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**.

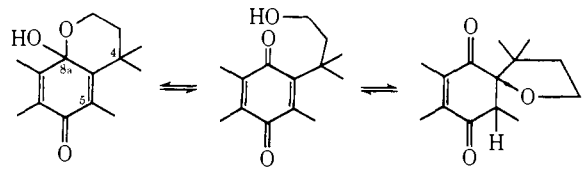
Stereopopulation Control. V. Facilitation of Intramolecular Conjugate Addition of an Aldehyde Hydrate and Hemiacetal

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).

Since the benzoquinone double bond has been found receptive to conjugate addition by a side-chain carboxyl group,[2] as well as by hydroxyl, it was of interest to examine the intermediate oxidation state (the aldehyde) as an example of a functional group which should be incapable of conjugate addition. This assumption proved to be only partially correct, since the solvated aldehyde (hemiacetal) is quite closely related to the hydroxyl species **1**, and does undergo conjugate addition in this form. This paper describes synthetic approaches to the propionaldehyde counterpart of **1**, and some unexpected transformations of this system which, as in numerous earlier cases, are attributable to stereopopulation control.[3]

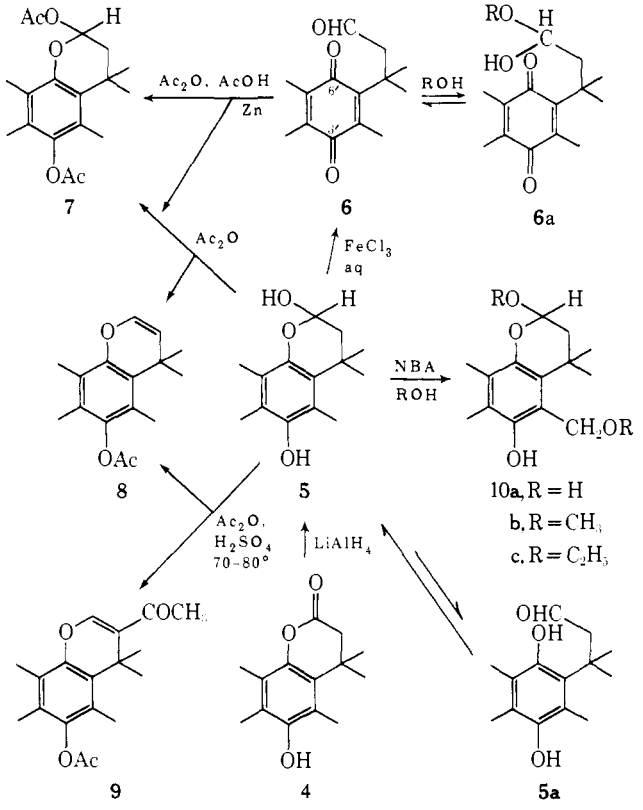
Results and Discussion

As noted previously,[1] routine reduction of the lactone **4**, with lithium aluminum hydride, stopped at the hemiacetal stage **5** because, fortuitously, a phenolate salt of **5** precipitated from the reaction medium. The species **5a**, the hydroquinonealdehyde tautomer of **5**, could not be detected spectroscopically, either by variation of solvent polarity or of pH,[4] nor was it possible to trap the aldehyde by formation of carbonyl derivatives. Acetylation of **5** at 25° led only to the corresponding diacetate **7**; at reflux temperature, the same reaction mixture also provided 20% of the olefinic product **8**. Acetylation of **5** in the presence of a trace of mineral acid (at 70–80°) provided equal amounts of 8 and of **9**, the latter apparently the result of further acylation of **8** by acetylium ion (Scheme I). Thus, it proved equally impossible to drive **5** into its acyclic form **5a** by blocking the hydroquinone phenolic groups.

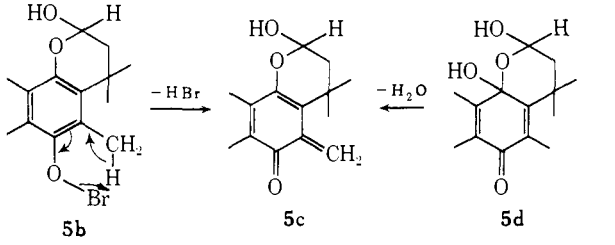
In all previously studied, fused bicyclic systems containing the trialkyl lock, C-2 has been either an sp^2 carbon (as in **4**) or a methylene carbon (as in the chroman analog of **4**). Compounds **5** and **7** are the first cases in which the methyl groups at C-4 show slight magnetic nonequivalence in their nmr signals.[5] Space-filling models suggest that magnetic nonequivalence at C-4 is more likely if the functional substituent at C-2 is assigned a pseudoaxial orientation. Such assignment is consistent with numerous precedents in carbohydrate chemistry, the preferred axial orientation being attributed to dipole repulsion between the lone pair electrons of the substituent and of the ring oxygen atom (the anomeric effect).[6]

It seemed reasonable that the oxidation of **5** to a quinone would force the side chain into its aldehydic form; however, oxidation of **5** with aqueous *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS) led to the *o*-hydroxymethyl derivative **10a**. Most likely, this product is formed by conjugate nucleophilic addition to the *o*-methylenequinone **5c**; the latter species

Scheme I



may be visualized as having been formed by dehydrohalogenation (**5b**) or, in view of the evidence presented in the preceding paper,[1] by vinylogous elimination of water from **5d**.



The same oxidants, in alcoholic media, produce the corresponding ether derivatives at C-5 (**10b**, **10c**). Simultaneously, the hydrogen bromide released during oxidation promotes the replacement of the hydroxyl group at C-2 by an alkoxy group. On the basis of the magnetic nonequivalence of the methyl groups at C-4 (nmr), the C-2 alkoxy group is assigned a pseudoaxial orientation. That the functionality is introduced at the C-5 position is readily demonstrable by nmr: the C-5 methyl group, by virtue of its extreme proximity to the C-4 methyl groups, always provides a δ value *ca.* 0.2 ppm downfield from those due to the C-7 and C-8 methyl groups;[7] accordingly, introduction of an electronegative atom at the C-5 methyl is readily distinguishable from any corresponding change at C-7 or C-8.

