indistinguishable from the band due to the α-hydrogens of **2** (and **3**), thus leading to erroneous values of (A/A_0). The extent of the supposed **2** → **7** rearrangement was estimated by comparing the intensities of the new high-field band and the band due to the exocyclic methylene hydrogens of $\mathbf{2}^{2-}$ (and $\mathbf{3}^{2-}$). This permitted calculation of the contribution of the α-hydrogen of **7**, which is probably unexchanged in the absence of excess deuterioxide, to the observed value of (α-H)/(*exo*-H). When (A/A_0) was determined from the corrected values of (α-H)/(*exo*-H), good straight lines were obtained from plots of ln (A/A_0) against time, thus permitting calculation of $k_s = 2k_2{}^1$. The effect of the presence of less than 5% of the nonionized acid was ignored.



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It should be noted that the rate of the **2** → **7** rearrangement was small relative to the rate of the carboxylate-catalyzed exchange; at the extreme temperatures of 93.0 and 117.8°, 50% exchange was accompanied by only 4 and 8% rearrangement, respectively. The failure to observe rearrangement with the much faster deuterioxide-catalyzed exchange is therefore not surprising. Interestingly, the rearrangement of **2** in deuterium oxide was observed to occur more rapidly for the free acid than for the salt. The origin of the new n.m.r. bands due to rearrangement of **2** was not investigated by means other than n.m.r. spectroscopy.

3-Methylenecyclopropane-*trans*-1,2-dicarboxylic Acid (Feist's Acid, 3).—The rates of exchange of $\mathbf{3}^{2-}$ were studied by following the decrease with time of (α-H)/(*exo*-H). The stability of the exocyclic hydrogens was checked by comparison of (*exo*-H) with the intensity

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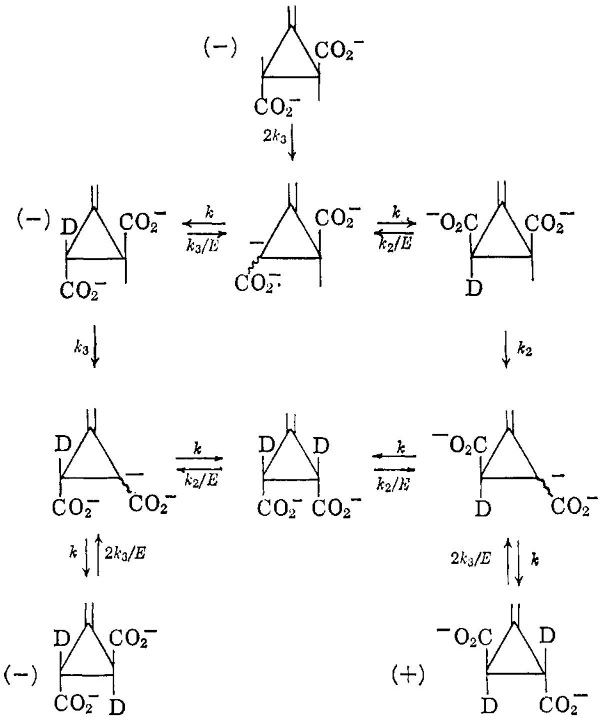
(10) Determined in the same manner as that employed by L. L. McCoy and G. W. Nachtigall [*J. Am. Chem. Soc.*, **85**, 1321 (1963)]. The first dissociation constant of **2** is 1.5 × 10^{-3} at 25° in water.

(11) *Cf.* E. F. Ullman, *ibid.*, **81**, 5386 (1959).

of the signal due to pivalic acid, which was added as an internal standard. No exchange of the exocyclic hydrogens was observed after 6 hr. at 118° in the presence of 0.1 N sodium deuterioxide. The rate of racemization of (−)-**3**$^{2-}$ was also measured at two temperatures by following the decrease with time of its specific rotation [α].

In Scheme II, which is suggested to accommodate the kinetics for the exchange and racemization of **3**$^{2-}$, the most important assumption made is that both **3**$^{2-}$ and **2**$^{2-}$ exchange through the same carbanionic intermediate, leading in both cases to equal retention and inversion at the reaction center. This assumption, which seems justified in light of the results obtained with **1**$^{-}$ and **2**$^{2-}$, permits calculation of k_3, the specific rate constant for the deuterioxide-catalyzed removal of one α-hydrogen from **3**$^{2-}$, from both the exchange and the racemization data. The treatment involves the use of a steady-state approximation for **2**$^{2-}$, which is reasonable because, at all temperatures used, **2**$^{2-}$ exchanges at rates greater than 60 times those of **3**$^{2-}$.

