Structural Studies on the Triterpenes of *Schinus terebinthefolius*

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A second triterpene, schinol (II), has been isolated from the berries in the ether extract. The relationship of II to previously reported terebinthone (I), has been demonstrated. Terebinthone (I) has been proven to be a triketo triterpene and schinol (II) to be a dihydroxy, keto triterpene. A unique type of dehydration has been discovered in II and a possible mechanism is discussed. Structures for I and II are proposed.

THE partial structural elucidation of a triterpene, terebinthone (I), isolated from the berries of *Schinus terebinthefolius* (Radd.), has been previously described (1). Terebinthone was found to be a 3,11-diketotriterpene with an ethylidene group in the side chain. The nature of a third oxygen function and an element of unsaturation were in doubt but a cyclic ether was proposed. In this present work, the authors have isolated a second triterpene, schinol (II), from this plant and present proposed structures for both compounds.

The triterpene (II), provisionally named schinol from the genus name of the plant, was found to be a $C_{30}H_{50}O_3$ dihydroxy ketone with one reactive double bond. A derivative of the two hydroxyl groups was prepared, but a derivative of the carbonyl group could not be prepared. This indicated that the carbonyl group was in a hindered position. This belief was substantiated by the presence of the carbonyl absorption band at 1690 cm.$^{-1}$ in the infrared which is characteristic for hindered carbonyl groups (2, 3). Except for the hydroxyl and carbonyl group regions, the infrared spectra of schinol (II) and terebinthol (I) were practically identical.

The presence of three carbonyl groups in terebinthone (I) was concluded by comparing the molar absorptivities, ϵ, of the compounds in Table I at 285 mμ. This wavelength was selected as being characteristic of isolated carbonyl groups in cyclohexanones (4). The value of ϵ for schinol was in close agreement with the values reported for one carbonyl group. The two compounds, 3-hydroxy-terebinthone (III) and 3-desoxydihydroterebinthone (IV) had ϵ values corresponding to two carbonyl groups. The ϵ value for terebinthone was in agreement with the presence of three carbonyl groups. These findings indicated that I and II might well be interconvertible or that both might be converted to a common intermediate.

TABLE I.

Compound	Gm./L., Dioxane	ϵ	Estd. No. of C=O
Schinol	4.06	14	1
3-Hydroxy-terebinthone	3.95	28	2
3-Desoxydihydro-terebinthone	4.05	28	2
Terebinthone	4.03	48	3

Oxidation with a chromium trioxide-pyridine complex (5) of II to I was successful though the yield was small. A higher yield was obtained by employing the Oppenauer method (6) with aluminum tertiary-butoxide. This gave conclusive evidence that terebinthone was a triketo compound.

It was necessary to re-examine terebinthol (V) and dihydroterebinthol (IV) since these were previously suspected to be dihydroxy ethers (1). If terebinthone is a triketone then hydride reduction should give a triol. Accordingly V and VI were carefully purified by repeated chromatography until a sharp consistent melting point was obtained. Elemental analyses now gave values which did not agree with those previously reported or those of the expected triol and dihydrol triol. Instead the values obtained for V and VI, $C_{30}H_{50}O_2$ and $C_{30}H_{52}O_2$ indicated that both compounds were missing the elements of water from the expected values. Peracid titration (7) indicated that a new double bond had been introduced in each compound.
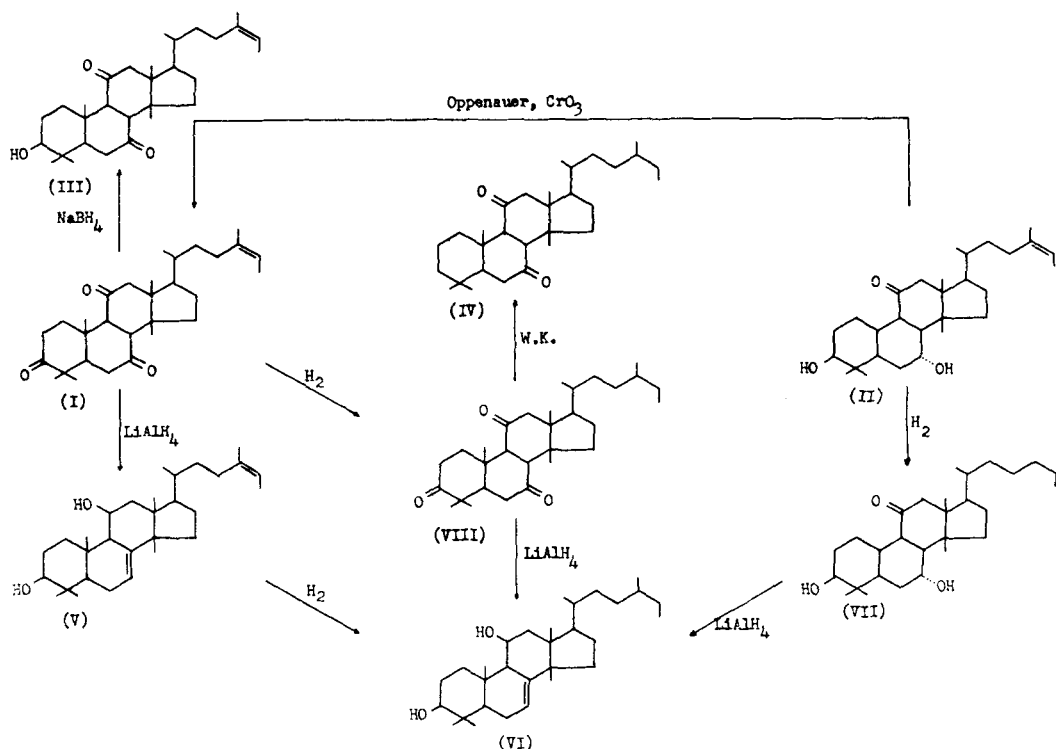
In an effort to determine if this unusual mechanism was operative in schinol (II), dihydroschinol (VII), from catalytic hydrogenation of schinol, was subjected to the same lithium aluminum hydride reduction previously reported (1). This gave a diol missing the elements of water from the expected formula. A comparison showed that this compound was identical with VI.

