

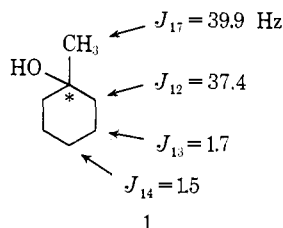
The Angular Dependence of Three-Bonded Carbon-Carbon Coupling Constants^{1a}

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Abstract: A correlation has been recognized between three-bonded carbon-13-carbon-13 coupling constants (${}^3J_{C-C}$) and the dihedral angle of the involved nuclei system of aliphatic carboxylic acids (*i.e.*, of the system ${}^{13}C-C-C-{}^{13}COOH$). This correlation was done through a study of $>90\%$ ${}^{13}C$ -carboxyl aliphatic carboxylic acids synthesized by a variety of methods. This correlation may prove to be useful for chemical shift assignments and conformational analysis.

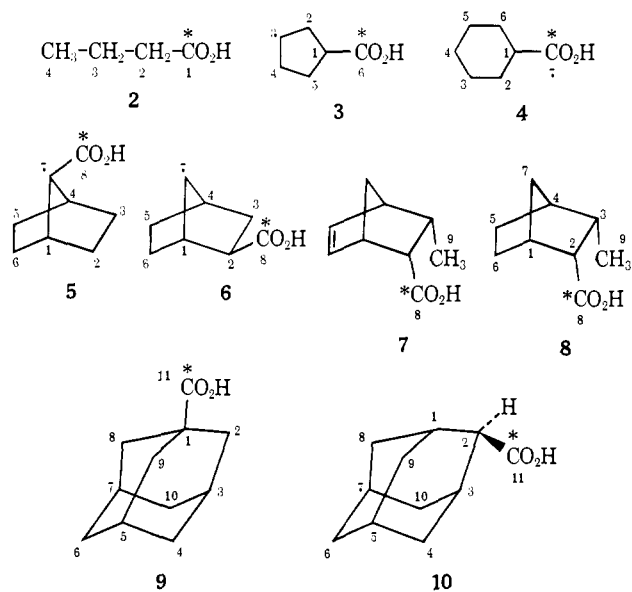
Three-bonded carbon-carbon coupling constants (${}^3J_{C-C}$) are larger than the respective two-bonded carbon-carbon coupling constants (${}^2J_{C-C}$) in all cases for a number of aliphatic and aromatic systems thus far studied.²⁻⁵ This observation is consistent with theoretical predictions⁶ that (at least in π systems) coupling constants should vary in an alternating fashion down a carbon chain. It was with surprise, therefore, that we observed⁷ in 1-methylcyclohexanol- ${}^{13}C$ (see **1**) that



${}^3J_{C-C}$ (J_{14}) was smaller than ${}^2J_{C-C}$ (J_{13}). We hypothesized that in **1** the small value for J_{14} might arise from an angular dependence, because in **1** we have the first instance in which the involved dihedral angle of a ${}^3J_{C-C}$ system is greatly different from 180° .

To test the idea that an angular dependence exists for ${}^3J_{C-C}$ values,⁸ we initiated a study of three-bonded

carbon-carbon coupling constants in certain selected aliphatic systems wherein all substituent and hybridization variables would be held constant while the dihedral angle of the ${}^3J_{C-C}$ in question was varied. In this study, various aliphatic and alicyclic carboxylic acids, labeled in the carboxyl position with $>90\%$ ${}^{13}C$ (**2-10**), were synthesized by reaction of the appropriate Grignard reagent with carbon- ${}^{13}C$ dioxide, except for 1-adamantanecarboxylic acid (**9**), which was synthesized by the reaction of 1-adamantyl bromide with carbon- ${}^{13}C$ monoxide under Lewis acid catalysis,²² and for *endo*-6-methyl-*endo*-5-norbornenecarboxylic acid (**7**) and the hydrogenated derivative (**8**), which were prepared *via* the Diels-Alder reaction of labeled isocrotonic acid with cyclopentadiene.²³ All ${}^3J_{C-C}$ values involving the labeled carboxyl carbons of **2-19** were then obtained



(1) (a) Presented in part at the 165th National Meeting of the American Chemical Society, Dallas, Texas, Apr 1973. (b) Robert A. Welch Predoctoral Fellow, 1971-1973.