The desired quinonepropionaldehyde **6** was eventually obtained, in high yield, by oxidation of **5** with aqueous ferric chloride. The variation in product with type of oxidant suggests that NBA oxidation may proceed *via* **5b**, while the ferric chloride process may involve **5d**.

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

(3) For a definition of this term, see S. Milstien and L. A. Cohen, *ibid.*, 94, 9158 (1972).

(4) The infrared spectrum of **5** shows no carbonyl band; the nmr spectrum shows no aldehydic proton; the ultraviolet spectrum shows no quinone band following aeration. This last test is based on the fact that hydroquinones are oxidized to quinones, at neutral or slightly alkaline pH, much more rapidly than are their monoethers or acetals.

(5) Magnetic nonequivalence at C-4 is also observed in the case of **2**, due to asymmetry at C-8a.

(6) J. T. Edward, *Chem. Ind. (London)*, 1102 (1955); R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, 47, 4427 (1969).

(7) The same downfield displacement has been observed in both monocyclic and fused, bicyclic systems containing the trialkyl lock.

That an hydroxydienone, such as **5d**, is an obligatory intermediate in the conversion of hydroquinone monoethers to quinones has been demonstrated in earlier studies.[8] Again, an attempt was made to generate and trap the hydroquinone aldehyde **5a** (as its diacetate) by reduction of **6**.[9] When the quinone was reduced with zinc in the presence of acetic anhydride, the only identifiable products were **7** and **8**.

While infrared and nmr spectra clearly indicate that the aldehyde group is present in aprotic media, solvation to **6a** probably occurs to a significant extent in water- or alcohol-containing media. In aprotic, and in neutral protic media, the aldehyde proved to be quite stable. A solution of **6** in methanol gave no evidence of change, according to its ultraviolet spectrum or tlc behavior; however, addition of dilute alkali to this solution effected discharge of the quinone color and formation of a colorless product, to which we have assigned the spiroacetal structure **11**. This assignment follows from the absence of hydroxyl absorption in the infrared, from a chromophore at 250 nm (α,β,β-trisubstituted enone),[10] from the absence of an aldehyde proton signal in the nmr spectrum, and from nmr evidence for an aliphatic methyl group (doublet) coupled to a single hydrogen atom (quartet) at C-10. In alkaline deuterium oxide, the C-10 proton is exchanged, the C-10 methyl group signal now appearing as a singlet. Following the analogy of conjugate addition of a side-chain hydroxyl function in alkaline media (**1** → **3**),[1] **11** must arise by conjugate addition of the methyl hemiacetal hydroxyl group in **6a**. The C-4 methyl groups in **11** show magnetic nonequivalence to the extent of 0.16 ppm; this effect may be due to the proximity of one of these methyls to the C-6 carbonyl group (as in the case of **3**),[1] or, less likely, to the asymmetry at C-2. In methanolic hydrogen chloride, **11** is stable for at least 72 hr; in aqueous acid, however, the compound is gradually transformed, without change in ultraviolet spectrum, into a more polar material, probably the spirohemiacetal **12**. Attempts to accelerate this reaction at elevated temperature, or to isolate the product, effected the conversion of **12** into two new products, as yet uncharacterized.

The addition of alkali to solutions of **6** in aqueous media did not result in its conversion to **12**, as might have been anticipated, but led to the isomer **13** (Scheme II). Although the ultraviolet spectrum of **13** is similar to that of **11** (α,β,β-trisubstituted enone), its nmr spectrum shows the methyl group at C-10 to be a singlet. A singlet proton (at C-5) is lost in alkaline deuterium oxide, this event having no effect on the C-10 methyl group. Infrared spectra show the hydroxyl groups at C-2 to be strongly hydrogen bonded intramolecularly, since the shape of the spectral envelope is unaltered by dilution. Molecular models show that facile hydrogen bonding between the C-2 hydroxyl and the C-9 carbonyl is possible if the C-10 oxygen and the C-5 hydrogen atoms are assigned trans-diequatorial orientations (Figure 1). This stereochemistry also provides

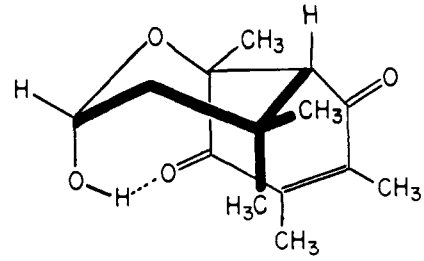
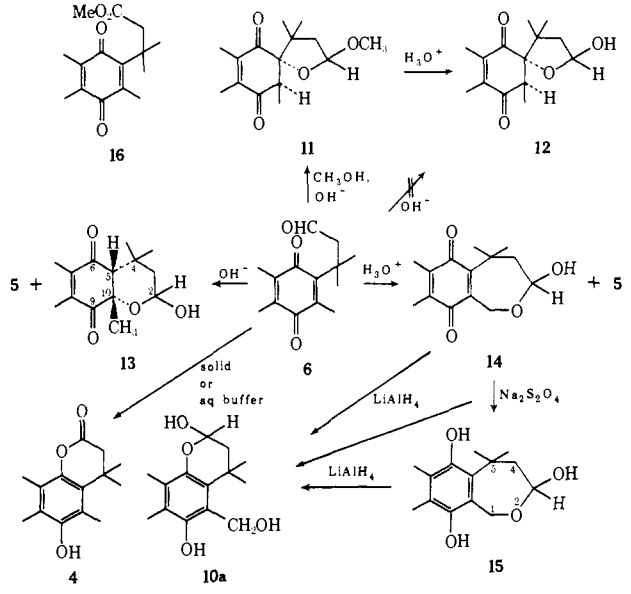


Figure 1. Three-dimensional structure of **13**, showing the ability of the C-2 hydroxyl group to form an intramolecular hydrogen bond with the C-9 carbonyl oxygen atom.