The conversion of I and II to a common product VI conclusively proved that terebinthone (I) and schinol (II) possessed the same ring system, side chain, and location of oxygen

Oppenauer, CrO₃

(III)

NaBH₄

(IV)

W.K.

(I)

H₂

(II)

LiAlH₄

H₂

(VIII)

(V)

LiAlH₄

H₂

(VII)

LiAlH₄

(VI)

functions. It was also obvious that the location of the newly introduced double bond in both V and VI would be invaluable in locating the position of the remaining oxygen function, if it was assumed the 3,11 assignment was correct.

Attempts to hydrogenate the new double bond in V and VI were unsuccessful which narrowed the possibilities to the Δ^7 and Δ^8 positions of a tetracyclic triterpene (8, 9, 10). Both V and VI gave negative Tortelli-Jaffe tests specific for a Δ^8 or a Δ^7 which can migrate to a $\Delta^{8,14}$ (11). This latter possibility can be discarded since this migration in a tetracyclic triterpene is prevented by the presence of a 14-methyl group. The nature of this double bond was further studied by plotting its molar absorptivity, ϵ, over the 205–225 mμ region (7). See Fig. 1. Samples of Δ^8-lanostanol and Δ^7-ergostene were used for direct comparison. Both Δ^7-ergostene and VI fell in the same region assigned to trisubstituted double bonds, while Δ^8-lanostanol fell in the same region assigned to tetrasubstituted double bonds (12, 13). Thus, it was concluded that the new double bond introduced in V and VI from hydride reduction is in the Δ^7 position.

In terebinthone (I) the three carbonyl groups must be in the ring system since the only unhindered group is in the 3 position. The infrared spectrum of terebinthone gave no evidence of a carbonyl group in ring D (14) hence the three six-membered rings were the only possible sites. Furthermore, the infrared and ultraviolet spectra of terebinthone (I) showed no absorption due to adjacent carbonyl groups (15) which indicated that the three carbonyl groups must be distributed in rings A, B, and C of the tetracyclic triterpene structure. This is consistent with the assignment of the new double bonds in V and VI to the Δ^7 position since this double bond must have been formed by a reduction of the carbonyl group at C-7 followed by a dehydration.

The possibilities that schinol (II) might be a 3,11-α-dihydroxy-7-keto or 3,11-β-dihydroxy-7-keto triterpene were considered but rejected. If the 11-β-hydroxyl group was present it would be unacylable (1). Schinol formed a derivative of both hydroxyl groups. If the 11-α-hydroxyl group was present a derivative of both hydroxyl groups could be prepared but hydride reduction of dihydroterebinthone (VIII) would not give dihydroschinol (VII) since lithium aluminum hydride reduction of an 11-keto group gives almost exclusively the 11-β-hydroxy compound (16, 17, 18).