(2) J. L. Marshall and A. M. Ihrig, *J. Amer. Chem. Soc.*, **94**, 1756 (1972).

(3) J. L. Marshall, A. M. Ihrig, and D. E. Müller, *J. Mol. Spectrosc.*, **43**, 323 (1972).

(4) J. L. Marshall and A. M. Ihrig, *Tetrahedron Lett.*, No. **21**, 2139 (1972).

(5) J. L. Marshall and A. M. Ihrig, *Org. Magn. Resonance*, **5**, 235 (1973).

(6) D. J. Sardella, *J. Amer. Chem. Soc.*, **95**, 3809 (1973).

(7) Unpublished results. This compound is in the synthetic sequence for toluene- ${}^{13}C$ (see ref 3).

(8) Precedents for an angular dependence of 3J exist for a number of nuclei. Leading references for the respective systems are given in ref 9-21.

(9) ${}^1H-C-C-{}^1H$: (a) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); (b) A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 195 (1965).

(10) ${}^1H-C-N-{}^1H$: V. F. Bystrov, V. T. Ivanov, S. L. Portnova, T. A. Balashova, and Y. A. Ovchinnikov, *Tetrahedron*, **29**, 873 (1973).

(11) ${}^1H-C-N^+-{}^1H$: W. F. Reynolds and T. Schaefer, *Can. J. Chem.*, **42**, 2119 (1964).

(12) ${}^1H-C-O-{}^1H$: (a) N. L. Bauld and Y. S. Rim, *J. Org. Chem.*, **33**, 1303 (1968); (b) R. D. Stolow and A. A. Gallo, *Tetrahedron Lett.*, No. **29**, 3331 (1968); (c) E. F. Kiefer, W. Gericke, and S. T. Amimoto, *J. Amer. Chem. Soc.*, **90**, 6246 (1968).

(13) ${}^{19}F-C-C-{}^1H$: (a) A. M. Ihrig and S. L. Smith, *ibid.*, **92**, 759 (1970); (b) M. S. Gopinathan and P. T. Narasimhan, *Mol. Phys.*, **21**, 1141 (1971); (c) K. Hirao, H. Nakatsuji, and H. Kato, *J. Amer. Chem. Soc.*, **95**, 31 (1973).

(14) ${}^{31}P-C-C-{}^1H$: A. A. Bothner-By and R. H. Cox, *J. Phys. Chem.*, **73**, 1830 (1969).

(15) ${}^{15}N-C-C-{}^1H$: see ref 14.

(16) ${}^{29}Si-C-C-{}^1H$: see ref 14.

(17) ${}^{13}C-C-C-{}^1H$: (a) see ref 14; (b) J. A. Schwarcz and A. S. Perlin, *Can. J. Chem.*, **50**, 3667 (1972); (c) R. Wasylshen and T. Schaefer, *ibid.*, **50**, 2710 (1972).

(18) ${}^{13}C-O-C-{}^1H$: see ref 17b.

(19) ${}^{13}C-N-C-{}^1H$: R. U. Lemieux, T. L. Nagabhushan, and B. Paul, *Can. J. Chem.*, **50**, 773 (1972).

(20) ${}^{13}C-C-O-{}^{31}P$: H. H. Mantsch and I. C. P. Smith, *Biochem. Biophys. Res. Commun.*, **46**, 808 (1972).

(21) ${}^{19}F-C-C-{}^{19}F$: (a) R. R. Ernst, *Mol. Phys.*, **16**, 241 (1969); (b) see ref 13c.

(22) Our procedure was a modification of that where formic acid is used rather than carbon monoxide: L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berberian, and R. G. Slighter, *J. Med. Chem.*, **10**, 517 (1967).

(23) K. Alder, *Justus Liebigs Ann. Chem.*, **514**, 9 (1934).