SCHEME II



For the deuterioxide-catalyzed exchange of **3**$^{2-}$ and for the racemization of **3**$^{2-}$, it can be shown that eq. 4 and 5 obtain, respectively. In eq. 4 and 5, E is,

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{E-1}{2E}(A/A_0) + \frac{E+1}{2E}(A/A_0)^{\frac{1+E}{1+2E}} \tag{4}$$

$$\frac{[\alpha]}{[\alpha]_0} = \frac{(1-E)^2}{E(2E-1)}(A/A_0) + \frac{E^2}{(2E^2-1)(2E-1)}(A/A_0)^{\frac{1}{2E}} + \frac{(E^2-1)(E+1)}{E(2E^2-1)}(A/A_0)^{\frac{E+1}{2E+1}} \tag{5}$$

as before, the kinetic isotope effect (k_H/k_D) for the deuterioxide-catalyzed removal of one α-hydrogen from either **2**$^{2-}$ or **3**$^{2-}$, A_0 is the initial concentration of unexchanged **3**$^{2-}$, A is its concentration at any subsequent time, $[\alpha]_0$ is the initial specific rotation, and $[\alpha]$ is the specific rotation at any subsequent time.

Using as before the value $E = 5$, eq. 4 and 5 become eq. 4a and 5a. A/A_0 was calculated from the various experimental values of both (α-H)/(*exo*-H) and $[\alpha]/[\alpha]_0$.

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{2}{5}(A/A_0) + \frac{3}{5}(A/A_0)^{6/11} \tag{4a}$$

$$\frac{[\alpha]}{[\alpha]_0} = \frac{16}{45}(A/A_0) + \frac{144}{245}(A/A_0)^{6/11} + \frac{25}{441}(A/A_0)^{1/10} \tag{5a}$$

For each kinetic run, the plot of ln (A/A_0) against time gave a good straight line from which was calculated $k_s = 2k_3$. The rate constants are summarized in Tables II and IV. At both 80.7 and 107.0°, the values of k_s as determined from rates of exchange and racemization differed by less than 5%. Using values determined from exchange experiments, ln $(k_s/2)$ was plotted against $1/T$, and the points were fitted by the least-squares method to a straight line, thereby permitting calculation of ΔH^* and ΔS^* for the deuterioxide-catalyzed removal of one α-hydrogen from **3**. These data are included in Table III.

For the exchange data, variation of E from 1 to 5 had a negligible effect on k_s. As determined from the racemization data, k_s was equally unaffected by variation of E from 3 to 5. Taking E equal to unity, so that $[\alpha]/[\alpha]_0 = (A/A_0)^{1/2}$, the values of k_s were increased by about 30%, and the plots of ln (A/A_0) against time showed deviations from linearity.

The Saturated Carboxylic Acids 4–6.—Cyclopropanecarboxylic acid (**4**), cyclopropane-*cis*-1,2-dicarboxylic acid (**5**), and cyclopropane-*trans*-1,2-dicarboxylic acid (**6**), as their sodium salts, were found to undergo deuterioxide-catalyzed exchange with deuterium oxide at exceedingly slow rates. After 100 hr. at 152 ± 2° and in the presence of >0.2 N sodium deuterioxide, **4**$^{-}$, **5**$^{2-}$, and **6**$^{2-}$ underwent exchange of their α-hydrogens to the extent of 0 ± 16, 3 ± 4, and 4 ± 4%, respectively. From these data, maximum values of the specific rate constants for the removal of one α-hydrogen were calculated for **4**$^{-}$, **5**$^{2-}$, and **6**$^{2-}$ by taking the extent of exchange as 16, 7, and 8%, respectively. For purposes of comparison, these maximum values of the rate constants for **4**, **5**, and **6** are included in Tables II and IV.

Discussion

Of particular interest is our finding that 2-methylenecyclopropane-1-carboxylic acid (**1**), which at 152° has a ΔF^* for exchange at least 8.3 kcal. less than ΔF^* for exchange of cyclopropanecarboxylic acid (**4**),[12] undergoes exchange and racemization at the same rate. This result can be contrasted with the observation that 2,2-diphenylcyclopropyl cyanide undergoes methoxide-catalyzed exchange of its α-hydrogen with

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[12] **1** and vinylacetic acid (**8**) undergo exchange at similar rates. Ives[13] determined at 100° a rate constant of 3×10^{-3} M^{-1} sec.$^{-1}$ for hydroxide-catalyzed exchange of the α-hydrogens of **8** with deuterium oxide; our interpolated value of the rate constant for **1** at the same temperature is 1.0×10^{-4} M^{-1} sec.$^{-1}$. We emphasize that these rate constants can only be compared qualitatively because markedly different conditions were used to study the exchange reactions of **1** (ionic strength = 2.26, $N_{D_2O} \sim 0.98$) and **8** (ionic strength = 1.05, $N_{D_2O} \sim 0.025$).

