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-bromonorbornane, 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*-^{13}C 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-^{13}C dioxide was delivered to the vacuum system, and then was condensed into the reaction vessel cooled with liquid nitrogen. The reaction vessel was then 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*-^{13}C acid (7)** was synthesized from labeled isocrotonic acid by reaction with cyclopentadiene according to the procedure of Alder.[23]

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

1-Adamantanecarboxylic-*carboxyl*-^{13}C acid (9) was synthesized in 75% yield using the procedure of Fieser,[22] except that the carbon-^{13}C monoxide (also purchased from Monsanto Research Corp., Mound Laboratory) was recycled through the reaction vessel *via* a continuous gas flow apparatus[40] 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 Program[31] used in these studies.

(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.

(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

Ronald T. Borchardt and Louis A. Cohen*

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 control[2] to facilitate the conjugate 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-

(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. Milstien and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970); (b) *J. Amer. Chem. Soc.*, **94**, 9158 (1972); (c) R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166 (1972).

pendence of the reaction rate on buffer catalysis. By virtue of these properties, the system provides us with a valuable model for enzyme-catalyzed reversible addition of nucleophiles to activated double bonds (lyases).[3] In metabolic pathways, however, carboxyl groups function in this capacity less often than do hydroxyl groups (*e.g.*, malic and isocitric acids) or amino groups (*e.g.*, aspartic acid and histidine). It was of interest, therefore, to attempt to facilitate the conjugate addition of the latter nucleophiles by similar utilization of the accelerating effect of severe conformational restriction.

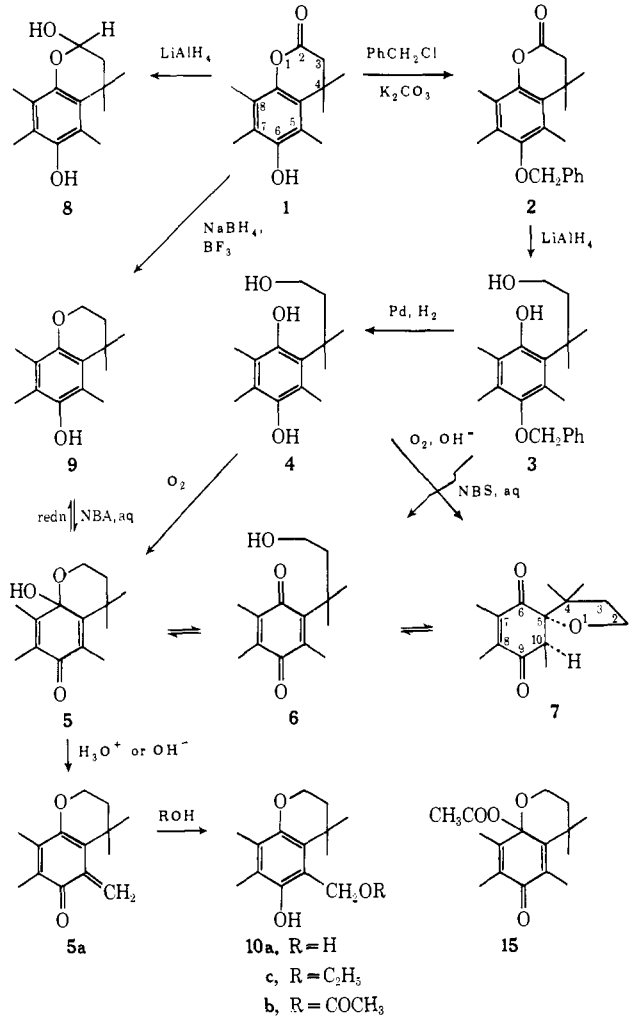
Our choice of model system for hydroxyl addition[4] was dictated by the availability of the lactone **1**[1,2b] and by the expectation that hydride reduction of this compound would provide **4**, the key material for our intended studies. Although the hydride reduction of **1** did not lead to **4**, the latter compound was obtained by an indirect route. This report deals with the unique chemical properties of **6**, the benzoquinone derived from **4**, as well as with those of several related compounds.

Results and Discussion

Attempts to reduce the 6-hydroxyhydrocoumarin **1** with lithium aluminum hydride (or with sodium bis(2-methoxyethoxy)aluminum hydride) failed to give the expected hydroxypropylhydroquinone **4**, reduction stopping at the hemiacetal stage **8**.[5] Incomplete reduction is due, apparently, to the precipitation of a salt of **8** from the reaction medium, this circumstance providing an unexpectedly facile route to the propionaldehyde counterpart (in its cyclic form) of **4**.[6] The desired product **4** was obtained by benzylation of **1** at the free phenolic group to produce **2**, hydride reduction of **2** to the diol **3**, and catalytic hydrogenolysis of **3** (Scheme I). Since the hydride reduction of **2** proceeds normally, the resistance to further reduction of **8** is attributable to salt formation at the free phenolic group.[7] Although **1** is unreactive toward sodium borohydride alone, it is reduced by the latter reagent in the presence of boron trifluoride (or by lithium aluminum hydride–boron trifluoride) to the chromanol **9**. As noted previously,[2c] reduction of phenolic lactones to cyclic ethers with hydride reagents and boron trifluoride appears to be a property unique to systems containing the "trialkyl lock."[8]