Table I. Carbon Chemical Shifts for 2-10

Compd	Solvent	Chemical shift ^a (ppm) for carbon atoms numbered respectively ^b											
		1	2	3	4	5	6	7	8	9	10		
2	Neat		36.4	18.6	13.6								
3	Neat	44.5	30.5	26.4	26.4	30.5							
4	Neat	43.6	29.4	26.0	26.5	26.0	29.4						
5	THF (50% w/v)	39.8	28.6	28.6	39.8	30.6	30.6	54.2					
6	C ₆ H ₁₂ (50% w/v)	41.7	47.1	34.5	36.9	29.2 ^c	30.0 ^c	37.0					
7 ^d	THF (50% w/v)											15.8	
8 ^d	THF (50% w/v)	42.1	48.0	35.9	44.0	23.2	24.5	41.1				14.9	
9	THF (40% w/v)	40.9	39.7	29.1	37.5	29.1	37.5	29.1	39.7	39.7		37.5	
10 ^d	THF (30% w/v)	31.0	50.8	31.0	34.9	29.0	38.7	29.0	39.3	34.9		39.3	

^a Downfield from TMS, converted from cyclohexane internal standard using $\delta_{C_6H_{12}}$ 27.6 [G. C. Levy and J. D. Cargioli, *J. Magn. Resonance*, **6**, 143 (1972)], except where noted. ^b For numbering of the carbon atoms, refer to the drawn structures. ^c Assignments reversed from reported values.²⁶ ^d Chemical shift converted from THF internal standard, using $\delta_{THF}(\beta-C)$ 26.7 (ref 24a, p 270).

Table II. J_{C-C} Values for 2-10^a

Compd	¹ J, Hz	² J, Hz	³ J, Hz	Dihedral angle ϕ , deg	⁴ J, Hz	⁵ J, Hz
2	55.4 (J_{12})	1.8 (J_{13})	3.6 (J_{14})	144 ^e		
3	56.5 (J_{18})	0.6 ($J_{26} = J_{56}$)	2.7 ($J_{36} = J_{46}$)	140 ^f		
4	55.7 (J_{17})	$\sim 0^b$ ($J_{27} = J_{57}$)	4.0 ($J_{37} = J_{57}$)	175 ^g	$\sim 0.5^c$ (J_{47})	
5	59.2 (J_{78})	$\sim 0^b$ ($J_{18} = J_{48}$)	$\sim 0^b$ ($J_{28} = J_{38}$)	57 ^h		
			5.6 ($J_{58} = J_{68}$)	164 ^h		
6	56.1 (J_{28})	1.0 (J_{18})	$\sim 0^b$ (J_{78})	83 ^h	$\sim 0.6^c$ (J_{58})	
		1.8 (J_{38})	$\sim 0.5^c$ (J_{48})	124 ^h		
			4.9 (J_{68})	172 ^h		
7			2.4 (J_{89})	3 ⁱ		
8	58.5 (J_{28})	$\sim 0^b$ (J_{38})	$\sim 0.5^c$ (J_{48})	132 ⁱ	$\sim 0.3^c$ (J_{58})	
		$\sim 0.4^c$ (J_{18})	$\sim 0.5^c$ (J_{68})	63 ⁱ		
			1.9 (J_{89})	6 ⁱ		
9	56.8 ($J_{1,11}$)	1.8 ($J_{2,11} = J_{8,11}$)	3.6 ($J_{3,11} = J_{5,11}$)	180	$\sim 0.6^c$ ($J_{4,11} = J_{6,11} = J_{10,11}$)	
10	54.4 ($J_{2,11}$)	$\sim 0.4^c$ ($J_{1,11} = J_{3,11}$)	$\sim 0.5^c$ ($J_{4,11} = J_{9,11}$)	67 ⁱ	$\sim 0^b$ ($J_{5,11}$)	0.4 ^d ($J_{6,11}$)
			4.2 ($J_{8,11} = J_{10,11}$)	176 ⁱ	$\sim 0^b$ ($J_{7,11}$)	

^a Compounds 2-4 were run neat; 5 and 7-10 were run saturated in tetrahydrofuran; and 6 was run saturated in cyclohexane. ^b No splitting, and little if any broadening. ^c No splitting, but appreciable broadening. Approximate value calculated using half-heights and line-shape behavior: D. J. Sardella, *J. Magn. Resonance*, **10**, 188 (1973). ^d Near limits of resolution. Splitting observed inconsistently. ^e See ref 27. ^f See ref 28. ^g See ref 29. ^h See ref 30. ⁱ Determined by force field calculations (see ref 31).

by recording the proton-decoupled carbon magnetic resonance spectra of these compounds and directly measuring the splittings of each of the natural abundance carbon signals.