[13] D. J. G. Ives, *J. Chem. Soc.*, 91 (1938).

methanol-*d* over 8000 times more rapidly than it racemizes.[14]

The equality of the exchange and racemization rates of **1** reveals that the double bond exocyclic to the three-membered ring has a marked effect in stabilizing the trigonal configuration of a cyclopropyl carbanion. However, the kinetic data does not allow us to state exactly the most stable hybridization of the α-carbon of the dianion formed by abstraction of a proton from the conjugate base of **1**. There are two alternative explanations that can accommodate the kinetic data, and these can be visualized with the aid of Figure 1. Interconversion of the enantiomers of the conjugate base of **1**, *i.e.*, *d*-$\mathbf{1}^-$ and *l*-$\mathbf{1}^-$, can be pictured as occurring *via* energetically identical transition states *d*-$\mathbf{1}^{-*}$ and *l*-$\mathbf{1}^{-*}$, in which the configuration at the α-carbon still resembles that of the anion in that it is not completely trigonal, and a symmetrical intermediate dianion (*d,l*-$\mathbf{1}^{2-}$), wherein the α-carbon is trigonal (*cf.* Figure 1A). Alternatively, the dianion *dl*-$\mathbf{1}^{2-}$ can be pictured as a transition state flanked by enantiomeric dianions (*d*- and *l*-$\mathbf{1}^{2-}$) wherein the configuration at the α-carbon resembles that in the enantiomeric monoanions. The important point made clear by our results is that the dianion *dl*-$\mathbf{1}^{2-}$, in which the configuration at the α-carbon is trigonal, be it a transition state or an intermediate, possesses less energy than the transition state for exchange.

The picture that emerges from study of the exchange reactions of 3-methylenecyclopropane-*cis*-1,2-dicarboxylic acid (**2**) and its *trans* isomer **3** is consistent with our interpretation of the kinetics and stereochemistry of exchange of **1**. Particularly revealing was the finding that the *cis*-diacid **2** is converted with deuterioxide in deuterium oxide to *trans*-diacid **3** that contains 73 ± 2 atom % deuterium in the α-positions. This indicates that the dianion of **2**, *i.e.*, $\mathbf{2}^{2-}$, is converted to at least one trianion intermediate that is transformed at essentially equal rates to $\mathbf{2}^{2-}$ and $\mathbf{3}^{2-}$. By using eq. 2, we calculate that, if the energy barrier separating the trianion from $\mathbf{2}^{2-}$ were 150 cal. greater than the barrier separating it from $\mathbf{3}^{2-}$, significantly less deuterium (<70 atom %) would have been incorporated in the α-position; if the barrier separating the trianion from $\mathbf{2}^{2-}$ were 150 cal. less than the barrier separating it from **3**, significantly more deuterium (>77 atom %) would have been incorporated in the α-position. The possibility that a measurable amount of the deuterium is incorporated in $\mathbf{3}^{2-}$ after $\mathbf{3}^{2-}$ is formed can be discounted because $\mathbf{3}^{2-}$ undergoes exchange at least 100 times more slowly than $\mathbf{2}^{2-}$ at the temperatures used to study the exchange of $\mathbf{2}^{2-}$.

As with the exchange reaction of $\mathbf{1}^-$, there are two alternative explanations that will account for the observed extent of the incorporation of deuterium at the α-position of $\mathbf{3}^{2-}$ formed from $\mathbf{2}^{2-}$. As the first and simpler explanation, we picture the high-energy portion of the energy configuration diagram separating $\mathbf{2}^{2-}$ and $\mathbf{3}^{2-}$ as consisting of a trianion intermediate, in which the configuration of the carbanionic α-carbon is trigonal, flanked by energetically similar (to ±150 cal.) transition states $\mathbf{2}^{2-*}$ and $\mathbf{3}^{2-*}$. In each of the transition states $\mathbf{2}^{2-*}$ and $\mathbf{3}^{2-*}$, the configuration of the carbon undergoing exchange still resembles that of the dianion from which the transition state was formed in that it is not completely trigonal. For the second explanation, our picture going from $\mathbf{2}^{2-}$ to $\mathbf{3}^{2-}$ consists of a transition state $\mathbf{2}^{2-*}$, a trianion $\mathbf{2}^{3-}$, a trianion with a trigonal carbanionic α-carbon, a third trianion $\mathbf{3}^{3-}$, and a second transition state $\mathbf{3}^{2-*}$. This picture requires the qualification that the high-energy configuration separating $\mathbf{2}^{3-}$ from the dianion of **3** ($\mathbf{3}^{2-}$) possesses to within 150 cal. the same energy as $\mathbf{2}^{2-*}$.

