Total Synthesis of Racemic Isochorismic Acid

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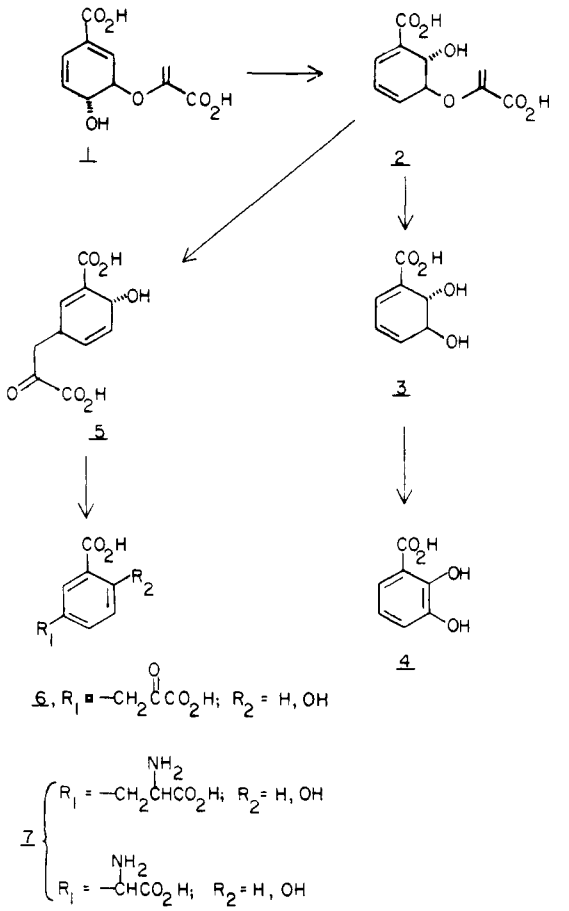
Chorismic acid (**1**) is the last common intermediate in the biosynthesis of aromatic substances through the shikimate pathway in bacteria, fungi, and higher plants.[1] One of the intriguing biosynthetic transformations of **1** is the enzyme-catalyzed isomerization to isochorismic acid (**2**).[2] The structure and absolute stereochemistry of **2** have been established by Gibson and co-workers.[2] The role of **2** as an intermediate in the biosynthesis of aromatic substances (Scheme I) has been reviewed.[3] Hydrolysis of the enol pyruvyl side chain of **2** affords **3**, which serves as the immediate precursor to 2,3-dihydroxybenzoic acid (**4**). Evidence suggests that **2** undergoes a Claisen rearrangement to isoprephenic acid (**5**), which subsequently is transformed into *m*-carboxy-substituted aromatic amino acids **7** via pyruvate derivatives **6**. The biosynthetic sequence resembles the conversion of **1** to tyrosine and phenylalanine.[1] Salicylic acid is derived from **2** in certain organisms.[3]

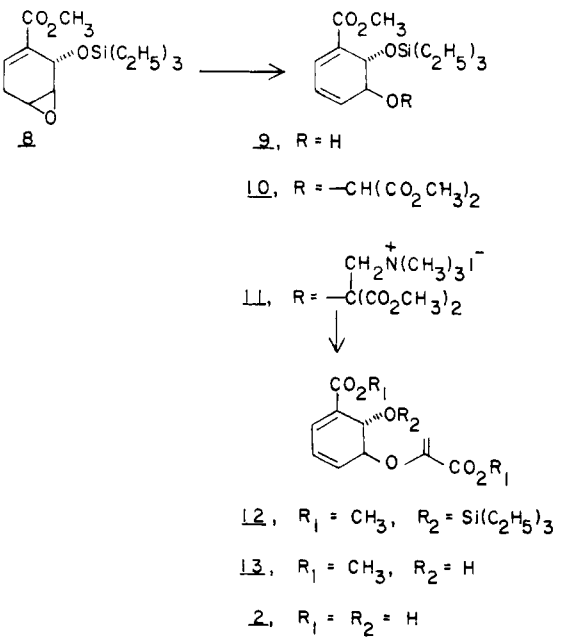
Racemic **3** has been prepared in our laboratory,[4] and recently the total synthesis of **1** has been accomplished in our laboratory[5] and in Ganem's laboratory.[6] The synthesis of **2** presents an interesting challenge since it is reported that **2** is an unstable substance that decomposes readily to a mixture of salicylate and 3-carboxyphenyl pyruvate at room temperature in aqueous solution a pH 7.[2] Described below is our total synthesis of racemic **2**.

