A Synthesis of Nezukone

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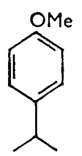
The action of silver salts, preferably the fluoroborate, on the adduct (3) of dichlorocarbene with 1-isopropyl-4-methoxycyclohexa-1,4-diene (2) results in the natural tropone nezukone (4).

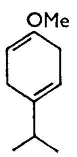
THE isolation of nezukone formulated as (4) was recently reported.[1] The structure seems well established on the basis of spectra and chemistry, but since it is the first terpenoid tropone (as distinct from tropolone) found in Nature, it has been synthesised. A simple synthesis of tropones consists [2] of addition of dihalogenocarbene to an enol ether resulting from metal–ammonia reduction of an anisole, and removal of halide anions by a silver salt [(1) ⟶ (2) ⟶ (3) ⟶ (4)].

Addition of dichlorocarbene (1·2 mol.) to (2) gave a mixed product containing about 80% of (3) and 20% of the bis-adduct, the former being separable by chromatography. Its structure was supported by spectra. Refluxing of (3) with silver nitrate in aqueous methanol gave the expected tropone (4) in poor yield, apparently because of secondary reactions due to the nitric acid produced. Reaction with silver fluoroborate gave the tropone (68% after redistillation). The mass spectrum, parent peak m/e 148, showed peaks at $M - 43$ (loss of $CHMe_2$) and $M - 28$ (loss of CO), in agreement with (4). The properties of the natural and synthetic compound are as follows: natural, b. p. 127—128°/5 mm., $\lambda_{max.}$ 230, 310—315 mμ (log ε 4·47, 4·17), τ (J in c./sec.) 8·79d (6H) (7), 7·3m (H) (7), 3·5—2·8m (5H), $\nu_{max.}$ 3520, 1635, 1580, 1457, 1237, 864 cm.$^{-1}$, n_D^{25} 1·5691; synthetic, b. p. 98—100°/0·5 mm., $\lambda_{max.}$ 232, 310—315 mμ (log ε 4·32, 3·90), τ (J in c./sec.) 8·78d (6H) (7), 7·3m (H) (7), 3·3—2·7m (5H), $\nu_{max.}$ 3500, 1640, 1582, 1455, 1232, 864 cm.$^{-1}$, n_D^{22} 1·5695.

The original workers [1] reported the preparation of a red semicarbazone, m. p. 174—176°, in the initial isolation but gave no experimental details; we could obtain only a red-brown gum.



(1)



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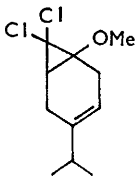

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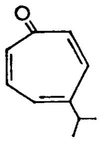
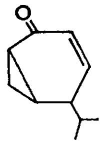


(4)



(5)

The occurrence of this tropone in association with related tropolones in a *Thuja* species known to produce bicyclic monoterpenes of the pinene and thujane type, reinforces the suggestion [3] that such terpenes lead to tropones by ring-expansion, possibly by cleavage of a double bond to a keto-aldehyde and recyclisation. An intermediate of type (5) would, after cyclopropane ring-cleavage, be a dihydronezukone.

EXPERIMENTAL

Reaction of 1-*Isopropyl*-4-*methoxycyclohexa*-1,4-*diene with Dichlorocarbene*.—Sodium (19 g.) was added to 4-isopropylanisole (20 g.) in liquid ammonia (300 ml.) and ethanol (110 ml.), to give the product (18 g.). The absence of aromatic material was shown by its transparence in the region $\lambda_{max.}$ 220—300 mμ, and other spectra were as expected: $\nu_{max.}$ 1698, 1667 cm.$^{-1}$, τ 4·70s (H), 5·45s (H), 6·55 (3H), 7·35 (4H), 7·9m (H) ($J = 6$ c./sec.), 9·05d (6H) ($J = 6$ c./sec.).

The diene (10 g.) in pentane was added to a stirred suspension of potassium t-butoxide (8·0 g.) in dry pentane (200 ml.) at −20° under nitrogen. Chloroform (8 g.) in pentane (20 ml.) was added dropwise during 45 min. After 12 hr. at room temperature the product was worked up, and chromatographed on alumina (Spence ' O '), the mono-adduct being eluted with 1 : 4 (v/v) benzene–ethyl acetate. It was distilled to give the adduct (10·3 g.), b. p. 100—105°/1·5 mm. as an unstable oil, τ 4·70s (H), 6·52s (3H), 7·2—8·25m (6H), 9·05d (6H).

Production of Nezukone.—Silver oxide (1·0 g.) was dissolved in fluoroboric acid (45%) (7·2 g.). To this solution was added the above adduct (1·0 g.) in ethanol (25 ml.), and the mixture refluxed for 5 hr. The precipitated silver chloride was equivalent to about 1·5 equiv. of chlorine. Saturated aqueous sodium chloride was added to precipitate the remaining silver ion, the solution neutralised with solid sodium hydrogen carbonate, and extracted with ethyl acetate (3 × 30 ml.). Removal of the solvent and extraction with pentane gave a soluble portion (0·74 g.) as a yellow liquid which was distilled, to give nezukone (0·5 g.), b. p. 98—100°/0·5 mm. (Found: C, 81·1; H, 8·4. Calc. for $C_{10}H_{12}O$: C, 81·1; H, 8·1%). Using silver nitrate instead of silver fluoroborate in a similar procedure gave the same product but it required initial chromatography and was obtained in 20% yield.

We are indebted to the S.R.C. for a scholarship (R. K.).

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[1] Y. Hirose, B. Tomita, and T. Nakatsuka, *Tetrahedron Letters*, 1966, 5875.

[2] A. J. Birch, J. M. H. Graves, and F. Stansfield, *Proc. Chem. Soc.*, 1962, 282.

[3] A. J. Birch, *Ann. Reports*, 1950, **47**, 193.