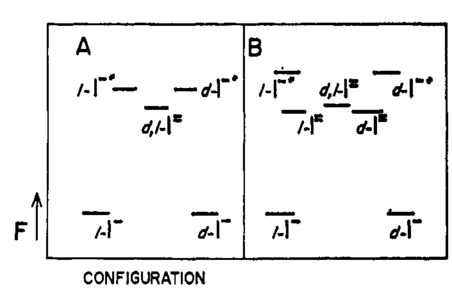

Figure 1.—Free energy–configuration diagram for exchange and racemization of 2-methylenecyclopropane-1-carboxylate (1^-) if the species with the trigonal configuration at the α-carbon of the dianion is (A) an intermediate or (B) a transition state.

For the admittedly complex treatment of the kinetics of exchange and racemization of the *trans*-diacid **3**, we assumed that $\mathbf{3}^{2-}$ is converted to a trianion intermediate which is converted to $\mathbf{2}^{2-}$ and $\mathbf{3}^{2-}$ at essentially equal rates; in other words, we assumed that $\mathbf{2}^{2-*}$ and $\mathbf{3}^{2-*}$ have essentially the same free energy. Using this assumption, the rate constant, k_3, for exchange of one α-hydrogen of $\mathbf{3}^{2-}$ was calculated using eq. 4 derived for exchange of $\mathbf{3}^{2-}$, and the same rate constant was calculated using eq. 5 derived for racemization of $\mathbf{3}^{2-}$. The excellent agreement of the values of k_3 calculated by the two methods gives a measure of assurance that the assumption is correct.

At the beginning of this discussion, we noted that at 152° the $\Delta\Delta F^*$ for the exchange reactions of **1** and **4** is at least 8.3 kcal. At the same temperature, we find for each of the unsaturated dicarboxylic acids that ΔF^* is at least 9 kcal. and probably more than 12 kcal. less than ΔF^* for the corresponding saturated dicarboxylic acid. The reduction of ΔF^* of ~12 kcal. can be taken as a conservative estimate of the resonance energy of the methylenecyclopropyl carbanion (**9**) in which the carbanionic carbon is trigonal.

Interestingly, an estimate of 6.3 kcal. can be made for the resonance energy of the transition state for nitrogen inversion in N-methylallenimine (**10**). The resonance energy possessed by **10** is taken to be the same as the $\Delta\Delta F^*$ for nitrogen inversion in N-methylallenimine and N-ethylethylenimine. By extrapolating data obtained at −53 to −30°,[15] one can estimate that the specific rate for inversion of N-methylallenimine is 2.3×10^5 sec.$^{-1}$ at 108°. At this temperature, the specific rate for inversion of N-ethylethylenimine is ~60 sec.$^{-1}$.[16] Note that the nitrogen atom in the transition state for inversion of N-methylallenimine is trigonal, and the transition state is isoelectronic with methylenecyclopropyl carbanion.

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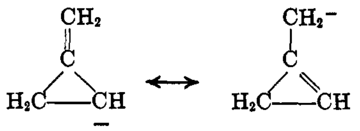
[14] H. M. Walborsky, A. A. Youssef, and J. M. Motes, *J. Am. Chem. Soc.*, **84**, 2465 (1962).

[15] A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960).

[16] A. T. Bottini and J. D. Roberts, *ibid.*, **80**, 5203 (1958).



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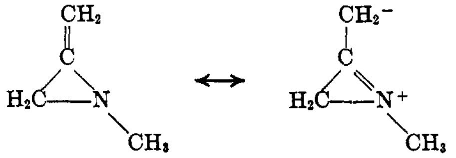

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It remains to be determined if an exocyclic methylene will impart sufficient stability to a cyclopropylcarbonium ion or a cyclopropyl carbon undergoing an SN2 reaction to allow nucleophilic substitution to occur at cyclopropyl carbon without rupture of the three-membered ring.