Oxidation of **3** with 1 equiv of *N*-bromosuccinimide (NBS) or of *N*-bromoacetamide (NBA) in aqueous acetonitrile provides the hydroxypropyl-*p*-benzoquinone **6** quantitatively.[9] Although **6** is stable in polar organic solvents and in neutral aqueous media, it is altered by acid or alkali. At pH values above 12, the quinone **6** undergoes very rapid intramolecular conjugate addition to form the spiroether **7**; conversion of the quinone into the enedione is followed readily by a shift in λ_{max} from 260–262 to 249–251 nm. At a pH value of *ca.* 13.2, the conversion is complete in 2 min. In the pH range 9.5–11.5, the reaction is subject to catalysis by phosphate buffer, presumably *via* a general base mechanism. Thus, conjugate intramolecular addition of the alkoxide ion (or incipient alkoxide ion) of **6** to the double bond provides the resonance-stabilized carbanion (or the enol) of **7**. The acidity of the one labile hydrogen atom of **7** is sufficient to permit rapid isotope exchange in deuterium oxide above pH 11.

Scheme I



The assignment of a spiroether structure for **7** follows from the absence of hydroxyl absorption in the infrared spectrum, from a chromophore at 249 nm (α,β,β-trisubstituted enone),[10] and from an nmr signal for an aliphatic methyl group (doublet) coupled to a single hydrogen atom (quartet). The single hydrogen atom is exchanged in alkaline deuterium oxide, the adjacent methyl group now appearing as a singlet in the nmr spectrum. The formation of **7** from **6** corresponds to the formation of a spirolactone from the propionic acid analog of **6**.[1] The arguments given in the earlier report for the formation of a spirocyclic system (five-membered ring) in preference to a fused, bicyclic system (six-membered ring) are equally applicable in the present case, as are the earlier conclusions regarding trans-

(3) H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1961, p 285.

(4) Studies on the addition of nitrogen nucleophiles are in progress.

(5) Attempted reduction of **1** with sodium in isoamyl alcohol gave a dark, intractable oil.

(6) The chemistry of this compound is described in the following paper: R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 8313 (1973).

(7) Hydride reduction of the 6-deoxy or 6-chloro analog of **1** to the corresponding diol proceeds without incident: ref 2c and unpublished results.

(8) Throughout this report, the term "trialkyl lock" refers to the unique combination of two alkyl groups at C-4 (in **1**) and an alkyl group at C-5 (or their steric equivalents).

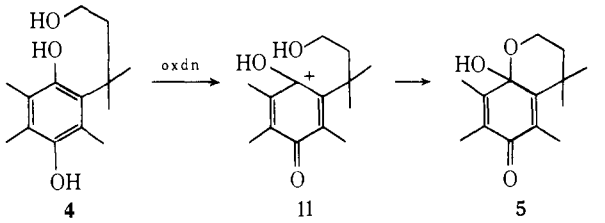
(9) For the mechanism of this oxidation, see W. Dürckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964).

(10) L. F. Fieser and M. Fieser, "The Steroids," Reinhold, New York, N. Y., 1959, p 19.

diaxial stereochemistry of the C-5 oxygen and the C-10 hydrogen atoms in the adduct.[1] It is likely that the stereochemistry of this product represents a thermodynamic preference, rather than a kinetically determined trans addition. All monocyclic and bicyclic compounds containing a trialkyl lock have been found, to date, to exhibit a sharp nmr singlet for the methyl groups at C-4. This symmetry is lost in the spirocyclic lactones and ethers; in the case of **7**, the methyl groups are separated by 0.10 ppm, presumably due to the proximity of one of these methyl groups to the C-6 carbonyl group (see numbering of **7**). This proximity is quite clear in Dreiding models with the stereochemistry specified.

In acidic media, **6** fails to undergo conjugate addition to form **7**. The quinone chromophore at 260 nm is gradually replaced by that of a phenolic chromophore at 290 nm; at pH 2, $t_{1/2}$ = *ca.* 3 hr, the rate of conversion increasing rapidly in more acidic media. The product of this transformation was the *o*-hydroxymethylphenol **10a**. The oxygen is on the C-5 methyl group, since the nmr spectrum shows the unique low-field C-5 methyl signal of **9** to have been replaced, in **10a**, by a methylene signal at much lower field. Tentatively, we formulate the mechanism of this transformation as an elimination–addition process, involving the hydroxy-dienone tautomer **5** and the *o*-methylenequinone **5a**. In protic solvents, the mole fraction of **5** present in equilibrium with **6** is too small to be detected by spectroscopic means; yet this ring-chain tautomerism must occur with ease, since **6** is reduced by ascorbic acid, dihydrolipoic acid, or sodium borohydride to **9** and not to the triol **4**.[11] The intermediacy of an *o*-quinonemethide (**5a**) is supported further by the cyclization of **6** in acidic ethanol to **10b**. Both **10a** and **10b** are hydrogenolyzed to **9**.