Scheme II



an explanation for the abnormally high field δ value of 0.70 ppm for one of the C-4 methyl groups,[11] which is constrained to lie directly over the 7,8-double bond and is subject to anisotropic displacement.[12] Clearly, our earlier explanation[2] for the preferential formation of spirocyclic products in these conjugate additions is not conclusive. The formation of a strong intramolecular hydrogen bond offers adequate thermodynamic compensation for whatever factors favor the spirocyclic fusion.[13] The formation of **11** in methanol indicates that a spirocyclic system is energetically preferred in the absence of compensating factors. A description of the stereochemistry of **11** is less certain than that of **13**, although conclusions have been drawn for analogous systems.[2] Hopefully, crystal structure analysis[14] will provide a clarification. An attempt to convert **12** into its thermodynamically preferable isomer **13** was unsuccessful; the alkaline conditions necessary to effect any transformation of **12** were severe enough to form many unidentified products not including **13**.

An additional product in the alkaline conversion of **6** into **13** is the hemiacetal **5**, isolated in 10% yield. This product may arise *via* intermolecular hydride transfer

(8) W. Dürckheimer and L. A. Cohen, *Biochem. Biophys. Res. Commun.*, **9**, 262 (1962); *Biochemistry*, **3**, 1948 (1964); *J. Amer. Chem. Soc.*, **86**, 4388 (1964).

(9) We had hoped to utilize the free aldehyde as a starting point for synthesis of the corresponding propylamine, *via* reduction of the aldoxime.

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

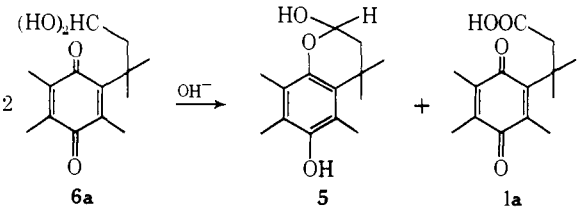
(11) The signal for the other C-4 methyl group appears at 1.08 ppm.

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 83.

(13) The transition from an sp^2 to an sp^3 carbon at C-5 or at C-10 provides sufficient freedom to open the lock.

(14) *Cf.* J. M. Karle and I. M. Karle, *J. Amer. Chem. Soc.*, **94**, 9182 (1972).

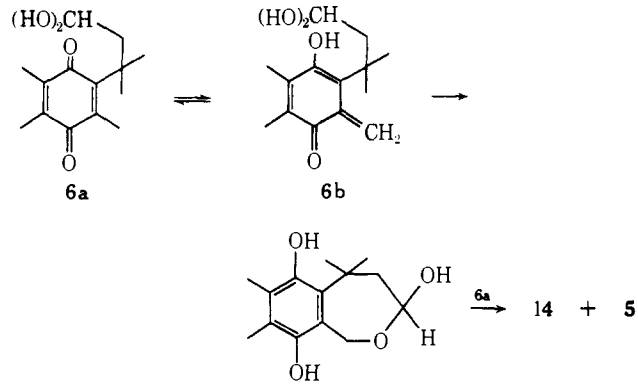
in a face-to-face dimer,[15] one molecule of quinone serving as an oxidant for the hydrated aldehyde. The other species postulated to result from this reaction, the quinone acid **1a**, was not sought among the reaction products.



6a **5** **1a**

Yet another mode of cyclization and hydride transfer occurs when **6** is exposed to aqueous acid, equivalent yields of **5** and a new quinonoid species **14** being obtained. The structure assigned to **14** follows from the presence of a tetraalkyl-*p*-benzoquinone chromophore, a nonassociated hydroxyl band in the infrared, and a shift, in the nmr spectrum, of the C-5 methyl signal (2.17 ppm; numbered as in **5**) to that of a low field methylene group (4.70 ppm). Mild reduction of **14** with sodium hydrosulfite leads to a mixture of the hydroquinone **15** and its tautomer **10a**, whereas reduction of **14** with lithium aluminum hydride produces **10a** almost exclusively. Although the tautomeric species **15** and **10a** are clearly different compounds on the basis of melting point, tlc behavior, and infrared spectrum, their nmr spectra are sufficiently similar to preclude direct structural assignment; these spectra differ, however, in the fact that the C-5 methylene signal is sharp in one and broad in the other species. When the isomer with the broad methylene signal is subjected to deuterium exchange under mild conditions, the band is sharpened considerably; similar treatment of the other isomer has no effect on its C-5 methylene signal. We assume, therefore, that the C-5 methylene signal in **10a** is broadened by coupling with the adjacent hydroxyl proton, this coupling being eliminated by deuterium exchange. Furthermore, the isomer considered to be the hydroquinone is readily reoxidized to **14** by aeration, while **10a** is unaltered under the same conditions. It appears that **10a** is the more stable of the two species since lithium aluminum hydride, acting as a strong base, transforms **15** into **19a** almost completely *via* the propionaldehyde intermediate. This transformation could not be demonstrated in aqueous base because of the high susceptibility of the hydroquinone to reoxidation to **14** under such conditions. Although hydrosulfite reduction of **14** provides a mixture of **15** and **10a**, **15** is not converted into **10a** under comparable conditions. This fact suggests that opening of the hemiacetal ring occurs more easily at the quinone than at the hydroquinone level of oxidation.