Results

Table I reports the chemical shift assignments for 2-10. The assignments for 2-5 and 7-10 were made by means of well-established additivity parameters²⁴ and steric perturbation effects²⁵ and by off-resonance decoupling experiments. The chemical shifts for 6 were as previously reported,²⁶ except that the assignments of C-5 and C-6 were reversed (*vide infra*).

Using the chemical shift assignments of Table I, the observed respective splittings are given in Table II. The values for the appropriate dihedral angles were obtained by a variety of methods. The dihedral angles for butanoic acid (2),²⁷ cyclopentanecarboxylic acid (3),²⁸

and cyclohexanecarboxylic acid (4)²⁹ were taken from thermodynamic data generated from conformational studies. The dihedral angles for the two norbornanecarboxylic acids (5 and 6) were taken from crystallographic data.³⁰ The dihedral angles for the methyl-norbornanecarboxylic acids (7 and 8) and for 2-adamantanecarboxylic acid (10) were adapted directly from force field calculations for the analogous methyl derivatives.³¹

(27) Conformational studies have not been done on butanoic acid itself, but a fairly accurate value would be expected as the average between that for butane [K. S. Pitzer, *J. Chem. Phys.*, **8**, 711 (1940); G. J. Szasz, N. Shepard, and D. H. Rank, *ibid.*, **16**, 704 (1948); D. W. E. Axford and D. H. Rank, *ibid.*, **18**, 51 (1950)] and for succinic acid [L. E. Erickson, *J. Amer. Chem. Soc.*, **87**, 1867 (1965)].

(28) I. O. C. Ekejiuba and H. E. Hallam, *J. Mol. Struct.*, **6**, 341 (1970); C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966). We estimate the dihedral angle to be 140° by assuming the compound is mostly in the half-chair conformation (C₂ symmetry).

(29) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 441. Calculations of the free energy differences between the axial and equatorial cyclohexane-carboxylic acid range from 0.7 to 1.86 kcal/mol. Our value was taken from the determination done for neat cyclohexanecarboxylic acid [B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964)], where the acid exists as a dimer and is 96% equatorial (the phase of our nmr sample was neat).

(30) A. C. MacDonald and J. Trotter, *Acta Crystallogr.*, **19**, 456 (1965); R. M. Wing, G. C. Tustin, and W. H. Okamura, *J. Amer. Chem. Soc.*, **92**, 1935 (1970).

(31) These force field calculations were done by means of the Lothar

(24) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972.

(25) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967); D. M. Grant and B. V. Cheney, *ibid.*, **89**, 5315 (1967); A. S. Perlin and H. J. Koch, *Can. J. Chem.*, **48**, 2639 (1970).

(26) J. B. Corutner, M. Jantelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7107 (1970).

Figure 1 shows a plot of the ${}^3J_{C-C}$ values of Table II vs. the corresponding dihedral angle. A definite trend emerges that is akin not to the usual Karplus-type relationship (where J is minimum when $\phi = 90^\circ$ and J is maximum when $\phi = 0, 180^\circ$)⁹⁻²⁰ but more to the ${}^3J_{F-F}$ relationship²¹ (where J_{\min} and J_{\max} are shifted to lower ϕ values). When the pattern of Figure 1 was recognized, it became apparent that the previous tentative assignments²⁶ for C-5 and C-6 carbons of *exo*-norbornanecarboxylic acid (**6**) were incorrect. Of the two signals in question (30.0 and 29.2 ppm downfield from TMS), the downfield signal, split into a doublet of 4.9 Hz, fitted the empirical curve of Figure 1 whereas the upfield signal with a much smaller J value clearly did not. Thus the assignments for C₅ and C₆ of **6** are reversed from the literature assignments.²⁶

