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THE BASE CATALYZED CONVERSION OF PREPHENATE TO p-HYDROXYPHENYLLACTIC ACID

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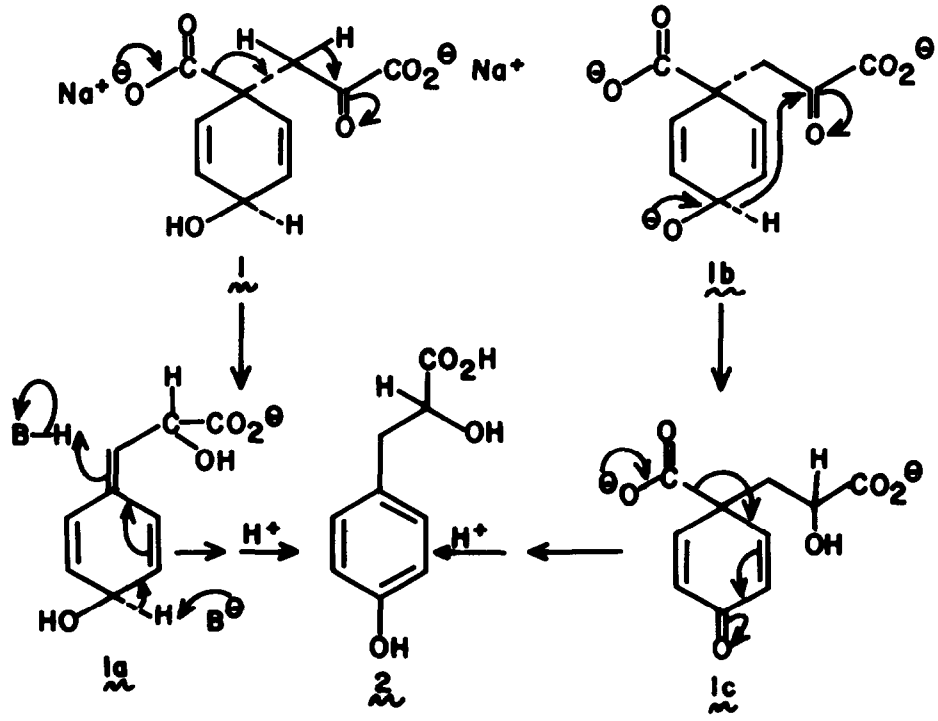
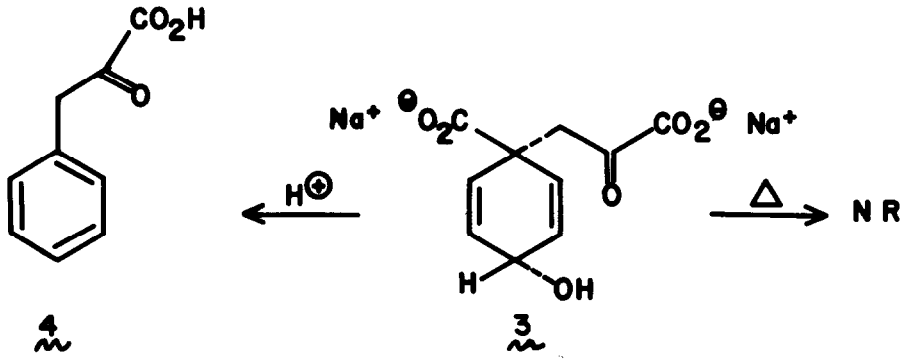
The conversion of the prephenate system (cf disodium salt, 1) to phenylpyruvic acid (4) by acid catalyzed decarboxylation-dehydration is well known.[1] Indeed, the rapidity of this process has thusfar prevented the characterization of the "free" prephenic diacid. Having recently[2] completed the total synthesis of disodium prephenate (1) as well as disodium epi-prephenate (3), we have undertaken to explore the chemistry of these interesting systems. In this connection, we have studied the conversion of 1 to 2 upon heating in alkali followed by acidification. This intriguing reaction was reported by Weiss[3], Gilvarg[4] and Plieninger.[1]

Plieninger[1] advanced two mechanisms to account for this transformation. These are shown below. The conversion, 1 → 1a, involves a 1,2-hydride shift driven by a decarboxylation. A prototropic variant (enolization of the side chain ketone and decarboxylation of the resultant glutaconate system) of this process was formulated by Gilvarg.[4] The pathway 1 → 1b → 1c involves a somewhat unusual[5] 1,6-hydride transfer followed by an easily justified decarboxylation.



