Ferruginol and Δ^9-Dehydroferruginol
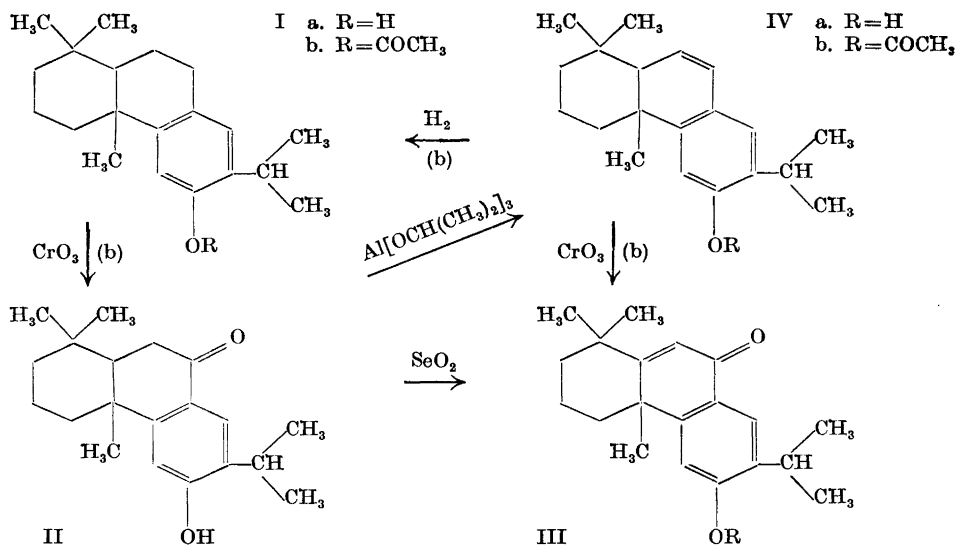
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The phenolic substance, acetate m. p. 92—93°, from the wood of *Juniperus communis* L. has been shown to be a mixture of ferruginol and Δ^9-dehydroferruginol. The previously isolated ferruginol from *Podocarpus ferrugineus* D. Don and *Dacrydium cupressinum* Solander also contains small amounts of Δ^9-dehydroferruginol. This compound has been synthesised.

The isolation of a phenolic substance in the form of a crystalline acetate, m. p. 92—93°, has previously been described [1]. This substance was at first thought to represent a pure compound "katajol" [2], but later this was doubted. In particular, the fact that only partial crystallisation of the phenol could be effected, was taken as an indication of non-homogeneity. It was suggested that the substance was a mixture of ferruginol (Ia) and a dehydro derivative [1]. Definite evidence of its nature came from an oxidation of the acetate with chromic oxide. After hydrolysis, this yielded a substance which was identified as a mixture of 9-ketoferruginol (II) and 9-keto- Δ^{10}-dehydroferruginol (III) by comparison of its ultraviolet and infrared spectra with those of the authentic compounds. On selenium dioxide dehydrogenation of the mixture, pure 9-keto- Δ^{10}-dehydroferruginol was obtained.

The acetate was subjected to catalytic hydrogenation, and it consumed 0.42 moles of hydrogen per mole of substance. The hydrogenated acetate formed rods, m. p. 81—82°, $[\alpha]_D^{20}$ +62° (ethanol). On hydrogenation, the ultraviolet spectrum (in ethanol) was altered from one absorption maximum at 268 mμ (log ε 3.71) to two maxima at 269 mμ (log ε 3.08) and 278 mμ (log ε 3.12). There is only one position, the conjugated 9-position, where the double bond could be placed in order to explain the large hypochromic shift in the ultraviolet spectrum and the formation of 9-keto- Δ^{10}-dehydroferruginol. During the chromic oxide oxidation the double bond in the 9-position obviously migrates to the 10-position. The acetate, m. p. 92—93°, thus consist of ferruginyl acetate (Ib) and Δ^9-dehydroferruginyl acetate (IVb). In order to verify this, Δ^9-dehydroferruginyl acetate was prepared in a 70 % yield by aluminium *iso*propoxide reduction of 9-ketoferruginol and acetylation of the reduced product. The reduction yielded in one stage the desired dehydro

derivative as a result of the easy dehydration that occurred in the intermediate 9-hydroxyferruginol. The Δ^9-dehydroferruginyl acetate had the constants m. p. 108—109°, $[\alpha]_D^{20}$ —92° (ethanol), λ_{max} (in ethanol) 220 mμ (log ε 4.39), 266 mμ (log ε 4.01), all of which are in good correlation with the constants

I a. R=H
b. R=COCH₃

IV a. R=H
b. R=COCH₃

calculated from the pure ferruginyl acetate, the acetate mixture and the hydrogen consumed by it. Ferruginyl acetate and Δ^9-dehydroferruginyl acetate were investigated by the contact method of Kofler [3] and found to form mixed crystals of Roozebom's type I.