The formation of **14** may begin with intramolecular conjugate nucleophilic addition in **6b**, the *o*-quinonemethide tautomer of **6a**, to form **15**, followed by oxidation of **15** to **14** by another molecule of **6a**. The hydride transfer portion of this scheme is supported by the fact that **14** and **5** are obtained in equivalent amounts; furthermore, a mixture of **15** and **6** is converted into **14** and **5** under the same reaction conditions. Quinone–*o*-quinonemethide tautomerism, such as that postulated for **6a–6b**, has been considered in various schemes involving biological quinones in mitochondrial oxidative phosphorylation.[16] Support for such tautomerism may be drawn from evidence that duroquinone is reported to undergo deuterium exchange under strongly alkaline conditions,[17a,18] and condenses with malonate carbanion[17b] and with amines[17c] at the methyl group. Trapping experiments with more complex alkylated quinones[19] provide additional evidence for such tautomerism. As a model for the present case, the quinone ester **16** was tested for deuterium isotope incorporation. In this compound, the reactivity of the quinone ring should be similar to that of **6**, without the complication of side-chain nucleophilicity, but with the loss of any role of the side chain as a general base. No isotope incorporation was observed under the conditions of the conversion of **6** into **14**, or under somewhat more drastic acidic or basic conditions. We do not consider this negative result to exclude the involvement of **6b**, since the structural and experimental conditions necessary to demonstrate isotope exchange or tautomerism in methylquinones are, as yet, poorly defined. A pathway involving **6a** ⇌ **5d** → **5c** → **6b** → **15** has not been considered, since the data already presented suggest that **5c** would proceed directly to **10a**.



The formation of **10a** by oxidation of **5** extends the frequently observed phenomenon that *o*-methylenequinone formation from 6-chromanols always involves the C-5 methyl group, never that at C-7; a justification for this selectivity has been presented previously.[1] The fact that the conversion of **6** into **15** also involves the C-5 methyl group does not, in any way, diminish the importance attributed[1] to the oxygen-containing ring of the chromanol in directing selectivity in *o*-methylenequinone formation, since the side chain of **6** can interact *only* with the C-5 methyl group.

(15) Other unusual reactions, which appear attributable to the existence of face-to-face dimers, have been found in these series; details will be published separately.

(16) E. Lederer and M. Vilkas, *Vitam. Horm. (New York)*, **24**, 409 (1966).

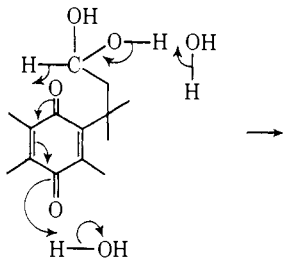
(17) (a) V. M. Clark, D. W. Hutchinson, and R. G. Wilson, *Chem. Commun.*, 52 (1968); (b) L. I. Smith and R O. Denyes, *J. Amer. Chem. Soc.*, **58**, 304 (1936); L. I. Smith, R. T. Arnold, and J. Nichols, *ibid.*, **65**, 2131 (1943); L. I. Smith, R. W. H. Tess, and G. E. Ullyot, *ibid.*, **66**, 1320 (1944); (c) D. W. Cameron, P. M. Scott, and L. Todd, *J. Chem. Soc.*, 42 (1964); see also G. Schill, *Justus Liebigs Ann. Chem.*, **693**, 182 (1966).

(18) On the other hand, isotopic exchange in methylquinones could not be detected chemically [A. Lapidot, B. L. Silver, and D. Samuel, *J. Biol. Chem.*, **241**, 5537 (1966)], or enzymatically [C. D. Snyder, S. J. DiMari, and H. Rapoport, *J. Amer. Chem. Soc.*, **88**, 3868 (1966)].

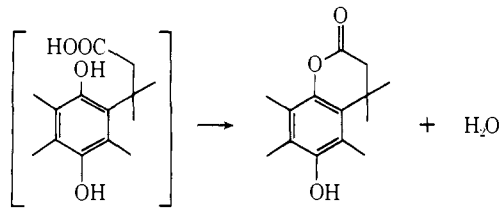
(19) See footnote 25 in ref 1. The Diels–Alder reaction has been used to trap the *o*-methylenequinone tautomers of methylquinones containing β,γ-olefinic side chains: P. Mamont, *Bull. Soc. Chim. Fr.*, 1568 (1970), and references cited therein.

Less alkylated benzoquinoneacetaldehydes or propionaldehydes have been prepared and studied to a limited extent.[20] Although these compounds were not subjected to the variety of conditions under which **6** shows its fascinating transformations, no instance of anomalous spectral or chemical properties has been reported. The difficulties inherent in the synthesis of less alkylated (and conformationally unrestrained) analogs of **6** have delayed our examination of their properties. Since the special properties of **1**, and of its carboxylic acid counterpart **1a**, could not be demonstrated at all in less alkylated analogs, the singularity created by the trialkyl lock probably extends to the aldehyde series as well.

Impressive support for this singularity arises from our observation of intramolecular hydride transfer in the quinone. A sample of **6**, which had been stored at −10°, was found, after several months, to have changed into the colorless lactone **4**. We propose that **6a** undergoes an intramolecular hydride transfer to form the unstable[3] hydroquinone acid **17**, as the basis for



6a



17 **4**

this cyclization. Since the water required for hydration of the aldehyde is regenerated in the lactonization step, it is clear that the small amount of water available in a closed vial could suffice to transform a large amount of aldehyde. In aqueous acidic or alkaline media, the hydrated aldehyde has already been shown to form the entirely different products, **14** and **13**, respectively. The mechanism proposed for this hydride transfer reaction indicates roles for both (general) acid and (general) base and suggests that selection among the pathways leading to **14**, **13**, or **4** may depend, not only on the pH of the medium, but on the catalytic species available. Indeed, whereas a solution of **6** in aqueous methanol appeared to be stable over several days at 25°, addition of acetate buffer (pH 4–5) effected considerable conversion to **4** in the same time period. Whether this reaction depends on the collaborative assistance of general acid *and* general base has not yet been determined, and will require detailed kinetic analysis. In any case, the propriety of this system as a model for hydride transfer in intermediary metabolism[21] is striking, and worthy of additional study.