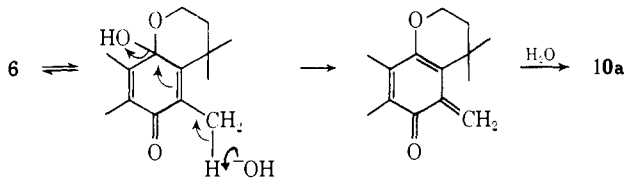
Aeration of the hydroquinone **4** in neutral media (methanol or acetonitrile) leads, not to the quinone **6**, but to its elusive tautomer **5**. This quinone hemiketal is easily differentiated from **6** by its ultraviolet absorption at 239 nm, corresponding in λ_{max} to that of the hemiketal obtained by two-electron oxidation of α-tocopherol.[12] In mildly alkaline media, **5** is converted, transiently, into its quinone tautomer **6**, and finally into **7**.[13] Aeration of **4** in alkaline media produces **7** in high yield, with **5** and **6** as presumed intermediates. In acidic media, **5** is converted to **10a** (in water) or to **10b** (in ethanol); in this case, **6** is not a requisite intermediate, nor can its transient presence be detected. We consider the oxidation of the hydroquinone **4** to proceed *via* the carbonium ion **11**. Solvolysis of **11** by water or methanol would lead directly to the quinone **6**, the normal course of events for most hydroquinone oxidations.[9,12] The trimethyl lock in **11**, however, maintains the side-chain hydroxyl group sufficiently close to the developing carbonium ion to effect intramolecular solvolysis exclusively. With α-tocopheryl-hydroquinone (or its simpler analogs), the side chain prefers an extended, nonparticipating conformation,



4 **11** **5**

and quinone is the only product of oxidation under comparable conditions,[14,15] or even in ether solution.[14b]

The present results stand somewhat in contrast to the facile conjugate addition observed with the propionic acid analog of **6**, and the facile elimination of the lactone analog of **7**, both reactions occurring in the pH range 4–8.[1] Apparently, the conversion of **6** to **7** requires the generation of an alkoxide ion; the resistance of **7** to elimination is probably due to the inferior leaving ability of the alkoxide ion, compared to that of carboxylate ion.[16] Although spectral data give no evidence of reconversion of **7** to **6** in alkaline media, the slow transformation of **7** into **10a** in 1 *N* sodium hydroxide ($t_{1/2}$ *ca.* 15 hr at 25°) reveals that conjugate elimination occurs, and that a pathway must exist for the base-catalyzed conversion of **6** (*via* **5** and **5a**) into **10a**.



5 **5a**

The spirocyclic ether **7** is stable in acidic media, at least as strong as 0.5 *N* hydrochloric acid.

In analogy with the behavior of α-tocopherol,[12] **9** is oxidized with NBS or NBA (in aqueous organic media) to **5**, as shown by ultraviolet spectra.[17] During storage of the reaction mixture, the hydrogen bromide formed during oxidation effects conversion of **5** into **10a** (or to **10b** in ethanol).[18] In an effort to avoid this complication,[19] oxidation of **9** was performed at pH 5–7 (acetate or phosphate buffers); surprisingly, **5** could no longer be detected spectroscopically, only quinone **6** being detected. The conversion of **5** to **6** is strongly sensitive to buffer catalysis, probably due to the independent action of both buffer species. In earlier studies[12] in the α-tocopherol series (or its 2,2-dimethyl model), the hydroxydienone **13** was obtained by NBS oxidation of the 6-hydroxychroman **12** in buffer media at pH 4–8. Although both hydroxydienones **5** and **13** are unstable in acid or alkaline media, the former appears to be much more sensitive to buffer catalysis

(11) The cyclodehydration of **4** to **9** does not occur under the reaction conditions. For analogous reductive cyclizations of α-tocopheryl-quinone, see M. A. Oxman and L. A. Cohen, *Biochim. Biophys. Acta*, **113**, 412 (1966).

(12) (a) W. Dürckheimer and L. A. Cohen, *Biochem. Biophys. Res. Commun.*, **9**, 262 (1962); (b) *J. Amer. Chem. Soc.*, **86**, 4388 (1964).

(13) As expected,[12b] borohydride reduction of **5** leads to the chromanol **9**.

(14) (a) Unpublished results; (b) M. Tishler and W. L. Wendler, *J. Amer. Chem. Soc.*, **63**, 1532 (1941).

(15) The observation that **3** and **4** lead to different oxidation products is not surprising: in the case of **3**, the oxidant can operate only at the one phenolic site; in the case of **4**, two sites are available for attack by the oxidant, the more sterically accessible site (C-6) differing from that in **3**.

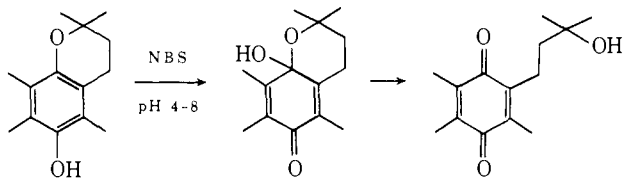
(16) Certainly the ease of carbanion formation from **7** cannot differ significantly from that of its spirolactone counterpart.

(17) The oxidation of **9** with ferric chloride in a water–benzene mixture leads to a novel dimer; details of this reaction will be published separately.

