Synthesis of Aleprestic Acid.

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Chain extension of *cyclo*pent-2-enylacetic acid by electrolysis with methyl hydrogen glutarate gives (±)-aleprestic acid. Evidence is presented for the position of the double bond in *cyclo*pent-2-enylacetic and aleprestic acid.

THE synthesis of saturated and unsaturated fatty acids by anodic cross-coupling of monocarboxylic acids with half esters of dicarboxylic acids (Linstead, Weedon, and Wladislaw, *J.*, 1955, 1097) led us to apply a similar procedure to the synthesis of some acids of chaulmoogra oil, containing the *cyclo*pent-2-enyl group. Interest in these compounds has grown recently, especially concerning the preparation of lower homologues not available from natural sources.

Aleprestic acid (δ-*cyclo*pent-2-enylvaleric acid), which occurs only in a very small amount (<0·5%) in *Hydnocarpus wightiana* oil, was first chosen because of its structural relation to thioctic acid.* It has been obtained by Cole and Cardoso (*J. Amer. Chem. Soc.*, 1939, **61**, 2349) by repeated fractional distillation of the ethyl esters. Comparison of its measured specific rotation with the estimated value seems to indicate that it was only about 70·5% pure; its synthesis, however, has not yet been reported.

Electrolysis in methanol of (±)-*cyclo*pent-2-enylacetic acid in the presence of an excess of methyl hydrogen glutarate, followed by alkaline hydrolysis of the ester formed, gave (±)-aleprestic acid in 27·5% yield. Of the two expected products of symmetrical coupling, suberic acid, but not 1 : 2-di*cyclo*pentenylethane, was identified.

Electrolysis of *cyclo*pent-2-enylacetic acid alone in methanol could not be performed owing to coating of the anode with insoluble polymers and consequent fall in the current. The same occurred when in place of the methyl half ester the benzyl half ester was employed.

Weedon (*Quart. Rev.*, 1952, **6**, 387) mentioned difficulties in the electrolysis of ethylenic acids due to coating of the anode with insoluble polymers, but to our knowledge complete inhibition has not been reported before. On the other hand, there are no references to the use of benzyl half esters in cross-coupling reactions with unsaturated acids. The complete inhibition observed cannot be explained at present.

No direct proof has yet been given that the double bond in the *cyclo*pentenylacetic acid is in the 2-position. Noller and Adams (*J. Amer. Chem. Soc.*, 1926, **48**, 2444), who described the preparation of *cyclo*pentenyl chloride and *cyclo*pentenylacetic acid, assumed the 2-position of the double bond on the basis of the chemical reactivities. We now provide a more rigorous proof. Of the three possible isomers only that with the double bond in the 2-position can exist in optically active forms. By treatment of our (±)-*cyclo*pentenylacetic acid with quinine we obtained the (+)-acid.

Although the anodic chain-extension method was shown in the erucic–brassidic series to give products without migration of the double bond (Bounds, Linstead, and Weedon, *J.*, 1953, 2393), it was necessary to prove that also for the *cyclo*pentenyl series. Use of (+)-*cyclo*pent-2-enylacetic acid in the anodic synthesis furnished (+)-aleprestic acid in 28% yield, proving that the 2-position of the double bond is maintained through the three-carbon homologation of its side chain. It confirms also the observation (Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95; Linstead, Lunt, and Weedon, *J.*, 1950, 3333; 1951, 1130) that optical activity involving an asymmetric carbon atom which is not directly attached to the carboxylic group eliminated in the reaction is preserved during the electrolysis.

The specific optical rotation of our aleprestic acid was $[\alpha]_D^{20}$ +74°, which is higher than that (+60·9°) of the aleprestic acid isolated from the *H. wightiana* oil (*loc. cit.*), but lower than that estimated (+100·5°) from the curve for the other homologues of this series. Our (+)-*cyclo*pent-2-enylacetic acid, with $[\alpha]_D^{20}$ +57°, may have been only partially resolved but we have no method of checking this. The anodic synthesis of the homologues of aleprestic acid and thioctic acid are being studied.

* The biological aspect of this relation is being studied.

Experimental

(±)-cyclo*Pentenylacetic Acid* (cf. Noller and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2444).—Freshly distilled *cyclo*pentadiene was converted into *cyclo*pent-2-enyl chloride by reaction with dry hydrogen chloride with cooling by solid carbon dioxide. The chloride, immediately after distillation (b. p. 27—29°/20 mm.) (yield 84·5%), was condensed with ethyl sodiomalonate with ice-cooling. The product, worked up in the usual way, gave diethyl *cyclo*pent-2-enylmalonate (84%), b. p. 120°/5 mm., n_D^{21} 1·4535. Hydrolysis by 20 hours' boiling with aqueous sodium hydroxide (15%) gave *cyclo*pent-2-enylmalonic acid (96·5%), m. p. 149—150° (from benzene). This acid at 190° gave *cyclo*pent-2-enylacetic acid (97%), b. p. 94·5°/3 mm., n_D^{20} 1·4684 (Found: C, 66·6; H, 7·9. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 7·9%).