Starting material for the synthesis (Scheme II) was **8** which was prepared in 63% overall yield from 1-(triethylsiloxy)-1,3-butadiene by the two-step procedure reported by Schlessinger and Lopes for the corresponding ethyl ester.[7] Epoxide **8** was isomerized to **9**[8,9] (82%) with 1,8-diazabicyclo[5.4.0]undec-7-ene in 95:5 ether/methanol at room temperature. Application of the elegant procedure developed by Ganem and co-workers[6] (dimethyl diazomalonate with 1 mol % rhodium acetate in benzene at 60 °C) afforded **10**[10] in nearly quantitative yield. Reaction of **10** with Eschenmoser's salt [$CH_2{=}N^+(CH_3)_2I^-$, $(C_2H_5)_3N$, CH_2Cl_2] and quaternization of the Mannich base (CH_3I, CH_2Cl_2) provided **11** (91% yield from **9**). Reaction of **11** with 1.1 equiv of NaOH in aqueous methanol at 0 °C effected fragmentation to **12**[11] (40-50%). Removal of the silyl protecting group from **12** (5:5:2 THF/HOAc/H_2O, 0 °C, 14 h) gave dimethyl isochorismate (**13**)[12]

Scheme I



Scheme II



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(9) **9**: IR (neat) 3420, 1710, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.12 (dd, 1 H, J = 5.0, 1.4 Hz) 6.28 (m, 2H), 4.69 (d, 1 H, J = 1.8 Hz), 4.14 (dd, 1 H, J = 4.8, 1.4 Hz), 3.78 (s, 3 H), 1.87 (br s, 1 H), 0.93 (m, 9 H), 0.65 (m, 6 H).

(10) **10**: IR(neat) 1740, 1710, 1645, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.13 (dd, 1 H, J = 6.0, 1.3 Hz), 6.42 (dd, 1 H, J = 9.4, 5.6 Hz), 6.22 (dd, 1 H, J = 9.0, 5.6 Hz), 4.81 (t, 1 H, J = 2.0 Hz), 4.60 (s, 1 H), 4.19 (dd, 1 H, J = 6.0, 2.1 Hz), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 0.92 (m, 9 H), 0.66 (m, 6 H).

(11) **12**: IR ($CHCl_3$) 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.11 (d, 1 H, J = 5.9 Hz), 6.37 (m, 1 H), 6.28 (m, 1 H), 5.55 (d, 1 H, J = 2.7 Hz), 4.86 (m, 2 H), 4.59 (d, 1 H, J = 2.7 Hz), 3.7. (s, 6 H), 0.92 (m, 9 H), 0.64 (m, 6 H).

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in 79% yield after chromatography (silica gel plate).

Saponification of **13** (NaOH in CH_3OH/H_2O) at 0 °C followed by acidification (Amberlite IR-120 resin) and concentration gave a mixture of **2** (80%) and aromatic product. Recrystallization from ethyl acetate gave pure, crystalline (±)-**2** (23%). Comparison of the spectral data (IR, UV, ^1H NMR)[13] of (±)-**2** with those reported for **2** isolated from *A. Aerogenes*[2] established their structural identity.

We have confirmed the instability of **2** described by Gibson and co-workers.[2] It is interesting to note that dimethyl ester **13** slowly undergoes Claisen rearrangement on standing in $CDCl_3$ solution at 0 °C to afford the dimethyl ester of **5**. Attempts to prepare the disodium salt of **5**, which has not been isolated from natural sources, are under investigation in our laboratory.

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(12) **13**: IR (neat) 3475, 1715, 1620, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.09 (dd, 1 H, J = 4.8, 1.6 Hz), 6.27 (m, 2 H), 5.56 (d, 1 H, J = 2.8 Hz), 4.96 (d, 1 H, J = 2.8 Hz), 4.88 (m, 2 H), 3.83 (s, 6 H), 3.31 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 167.0 (s), 163.4 (s), 149.2 (s), 132.2 (d), 129.3 (d), 125.0 (d), 97.4 (t), 76.4 (d), 66.3 (d), 52.2 (q), 51.8 (q), the signal for C_1 is not observed perhaps due to overlap with other absorption in the region of 130 ppm.

(13) (±)-**2**: mp 116–117 °C; IR (KBr) 3400, 1695, 1625, 1585 cm^{-1}; UV (H_2O), 280 nm (ε 12 200); ^1H NMR (9:1 acetone-d_6/CD_3CO_2D, 250 MHz) δ 10.1 (br s), 7.11 (1 H, dd, J = 5.4, 1.2 Hz), 6.37 (1 H, dd, J = 9.7, 5.4 Hz), 6.32 (1 H, dm, J = 9.7 Hz), 5.44 (1 H, d, J = 2.4 Hz), 4.96 (1 H, d, J = 2.4 Hz), 4.74 (2 H, m).

When Is Allylic Resonance Unimportant?