Ferruginol, $[\alpha]_D^{18}$ +65° (ethanol), λ_{max} (in ethanol) 284 mμ (log ε 3.50) prepared from ferruginyl acetate resisted crystallisation. By prolonged chromatography a few crystals, m. p. 56—57°, could be obtained, but the greater part could not be crystallised. Even a trace of impurity seems to be able to inhibit crystallisation. Δ^9-Dehydroferruginol, $[\alpha]_D^{20}$ —60° (ethanol), λ_{max} (in ethanol) 218 mμ (log ε 4.29), 280 mμ (log ε 3.97) also resists crystallisation.

The formation of mixed crystals between ferruginyl acetate and its dehydro derivative explains some discrepancies in the literature and our observations. From *Podocarpus ferrugineus* D. Don, Brandt and Neubauer [4] isolated ferruginol, $[\alpha]_D^{16}$ +40.6° (ethanol). A sample of the acetate from this ferruginol was kindly supplied by Prof. H. Erdtman. After catalytic hydrogenation, this acetate, m. p. 82—83°, $[\alpha]_D^{20}$ +57° (ethanol), λ_{max} (in ethanol) 269 mμ (log ε 3.19), 278 mμ (log ε 3.19) gave the values m. p. 81—2°, $[\alpha]_D^{20}$ +62° (ethanol), λ_{max} (in ethanol) 269 mμ (log ε 3.09), 278 mμ (log ε 3.12). Hence it contained about 3 % Δ^9-dehydroferruginyl acetate. For the acetate of ferruginol obtained from *Dacrydium cupressinum* Solander, Brandt and Thomas [5] reported

log ε 3.3 at λ_{max} 269 mμ (in ethanol). This would be equivalent to a content of about 9 % of the dehydro form.

In the partial synthesis of ferruginol from dehydroabietic acid and podocarpic acid, Campbell and Todd [6] reported rotations of the ferruginyl acetates and of the crude ferruginols, which are in good correlation with the present values, but in the purification of ferruginol from podocarpic acid the rotation was lowered from $[\alpha]_{Hg}^{25}$ +59° to $[\alpha]_{Hg}^{27}$ +37.8° (ethanol). No explanation for this behaviour has been found.

The isolation of ferruginol from the wood of *Juniperus communis* L. in a yield of 0.1 % would at least partially explain the durability of the wood, for this phenol is a fungicide [7].

EXPERIMENTAL

(All m. p.'s are determined on a Kofler microscope. The microanalyses have been performed by Dr. A. Bernhardt, Mülheim.)

Oxidation of the acetate, m. p. 92—93°, with chromic oxide. The acetate (200 mg) and chromic oxide (80 mg) in acetic acid (10 ml) were heated on the water bath for 45 min. After dilution with water, the product was extracted with ether. The crystals obtained from the ether melted after recrystallisation between 115 and 130°. This mixture was chromatographed, yielding 48 mg of colourless prisms, m. p. 287—289°. Both the UV- and the IR-spectrum proved that the crystals consisted of a mixture of 9-ketoferruginol and 9-keto-Δ^{10}-dehydroferruginol.

9-Keto-Δ^{10}-dehydroferruginol (III). 9-Ketoferruginol (30 mg) and selenium dioxide (11 mg) in nitrobenzene (2 ml) were heated at 190° for 2 h. The dark-coloured solution was filtered and the precipitate washed with ether and ethanol. The combined filtrates were washed with sodium carbonate, and the ether and ethanol evaporated. After chilling, 13 mg of pink-coloured rods, m. p. 281—283°, crystallised out. Recrystallisation from benzene-light petroleum yielded colourless crystals, m. p. 288—290°. (Found C 80.2; H 8.9. Calc. for $C_{20}H_{26}O_2$ C 80.5; H 8.8.) UV-spectrum: λ_{max} (in ethanol) 246 mμ (log ε 4.21), 316 mμ (log ε 4.02); (in 0.05 N Na_2CO_3) 245 mμ (log ε 4.30), 381 mμ (log ε 4.18). IR-spectrum, principal bands (KBr): 3 060 (s), 2 905 (s), 2 840 (m), 1 630 (s), 1 610 (s), 1 575 (s), 1 555 (s), 1 500 (s), 1 460 (s), 1 383 (s), 1 340 (s), 1 310 (s), 1 282 (s), 1 258 (s), 1 178 (s), 1 150 (m), 1 090 (m), 887 (s), 875 (m) and 866 cm^{-1} (s).