These facts present the interesting conclusion that lithium aluminum hydride dehydrates a 7-hydroxyl group in schinol (II) while in terebinthone (I), this reagent first must reduce the carbonyl group to a 7-hydroxyl group then de-
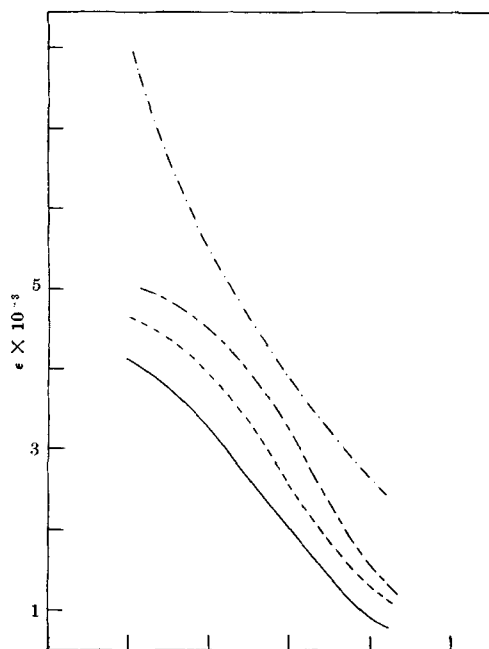
Fig. 1.—Ultraviolet absorption of —— dehydro-dihydroschinol (VI), — · — lanostenol, — · — 7-ergostenol, - - - dihydroterebinthol (VI).

hydrate it by a similar mechanism. There is no precedence for this reaction in the literature though recent work (19), has shown that 3-α-p-toluene sulfonates of steroids can be dehydrated with lithium aluminum hydride to Δ^2 compounds very readily. This is a *trans* elimination with the large ester forming the leaving group and the hydride abstracting the adjacent proton. On this basis we would like to propose a similar mechanism (IX) with some form of an aluminum alcoholate forming the leaving group and a second mole of the hydride serving as the proton abstracting base. If this likely mechanism is operative, then the 7-hydroxyl group involved must be α-oriented, for a 7-β-hydroxyl group would be cisoid to the 8-hydrogen and a *cis* elimination mechanism would probably proceed with much more difficulty, if at all, at 36°.

There remained the necessity of proving the orientation of the 3-hydroxyl group of schinol (II). This was determined by treating dihydroschinol (VII) with phosphorus pentachloride. If the 3-β-hydroxyl group is present then X should suffer ring contraction with the formation of an isopropylidene group (XI) (20). Ozonolysis of the product from treatment of VII gave acetone proving a 3-β-hydroxyl group. This assignment of a β orientation is consistent with the fact that hydride reduction of dihydroterebinthone (VIII) should give almost exclusively a

3-β-hydroxyl group (21) which resulted in a compound VI which could also be obtained from schinol (II).

From these findings the authors propose the structures I and II to terebinthone and schinol, respectively.

EXPERIMENTAL[1]

Isolation of Schinol (II).—The hexane marc of the berries of *Schinus terebinthefolius* was extracted with ether in a Soxhlet extractor for 24 hr. The ether was allowed to evaporate leaving a crude crystalline residue. This residue was crystallized several times from ethyl acetate to give a 0.35% yield of schinol, m.p. 145–146.5°, $[\alpha]_D^{23}$ -39.7° (chloroform).

Anal.—Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99; 4 C-CH₃, 13.10. Found: C, 78.74; H, 10.74; C-CH₃, 11.98 (Kuhn-Roth).

Schinol was found to be slightly soluble in hexane, ethanol benzene, and chloroform but insoluble in aqueous acid and base. Infrared analysis in nujol showed absorption at 3500^{-1} cm. (hydroxyl), 1700^{-1} cm. (carbonyl), and 1645^{-1} cm. (alkene). The region 1400–650⁻¹ cm. was practically identical to that of terebinthone (I). Schinol (II) gave positive Liebermann-Burchard, Salkowski, and tetranitromethane tests but gave negative Zimmermann and Tortelli-Jaffe tests.
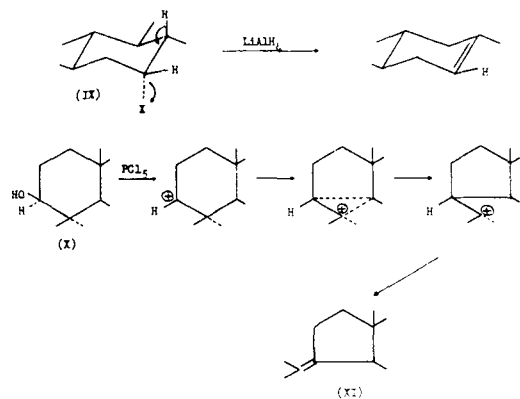
Schinol Dibenzoate.—One gram of schinol in 10 ml. of anhydrous pyridine was treated with 2 ml. of benzoyl chloride and the product isolated in the usual way, m.p. 125–127°.