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Electron delocalization (resonance) has important consequences for both the structure and stability of the allyl radical.[1] EPR spectroscopy indicates that the allyl radical possesses C_{2v} symmetry[2] and that the barrier to rotation of one methylene group out of conjugation is greater than 15 kcal/mol.[3] When π-electron correlation is included in the wave function for the radical, ab initio calculations are successful in reproducing both the C_{2v} geometry of, and substantial barrier to, rotation in allyl.[4]

Given these experimental and theoretical indications of the importance of resonance in allyl, we were surprised to discover in our calculations on the lowest π state of the isoelectronic formyloxyl radical that there was little preference for a C_{2v} geometry over one with unequal C–O bond lengths.[5] In this communication we present a simple explanation of the apparently small amount of resonance stabilization in the lowest π state of formyloxyl. This explanation can be used to predict with generality the types of molecules containing three electrons in three p–π orbitals in which allylic resonance will be relatively unimportant.

Formyloxyl differs from allyl in that the two terminal heavy atoms are much more electronegative than the central atom. Consequently, in formyloxyl the nonbonding π MO ($1a_2$), which is confined to these two atoms, is separated from the bonding π MO ($1b_1$) by a smaller energy gap than in allyl. The $1a_2$–$1b_1$ orbital energy difference, calculated with the 3-21G basis set,[6] is 0.052 hartree in formyloxyl, which is less than half of the 0.124 hartree computed with the same basis set for allyl.

Because of the relatively low energy of the $1b_1 \rightarrow 1a_2$ excitation in formyloxyl, the excited $^2B_1$ π configuration, $1b_1 1a_2^2$, in this radical is separated from the lowest π configuration, $1b_1^2 1a_2$ ($^2A_2$), by a relatively small energy gap. These two configurations can be mixed by a b_2 distortion that shortens the bond to one terminal heavy atom and lengthens the bond to the other. The mixing between $^2B_1$ and $^2A_2$ lowers the energy required for this type of distortion in the ground state. The closer in energy that these two configurations are, the greater the effect that their mixing will have on facilitating asymmetric bond length distortion from C_{2v} symmetry.[7] Therefore, the propensity of formyloxyl for undergoing distortion from C_{2v} symmetry may be attributed to the existence of a low-lying $^2B_1$ configuration in this radical.

A decrease in the importance of allylic resonance is also anticipated when the central atom is more electronegative than the heavy atoms at the termini. This expectation is based on the fact that another excited $^2B_1$ configuration, $1b_1^2 2b_1$, differs from the lowest configuration by the excitation $1a_2 \rightarrow 2b_1$. Consequently, a small energy for this excitation will facilitate mixing between these two configurations on a b_2-type distortion. Since $2b_1$ has density on the central atom, where $1a_2$ has a node, the energy difference between these two MO's will be reduced when the central atom is more electronegative than the two terminal heavy atoms.

In order to test the prediction that substitution of the central carbon in allyl by a more electronegative element would also lead to a decrease in the importance of allylic resonance, we have carried out calculations on $O(CH_2)_2^+$, a radical that is isoelectronic with allyl. A previous theoretical study by Radom and co-workers led to the intriguing result that $O(CH_2)_2^+$ prefers a geometry with one methylene group twisted out of conjugation.[8] The apparent preference for this geometry over a planar one, in which the radical might have been stabilized by allylic resonance, was not commented upon.

The optimal C_{2v} structure for $O(CH_2)_2^+$ was found by MC-SCF calculations[9] with the 3-21G basis set. Evaluation of the Hessian matrix at this geometry[10] showed one negative eigenvalue, corresponding to asymmetric stretching of the C–O bonds. Thus, at this level of theory the C_{2v} structure represents the transition state for interconversion of two mirror image structures with unequal bond lengths. Optimization of one of these two structures gave an MC-SCF energy of -115.7370 hartrees, which is lower than that of the optimal C_{2v} structure, although by only 0.4 kcal/mol. The surface for the planar molecule is sufficiently flat that higher quality calculations could find a C_{2v} geometry to be the energy minimum instead of a transition state. Nevertheless, the flatness of the surface indicates that allylic resonance in the planar radical is relatively unimportant.

A geometry with one methylene group twisted out of a conjugation was also optimized, by using an MC-SCF wave function that correlated two of the four electrons that occupy orbitals of a″ (π) symmetry. The resulting structure is similar to those obtained by Radom et al.[8] However, unlike Radom and coworkers, we find this structure to be 1.9 kcal/mol above the energy of the lower of the two planar structures. Higher quality calculations would be necessary in order to predict unequivocally the equilibrium geometry of $O(CH_2)_2^+$, but it appears that methylene group rotation from planarity in this allylic radical costs little, if any, energy. This situation contrasts with that in allyl, where resonance stabilization of the planar radical results in a barrier to methylene group rotation of more than 15 kcal/mol.

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