(20) K. Ley and R. Nast, *Angew. Chem.*, **79**, 150 (1967); J. M. Bruce and D. Creed, *J. Chem Soc. C*, 649 (1970); G. R. Allen, Jr., *J. Org. Chem.*, **33**, 3346 (1968).

Experimental Section[22]

2,6-Diacetoxy-4,4,5,7,8-pentamethylchroman (7) and 6-Acetoxy-4,4,5,7,8-pentamethyl-4*H*-1-benzopyran (8). To a solution of **5** (0.47 g, 2.0 mmol)[1] in 5 ml of acetic anhydride and 3 ml of acetic acid was added 0.15 g of anhydrous sodium acetate. The mixture was stirred and heated at reflux for 30 min, and was then diluted with 20 ml of water. When hydrolysis of acetic anhydride was complete, the mixture was extracted with several portions of ether. The combined ether extracts were washed with water, 5% sodium bicarbonate, and saturated brine, and were dried ($MgSO_4$). Removal of solvent afforded a colorless oil which was separated into two fractions by chromatography on silica gel (eluent, 5% ethyl acetate in hexane); fraction A crystallized from hexane and consisted of 0.105 g (20%) of **8**: mp 47–49°; ir ($CHCl_3$) 1748 (C=O) and 1685 (C=C) cm^{-1}; nmr ($CDCl_3$) δ 1.47 (s, 6 H, C-4 CH_3's), 2.03 and 2.15 (2 s, 6 H, C-7 and C-8 CH_3's), 2.22 (s, 3 H, C-5 CH_3), 2.32 (s, 3 H, acetoxy CH_3),[23] 4.60 (d, J = 6 Hz, 1 H, C-3 CH), and 6.43 ppm (d, J = 6 Hz, 1 H, C-2 CH).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.30; H, 7.40.

Fraction B also crystallized from hexane and afforded 0.31 g (48%) of **7**: mp 76–78°; ir ($CHCl_3$) 1770 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.48 and 1.52 (2 s, 6 H, C-4 CH_3's), 1.95 (d, J = 5 Hz, 2 H, C-3 CH_2), 2.03 and 2.12 (2 s, 6 H, C-7 and C-8 CH_3's), 2.23 (s, 3 H, C-5 CH_3), 2.09 and 2.31 (2 s, 6 H, acetoxy CH_3's),[23] and 6.38 ppm (t, J = 5 Hz, 1 H, C-2 CH).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.43; H, 7.37.

When the same reaction mixture was stored overnight at 25°, the diacetoxychroman **7** was obtained in 70% yield, no olefinic material being detected.

Conversion of 5 to a Mixture of 8 and the Ketone 9. To a solution of **5** (0.50 g, 2.12 mmol) in 10 ml of acetic anhydride was added a drop of concentrated sulfuric acid. The mixture was heated at 70–80° for 18 hr and was poured onto ice. After decomposition of the excess anhydride, the aqueous mixture was extracted with several portions of benzene, and the extract was worked up as for **7**. Removal of solvent afforded a colorless oil which crystallized on storage. Recrystallization (acetone–hexane) afforded 0.25 g (40%) of the ketonic substance **9**: mp 119–121°; ir ($CHCl_3$) 1760 and 1655 (C=O) cm^{-1}; nmr (acetone-d_6) δ 1.65 (s, 6 H, C-4 CH_3's), 1.93 and 2.07 (2 s, 6 H, C-7 and C-8 CH_3's), 2.13 (s, 3 H, C-5 CH_3), 2.18 and 2.23 (2 s, 6 H, acetyl and acetoxy CH_3's), and 7.52 ppm (s, 1 H, C-2 CH).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.44; H, 7.24.

Purification of the mother liquor by preparative tlc on silica gel (eluent, 15% ethyl acetate in hexane) afforded a colorless oil which crystallized (hexane) to yield 0.20 g (39%) of **8**, mp 47–48°.

5-Hydroxymethyl-4,4,7,8-tetramethyl-2,6-chromandiol (10a). To a stirred solution of 0.24 g (1 mmol) of **5** in 15 ml of 10% aqueous acetonitrile was added, dropwise at 25°, 5 ml of acetonitrile containing 1 equiv of NBA or NBS.[24] The mixture was stirred for 1 hr and was diluted with water, and the aqueous mixture was worked up as for **7**. After removal of solvent, there was obtained a red oil which was purified by chromatography on silica gel (eluent, 30% ethyl acetate in hexane); a semisolid, colorless fraction was obtained which crystallized from chloroform to give a 64% yield of **10a**: mp, 144–146°; ir ($CHCl_3$) 3610 and 3400 (OH) cm^{-1}; nmr ($CDCl_3$) δ 1.42 (s, 6 H, C-4 CH_3's), 1.76 (d, 1 H, C-3 CH), 1.85 (s, 1 H, C-3 CH), 2.10 (s, 6 H, C-7 and C-8 CH_3's), 4.98 (s, 2 H, C-5 CH_2), and 5.28 ppm (m, 1 H, C-2 CH).

(21) H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966, Chapters 13 and 14, and references cited therein.

(22) 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. The identity and homogeneity of each species isolated were confirmed by mass spectrum and tlc.

(23) Signals due to the acetoxy methyl groups were differentiated from those due to aryl methyl groups by examination of expanded scale nmr spectra: the aryl methyl signals are broader and shorter than those of acetoxy methyl, and show fine structure.

(24) These oxidants may be used interchangeably.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.56; H, 8.02.

2-Methoxy-5-methoxymethyl-4,4,7,8-tetramethyl-6-chromanol (10b). Oxidation of **5** in 10% methanolic acetonitrile, using the procedure described above, provided a 55% yield of **10b**: bp 154–155° (0.3 mm); ir (neat) 3380 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.47 and 1.43 (2 s, 6 H, C-4 CH_3's); 1.88 (d, J = 5 Hz, 2 H, C-3 CH_2), 2.17 (s, 6 H, C-7 and C-8 CH_3's), 3.47 and 3.53 (2 s, 6 H, OCH_3's), 4.83 (s, 2 H, C-5 CH_2), and 4.95 ppm (t, J = 5 Hz, 1 H, C-2 CH).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.49; H, 8.79.