(18) The oxidation of **9** to **10b** is also observed with ethanolic silver nitrate at 80°.

(19) The isolation of **5** from oxidation of **4** presents no such difficulty, since no acid is released during the air oxidation step.

in its breakdown.[20] At present, the only explanation we can offer for this variation in behavior is that **13**



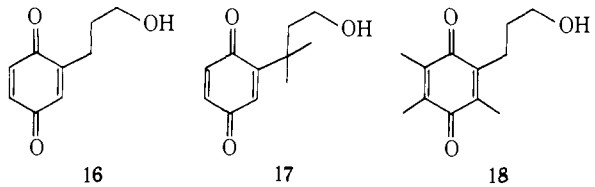
12 13 14

offers steric hindrance (*via* the 2,2-dialkyl groups) to association of the hemiketal with the buffer species.

Although the chromanol **9** is stable to NBS in dry acetonitrile (at least for 4 hr), addition of acetate ion leads to a species whose ultraviolet spectrum corresponds to that of **5**; while this product, probably the 8a-acetoxydienone **15**, shows a lability toward acid roughly comparable to that of **5**, it is significantly more stable than **5** toward mild alkali or toward buffer species. In acetonitrile containing acetate ion and a trace of trifluoroacetic acid, **15** is transformed into a product with λ_{max} 288 nm, presumably the acetate ester **10c**.

A significant expression of stereopopulation control is found in the observation that **5** is readily regenerated from **6** in nonpolar media or in the neat state. A solution of the quinone in cyclohexane shows ultraviolet spectral peaks at both 260 and at 239 nm, of roughly equal intensity. Slight dilution of this solution with alcohol promotes a slow shift in the equilibrium toward **6**. Immediately following solution of neat **6** in methanol, the presence of **5** can be seen spectroscopically. In this medium, the shift toward **6** occurs more rapidly and, upon addition of water ($t_{1/2}$ = *ca.* 1 hr) or of aqueous buffer, much more rapidly. In the neat state, **5** and **6** may be present in roughly equal amounts.[21,22] The displacement toward **6** in polar media must be due, therefore, not to the greater thermodynamic stability of **6** over **5**, but to the more effective hydrogen bonding to solvent in the former case.

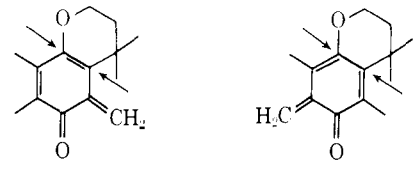
The chemical properties of the quinone containing a trialkyl lock (**6**) stand in contrast, in several respects, to those of the isomeric unlocked quinone **14**, as well as to those of less alkylated quinones with two-[23] and three-carbon side chains (*e.g.*, **16–18**).[24] All these



16 17 18

quinones appear to be stable to acid or alkali under the conditions applied to **6**. Although the transformation **12** → **13** → **14** has been demonstrated,[12] a spectroscopically detectable equilibrium concentration of **13** could not be realized. The facile transformation of **6** into **10**, a reaction intensively sought for biologically significant quinones,[25] occurs because of the facile reconversion of **6** into **5**, and an equilibrium reasonably favorable to the latter species. This kinetic and thermodynamic advantage may be attributed to the conformational freezing of the side chain of **6** in the cisoid form by the trialkyl lock. While the methylenequinone **5a** undergoes nucleophilic addition to form **10**, the analogous *o*-methylenequinone of the α-tocopherol series prefers to dimerize *via* a Diels–Alder process.[26,27] The reluctance of **5a** to dimerize may be due to the steric effect of the 4,4-dimethyl groups.

In one respect, **5** and **13** show a striking similarity: the tendency to undergo methylenequinone formation (and subsequent nucleophilic addition or dimerization) at C-5 rather than at C-7. This phenomenon has been observed repeatedly in the chemistry of alkylated 6-chromanols, both its generality and singularity having been verified in numerous and careful studies.[28] We feel this selectivity to be best explained by consideration of the thermodynamic stabilities of the isomeric methylenequinones (or of the carbonium ion or radical species related to them). Accommodation for the normal bond angles of an ethylenic group is achieved with less strain or distortion in the intercyclic arrangement of **5a** than in the exocyclic arrangement of **5b**.[29]



5a 5b

Apparently, the energy difference between the two forms is greater in the presence of the ring heteroatom than in a purely carbocyclic system, since greater selectivity is observed in the former case.[23b,30] Yet, it is surprising that this energy difference is sufficiently large to direct **5** exclusively to **10**, in which the creation of functionality at the C-5 methyl group must surely meet with serious steric opposition by the *gem*-dimethyl groups at C-4.

(20) In the earlier studies with **13** (as in the case of **5**), no effort was made to obtain specific rate constants for buffer catalysis of ring opening, although a sensitivity to both buffer species was expected on the basis of numerous studies with sugar hemiacetals. Quantitative data (for **13**) have been reported recently: M. F. Marcus and M. D. Hawley, *J. Org. Chem.*, **35**, 2185 (1970).

(21) Nmr spectra in C_6D_{12} indicate *ca.* 40% of **5** in the equilibrium mixture.