(+)-cyclo*Pent-2-enylacetic Acid.*—The (±)-acid (20 g., 0·16 mole) was dissolved in a solution of sodium hydroxide (6·3 g., 0·16 mole) in water (250 c.c.) and added gradually to a warm solution of quinine hydrochloride (31 g., 0·08 mole) in water (2·5 l.). The solution was boiled for 5 min., then cooled. The quinine salt of the (+)-acid separated and after recrystallization once from water (*ca.* 3·5 l.) was obtained as colourless crystals (14·4 g.), m. p. 113—115°, $[\alpha]_D^{18}$ −114·6° (*l*, 1; *c*, 2 in EtOH). The rotation remained constant on further recrystallization.

The quinine salt (14·4 g.) was dissolved in warm water (*ca.* 1·6 l.) and, after the solution had been cooled rapidly, the equivalent amount of 2N-hydrochloric acid was added. The regenerated acid was extracted with ether, and the ethereal solution was washed with a small volume of water, dried, and evaporated. Distillation of the residue gave (+)-*cyclo*pent-2-enylacetic acid (3·4 g., 34%), b. p. 110°/6 mm., $n_D^{19·5}$ 1·4684 (Found: C, 66·5; H, 7·7%), $[\alpha]_D^{20}$ +57° (*l*, 1; *c*, 2 in $CHCl_3$).

The mother-liquors were evaporated in a vacuum to 1 l. and more quinine salt was separated; this had m. p. 107—112°, which was not improved by further crystallizations. Further concentration gave no more quinine salt.

(−)-cyclo*Pentenylacetic Acid.*—After separation of the quinine salt, a small portion of the mother-liquor was added to a warm solution of quinidine sulphate, but only an oil separated. Then the whole of the mother-liquor was treated with hydrochloric acid and the crude (−)-*cyclo*pent-2-enylacetic acid extracted with ether. The ethereal solution was washed with a small volume of water, dried, and evaporated. Distillation of the residue gave (−)-*cyclo*pent-2-enylacetic acid (6·4 g., 64%), b. p. 90·5°/2·5 mm., n_D^{23} 1·4675, $[\alpha]_D^{20}$ −33·1° (*l*, 1; *c*, 2·4 in $CHCl_3$).

(±)-*Aleprestic Acid.*—A mixture of (±)-*cyclo*pent-2-enylacetic acid (6 g., 0·047 mole) and methyl hydrogen glutarate (b. p. 124°/4 mm., $n_D^{23·5}$ 1·4372; prepared from the anhydride and methanol in 98% yield) (21·1 g., 0·144 mole) in methanol (80 c.c.) was electrolysed (current 0·6 amp.; cf. Linstead, Weedon, and Wladislaw, *loc. cit.*). The cell contents were filtered from a colourless polymer, acidified with glacial acetic acid, and evaporated. The residue was extracted with ether (500 c.c.), and the solution was washed with 2N-sodium hydroxide, then dried (Na_2SO_4) and evaporated. By the distillation of the residue, 0·5 g. of a fraction, b. p. 47—48°/15 mm., was removed. The remaining liquid (12 g.) was hydrolysed by stirring it under reflux for 4 hr. with a 2N-solution of sodium hydroxide in methanol–water (4 : 1) under nitrogen. After addition of water, the methanol was distilled off in nitrogen and the aqueous solution was extracted with ether and then with benzene. Evaporation of both extracts gave no residue. The ether- and benzene-insoluble material was treated with excess of 30% hydrochloric acid and the resulting acids were extracted with ether. The residue left on evaporation of ether was extracted with chloroform. Separation of the insoluble material gave suberic acid (5 g., 39·6%), m. p. 139—140°. The chloroform solution was evaporated and the distillation of the residue gave (±)-aleprestic acid (2·2 g., 27·5%), b. p. 126—127°/3 mm., n_D^{22} 1·4711 (Found: C, 71·3; H, 9·5. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·6%).

(+)-*Aleprestic Acid.*—(+)-*cyclo*Pent-2-enylacetic acid (2·55 g., 0·020 mole) and methyl hydrogen glutarate (11 g., 0·075 mole) in methanol (40 c.c.) were electrolysed (current 0·6 amp.) as in the preceding experiment. (+)-Aleprestic acid (0·95 g., 28%), b. p. 139—140°/5 mm., $n_D^{20·5}$ 1·4690, $[\alpha]_D^{20}$ +74° (*l*, 1; *c*, 1·3 in $CHCl_3$) (Found: C, 71·65; H, 9·6%), and suberic acid (2·4 g., 36·9%), m. p. 139—140°, were obtained.

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