Oxidation of **5** in ethanolic acetonitrile afforded the analogous diethoxy compound **10c**: bp 150–155° (0.3 mm); ir (neat 3330 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.45 (s, 6 H, C-4 CH_3's), 1.87 (d, J = 4 Hz, 2 H, C-3 CH_2), 2.17 (s, 6 H, C-7 and C-8 CH_3's), 4.85 (s, 2 H, C-5 CH_2), and 5.02 ppm (t, J = 4 Hz, C-2 CH).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.92; H, 9.13.

3-(3′,6′-Dioxo-2′,4′,5′-trimethylcyclohexa-1′,4′-diene)-3,3-dimethylpropionaldehyde (6). To a solution of ferric chloride hexahydrate (4.52 g, 16.8 mmol) in 20 ml of water was added, at 25°, a solution of **5** (2.02 g, 8.4 mmol) in 20 ml of benzene and 20 ml of tetrahydrofuran. The mixture was shaken vigorously for 14 hr, while progress of the reaction was followed by tlc (silica gel, 30% ethyl acetate in hexane). The organic layer was separated and the aqueous layer was extracted with fresh benzene. The combined extracts were worked up as for **7**. Removal of solvent afforded a yellow oil which was purified by chromatography on silica gel (eluent, 15% ethyl acetate in hexane). A yellow solid was obtained which was recrystallized from hexane (1.62 g, 82%): mp 50–52°; ir ($CHCl_3$) 1720 and 1642 cm^{-1} (C=O); uv max (CH_3OH) 257 nm (ϵ 15,000); nmr ($CDCl_3$) δ 1.43 (s, 6 H, C-4 CH_3's), 1.90 (s, 6 H, C-7 and C-8 CH_3's), 2.17 (s, 3 H, C-5 CH_3), 3.17 (s, 2 H, C-2 CH_2), and 9.66 ppm (s, 1 H, CHO).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.83; H, 7.77.

Reductive Conversion of 6 into 7 and 8. To a mixture of **6** (0.47 g, 2.0 mmol) and 0.15 g of anhydrous sodium acetate in 5 ml of acetic anhydride and 3 ml of acetic acid was added 0.5 g of zinc dust. The reaction mixture was stirred and heated at reflux for 0.5 hr, and filtered, while hot, into 20 ml of water. After hydrolysis of the acetic anhydride was complete, the mixture was worked up as for **7**. Removal of solvent afforded a colorless oil. Tlc (silica gel, 15% ethyl acetate in hexane) showed two major products, which were separated by column chromatography on silica gel (eluent, 5% ethyl acetate–hexane). Fraction A consisted of 0.105 g (20%) of **8**, mp 47–49° (hexane); fraction B afforded 0.31 g (48%) of **7**, mp 76–78° (hexane).

2-Methoxy-4,4,7,8,10-pentamethyl-1-oxaspiro[4.5]dec-7-ene-6,9-dione (11). To a solution of **6** (0.30 g, 1.28 mmol) in 15 ml of methanol was added dropwise 2 ml of 0.5% sodium hydroxide. The reaction mixture was stirred at 25° for 15 min and was diluted with water, and the mixture was worked up as for **7**. Removal of solvent afforded a colorless oil which was purified by thick-layer chromatography on silica gel (eluent, 15% ethyl acetate–hexane). The major band was extracted with ethyl acetate and provided, after crystallization from hexane, 0.20 g (64%) of **11**: mp 81–83°; ir ($CHCl_3$) 1679 cm^{-1} (C=O); uv max (CH_3OH) 250 nm (ϵ 12,700); nmr ($CDCl_3$) δ 1.02 and 1.18 (2 s, 6 H, C-4 CH_3's), 1.27 (d, J = 7 Hz, 3 H, C-10 CH_3), 2.01 and 2.05 (2 s, 6 H, C-7 and C-8 CH_3's), 2.03 (m, 2 H, C-2 CH_2), 3.03 (q, J = 7 Hz, 1 H, C-10 CH), 3.42 (s, 3 H, C-2 OCH_3), and 5.08 ppm (m, 1 H, C-2 CH). The nmr spectrum of a solution of **11** in CD_3OD containing 5 drops of 1 N NaOD (in D_2O) lacked the signal at 3.03 ppm and gave a signal at 1.29 ppm (s, 3 H, C-10 CH_3).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.64; H, 8.48.

A solution of **11** in methanol containing *ca.* 5% hydrogen chloride showed no change in uv spectrum or in tlc behavior over a 72-hr period at 25°, or even after 30 min at reflux. In a 1:1 mixture of methanol and 1 N hydrochloric acid, at 25°, again no spectral change was observed; however, a slower moving material soon became evident on silica gel plates. After 24 hr at 25°, **11** had almost entirely disappeared; the new species (which we consider to be **12**) was the only significant material evident by tlc. After an additional 24 hr storage, two new spots began to appear, whose R_f values differed only slightly from that of **12** in a 20 or 30% ethyl acetate–hexane system. At elevated temperature, the conversion of **11** to **12** was more rapid, but **12** was rapidly replaced by the two unidentified products. Throughout these transformations, no significant uv changes were discernible.