(22) Since the conversion of **5** to **6** is subject to buffer catalysis, the same condition must hold for the reverse reaction. The overwhelming preponderance of **6** in aqueous buffer media rules out any demonstration of the principle of microscopic reversibility.

(23) (a) G. Wegner, T. F. Keyes, N. Nakabayashi, and H. G. Cassidy, *J. Org. Chem.*, **34**, 2822 (1969); (b) J. L. G. Nilsson, H. Selander, H. Sievertsson, and I. Skånberg, *Tetrahedron*, **26**, 879 (1970).

(24) Synthesis of these simpler quinones will be reported separately.

(25) The conversion of **6** into **10** (*via* **5** and **5a**) parallels the key steps in several mechanisms postulated for mitochondrial oxidative phosphorylation; for a summary, see E. Lederer and M. Vilkas, *Vitam. Horm. (New York)*, **24**, 409 (1966). The feasibility of this sequence has been demonstrated in the vitamin K and ubiquinone series by trapping the products (corresponding to **10**, R = Cl) with acetyl chloride:[26] A. F. Wagner, A. Lusi, C. H. Shunk, B. O. Linn, D. E. Wolf, C. H. Hoffman, R. E. Erickson, B. Arison, N. R. Trenner, and K. Folkers, *J. Amer. Chem. Soc.*, **85**, 1534 (1963); A. F. Wagner, A. Lusi, R. E. Erickson, B. Arison, N. R. Trenner, and K. Folkers, *ibid.*, **85**, 3793 (1963).

(26) We suspect that many, if not all, oxidative conversions (in media containing nucleophiles) of 6-chromanols to *o*-methylenequinone intermediates pass through a stage corresponding to **5**, and that 8a-hydroxydienones are the true substrates in trapping experiments with acetyl chloride.[25] Additional support for this thesis appears in papers V (ref 6) and VI (R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 8319 (1973)) of this series.

(27) J. L. G. Nilsson, H. Sievertsson, and H. Selander, *Acta Chem. Scand.*, **23**, 268 (1968), and references cited therein.

(28) J. L. G. Nilsson, *Acta Pharm. Suecica*, **6**, 1 (1969).

(29) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954); (b) L. Pauling in "Theoretical Organic Chemistry, The Kekule Symposium," Butterworths, London, 1959, pp 2–5; (c) H. H. Jaffe and M. Orchin, "Theory and Practice of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 197.

(30) J. L. G. Nilsson, H. Selander, H. Sievertsson, and I. Skånberg, *Acta Chem. Scand.*, **24**, 580 (1970).

Experimental Section[31]

4,4,5,7,8-Pentamethyl-2,6-chromandiol (8). Lithium aluminum hydride (1.52 g, 0.04 mol) was added to 100 ml of anhydrous ether and the mixture was heated at reflux for 2 hr. To the resulting solution was added dropwise a solution of **1**[1,2b] (5.0 g, 0.02 mol) in 50 ml of anhydrous tetrahydrofuran at such a rate as to maintain reflux. After addition was complete, reflux was continued for 2 hr. Addition of "wet" ether, followed by water, was used to decompose the excess hydride. The aqueous layer was extracted with several portions of ether, and the combined ether fractions were washed with water and saturated NaCl and were dried ($MgSO_4$). Removal of the ether and crystallization of the residual solid (benzene) afforded 4.25 g (85%) of **8**:[32] mp 165–167°; ir ($CHCl_3$) 3620 (sh) and 3400 (br) cm^{-1} (OH); nmr (acetone-d_6) δ 1.43 (s, 6 H, C-4 $(CH_3)_2$), 1.75 (d, 1 H, J = 2 Hz, C-3 CH_2), 1.85 (s, 1 H, C-3 CH_2), 2.07 (s, 3 H, C-7 CH_3), 2.13 (s, 3 H, C-8 CH_3), 2.34 (s, 3 H, C-5 CH_3), and 5.28 ppm (m, 1 H, C-2 CH); in $CDCl_3$, the C-4 methyl groups are split into a doublet (δ 1.47 ppm, J = 1.5 Hz).[33]

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.17; H, 8.38.

4,4,5,7,8-Pentamethyl-6-chromanol (9). To a stirred solution of sodium borohydride (1.52 g, 0.04 mol) in 100 ml of anhydrous diglyme was added dropwise, at ice-bath temperature, a mixture of **1** (5.00 g, 0.02 mol) and boron trifluoride etherate (85.0 g, 0.6 mol) in 100 ml of anhydrous tetrahydrofuran.[2a,34,35] The mixture was maintained at this temperature for 45 min and was then heated at reflux for 3 hr. Excess hydride was decomposed by dropwise addition of 5% hydrochloric acid. The reaction mixture was worked up as for **8**. Removal of solvent and distillation of the residual oil provided 4.20 g (88%) of **9**: bp 121–122° (0.3 mm);[36] ir (neat) 3450 cm^{-1} (broad OH); nmr ($CDCl_3$–D_2O)[37] δ 1.43 (s, 6 H, C-4 CH_3's), 1.78 (m, 2 H, C-3 CH_2), 2.13 (s, 6 H, C-7, C-8 CH_3's), 2.33 (s, 2 H, C-5 CH_3), and 4.08 ppm (m, 2 H, C-2 CH_2).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.35; H, 9.04.