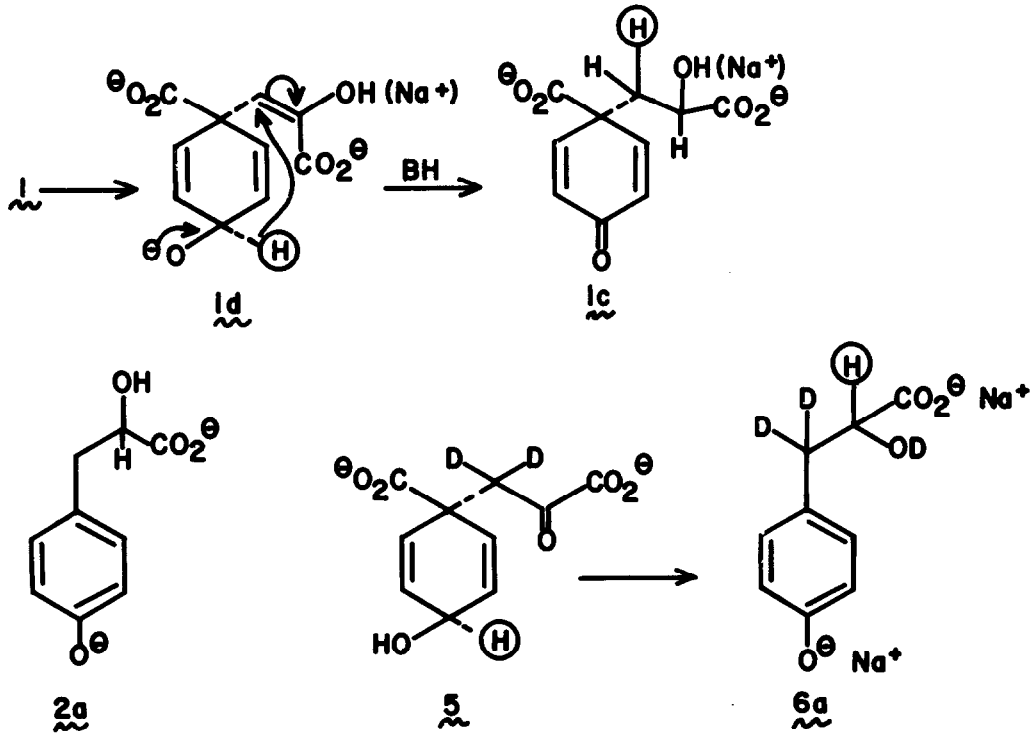
We first verified the reaction on pure synthetic 1 and subsequently worked with barium prephenate obtained from natural sources[6], under conditions similar to those described by Gilvarg, (heating the prephenate in 2N sodium hydroxide, 100°). After heating for 20 minutes followed by acidification, there was obtained a 90-98% yield of virtually homogeneous 2. $\delta((CD_3)_2C=O)$ 2.78 (1H, dd, J_1 = 14Hz, J_2 = 7Hz), 3.04 (1H, dd, J_1 = 14Hz, J_2 = 5Hz), 4.29 (1H, dd, J_1 = 7Hz, J_2 = 5Hz), 6.69 (2H, d, J = 8Hz), 7.04 (2H, d, J = 8 Hz); ppm. Recrystallization ($CHCl_3$-EtOAc) gave pure 2, mp 147.5-149°, lit[7] 143-145°.

Attempts to effect similar reaction of the synthetic epi system, 3 were unsuccessful. Upon acidification, the only product obtained (99%) was phenylpyruvic acid, 4. Of the mechanisms described above, it would appear that the Cannizzaro-like process (1b → 1c) would most readily accommodate the configurational dependence of the transformation.



It should be noted that in addition to the 1,6-hydride mode suggested by Plieninger, a 1,5-hydride shift can be envisioned via 1d. The transformation of 1d → 2 would, in essence, correspond to a Michael addition to an α,β-unsaturated carboxylate. An operational distinction between these pathways could be exploited. Of the mechanisms considered, the 1,6-hydride transfer (1b → 1c) uniquely predicts emergence of the original carbinyl proton as of the carbinyl proton of 2. In all other mechanisms this proton either exchanges with the bulk solvent or is incorporated at the benzylic carbon.

Fortunately, this distinction could be subjected to scrutiny. As we have previously described,[2] 1 is rapidly converted to its dideutero derivative, 5 at room temperature in NaOD-D_2O. However, 2a does not suffer a noticeable (by nmr analysis) exchange of any carbon bound protons after 20 minutes, even at 100°, in 2N NaOD-D_2O. Accordingly, 5 was subjected to the action of 2N NaOD-D_2O as described above. Nmr analysis of the resultant D_2O solution demonstrated the exclusive emergence of p-hydroxyphenyllactate salt of the labelling pattern shown in 6a. $\delta(D_2O)$ 4.14 (1H, s), 6.54 (2H, d, J = 8Hz), 6.98 (2H, d, J = 8Hz); ppm.



Given the failure of 3 to suffer any conversion to 2, the intramolecular nature of the hydride transfer seems securely established. Given the clean conversion of 5 → 6a, the 1,6-hydride transfer mechanism postulated by Plieninger[1] is thus established.

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REFERENCES

1. H. Plieninger, Angew. Chem. Internat. Edn. (Eng), 1, 367 (1962).

2. S. Danishefsky and M. Hirama, J. Amer. Chem. Soc., In Press.

3. Quoted by H. Plieninger as a personal communication from U. Weiss. See: ref. 1, footnote 13.

4. C. Gilvarg in W. D. McElroy and H. B. Glass, "A Symposium on Amino Acid Metabolism", Johns Hopkins Press, Baltimore, Md. pp. 812-814 (1955).

5. V. Prelog and W. Küng, Helv. Chim. Acta , 39, 1394 (1956).

6. Available from the Sigma Chemical Co., St. Louis, Mo.

7. T. Matsuura and H. J. Cahnmann, J. Amer. Chem. Soc., 81, 871 (1959).