2-Hydroxy-4,4,7,8,10-pentamethyl-1-oxa-*cis*-bicyclo[4.4.0]dec-7-ene-6,9-dione (13). To a solution of **6** (0.30 g, 1.28 mmol) in 10 ml of acetonitrile and 5 ml of water was added dropwise 1 ml of 0.5% sodium hydroxide. The reaction mixture was stirred at 25° for 1 hr and was diluted with 25 ml of water, and the mixture was worked up as for **7**. Removal of solvent afforded a red oil which was further purified by chromatography on silica gel (eluent, 30% ethyl acetate–hexane). Crystallization of the slower running major fraction (benzene–hexane) afforded 0.20 g (63%) of **13**: mp 86–88°; ir ($CHCl_3$) 3620 (sh), 3510 (m) (OH), and 1660 (C=O) cm^{-1}; uv max (CH_3OH) 252 nm (ϵ 11,900); nmr ($CDCl_3$) δ 0.70 and 1.08 (2 s, 6 H, C-4 CH_3's), 1.23 (s, 3 H, C-10 CH_3), 1.93 (m, 2 H, C-3 CH_2), 2.03 (s, 6 H, C-7 and C-8 CH_3's), 2.52 (s, 1 H, C-5 CH), and 4.75 ppm (m, 1 H, C-2 CH). In CD_3OD–5% CD_3ONa, the signal at 2.52 ppm (C-5 CH) was lost and the signal at 1.23 ppm (C-10 CH_3) remained essentially unaltered.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.64; H, 7.69.

From the chromatographic forerun, there was obtained a 10% yield of **5**, mp 167–170° (chloroform–hexane).

Acid-Catalyzed Cyclization of 6 to 5 and 3-Hydroxy-5,5,8,9-tetramethyl-2-oxabicyclo[4.5.0]undec-6,8-diene-7,10-dione (14). To a solution of **6** (0.40 g, 1.70 mmol) in 10 ml of acetonitrile was added 10 ml of 0.1 N hydrochloric acid and the reaction mixture was stirred at 25° for 15 hr. Water was added and the mixture was worked up as for **7**. Removal of solvent afforded a reddish oil which, after solution in benzene, deposited 0.15 g (38%) of a colorless product, mp 162–165°; this material was identified as **5** on the basis of ir, nmr, and mass spectra, and mixture melting point. Purification of the mother liquor by preparative tlc on silica gel (eluent, 10% ethyl acetate–chloroform) provided, after crystallization from chloroform–hexane, 0.17 g (40%) of **14**: mp 115–117°; ir ($CHCl_3$) 3600, 3410 (OH), and 1660 cm^{-1} (C=O); uv max (CH_3OH) 261 nm (ϵ 14,450); nmr (acetone-d_6) δ 1.26, 1.53 (2 s, 6 H, C-5 CH_3's), 1.77 (d, 1 H, C-4 CH), 1.95 (s, 6 H, C-8 and C-9 CH_3's), 2.10 (s, 1 H, C-4 CH), 4.67 and 4.72 (2 s, 2 H, C-1 CH_2), and 5.30 ppm (m, 1 H, C-3 CH).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.41; H, 7.14.

Hydride Reduction of 14 to 10a. Lithium aluminum hydride (0.114 g, 3.0 mmol) was added to 15 ml of anhydrous ether, and the mixture was heated at reflux for 2 hr. To the solution was added dropwise a solution of **14** (0.20 g, 0.8 mmol) in 15 ml of anhydrous tetrahydrofuran. The reaction mixture was heated at reflux for 2 hr, "wet" ether was then added to decompose excess hydride, and finally the mixture was diluted with 5% hydrochloric acid. The mixture was extracted with several portions of ether, and the combined ether extracts were washed with 5% hydrochloric acid, water, and saturated brine, and were dried ($MgSO_4$). Removal of solvent afforded a reddish oil which was purified by preparative tlc on silica gel (eluent, 30% ethyl acetate–hexane). Crystallization (chloroform) of the major fraction afforded 0.10 g (50%) of **10a**, mp 146–147°; ir, nmr, and mass spectra were identical with those of an authentic sample.

Hydrosulfite Reduction of 14 to 10a and 15. To a solution of sodium hydrosulfite (1.35 g, 7.2 mmol) in 30 ml of water was added a solution of **14** (0.60 g, 2.4 mmol) in 45 ml of ether. The reaction mixture was shaken at 25° for 1 hr. The ether layer was separated and the aqueous layer was extracted with two portions of ether. The combined ether extracts were washed with water and saturated brine, and were dried ($MgSO_4$). Removal of solvent yielded a yellowish foam which was separated into two principal fractions by preparative thick-layer chromatography on silica gel (eluent, 30% ethyl acetate–hexane). The faster moving material, which was identified as **10a**, was obtained in 59% yield, mp 145–147°. Comparison with an authentic sample was made by means of ir, nmr, and mass spectra, as well as by tlc behavior and mixture melting point. The slower moving fraction was crystallized from chloroform (0.145 g, 24%): mp 135–137°; nmr (acetone-d_6) δ 1.45 (s, 6 H, C-5 CH_3's), 1.80 (m, 2 H, C-4 CH_2), 2.05 and 2.09 (2 s, 6 H, C-8 and C-9 CH_3's), 4.91 (s, 2 H, C-1 CH_2), and 5.25 ppm (m, 1 H, C-3 CH). Addition of D_2O to this nmr solution produced no significant alteration in the spectrum. When the nmr solution of **10a** (in $CDCl_3$) was shaken with a drop of D_2O, the C-5 CH_2 band at 4.98 ppm was sharpened significantly. These data, together with the absence of ir carbonyl bands and the presence of a phenolic chromophore in the uv spectrum, are consistent with structure **15**.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.71; H, 7.72.

When a solution of **15** in aqueous methanol is aerated for 1–2 hr, the quinone **14** is regenerated; under the same conditions, **10a** shows no tendency to undergo air oxidation. When a solution of **15** in tetrahydrofuran is heated at reflux for 2 hr with lithium aluminum hydride, the principal product present, according to tlc, is **10a**, only a trace of **15** remaining; however, when a solution of **15** in ether is shaken with aqueous sodium hydrosulfite, no conversion to **10a** can be detected. Equivalent amounts of **15** and **6** were dissolved in 10 ml of acetonitrile and the solution was diluted with 10 ml of 0.1 *N* hydrochloric acid. After 15 hr, tlc showed **14** and **5** to be the major products present (in roughly equal amount), with only traces of the initial components.

