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Pyrrolizidine Alkaloids: The Synthesis and Stereochemistry of α- and β-Retusanecic Acids

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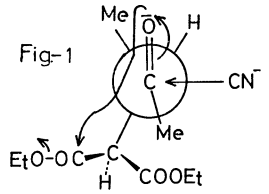
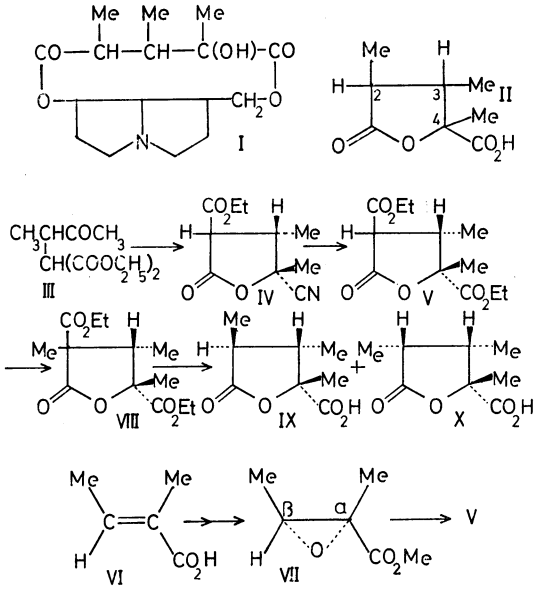
Retusine (I) was isolated from *Crotalaria retusa* L. by Culvenor and Smith,[1] the alkaline hydrolysis of I gave two acids, named α- and β-retusanecic acids. These acids agreed with the epimeric 2,3,4-trimethyl-4-hydroxyglutaric acid 1,4-lactones synthesized by Adams and Hauseman.[2] They have shown that the isomeric acids differ in the configuration of the carbon (C_2) alpha to the lactone and that the interconversion between α- and β-acids caused by refluxing with concentrated hydrochloric acid proceeds to an equilibrium wherein the β-acid predominates. Since the β-acid is thermodynamically more stable than the α-acid, the *trans*-cofiguration of the C_2–CH_3 group relative to the C_3–CH_3 group in the β-acid can be presumed. However, they have not referred to the relation between two methyl groups at C_3 and C_4. This note will discuss the new synthesis of α- and β-retusanecic acids and their stereochemistry. III was chosen as the starting material because an active hydrogen of the malonyl group would be available for alkylation after a ring-closure reaction. Cyano-lactone (IV) was obtained as the only product by the addition of HCN to the keto-ester (III). Moreover, IV was converted to the ester-lactone (V) by the usual method. In order to confirm the configuration of the two methyl groups at C_3 and C_4 in V, another synthesis of V was carried out. It is known that epoxide ring opening[3] by nucleophilic attack proceeds in a *trans* manner. Epoxide (VII) obtained from tiglic acid (VI) was reacted with sodium diethyl malonate to give a lactone compound. Moreover, it was identical with V (bp, IR, NMR). Therefore, the two methyl groups at C_3 and C_4 in V must be in *trans*-configuration. It was assumed that the formation of IV from III was begun by the attack of cyanide on the less hindered side, followed by ring closure, as if shown in Fig. 1. VIII

Fig-1



was obtained by the methylation of V. After acid hydrolysis and decarboxylation, two isomeric acids were given in a 17: 1 ratio by fractional crystallization. The IR spectrum ($CHCl_3$) of the (±)major product of IX was superimposable with that of β-retusanecic acid. Also, the IR spectrum ($CHCl_3$) of the (±)minor product of X was superimposable with that of α-retusanecic acid. Consequently, it is confirmed that the configuration of the two methyl groups at C_3 and C_4 in α- and β-retusanecic acids is *trans*.



