Acknowledgment. This work was supported by Grant-in-Aid 447017 from the Ministry of Education, Science and Culture of Japan. We thank Dr. Y. Senda for his gift of rhodium complex catalyst and Mrs. Hoevers of TNO for her help in analysis and bioassay.

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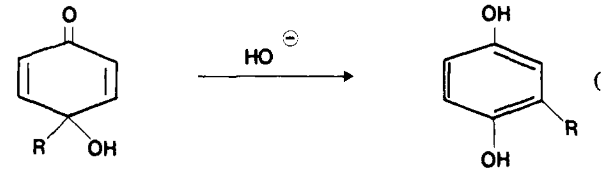
Received March 31, 1980

Conformational and Electronic Control of Anionic Rearrangements of 4-Hydroxycyclohex-2-en-1-ones

Sir:

4-Substituted 4-hydroxycyclohexa-2,5-dien-1-ones (**1**) have long been known to undergo rearrangement to 2-substituted hydroquinones (**2**) upon treatment with base.[1] This transformation, which may be termed a vinylogous acyloin rearrangement, presumably owes its driving force to the attainment of the hydroquinone product aromaticity.



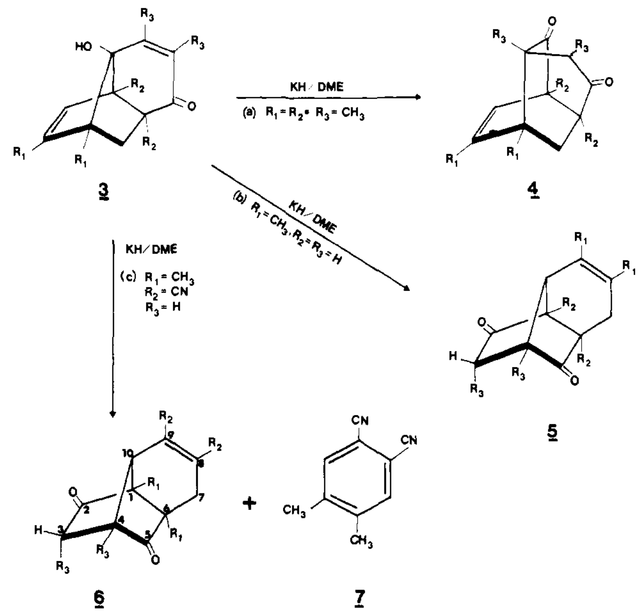
(1)

1 **2**

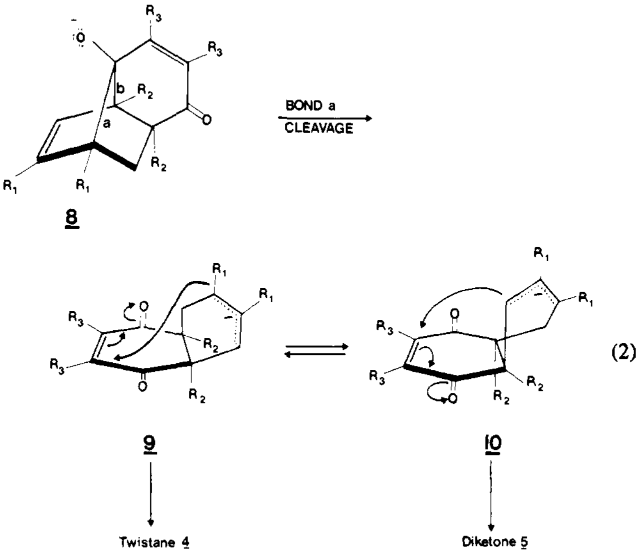
We recently discovered what appeared to be a novel, nonaromatic version of this rearrangement, namely, the conversion of 4-hydroxycyclohexenone **3a** ($R_1 = R_2 = R_3 = CH_3$) into the twistane derivative **4** upon treatment with potassium hydride in dimethoxyethane (Scheme I).[2] However, in this communication, we report that (1) twistane formation is *not* a general process for compounds of general structure **3** when treated similarly, (2) alternative, highly unusual anionic rearrangements occur under these conditions, and (3) the divergent rearrangement pathways can be understood on the basis of the conformational and electronic effects exerted by the substituents present in **3**.

For example, treatment of substrate **3b**[3] ($R_1 = CH_3$, $R_2 = R_3 = H$) with potassium hydride in dimethoxyethane gave a 35% isolated yield (after recrystallization) of the diketone **5** (Scheme I).[3] Gas chromatography indicated that **5** constituted >95% of the total volatile products formed. Even more intriguingly, hydroxycyclohexenone **3c** ($R_1 = CH_3$, $R_2 = CN$, $R_3 = H$)[4] afforded diketone **6** (90% by GC, 34% isolated) plus dinitrile **7** (5% by GC, 2% isolated) when treated under similar conditions (Scheme I). Note that while products **5** and **6** have identical ring skeletons, they possess different substitution patterns, indicating they are formed by different mechanisms. The structure of **6** was deduced from its spectral data,[5] and **7** is a known compound, mp 179–180 °C (lit.[6] mp 178–179 °C).