Discussion

The general trend of Figure 1 suggests that this correlation may serve as a sensitive tool in conformational analysis. Considering the two adamantyl derivatives **9** and **10**, the different ${}^3J_{C-C}$ values for the two anti C-C-C-C systems ($J_{\beta,11}$ and $J_{\delta,11}$, respectively) correspond nicely with the small difference in the dihedral angles.³² For the 1-adamantane derivative (**9**), the carboxyl group is in a symmetrical environment and will be in an angle exactly 180° with the γ -carbon atoms, whereas in the 2-adamantane derivative (**10**), the axial (γ -syn) hydrogens sterically interacting with the carboxyl group push the group away and reduce the anti angle a few degrees from 180° . The correlation of the size of ${}^3J_{C-C}$ with the dihedral angle appears to be just as sensitive at the other end of the scale, in the case of the *endo*-methyl-*endo*-carboxylic acid derivatives **7** and **8**. In these compounds, the carboxylic acid group forms an angle near 0° with the eclipsing methyl group, but the respective eclipsed ${}^3J_{C-C}$ values of **7** and **8** are distinctly different, reflecting a smaller angle in **7**, where the olefin inhibits overall twisting of the norbornane skeleton.

It would be of theoretical interest to know the signs of the coupling constants reported herein. From the known sign of ${}^1J_{C-C}$ values³³ and from the expected alternating fashion of signs of J_{C-C} values down a carbon chain,⁶ a positive sign is to be expected for the present ${}^3J_{C-C}$ values. The trend of Figure 1 suggests that at the minimum (at $\phi \approx 65^\circ$) the ${}^3J_{C-C}$ value briefly changes signs. Verification of a positive ${}^3J_{C-C}$ value awaits theoretical calculations and/or experimental sign determinations.

Using the correlation of Figure 1 to reexamine the ${}^3J_{C-C}$ value of **1** ($J_{1,4}$), we would expect **1** with a dihedral angle of 60° to certainly have a low value. In fact, it is surprising that the observed ${}^3J_{C-C}$ value for **1** is as large

Schäfer and Wolfgang Schubert Conformational Program [adapted from S. Lifson and A. Marshal, *J. Chem. Phys.*, **49**, 5116 (1968)] with Variable Minimization Routine, supplied by L. Schäfer, Department of Chemistry, University of Arkansas, Fayetteville, Ark. In these calculations, the methyl-substituted analog was treated, owing to the difficulties in treating the carboxyl-substituted compound precisely. Nevertheless, for those compounds for which force field calculation data are used, the dihedral angle values utilized should be quite close to the true values.

(32) This difference should not be due to an alkyl substituent effect, for the ${}^3J_{C-C}$ values are the same in butanoic acid and pentanoic acid (see ref 4).

(33) H. Dreeskamp, K. Hildenbrand, and G. Pfisterer, *Mol. Phys.*, **14**, 295 (1968); K. A. McLaughlan, *Chem. Commun.*, 105 (1965); D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 2228 (1967).

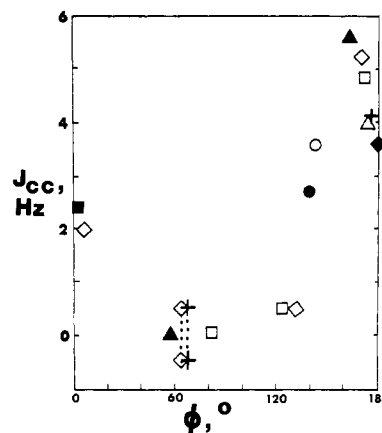


Figure 1. Plot of ${}^3J_{C-C}$ vs. the dihedral angle ϕ , from the respective compounds: **2** (○), **3** (●), **4** (△), **5** (▲), **6** (□), **7** (■), **8** (◇), **9** (◆), **10** (+).

as it is. Perhaps this ${}^3J_{C-C}$ is larger than expected (1) because there are two coupling pathways or (2) because the correlation of aliphatic carboxylic acids cannot be carried over to substituted hydrocarbons. We are currently exploring this second possibility.

Considering values in Table II other than ${}^3J_{C-C}$ values, of particular interest is the ${}^3J_{C-C}$ value in 2-adamantanecarboxylic acid (**10**), because it would be the first ${}^3J_{C-C}$ value measured to further test the idea⁶ that coupling constants, like chemical shifts, should vary in an alternating fashion down a carbon chain. Indeed, this ${}^3J_{C-C}$ value measured for **10** ($J_{\delta,11}$) is as large as the ${}^4J_{C-C}$ values, thus supporting theoretical considerations.⁶

Also of interest are the ${}^1J_{C-C}$ values. One would expect these values to increase with increased strain of the respective ring system, reflecting the increased s character of the C-CO₂H bond.³⁴ Inspection of Table II shows that this expected trend is only an approximate one: indeed, **5** with the greatest strain does have the greatest ${}^1J_{C-C}$ value (59.2 Hz), followed by **8** (58.5 Hz), but the remaining compounds (with 1J in the range 54.4–56.8 Hz) show some inconsistencies (compounds **2**, **6**, and **9**). There are apparently additional unknown factors operating in this series.

