Synthesis of 3-n-Butyltetrahydrophthalides

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CNIDILIDE, neocnidilide, and isocnidilide, which occur in the roots of *Cnidium officinale*[1] are 3-n-butyltetrahydrophthalides with the configurations shown[1,2] in (I; R = β-H), (II; R = α-H) and (II; R = β-H) respectively.

We now describe a synthesis of lactones having the gross structure of (I) and (II).

Reaction of ethyl pentadienoate (III)[3] with acraldehyde at 90° for 9 hr. gave a 40% yield of ethyl 2-formylcyclohex-5-enoate (IV), b.p. 83°/0·3

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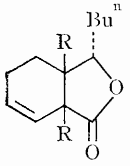
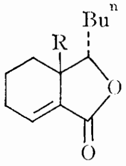
[1] H. Mitsuhashi and T. Muramatsu, *Tetrahedron*, 1964, **20**, 1971, where earlier references are given.
[2] U. Nagai and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1433.
[3] R. G. Glushkov and O. Yu. Magidson, *Med. Prom. S.S.S.R.*, 1962, **16**(3), 27; *Chem. Abs.*, 1963, **58**, 442b.

mm., ν_{max} (1) 1725 cm.$^{-1}$ (C=O) and 1650 cm.$^{-1}$ (weak; C=C), τ 4·2 (2 olefinic protons) and 0·4 (aldehyde proton). Gas–liquid chromatography (g.l.c.), of what must initially have been a *cis*-ester, showed that it consisted of a mixture of *cis*- and *trans*-forms. Attempts to separate the isomers by preparative g.l.c. led to further isomerisation on the column. Equilibration (95% *trans*-) was effected by treatment in benzene with alumina.

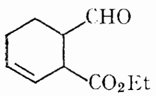


(I)

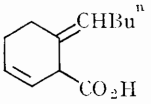


(II)

$CH_2=CH-CH=CHCO_2Et$ (III)



(IV)



(V)

The identity of the *trans*-formyl ester was established (*a*) by oxidation with chromic acid followed by alkaline hydrolysis, with concomitant double bond migration, to Δ^2-tetrahydrophthalic acid, (*b*) by hydrogenation over palladised charcoal followed by oxidation and then hydrolysis to *trans*-hexahydrophthalic acid.

Reaction of the Diels–Alder product with n-butylmagnesium bromide gave a mixture of lactone and unchanged ester which when chromatographed on silica gel gave the lactone (I; R = H), b.p. 109°/0·4 mm., n_D^{20} 1·4815, no max. in the ultraviolet range but log ϵ = 2·627 at 2200 Å, ν_{max} (1) 1760 (lactone) and 1650 cm.$^{-1}$ (weak; C=C), τ 4·2 (2 olefinic protons). The infrared spectrum was identical with the published[1] spectrum of cnidilide (I; R = H).

When the product of the Grignard reaction was chromatographed first on alumina and then on silica gel the lactonic product (II), which had a strong celery smell,[4] had b.p. 112°/0·4 mm., n_D^{21} 1·4953, λ_{max} (EtOH) 2200Å (log ϵ 4·01), ν_{max} (1) 1755 (lactone) and 1680 cm.$^{-1}$ (conj. C=C), τ 3·35 (1 olefinic proton). The infrared spectrum was identical with that of neocnidilide (II; R = H) already published;[1] the physical constants agreed closely with those given[4] for sedanolide. When our lactone (I) was treated, in ether, with alumina it afforded its double-bond isomer (II). Both products were chromatographically pure (g.l.c.) and their n.m.r. spectra supported this.

All compounds gave satisfactory analyses.

The stereochemistry of the synthetic lactones remains to be investigated.

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[4] D. H. R. Barton and J. X. de Vries, *J. Chem. Soc.*, 1963, 1916.