The Total Synthesis of (±)-Carabrone

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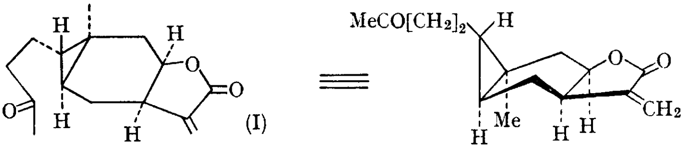
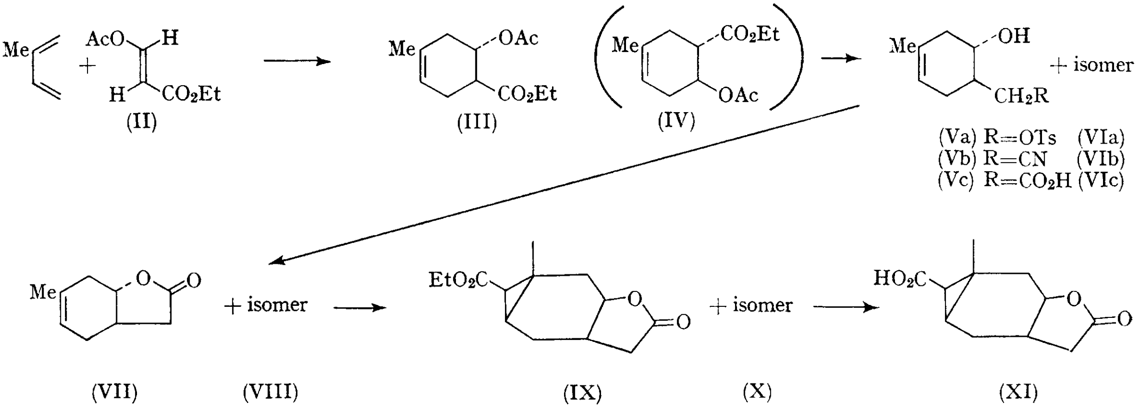
THE structure[1] and stereochemistry[2] of carabrone have been established as (I). It is an interesting cyclopropanoid lactone which could arise from fission of the five-membered ring of a normal guaianolide, and the purpose of this Communication is to describe a total synthesis of (±)-carabrone. Diels–Alder reaction of isoprene and ethyl β-acetoxyacrylate[3] (II) yielded a mixture[*] of (III) and (IV) (about 3 : 1) in 48% yield, which gave an acid mixture (Vc and VIc) on lithium aluminium hydride reduction followed by treatment of the monotosylate (Va and VIa) with sodium cyanide and hydrolysis with 10% sodium hydroxide in ethanol, in 45% overall yield. The acid mixture was heated at 195—200° for 1·5 hr. to give an oily lactone mixture[†] (VII and VIII) in 71% yield.

Treatment of the lactone mixture with ethyl diazoacetate and copper powder in Diglyme at 170° furnished a mixture[‡] of cyclopropane derivatives [(IX) : (X) = 87 : 13] b.p. 140—143°/0·2 mm., ν_{max} 1785 and 1727 cm.$^{-1}$, in 53% yield, from which an acid-lactone (XI), m.p. 219—220°, ν_{max} 1790 and 1705 cm.$^{-1}$, was obtained by hydrolysis with 10% sodium hydroxide–ethanol followed by lactonisation, in 41% yield. As the acid lactone was obtained from the lactone mixture (IX : X = 87 : 13) in the above-mentioned yield, its structure should be represented by formula (XI).

Although the acid-lactone (XI) is an *exo*-derivative (a), either (XII) or (XIII) is expected for this lactone, owing to the direction of attack of ethyl diazoacetate on the double bond. A suspension of the sodium salt of (XI) in benzene and pyridine was treated with oxalyl chloride to give the corresponding acid chloride (XIVa), which was immediately converted into a thiolester (XIVb), m.p. 134—135°, ν_{max} 1776 and 1679 cm.$^{-1}$, by treatment with ethanethiol in benzene, in 55% overall yield. Its n.m.r. spectrum shows



(I)



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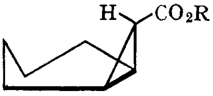
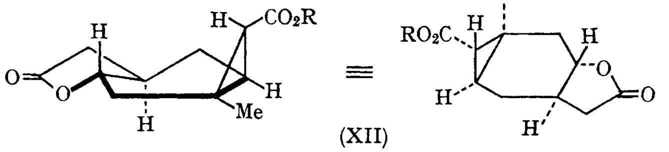
[*] Dehydrogenation of this mixture with 10% palladised charcoal at 320—325° gave an oily product, which showed two peaks at retention times of 23·0 and 20·7 min. in 74 and 26% yield in the gas chromatogram. Since the former showed a band (ref. 6) at 758·5 and the latter at 749 cm.$^{-1}$, these compounds were considered to be ethyl *p*-toluate and ethyl *m*-toluate, respectively.

[†] Although this lactone shows only one peak in the gas chromatogram, it is a mixture of (VII) and (VIII) since the starting material is a mixture of (III) and (IV) at *ca.* 3 : 1.

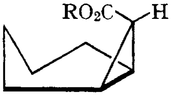
[‡] This product showed two main peaks at retention times of 11·6 and 7·7 min. in 87 and 13% yield in the gas chromatogram. As the reaction of cyclohexene derivatives with ethyl diazoacetate and copper powder give a mixture of the *exo*- (a) and the *endo*-derivative (b) at the ratio of 16 : 1 (ref. 7) or 85 : 1·5 (ref. 8), this lactone mixture is not a mixture of stereoisomers and peaks at retention times of 11·6 and 7·7 min. are assigned to (IX) and (X), respectively.