Experimental

Diethyl 1-Methyl-2-oxo-propylmalonate (III). Twelve grams of sodium were added to a solution of 85 g of diethyl malonate in 450 ml of dry ether. The solution was then refluxed for 8 hr until the sodium had completely dissolved, and then it was cooled. To the cooled solution, 75 g of methyl α-bromoethyl ketone were added all at once. The mixture was then refluxed for 2 hr. The ether solution was washed with ice cold water, and then dried with calcium chloride. After the solvent had been distilled, the residue was distilled at 144—149 °C (18 mmHg) to give 64 g of III (52% yield). IR (neat): 1760—1740 cm^{-1} (broad); NMR ($CDCl_3$) (δ): 2.30 ($-COCH_3$). Found: C, 57.37; H, 7.93%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

β-Methyl-α-ethoxycarbonyl-γ-cyano-γ-valerolactone (IV). Twenty grams of III, 2.5 g of powdered CaO, and 8.6 g of HCN were placed in a flask in an ice bath. The flask was sealed and warmed at 50 °C for 3 hr. The excess HCN was then evaporated *in vacuo*. To the residue, 20 ml of chloroform were added. The chloroform solution was separated from an inorganic substance. After the solvent had been removed, 17 g of a dark-colored oil was obtained and chromatographed over a silica-gel column. Elution with chloroform gave a

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1) C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, **10**, 464 (1957).

2) R. Adams and F. B. Hauserman, *J. Amer. Chem. Soc.*, **74**, 694 (1952).

3) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons Inc, New York (1956), p. 106.

colorless oil. The oil was distilled at 120—122 °C (3 mmHg) to give 7 g of IV (50% yield). IR (neat): 1815, 1750 cm^{-1}; Found: C, 56.88; H, 6.05; N, 6.25%. Calcd for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63%.

β-Methyl-α,γ-diethoxycarbonyl-γ-valerolactone (V). A cold solution (0 °C) of 2 g of IV, 1 ml of absolute ethanol, and 1 ml of dry ether were saturated with dry hydrogen chloride, allowed to stand at 0 °C overnight, and then neutralized with a saturated solution of potassium carbonate. After extraction with ether, the ether solution was dried with anhydrous sodium sulfate. After the ether had been removed, the residue was distilled at 150—153 °C (4 mmHg) to give 1.2 g of V (50% yield). IR (neat): 1800, 1745 cm^{-1}; NMR ($CDCl_3$) (δ): 1.60 (-C(COOC$_2$H$_5$)-CH$_3$). Found: C, 55.57; H, 7.10%. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03%.

V from Methyl α-Methyl-α,β-epoxy-butyrate (VII). To solution of 0.288 g of sodium in 30 ml of absolute ethanol, 1.98 g of diethyl malonate were added. After 1 hr, 1.6 g of VII were added to the solution. The mixture was then refluxed for 35 hr, and the ethanol was evaporated *in vacuo*. After the residue had been extracted with ether, the solution was dried with anhydrous sodium sulfate. After the distillation of the solvent, 1.3 g of a colorless oil was given. The oil was chromatographed over a silica-gel column and eluted with chloroform. The first fraction (1200 ml) was concentrated to give 0.7 g of an oily product which was identical with V (bp, IR, NMR).

α,β-Dimethyl-α,γ-diethoxycarbonyl-γ-valerolactone (VIII). One gram of V was added to a solution of 0.1 g of sodium in 25 ml of absolute ethanol. After 1 hr, 0.63 g of methyl iodide in 2 ml of absolute ethanol was added to the solution. The mixture was then refluxed for 25 hr, and the ethanol was evaporated *in vacuo*. After the residue had been extracted with ether, the ether solution was dried with anhydrous sodium sulfate. After the evaporation of the solvent, the residual oil was distilled at 133 °C (2 mmHg) to give 0.93 g of VIII (88% yield). IR (neat): 1795, 1750 cm^{-1}. Found: C, 57.56; H, 7.57%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

2,3,4-Trimethyl-4-hydroxy-glutaric Acid-1,4-lactone, IX and X. A solution of 2.565 g of VIII in 25 ml of conc. hydrochloric acid was refluxed for 15 hr. After the evaporation of the solvent, the residue was heated on an oil bath at 170—190 °C to give 1.385 g of a solid. Fractional crystallization with benzene gave 0.85 g of plate crystals (mp 117—118 °C) of IX and 0.05 g of needle crystals (mp 129—130 °C) of X. IX: IR ($CHCl_3$): 1790, 1738 cm^{-1}; NMR (pyridine-d_5) (δ): 1.75 (-C(COOH)-CH$_3$). Found: C, 55.93; H, 7.10%. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03%. *δ*: IR ($CHCl_3$): 1790, 1742 cm^{-1}; NMR (pyridine-d_5) (δ): 1.70 (-C(COOH)-CH$_3$). Found: C, 55.87; H, 6.97%. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03%.