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A Reversible Rearrangement of Dendrobinic Acid to a Lactam Derivative

We wish to report an example of a reversible skeletal rearrangement in which a proximity effect has an important role.

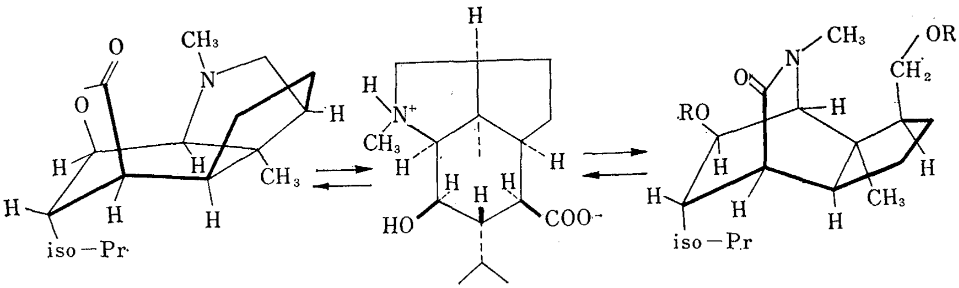
Dendrobinic acid1) (I), m.p. 240~242°, IR (Nujol): 1570 cm^{-1} (COO^-), when warmed with acetic anhydride for 1 hour on a water-bath, changed into a neutral substance in over 70% yield with a small recovery of dendrobine. The homogeneous neutral product, though it failed to crystallize, showed two intense carbonyl absorptions at 1730 and 1664 cm^{-1} in the infrared spectrum in chloroform. Its nuclear magnetic resonance spectrum indicated the presence of $-CH(\underline{CH_3})_2$ (6H, 9.07, d, J=6 c.p.s.), $-\overset{|}{\underset{|}{C}}-\underline{CH_3}$ (3H, 8.72, s), $2 \times COCH_3$ (3H, 7.92, s; 3H, 7.97, s), and $CO-\overset{|}{N}-\underline{CH_3}$ (3H, 7.05, s) with additional signals at 7.38 (1H, t, J=2.3 c.p.s.), 6.58 (1H, d, J=2.5 c.p.s.), 5.87 (2H, d, J=7.5 c.p.s.), and 4.86 τ (1H, t, J=2.5 c.p.s.). Therefore the compound is a diacetate. Mild methanolysis of this diacetate furnished a crystalline diol, m.p. 163~166°, $C_{16}H_{27}O_3N$ (M^+ 281), which showed a single carbonyl absorption at 1660 cm^{-1} in the infrared spectrum ($CHCl_3$) but lacked acetyl signal in the nuclear magnetic resonance spectrum. Reacetylation of the diol with acetic anhydride and pyridine regenerated the diacetate as shown by infrared and thin-layer chromatography comparisons. The N-acetyl structure for the diacetate was thus excluded. The rearranged lactam structures (Ⅲ) for the diacetate, and (Ⅳ) for the diol were concluded by the comparison of the nuclear magnetic resonance spectra of (Ⅲ) and (Ⅳ). The diol exhibited peaks at 9.10, 8.93 (6H, two doublets of J=6 c.p.s., $-CH(\underline{CH_3})_2$), 8.72 (3H, s, $-\overset{|}{\underset{|}{C}}-\underline{CH_3}$), 6.98 (3H, s, $CO-\overset{|}{N}-\underline{CH_3}$), 7.49 (1H, t, J=2 c.p.s.), 6.40 (2H, d, J=8 c.p.s.), 6.60 (1H, d, J=2.5 c.p.s.), and 5.99 τ (1H, t, J=2.5 c.p.s.). The peaks at 6.58 and 7.38 τ in (Ⅲ) must be attributable to $CO-\overset{|}{N}-C\underline{H}\langle$ and $\rangle C\underline{H}-CO-\overset{|}{N}-$ respectively, since they showed little shifts by hydrolysing the acetate into the diol (Ⅳ). While those at 5.87 τ and 4.86 τ in (Ⅲ) shifted considerably to higher field (0.53 and 1.13 p.p.m., respectively) indicating that they are the protons geminal to acetoxyl groups, *i.e.* $\rangle C\underline{H}-OAc$ and $-C\underline{H}_2OAc$, respectively. Coupling patterns of all the protons above indicated are also well explainable by the formulations (Ⅲ) and (Ⅳ) for the diacetate and the diol, respectively.

The extremely facile lactam cleavage and a reverse rearrangement were observed in these compounds. The rearranged lactam (Ⅲ) when heated in 1.5% methanolic hydrochloric acid for 2 hours quantitatively regenerated dendrobinic acid (I) which then slowly cyclized into dendrobine (Ⅱ). More strikingly, the diol (Ⅳ), when stored in a chloroform solution, slowly deposited a crystalline dendrobinic acid hydrochloride, m.p. 160~165° and 239~240° (decomp.), IR (Nujol): 1724 cm^{-1} (COOH). The fact that the first product in the rearrangement is dendrobinic acid but dendrobine may exclude the possibility of acyl migration step in the reverse reaction.

Suitable proximity of both the carboxylate and free electrons on nitrogen seems to be necessary and acetic anhydride is also indispensable as a reagent for the rearranged lactam formation, because mineral acids only cyclized dendrobinic acid (I) into dendrobine (Ⅱ), and the betaine (V),[*1] m.p. 257~258° (decomp.), IR (Nujol): 1573 cm^{-1}

[*1] The betaine was first designated as methyldendrobinium hydroxide (m.p. 251° (decomp.)), by Suzuki, *et al.*1)

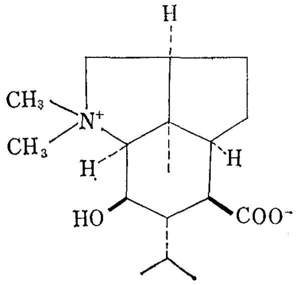
1) H. Suzuki, I. Keimatsu, K. Ito: Yakugaku Zasshi, 54, 801 (1934).



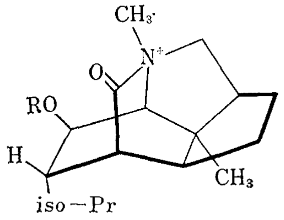
II I

III : R=COCH$_3$

IV : R=H



V



VI

(COO^-), was recovered unchanged on the same treatment with acetic anhydride. A simple acetolysis took place when V was heated with the same reagent under reflux and furnished dendrobine (II). Following mechanism may be suggested; that is, the initially formed anhydride will cyclize into a labile intermediate (VI) which will be also formed from III or IV and cleave into two directions depending upon the condition used.

This reversible rearrangement is essentially analogous to that of solanidane-18-oic acid to 16α-acetoxy-18-oxocevanidane[2] but the more drastic condition (*i.e.* hydrolysis with acetic acid-hydrochloric acid under reflux for 6 days) was used for the reverse rearrangement by the earlier authors.

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[2] J.C. Sheehan, R.L. Young, P.A. Cruickshand : J. Am. Chem. Soc., **82**, 6147 (1960).