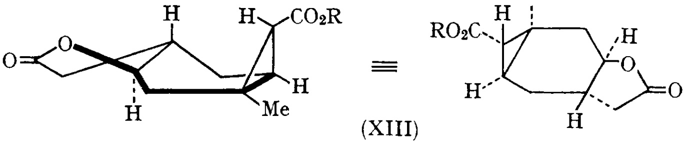
(a)



(XII)



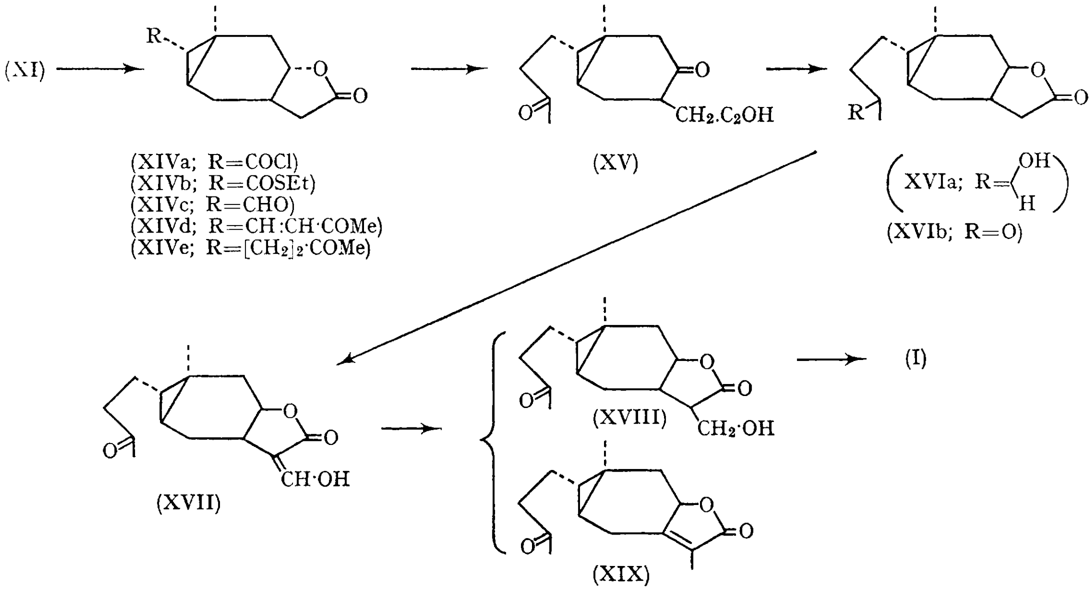
(b)



(XIII)

a signal at τ 6·20 (multiplet) due to a proton attached to the carbon atom carrying the lactonic oxygen, whereas that proton in carabrone (I) appears at τ 5·22. This leads to the conclusion that the proton in (XIVb) appears at such a high field since it has axial-like conformation and is shielded by the cyclopropane ring. Therefore compound (XIVb) is not represented by formula (XIII) but by (XII).

Treatment of (XIVb) with deactivated Raney nickel in acetone furnished an aldehyde derivative (XIVc), m.p. 94—96°, ν_{max} 2746, 1782, and 1702 cm.$^{-1}$, in 70% yield. On Witting reaction with acetylmethylenetriphenylphosphorane[4] this gave an oily product (XIVd), ν_{max} 1779, 1667, and 1607 cm.$^{-1}$, λ_{max} 256 mμ (ϵ 20,200), in 75% yield, which was hydrogenated with 10% palladised charcoal in ethanol to give (XIVe), ν_{max} 1774 and 1713 cm.$^{-1}$. The *trans*-lactone thus obtained (XIVe) must be converted into the *cis*-lactone (XVIb). Hydrolysis of (XIVe) followed by chromium trioxide oxidation afforded a keto-acid (XV), which was reduced with sodium borohydride to give a mixture of *trans*- and *cis*-hydroxy-acids. One of these was easily lactonised to give a *cis*-lactone (XVIa) in 27% overall yield, which was oxidised with chromium trioxide yielding the *cis*-keto-lactone (XVIb), m.p. 74—75°, ν_{max} 1766 and 1714 cm.$^{-1}$. The ketalisation product of (XVIb) was converted into (±)-carabrone (I) by our method,[5] that is, it was treated with ethyl formate and sodium hydride in dry ether to give the sodium salt of the α-formyl-lactone, which was acidified with hydrochloric acid in ether



affording (XVII), ν_{max} 1714 and 1682 cm.$^{-1}$, in 90% yield. Hydrogenation of (XVII) with 10% palladised charcoal in ethyl acetate gave the desired hydroxy-lactone (XVIII) and an $\alpha\beta$-unsaturated lactone[1]§ (XIX). The former was treated with tosyl chloride in pyridine to give an exocyclic-methylene $\alpha\beta$-unsaturated lactone (I), m.p. 89—91°, which was shown to be identical with carabrone by comparison of the infrared spectra and gas-chromatographic retention times.

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§ This compound was shown to be identical with the natural product obtained from carabrone (I) by comparison of the i.r. spectra and gas-chromatographic retention times.

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