3-(2′,5′-Dihydroxy-3′,4′,6′-trimethylphenyl)-3,3-dimethyl-1-propanol (4). A solution of **3**[2c] (0.33 g, 1.0 mmol) in 15 ml of methanol was subjected to catalytic hydrogenation over 100 mg of 10% palladium/charcoal. Following separation of catalyst and evaporation of solvent, a pale yellow oil was obtained. Crystallization (benzene–hexane) afforded 0.14 g (63%) of **4**: mp 115–118°; nmr (acetone-d_6) δ 1.57 (s, 6 H, C-3 CH_3's), 2.11 (s, 6 H, C-3′ and C-4′ CH_3's), 2.35 (s, 3 H, C-6′ CH_3), and 3.53 ppm (t, 2 H, C-1 CH_2); the triplet due to the methylene group at C-2 is masked by the signals of the methyl groups at C-3′ and C-4′.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.79; H, 9.05.

8a-Hydroxy-4,4,5,7,8-pentamethyl-6-chromanone (5). Oxygen was bubbled through a solution of **4** (0.48 g, 2.0 mmol) in 40 ml of methanol for 18 hr. Progress of the reaction (disappearance of **4**) was followed by tlc (silica gel, ethyl acetate–hexane, 1:3). The solvent was removed *in vacuo* to yield a pale yellow oil. Efforts to purify the product further by chromatography on silica gel or on alumina resulted in partial conversion to **10a** or to **7**, respectively. Fresh preparations of **5** show ir (neat) 3420 (OH) and 1650 (C=O) cm^{-1}; uv max (CH_3OH) 239 nm (ϵ 11,300) and no significant absorption in the 250–270-nm range;[38] nmr ($CDCl_3$) δ 1.39 and 1.47 (2 s, 6 H, C-4 CH_3's),[39] 1.80 (m, 2 H, C-3 CH_2), 1.94 and 2.00 (2 s, 6 H, C-7 and C-8 CH_3's), 2.16 (s, 3 H, C-5 CH_3), and 3.88 ppm (m, 2 H, C-2 CH_2).

Addition of excess sodium borohydride to an ice-cold solution of **5** in 50% aqueous acetonitrile resulted in the formation of **9**, identified by tlc and mass spectrum.

3-(3′,6′-Dioxo-2′,4′-5′-trimethylcyclohexa-1′,4′-diene)-3,3-dimethyl-1-propanol (6). To a solution of 328 mg (1 mmol) of **3** and 600 mg (2 mmol) of tetrabutylammonium acetate in 10 ml of 30% aqueous acetonitrile was added, at 0°, a solution of 196 mg (1.1 mmol) of NBS in 5 ml of acetonitrile. After 30 min, the bright yellow solution was concentrated *in vacuo*, at low temperature, to remove acetonitrile. The oily, aqueous mixture was extracted with two 50-ml portions of dichloromethane; the combined extracts were washed with 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated. The residual oil was kept under high vacuum at 50° for 24 hr to remove residues of benzyl alcohol and benzaldehyde. The product, which could not be crystallized, was homogeneous by tlc and gave a parent peak in its mass spectrum only at m/e 236. An attempt was made to purify the material further by chromatography on silicic acid; however, an exothermic reaction ensued on the column, and the quinone which was eluted proved to be trimethyl-*p*-benzoquinone. The reverse Friedel–Crafts reaction was due, evidently, to the acidity of the silicic acid. Uv max (CH_3OH) 262 nm (ϵ 13,800); in cyclohexane, the compound shows peaks at 239 and at 260 nm, of approximately equal intensity; nmr (CD_3OD) δ 1.49 (s, 6 H, C-3 CH_3's), 1.94 (s, 6 H, C-3′ and C-4′ CH_3's), 2.09 (t, 2 H, C-2 CH_2), 2.14 (s, 3 H, C-6′ CH_3), and 3.51 ppm (t, 2 H, C-1 CH_2); in cyclohexane-d_{12}, the nmr spectrum is very complex, showing signals attributable both to **5** and **6**; the greatest difference in δ is due to the C-1 methylene group; by integration of peak areas, the equilibrium mixture was estimated to contain *ca.* 40% of **5**.

The quinone **6** was also obtained by NBS oxidation of **9** in acetate buffer (pH 4.8, 0.05 *M*) or in phosphate buffer (pH 7.0, 0.05 *M*), each containing 10% acetonitrile. The hydroxydienone **5** was observed, by its ultraviolet spectrum, as a transient intermediate with $t_{1/2}$ = 5–10 min. The rate of disappearance of **5** increased with increasing buffer concentration; **5** could no longer be detected spectrally when oxidation of **9** was performed in 0.3 *M* buffer.

To separate solutions of the quinone in 20% aqueous acetonitrile were added 10 equiv each of ascorbic acid, dihydrolipoic acid, and sodium borohydride. After 24 hr, tlc showed **6** to have been reduced entirely to **9** in the latter two mixtures, and partially in the first (ascorbic acid); the triol **4** was not detected in any of these reaction mixtures.

