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SYNTHESES OF CADINANES (1). A STEREOSPECIFIC TOTAL SYNTHESIS OF CADINENE DIHYDROCHLORIDE

Milton D. Soffer and Güniz E. Günay
Department of Chemistry, Smith College, Northampton, Mass.

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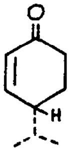
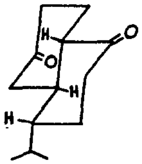
The cadinanes probably constitute the most widespread group of sesquiterpenoids found in nature, and their common crystalline derivative, cadinene dihydrochloride, occupies a central position in their structural investigation. We have reported previously convenient syntheses (2) of the monoterpenoid (±)-cryptone, and the stereospecific conversion (3) of (-)-cryptone (I) into the (+)-dicyclic diketone (II). We wish to report now the closing of the links in the total synthesis of (+)-cadinene dihydrochloride (III) by the resolution of (±)-cryptone and the conversion of the diketone into the dihydrochloride (4).

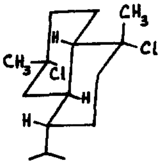
(±)-Cryptone in the form of its *p*-carboxyphenylhydrazone, m.p. 221-223° (dec.), ν_{max}(KBr) 1673, 1607, 1260 cm^{-1}, λ_{max} (95% EtOH) 340 mμ (ε 41,009), 231 mμ (ε 13,809), anal. C 70.18, H 7.48, N 10.36, gave readily with quinine one easily isolated salt, m.p. 189-191° (dec.), $[\alpha]_D^{21}$ -89°, anal. C 72.33, H 7.51, N 9.07, from which the free hydrazone was regenerated in the usual way, m.p. 217-218° (dec.), $[\alpha]_D^{24}$ +95.7°, with absorption spectra identical with those of the racemic form, anal. C 70.62,



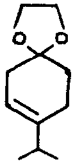
I



II



III



IV

H 7.50, N 10.18, and this could be reconverted into (-)-cryptone, $[\alpha]_D^{20}$ -72° (5), $\nu_{max}(CCl_4)$ 1683 cm^{-1}, λ_{max}(95% EtOH) 227 mμ (ε 12,600), by conditions of acid hydrolysis used previously on the (±)-semicarbazone (6).

The (+)-diketone (II), with methyllithium and direct treatment with hydrogen chloride, readily gave (+)-cadinene dihydrochloride, m.p. 116-117°. The product was identical with an authentic sample prepared from (-)-γ_2-cadinene (7) according to its optical rotation, infrared absorption spectrum, melting point and mixed melting point. Similarly the enantiomeric (-)-diketone obtained by degradation of (+)-ε-muurolene (8,9), gave (-)-cadinene dihydrochloride with the same infrared spectrum and melting point, and the same mixed melting point with an authentic sample (10). These conversions provide a synthetic path to "β-cadinene" (10,11,12) and to ε-cadinene (8,9), both of which are now available by different methods from cadinene dihydrochloride (9,10,11), and they also make accessible the synthetic cadinanes of both enantiomeric series, since both enantiomers of cryptone are available from different botanical sources (13).

The method of resolution through the p-carboxyphenylhydrazone, using readily available reagents and mild conditions, may have general application, especially for α,β-unsaturated ketones and in cases where the formation of the enolate must be avoided for retention of asymmetry (6). In the present case, the dioxolane method of Casanova and Corey (14) appeared to be inapplicable since in the formation of the simple ethylene ketal the double bond was found to migrate to the β,γ-position with complete destruction of asymmetry. In fact, in the present work the racemic cryptone required was obtained from its abundant (-)-isomer (5) via the Δ^3-dioxolane (IV), b.p. 80-82° at 2.5 mm., NMR, one vinyl proton centered at τ 4.78 and five allylic protons centered at τ 7.90, anal. C 72.79, H 10.18, which on hydrolysis followed by gas chromatography (carbowax 20 M) gave, in a ratio of 3:1, the (±)-cryptone, identical with the natural ketone in its IR and UV absorption, and the β,γ-unsaturated isomer (6), $\nu_{max}(CCl_4)$ 1718 cm^{-1}, no UV max.

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