A sample of the previously obtained mixture of 9-ketoferruginol and 9-keto-Δ^{10}-dehydroferruginol (25 mg) was oxidised with selenium dioxide (9 mg) as described above. After purification, 9 mg of rods, m. p. 287—289°, were isolated. The IR- and UV-spectra of this product were identical with those of authentic 9-keto-Δ^{10}-dehydroferruginol.

Hydrogenation of the acetate, m. p. 92—93°. The acetate (300 mg) in ethanol (10 ml) was subjected to catalytic hydrogenation with a Pt-catalyst (16 mg PtO$_2$). The reduction stopped after 1 h, 0.38 mmoles of hydrogen having been consumed. The product (290 mg) crystallised from ethanol as rods, m. p. 81—82°, $[\alpha]_D^{20}$ +62° $\pm$ 2° (ethanol, c 2.2). (Found C 80.1; H 9.8. Calc. for $C_{22}H_{32}O_2$ C 80.4; H 9.8), λ_{max} (in ethanol) 269 mμ (log ε 3.08), 278 mμ (log ε 3.12).

Hydrogenation of the "Brandt-Neubauer" ferruginyl acetate. The ferruginyl acetate, m. p. 82—83°, $[\alpha]_D^{20}$ +57° $\pm$ 2° (ethanol, c 2.3), λ_{max} (in ethanol) 269 mμ (log ε 3.19), 278 mμ (log ε 3.19), was hydrogenated as above, yielding crystals, m. p. 81—82°, $[\alpha]_D^{20}$ + 62° $\pm$ 2° (ethanol, c 2.1), λ_{max} (in ethanol) 269 mμ (log ε 3.09), 278 mμ (log ε 3.12). The mixed m. p. of the hydrogenated acetates was 81—82°.

Ferruginol (Ia). Ferruginyl acetate (hydrogenated) (100 mg) was refluxed in N potassium hydroxide (20 ml) for 40 min. The product, 85 mg of a nearly colourless resin, $[\alpha]_D^{18}$ + 65° $\pm$ 2° (ethanol, c 2.4), λ_{max} (in ethanol) 284 mμ (log ε 3.50), resisted crystallisation. By chromatography a few crystals, m. p. 56—57°, could be obtained in one fraction, but crystallisation could not be effected by seeding in the bulk.

Δ^9-*Dehydroferruginyl acetate* (IVb). 9-Ketoferruginol (145 mg) and aluminium *iso*-propoxide (350 mg) (Riedel-de Haën) in abs. *iso*propanol (5 ml) were heated on a water bath in a flask equipped with a 40 cm Vigreux column. After 5 h, no acetone could be detected in the distillate. Abs. *iso*propanol (5 ml) was added and the solution was kept at total reflux for 1 h. The acetone reaction was negative in the distillate taken after this time. The cooled solution was hydrolysed with 2 N hydrochloric acid (30 ml) and extracted with ether. The ether was evaporated on the water bath and the residue was acetylated with acetic anhydride and pyridine at room temperature (two days). The mixture was poured into water and the precipitate crystallised from aqueous ethanol, giving

110 mg (70 %) of prisms, m. p. 108—109°, $[a]_D^{20}$ —92° $\pm$ 2° (ethanol, c 2.3), λ_{max} (in ethanol) 220 mμ (log ε 4.39), 266 mμ (log ε 4.01), inflexion at 298 mμ (log ε 3.2). (Found C 80.3; H 9.3. Calc. for $C_{22}H_{30}O_2$ C 80.9; H 9.3). The acetate was partially hydrolysed by chromatography on alumina.

Δ^9-*Dehydroferruginol* (IVa). Δ^9-Dehydroferruginyl acetate (90 mg) was refluxed in N potassium hydroxide (10 ml) for 30 min. The product (75 mg) was a light yellow resin, $[a]_D^{20}$ —60° $\pm$ 2° (ethanol, c 3.2), λ_{max} (in ethanol) 218 mμ (log ε 4.29), 280 mμ (log ε 3.97). All attempts to effect crystallisation failed.

Isomorphy of ferruginyl acetate and Δ^9-*dehydroferruginyl acetate.* The acetates were brought into contact by the method of Kofler [3]. On cooling and heating the acetates formed mixed crystals of Roozebom's type I.

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