4,4,7,8,10-Pentamethyl-1-oxaspiro[4.5]dec-7-ene-6,9-dione (7). A solution of 6 mmol of **3**, in 60 ml of methanol, was subjected to hydrogenolysis, as described above, to generate **4**. After removal of the catalyst, 0.25 ml of 5% sodium hydroxide was added and oxygen was bubbled through the methanol solution for 5 hr. The solvent was evaporated and the residual oil was distilled to yield 1.10 g (77%) of **7**: bp 108–110° (0.3 mm); ir ($CHCl_3$) 1679 cm^{-1} (C=O); uv max (CH_3OH) 249 nm (ϵ 12,000); nmr ($CDCl_3$) δ 0.95 and 1.05 (2 s, 6 H, C-4 CH_3's), 1.33 (d, 3 H, J = 7 Hz, C-10 CH_3), 1.90 (m, 2 H, C-3 CH_2), 2.05 (s, 6 H, C-7 and C-8 CH_3's), 3.07 (q, 1 H, C-10 CH), and 4.06 ppm (m, 2 H, C-2 CH_2).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.91; H, 8.75.

In a 0.1 *M* solution of NaOD in CD_3OD, the quartet at 3.07 ppm is lost and the doublet at 1.33 ppm becomes a singlet. This exchange occurs, more slowly, in more dilute solutions of NaOD in CD_3OD or in CD_3OD–D_2O mixtures. In media less alkaline than 0.01 *N* NaOD, exchange becomes very slow. An attempt to follow the rate of exchange by nmr was complicated by the competitive transformation of **7** into **10a**.

Conversion of 5 or 6 into 7. To a solution of the hydroxydienone **5** (0.94 g, 4.0 mmol) in 100 ml of methanol was added 0.2 ml of 5% sodium hydroxide. The reaction mixture was stirred at 25° for 4 hr, progress of the reaction being followed by tlc (silica gel, ethyl acetate–hexane, 1:3). Work-up of the reaction mixture, as above, gave, after distillation, a 58% yield of **7**, bp 107–110° (0.3 mm). By the same procedure, **6** was converted into **7** in alkaline methanol; in 0.1 *M* sodium hydroxide containing 20% methanol, the conversion required 2–3 min for completion. The reaction was significantly slower in phosphate buffer (pH 9.5–11.5)–20% methanol, the rate of formation of **7** increasing with buffer concentration.

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(31) Microanalyses and spectral measurements were performed by the Microanalytical Services and Instrumentation Section of this laboratory, under the direction of Dr. D. F. Johnson. Melting points and boiling points are uncorrected.

(32) A somewhat lower yield was obtained by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al).

(33) Magnetic nonequivalence of the methyl groups is due to the asymmetry introduced at C-2.

(34) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962).

(35) Omission of boron trifluoride gave complete recovery of the lactone. The cyclic ether **9** is also obtained by reduction of **1** with lithium aluminum hydride–boron trifluoride, but in much lower yield.

(36) In subsequent preparations of **9**, the liquid product was subjected to chromatographic purification (silica gel; eluent, ethyl acetate–hexane, 1:9). The resulting oil solidified on storage and was recrystallized from hexane, mp 79–80° (Paul S. Hillery).

(37) In $CDCl_3$ (or CCl_4) alone, the aryl methyl signals are very broad; addition of 1 drop of D_2O (or of any other hydrogen-bonding solvent) normalizes the signals to their expected sharpness. This phenomenon is under further investigation.

(38) Absorption in the latter region indicates contamination by the enedione **7** or the quinone **6**, or both.

(39) Magnetic nonequivalence of the methyl groups is due to the asymmetry at C-8a.

5-Hydroxymethyl-4,4,7,8-tetramethyl-6-chromanol (10a). To a stirred solution of **9** (0.24 g, 1.1 mol) in 15 ml of 10% aqueous acetonitrile was added dropwise, at 25°, 5 ml of acetonitrile containing 1 equiv of NBA or NBS. The reaction mixture was stirred for 1 hr. Initially, the mixture showed a spectral band at 239 nm, which disappeared gradually and was replaced by a band at 290 nm. Water was then added and the aqueous mixture was worked up as for **8**. Removal of solvent left a reddish oil which was purified by chromatography on silica gel (eluent, 15% ethyl acetate in hexane), affording 0.20 g (75%) of a colorless oil. Attempts to purify the product further by distillation resulted in decomposition. Purification for analysis was achieved by preparative thick layer chromatography on silica gel (eluent as above): uv max (CH_3OH) 290 nm (ϵ 1650); ir (neat) 3410 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.36 (s, 6 H, C-4 CH_3's), 1.76 (m, 2 H, C-3 CH_2), 2.10 (s, 6 H, C-7 and C-8 CH_3's), 4.02 (m, 2 H, C-2 CH_2), and 4.91 ppm (s, 2 H, C-5 CH_2).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.31; H, 8.58.

In a similar manner, oxidation of **9** with NBA in ethanol at 25° or with silver nitrate at 80° led to the 5-ethoxy analog **10b**, mass spectrum *m/e* 264. Catalytic hydrogenolysis of **10a** or **10b** with palladium/charcoal in ethanol provided **9**, which was identified by tlc and by mass and nmr spectra.