Experimental Section

Nmr Spectra. The carbon magnetic resonance spectra, all proton-irradiated, were recorded by a single scan on a JEOL PS-100 nmr spectrometer, using 8 mm o.d. rotating samples. Each sample was run 5–10 times and the final value of J was taken as an arithmetical average. The maximum deviation was 0.2 Hz for individual runs and the accuracy of the final J values is thus placed at ≤ 0.2 Hz. The resolution depended upon the concentration and the complexity of the molecule. Independent studies with a variety of labeled compounds²⁻⁵ have shown that resolution for relatively simple compounds like **2** which can be run neat can give a resolution of ≤ 0.5 Hz, while for more complicated compounds like **9** which are run as $<50\%$ solutions, the resolution may be as low as 0.8 Hz.

Introduction of Carbon-¹³C Dioxide. Labeled carbon dioxide ($>90\%$) was purchased from Monsanto Research Corp., Mound Laboratory, Miamisburg, Ohio. Compounds **2–6**, **10**, and labeled isocrotonic acid (the precursor for compounds **7** and **8**) were synthesized by reacting labeled carbon dioxide with the appropriate Grignard reagent. The Grignard reagents were prepared in the

(34) These ${}^1J_{C-C}$ values should approach that observed in cyclopropane (72.5 Hz): J. D. Roberts and J. Weigert, *J. Amer. Chem. Soc.*, **94**, 6021 (1972).

usual manner^{35,36} from the respective hydrocarbon bromides. All bromides were purchased from Aldrich Chemical Co., Milwaukee, Wis., except for 1-propenyl bromide, which was purchased from Chemical Samples Co., Columbus, Ohio, and for 7-bromonorborene, which was synthesized according to the procedure of Marchand.³⁷ The carbonation of the norbornyl bromides (to give **5** and **6**) were conducted under high dilution to minimize coupling of the Grignard reagent. A typical carbonation procedure follows.

Cyclohexanecarboxylic-carboxyl-¹³C Acid (4).³⁸ A solution of cyclohexylmagnesium bromide was prepared under an argon atmosphere in a 250-ml erlenmeyer flask with a 24/40 joint adaptable to a high vacuum system, using 10.0 g of cyclohexyl bromide (0.061 mol), 1.51 g of magnesium turnings (0.062 mol), and 150 ml of anhydrous ether. A magnetic stirrer bar was placed in the reaction flask, and the flask was connected to the vacuum system. The Grignard solution was degassed twice at 10⁻⁵ Torr by the liquid nitrogen freeze-thaw technique. The Grignard solution was then sealed from the vacuum system by closing the appropriate stopcock.

The volume of the vacuum system had been previously determined so that the weight of carbon dioxide introduced to the system could be determined by measuring the pressure of the manometer. One gram (0.0223 mol) of carbon-¹³C dioxide was delivered to the vacuum system, and then was condensed into the reaction vessel cooled with liquid nitrogen. The reaction vessel was then

(35) J. Cymeran-Craig and J. W. Loder, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 667.

(36) Labeled isocrotonic acid was synthesized using tetrahydrofuran solvent, owing to the greater difficulty of initiating a vinyl bromide: D. Seyferth in ref 35, p 258.

(37) A. P. Marchand and W. R. Weimer, Jr., *Chem. Ind. (London)*, 200 (1969).