Scheme I



The divergent results for **3a**, **3b**, and **3c** can be nicely rationalized if one makes the unifying assumption that the initial step following proton removal in each case is cleavage of either bond a or bond b of alkoxide **8**. Whether bond a or bond b cleaves depends in turn on the nature of R_2. When $R_2 = CN$ as in **3c**, bond b cleaves for reasons of carbanion resonance stabilization whereas in the absence of this effect ($R_2 = H$ or CH_3, compounds **3b** and **3a**, respectively) cleavage of bond a is intrinsically favored.



Cleavage of bond a leads to an allyl anion having conformation **9** which can close directly to the twistane product **4** via an internal

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(1) (a) Bamberger, E. *Chem. Ber.* **1900**, *33*, 3600–3622. (b) Goodwin, S.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 179–185. (c) Nishinaga, A.; Itahara, T.; Matsuura, T. *Chem. Ber.* **1976**, *109*, 1530–1548.

(2) Greenhough, T. J.; Scheffer, J. R.; Trotter, J.; Wong, Y-F. *J. Chem. Soc., Chem. Commun.* **1979**, 933–934.

(3) The preparation and characterization of compounds **3b** and **5** are described in Scheffer, J. R.; Bhandari, K. S.; Gayler, R. E.; Wostradowski, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 2178–2189.

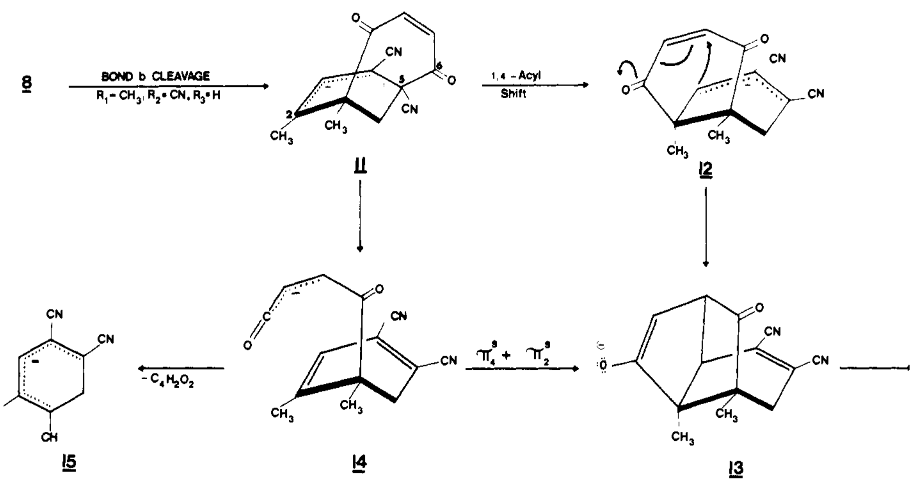
(4) Scheffer, J. R.; Jennings, B. M.; Louwerens, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 7040–7048.

(5) Compound **6**: mp 225–226 °C; UV (MeOH) λ_{max} 234 nm (ϵ 7900); IR (KBr) 1739 (C=O), 2232 cm^{-1} (CN); 270-MHz NMR (acetone-d_6) δ 0.95 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 2.30 (d, J = 18 Hz, 1 H, C(3) endo), 2.59 (d, J = 20 Hz, 1 H, one of C(7) methylenes), 2.77 (d, J = 20 Hz, 1 H, one of C(7) methylenes), 2.81 (dd, J = 18, 5 Hz, 1 H, C(3) exo), 3.40 (s, 1 H, C(10) methine), 3.59 (d, J = 5 Hz, 1 H, C(4) methine); mass spectrum parent (70 eV), m/e 240. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.70; H, 5.19; N, 11.71. The location of the methyl groups in **6** follows from their NMR high-field chemical shifts and lack of coupling. The location of the nitrile groups is indicated by their red-shifted IR bands as compared to saturated nitriles. For example, the CN stretching frequency for **3c** is 2270 cm^{-1}.

(6) Mikhalenko, S. A.; Gladyr', S. A.; Luk'yanets, E. A. *Zh. Org. Khim.* **1972**, *8*, 341–343.