The quinone **6**, or the hydroxydienone **5**, was transformed into **10a** in 0.01 *N* hydrochloric acid containing 10% acetonitrile. For this conversion, $t_{1/2}$ = *ca.* 3 hr at 25°; in more acidic media, the rate of conversion increases rapidly. In ethanol as solvent (and trifluoroacetic acid as catalyst), the same compounds are converted into **10b**. A solution of **7** in 1 *N* sodium hydroxide–20% ethanol was converted into **10a** during storage at 25° ($t_{1/2}$ = *ca.* 15 hr).

Oxidation of 9 in the Presence of Acetate Ion. Addition of 1 equiv of NBS to a solution of **9** in dry acetonitrile produced no ultraviolet spectral change over a 4-hr period. Upon addition of 2 equiv of tetrabutylammonium acetate to this reaction mixture, the phenolic spectrum disappeared rapidly and was replaced by a high intensity peak at 238 nm. The same spectrum was obtained when tetrabutylammonium acetate was added prior to NBS. Since the oxidation product was unaffected (in its spectrum) by dilution of its solution in acetonitrile with water, acetate buffer (pH 5), or phosphate buffer (pH 7.5) for at least 2 hr, it could not be **5**, and is, therefore, considered to be the acetoxydienone **15**. Addition of a trace of trifluoroacetic acid to the original reaction mixture resulted in a rapid loss of absorption at 238 nm, and formation of a new peak at 288 nm. The transformation product is considered to be **10c**, the acetate ester of **10a**. No attempt was made to isolate either **15** or **10c**.

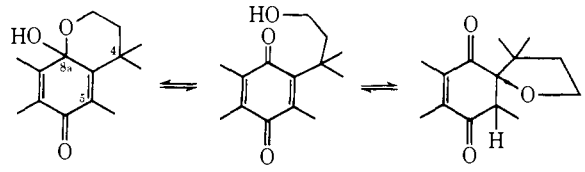
Stereopopulation Control. V. Facilitation of Intramolecular Conjugate Addition of an Aldehyde Hydrate and Hemiacetal

Ronald T. Borchardt and Louis A. Cohen*

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 lactone function in 6-hydroxy-4,4,5,7,8-pentamethylhydrocoumarin (**4**) is reduced by lithium aluminum hydride only to the hemiacetal stage **5**, 4,4,5,7,8-pentamethyl-2,6-chromandiol. Several attempts to trap **5a**, the hydroquinonepropionaldehyde tautomer of **5**, by acylation failed, reaction occurring only in the hemiacetal form. Oxidation of **5** with positive halogen reagents failed to produce the benzoquinonepropionaldehyde **6**, but resulted in the conversion of the C-5 methyl group into an hydroxy- or methoxymethyl group (**10**). Formation of **6** was finally achieved by ferric chloride oxidation. In alkaline methanol, the solvated form of **6** undergoes intramolecular conjugate addition to form a spirocyclic ether–acetal **11**, 2-methoxy-4,4,7,8,10-pentamethyl-1-oxaspiro[4.5]dec-7-ene-6,9-dione. In aqueous acid, the methoxy group of **11** is replaced by hydroxyl (**12**); however, the hydrate of **6** does not cyclize to **12** in alkaline media, but to the fused, bicyclic system **13**, 2-hydroxy-4,4,7,8,10-pentamethyl-1-oxa-*cis*-bicyclo[4.4.0]dec-7-ene-6,9-dione. This unique product owes its stability to the presence of a strong hydrogen bond between the C-2 hydroxyl and the C-9 carbonyl groups. In aqueous acid, the hydrate of **6** is converted into an equimolar mixture of **5** and the bicyclic quinone **14**, 3-hydroxy-5,5,8,9-tetramethyl-2-oxabicyclo[4.5.0]undec-6,8-diene-7,10-dione. Hydrosulfite reduction of **14** provides the hydroquinone analog **15**, together with **10** (R = H). Hydride reduction of **14** gives only **10**. Of the ring isomers **15** and **10**, the latter is the more stable since **15** is converted into **10** by lithium aluminum hydride acting as a strong base. Upon storage of the solid **6**, an intramolecular hydride transfer slowly regenerates **4**; the same transformation is effectively catalyzed by aqueous buffers. Mechanisms are proposed for this variety of transformations, all of which are unique to systems subject to severe stereopopulation control.

In the preceding paper of this series,[1] we described the unique ability of the hydroxypropyl-*p*-benzoquinone **1** to cyclize reversibly either to **2** or to **3**.



2 **1** **3**

Both the rate constants and the equilibria for these cyclizations exceed immeasurably those of simpler homologs lacking the full set of alkyl groups at C-4 and C-5 (the trialkyl lock, numbering as in **2**). By limiting the rotational freedom of covalent bonds in the side chain of **1**, and thus the variety of principal conformers (all of the productive cisoid type), and by bringing the ground state closer than normal to the transition state (with respect to overall geometry, electron density distribution, solvation, and free energy content), the trialkyl lock achieves, *via* nonbonded repulsion, the results which, classically, have been sought through covalent, electronic, or thermal activation.

(1) R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 8308 (1973).