Test for Proton Exchange in 16. Solutions of the quinone **16**[2] in CD_3OD, 0.5 *N* in deuterium chloride or $NaOCD_3$, were examined by nmr over a 24-hr period at 30–35°; there was no significant spectral change in either solution. The same solutions were maintained at 50–55° for 1 hr; again there was no evidence for exchange at the methyl groups.

Conversion of 6 to 4. A sample of **6**, which had been stored in the crystalline state (in a capped vial) for approximately 1 month was observed to have undergone a transformation, resulting in contamination with a colorless, more polar substance. Separation of 0.20 g of the mixture on silica gel (eluent, 25% ethyl acetate–hexane) afforded, after crystallization from acetone–hexane, 0.046 g (24%) of **4**, mp 185–187°. Identity with an authentic sample was confirmed by means of ir and nmr spectra, and mixture melting point. After 3 months, the same sample consisted almost entirely of **4**, as determined by tlc and uv spectral analysis. A solution of **6**, freshly prepared, in 80% aqueous methanol showed no loss of the quinone chromophore over 3 days at 25°. Solutions of **6** in acetate buffer (0.2 *M*, pH 4 or 5)–methanol (4:1) showed a loss of 50–75% of the quinone chromophore in the same 3-day period; the presence of **4** in these reaction mixtures was demonstrated by tlc.

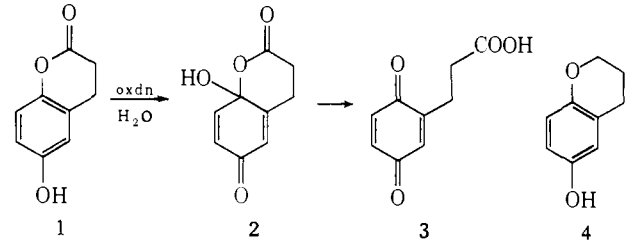
Stereopopulation Control. VI. Conformational Selection of Alternative Oxidation Pathways

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: Aqueous oxidation of 6-hydroxy-4,4,5,7,8-pentamethylhydrocoumarin (**5**) or of 5,7-dibromo-4,4-dimethyl-6-hydroxyhydrocoumarin (**7**) results in the formation of the corresponding quinonepropionic acids. In the presence of $H_2{}^{18}O$, isotopic oxygen is found only in the quinone carbonyl, implicating a *p*-hydroxydienone intermediate in the oxidation pathway. Under the same conditions, the oxidation of 5,7-dibromo-6-hydroxyhydrocoumarin (**10**) provides a quinonepropionic acid with label only in the carboxyl group. In this case, an acylium ion intermediate is proposed. In ethanol as solvent, all three hydrocoumarins form *p*-ethoxydienones on oxidation; in the case of **10**, an equivalent amount of the quinonepropionic ester is also formed; in this reaction, both pathways are followed competitively. In the presence of acetate ion, **5** and **7** form *p*-acetoxydienones while **10** forms a mixed anhydride between acetic acid and the quinonepropionic acid. The *p*-acetoxydienone of **5** rearranges to the thermodynamically preferable *o*-acetoxydienone *via* an SN2′ displacement with acetate ion as nucleophile. The reaction is considerably accelerated upon addition of acetic acid. With acetic acid alone, the *p*-acetoxydienone of **5** rearranges to a quinone mixed anhydride, as does that of **7**. The *p*-acetoxydienone of **7**, however, is not converted into an *o*-acetoxydienone in acetic acid–sodium acetate. Toward aqueous acid hydrolysis, the *p*-ethoxydienone of **10** is more labile than that of **7** by a factor of 5300. The results of labeling in $H_2{}^{18}O$, the differences in oxidation pathways, and the differences in stability to hydrolysis are all attributed to the influence of stereopopulation control. The 4,4,5 trisubstitution in **5** and **7** represses formation of the acylium ion which would lead to quinone esters and anhydrides and, instead, promotes reactions of the cyclic carbonium ion, leading to para-substituted dienones.

Oxidation of 6-hydroxyhydrocoumarins **1**[1] in water-containing media proceeds, as expected, to form the corresponding quinonepropionic acids **3**.[2] Generally, the quinone acids are obtained in good yield and are free of significant side products.[3] It is logical to assume that oxidations of all 6-hydroxyhydrocoumarins follow a common mechanism, involving the thermodynamically unstable *p*-hydroxydienone **2**. The assumption of this intermediate is based on the demonstration of a parallel pathway in the oxidation of 6-chromanols **4**, since their moderately stable *p*-hydroxydienones have been isolated in three cases.[4] In the course of our studies on stereopopulation control[2a] and on conservation of oxidative free energy[5] in such systems, it became apparent that the assumption of a



1 2 3 4

(1) Structures **1–4** are intended to represent general classes of compounds, of which they are the least substituted members.

(2) (a) R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9175 (1972); (b) M. Asano and T. Kawasaki, *J. Pharm. Soc. Jap.*, **70**, 480 (1950); (c) L. I. Smith and R. O. Denyes, *J. Amer. Chem. Soc.*, **58**, 304 (1936).

(3) This generalization ignores the fact that certain members of series **3** are unstable,[2a] and are consumed in subsequent transformations.

(4) (a) R. T. Borchardt and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 8308 (1973); (b) W. Dürckheimer and L. A. Cohen, *ibid.*, **86**, 4388 (1964); (c) N. I. Bruckner and N. L. Bauld, *J. Org. Chem.*, **36**, 4045 (1971).

(5) J. W. Thanassi and L. A. Cohen, *J. Amer. Chem. Soc.*, **89**, 5733 (1967); *Biochim. Biophys. Acta*, **172**, 389 (1969).