0002-7863/80/1502-6604$01.00/0

Scheme II



Michael addition as shown in the above reaction. Formation of diketone **5**, however, is impossible from **9** and requires an intervening isomerization of **9** into conformation **10** followed by the alternative intramolecular Michael addition shown. Similarly, a crossover closure from anion **10** to twistane **4** is geometrically prohibited. This scheme can be used to explain the **4**:**5** product ratio differences observed between substrates **3a** and **3b**, namely, that **3b** gives products of type **5** only and that **3a** gives both types.[7]

It appears that once again the dominant influence is the nature of R_2, in this case its steric effect. The simplest interpretation is that when $R_2 = H$ (substrate **3b**) conformational equilibration of **9** and **10** is rapid relative to the rates of closure of **9** to **4** and **10** to **5**, but when $R_2 = CH_3$ (substrate **3a**), conformational equilibration is slower than closure. This effect stems from the fact that the equilibration necessarily involves eclipsing of the bridgehead R_2 groups. As a result, the **4**:**5** ratio for **3b** ($R_2 = H$) will be governed by the difference in the activation energies for the processes **9** → **4** and **10** → **5** (Curtin-Hammett principle).[8] Two factors lead to the clear prediction that the **10** → **5** closure should be favored as is observed experimentally. (1) The twistane ring system of **4** possesses a greater strain energy than the tricyclo[4.4.0.0^{3,7}]decane ring system of **5**,[9] and (2) bonding in **9** occurs between atoms which are not only further apart but more highly substituted ($R_1 = CH_3$) than in the case of **10**. In contrast, when equilibration between two conformers is *slower* than the rate of reaction of either, the product ratio depends on the relative conformer populations.[10] Thus, **3a** ($R = CH_3$) leads to twistane **4** via initially formed anion **9** before **9** can isomerize appreciably to **10**. As is observed experimentally,[7] this mechanism predicts larger amounts of product **5** at higher temperatures. We have observed similar methyl group eclipsing effects in some of our photochemical studies.[4]

Turning now to a discussion of the mechanism of the rearrangement of substrate **3c**, we suggest that the corresponding alkoxide undergoes preferential bond b cleavage to afford allyl anion **11** (Scheme II). There are several plausible mechanisms by which intermediate **11** can proceed on to final product **6**. One involves a symmetry-allowed[11] 1,4-sigmatropic acyl shift of **11** to give **12**. Carbanion **12** can in turn close to give **13** (the enolate of diketone **6**) via an internal Michael addition process exactly analogous to the conversion of **10** to **5** as previously shown. Anionic 1,4-sigmatropic rearrangements, while rare,[12] have been established for 2-alkoxypyridine *N*-oxides (migration from one oxygen atom to another).[13] Carbanion **11** could also rearrange to **12** via a nonconcerted process involving nucleophilic attack by C(2) on C(6) followed by C(5)–C(6) bond cleavage. A third possibility for the formation of **6** involves ring opening of **11** to give ketene enolate **14** followed by symmetry-allowed[11] [4 + 2] cycloaddition to afford, once again, enolate **13**. Intermolecular cycloadditions of allyl anions to olefins are well-established provided the product anion is resonance stabilized.[14] This condition is met in the conversion of **14** to **13**.

Finally, turning to the formation of 4,5-dimethylphthalonitrile (**7**) which is produced in 5% yield along with diketone **6** in the reaction of **3c**, we suggest that it arises via protonation of anion **15** followed by aromatization during workup. Anion **14** (as well as anion **12**) represents a possible precursor of carbanion **15** via expulsion of the bis ketene fragment $C_4H_2O_2$. No products resulting from reaction of this interesting species could be isolated, however.

In summary, the results provide novel examples of the ways in which substituents can affect anionic rearrangement pathways. Particularly intriguing are the unusual mechanistic possibilities presented by the rearrangement of dinitrile **3c**. Further work aimed at differentiating among these possibilities is under way.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

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(7) The ratio of **4**:**5** ($R_1 = R_2 = R_3 = CH_3$) was found[2] to be 8:1 at 83 °C (potassium hydride in refluxing dimethoxyethane) and 1:1 at 101 °C (potassium *tert*-butoxide in refluxing dioxane). The 1:1 ratio includes a side product derived from **4** in potassium *tert*-butoxide–dioxane. Compounds **4** and **5** did not interconvert under either set of reaction conditions.

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(9) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005–8025.

(10) Lewis, F. D.; Johnson, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 8914–8916.

(11) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry", Academic Press: New York, 1970.

(12) Grovenstein, E., Jr. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 313–332.

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Received June 19, 1980

Biosynthesis of Lipoic Acid: Extent of Incorporation of Deuterated Hydroxy- and Thiooctanoic Acids into Lipoic Acid

Sir:

It has been demonstrated that lipoic acid can be biosynthesized in *Escherichia coli* from octanoic acid.[1,2] It has also been dem-