(38) This procedure is a modification of syntheses for carbon-14 labeled compounds: A. Murray, III, and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, pp 34, 35, 86-88.

sealed from the vacuum system and allowed to warm by substituting a Dry Ice-isopropyl alcohol bath for the liquid nitrogen. After about 20 min the Grignard solution thawed sufficiently to permit stirring. The reaction mixture was then allowed to warm to 0° with stirring over a period of 1 hr. The system was opened and water was added dropwise to the reaction mixture to react excess Grignard reagent. The reaction mixture was dissolved in 6 N hydrochloric acid and extracted with four 50-ml portions of ether. The ether was evaporated to give 2.52 g (86%, based on the carbon dioxide).

endo-6-Methyl-endo-5-norbornenecarboxylic-carboxyl-¹³C acid (7) was synthesized from labeled isocrotonic acid by reaction with cyclopentadiene according to the procedure of Alder.³³

endo-3-Methyl-endo-2-norbornanecarboxylic-carboxyl-¹³C acid (8) was prepared in quantitative yield from **7** by catalytic hydrogenation.³⁹

1-Adamantanecarboxylic-carboxyl-¹³C acid (9) was synthesized in 75% yield using the procedure of Fieser,²² except that the carbon-¹³C monoxide (also purchased from Monsanto Research Corp., Mound Laboratory) was recycled through the reaction vessel via a continuous gas flow apparatus⁴⁰ until uptake of the labeled carbon monoxide was complete.

Acknowledgments. The authors are indebted to the Robert A. Welch Foundation (Grant No. B-325) and to North Texas University Faculty Research for financial support of this research. The authors are also grateful for the help of Dr. Michael Barfield of the University of Arizona in obtaining the carbon magnetic resonance spectrum of **10**, and Dr. Lothar Schäfer of the University of Arkansas for providing the Conformation Program³¹ used in these studies.

(39) A. C. Cope and E. C. Herrick in ref 35, p 304.

(40) A. D. Berry and T. L. Brown, *Inorg. Chem.*, **11**, 1165 (1972).

Stereopopulation Control. IV. Facilitation of Intramolecular Conjugate Addition of the Hydroxyl Group

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Contribution from the Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. Received June 22, 1973

Abstract: The hydroquinone ether 4,4,5,7,8-pentamethyl-6-chromanol (**9**) is oxidized in aqueous media to the corresponding benzoquinone **6**, 3-(3',6'-dioxo-2',4',5'-trimethylcyclohexa-1',4'-diene)-3,3-dimethyl-1-propanol. Above pH 12, **6** undergoes rapid intramolecular conjugate addition to the spirocyclic ether **7**, 4,4,7,8,10-pentamethyl-1-oxaspiro[4.5]dec-7-ene-6,9-dione. In less alkaline media, the same reaction is subject to general base catalysis. In aqueous acid, this quinone is converted into 5-hydroxymethyl-4,4,7,8-tetramethyl-6-chromanol (**10a**). The mechanism of this transformation involves conversion of **6** into its cyclic tautomer **5**, 8a-hydroxy-4,4,5,7,8-pentamethyl-6-chromanone, vinylogous loss of water from **5** to form a transient *o*-methylenequinone, and conjugate addition of solvent to the latter species. The labile hydroxydienone **5** can be generated by aeration of solutions of the hydroquinone **4**, 3-(2',5'-dihydroxy-3',4',6'-trimethylphenyl)-3,3-dimethyl-1-propanol. In non-hydrogen-bonding solvents, **5** and **6** coexist in approximately equal amounts; in hydrogen-bonding solvents, the equilibrium is overwhelmingly in favor of **6**. In water, the ring opening of the hemiketal **5** is strongly sensitive to buffer catalysis. Hydroxypropylquinones lacking any element of the trialkyl lock (4,4,5-substitution in **9**) do not undergo conjugate addition to form spirocyclic ethers (as **7**), do not exhibit ring-chain tautomerism (as **5** ⇌ **6**), and do not recyclize readily to functionalized 6-chromanols (as **10**). An explanation is offered for the remarkable difference in reactivity between methyl groups at C-5 and at C-7 in polymethylated 6-chromanols.

In paper III of this series,¹ we described the application of stereopopulation control² to facilitate the con-

(1) R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9175 (1972).

(2) This term is defined in earlier papers: (a) S. Müstien and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S. A.*, **67**, 1143 (1970); (b) *J. Amer. Chem.*

ugate addition of a side-chain carboxyl group to a *p*-benzoquinone double bond, the facile reversibility of the reaction in the pH range 4-8, and the strong de-

Soc., **94**, 9158 (1972); (c) R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166 (1972).