Appendix

Kinetic Treatment for the Deuterioxide-Catalyzed Exchange of 2^{2-} with Deuterium Oxide.—Scheme I was assumed. It was further assumed that 3^{2-} undergoes no observable exchange under the reaction conditions, and that the trianion intermediate in the reaction is converted to 2^{2-} and 3^{2-} at essentially equal rates, *i.e.*, $k = k'$. Justification for the latter two assumptions is given in the text.

With k, k', and E as defined previously, and A_0 = the initial concentration of nondeuterated 2^{2-}, A = the concentration of nondeuterated 2^{2-} at time t, B = the concentration of monodeuterated 2^{2-} at time t, C = the concentration of monodeuterated 3^{2-} at time t, and X = the concentration of the first trianion intermediate at time t, rate equations for A, B, and C are

$$\frac{dA}{dt} = -2k_2A$$

$$\frac{dB}{dt} = kX - k_2\left(\frac{E+1}{E}\right)B$$

$$\frac{dC}{dt} = kX$$

A steady-state approximation may be applied for X to give

$$2k_2A + \frac{k_2}{E}B - 2kX = 0$$

The last four equations were solved for A, B, and C by the operator method[17] to obtain

$$A = A_0e^{-2k_2t}$$

$$B = \frac{2E}{2E-1}A_0e^{-2k_2t}\left[e^{\frac{2E-1}{2E}k_2t} - 1\right]$$

$$C = A_0\left[\frac{1+E}{1+2E} + \frac{1-E}{2E-1}e^{-2k_2t} - \frac{2E}{(2E-1)(2E+1)}e^{-\frac{(2E+1)}{2E}k_2t}\right]$$

Now

$$\frac{(\alpha\text{-H})}{(exo\text{-H})} = \frac{2A + B + C}{2A_0}$$

but instead of solving directly for k_2, it was found more convenient to express (α-H)/(*exo*-H) in terms of A/A_0, thereby obtaining eq. 3 (see Results).

Equation 3 was solved by machine computation for each value of (α-H)/(*exo*-H), and ln (A/A_0) was plotted against t to obtain k_2.

[17] N. M. Rodiguin and E. N. Rodiguina, "Consecutive Chemical Reactions," D. Van Nostrand Co., New York, N. Y., 1964.

Synthesis of *cis*- and/or *trans*-Dispiro[3.1.3.1]decane-2,8-dicarboxylic Acid[1]

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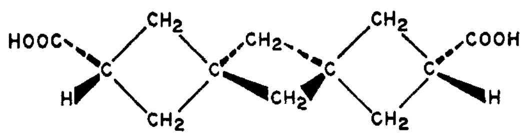
The *cis* and/or *trans* isomers of dispiro[3.1.3.1]decane-2,8-dicarboxylic acid (I) have been synthesized for use in future physical organic studies. Pentaerythritol was converted in three steps into a new compound, 1,1,3,3-tetrakis(hydroxymethyl)cyclobutane (II), *via* the intermediates, 2,2-bis(bromomethyl)-1,3-propanediol, 2-phenyl-5,5-bis(bromomethyl)-1,3-dioxacyclohexane, and diisoamyl 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylate. Reaction of II with excess *p*-toluenesulfonyl chloride gave 1,1,3,3-tetrakis(hydroxymethyl)cyclobutane tetra-*p*-toluenesulfonate which was then condensed with 2 moles of diethyl malonate to give tetraethyl dispiro[3.1.3.1]decane-2,2,8,8-tetracarboxylate (III). Saponification of III led to dispiro[3.1.3.1]decane-2,2,8,8-tetracarboxylic acid which, when heated under reduced pressure at a temperature above its melting point (210°), underwent decarboxylation to give *cis*- and/or *trans*-dispiro[3.1.3.1]decane-2,8-dicarboxylic acid.

The isomeric compounds *cis*- and/or *trans*-dispiro[3.1.3.1]decane-2,8-dicarboxylic acids have been synthesized as intermediates for conversion into compounds of interest for physical organic studies. It is hoped that the unique, fixed, geometrical relationships in 2,8-disubstituted dispiro[3.1.3.1]decanes will permit a study of group interactions where the inductive and resonance effects have been minimized and where spacial orientations can be calculated with a reasonable degree of confidence. The primary purpose of this paper is to report the synthesis of *cis*- and/or *trans*-dispiro[3.1.3.1]decane-2,8-dicarboxylic acids (I).



I

Successful synthesis of I was accomplished using methods of synthesis developed earlier by Buchman

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[1] Presented to the Organic Chemistry Division at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964; Abstracts, p. 98.