Anal.—Calcd. for $C_{44}H_{58}O_5$: C, 79.24; H, 8.77. Found: C. 79.63; H, 9.11.

Perebenzoic Acid Titration of Schinol (II).—The titration was conducted according to the method previously described (7). The perbenzoic acid consumed was equivalent to 1.2 double bonds.

Dihydroschinol (VII).—A solution of 0.8 Gm. of schinol (II) in 50 ml. of ethyl acetate was hydrogenated at atmospheric pressure using pre-reduced platinum oxide as a catalyst. The consumption of hydrogen was equivalent to 94% of the theoretical amount for one double bond. The ethyl acetate was removed under a vacuum and the residue crystallized from benzene to give 0.78 Gm. of VII, m.p. 148.5–150°, $[\alpha]_D^{23}$ -37.3° (chloroform).

Anal.—Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38; two active hydrogens, 0.43. Found: C, 78.53; H, 11.12; active hydrogen, 0.47.

The compound gave no tetranitromethane test and showed no infrared absorption for a double bond.

3-Hydroxy-terebinthone (III).—The method described by Rao (22) was used to reduce 1.5 Gm. of terebinthone (I). The reduction was conducted with sodium borohydride in aqueous dioxane. The crude product was chromatographed on a Celite-magnesium trisilicate (1:1) column, eluting with hexane. The purified compound was crystallized from benzene, m.p. 197–199°, $[\alpha]_D^{23}$ –23.4° (chloroform).

Anal.—Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.84; H, 10.73.

The infrared spectrum showed absorption at 3400 cm.$^{-1}$ (hydroxyl) and 1690 cm.$^{-1}$ (carbonyl). The compound gave no Zimmermann reaction.

3-Hydroxy-terebinthone Mono-*p*-nitrobenzoate. —A quantity of III was converted to the *p*-nitrobenzoate in the usual way. The crude product was chromatographed on alumina and crystallized from methanol to give crystals, m.p. 115–117° (capillary).

Anal.—Calcd. for $C_{37}H_{51}NO_6$: N, 2.31. Found: N, 2.55.

The infrared analysis showed no absorption for an hydroxyl group.

Ultraviolet Studies of I, II, III, and IV.—The ultraviolet absorptions of terebinthone (I), schinol (II), 3-hydroxy-terebinthone (III), and 3-desoxy-terebinthone (IV) were measured at 285 mμ using 0.01 molar concentrations in dioxane. The molar absorptivities, ϵ, were calculated. See Table I.

Chromic Acid Oxidation of II to I.—A solution of 1 Gm. of schinol (II) in 20 ml. of anhydrous pyridine was added to a solution of 1 Gm. of chromium trioxide in 20 ml. of anhydrous pyridine. The solution was allowed to stand for 24 hours at room temperature. It was then diluted with 100 ml. of water and extracted with ethyl acetate and this in turn washed with dilute acid. The ethyl acetate was evaporated and the residue chromatographed on a Celite-magnesium trisilicate (1:1) column. A crystalline product weighing 50 mg. was obtained, m.p. 177–179°. A mixed melting point with terebinthone (I) gave no depression and the infrared spectra were identical.

Oppenauer Oxidation of II to I.—A solution of 4 Gm. of schinol (II) and 40 ml. of freshly distilled cyclohexanone in 400 ml. anhydrous toluene was distilled until 150 ml. of toluene was removed. To the remaining solution was added dropwise, 4 Gm. of aluminum tertiary-butoxide in 150 ml. of dry toluene. This solution was refluxed 45 minutes then allowed to stand 12 hours. The reaction mixture was then diluted with water and steam distilled to remove volatile solvents. The precipitate which formed was filtered off then chromatographed on Celite-magnesium trisilicate (1:1). The hexane eluate was recrystallized from ethanol to give 2.5 Gm. of crystals, m.p. 178–179°. A mixed melting point with terebinthone (I) gave no depression and the infrared spectra were identical.

Purification of Terebinthol (V).—A 0.5-Gm. quantity of terebinthol (V), previously prepared, (1) was chromatographed several times on columns

of Celite-magnesium trisilicate (1:1) until a fraction was obtained, m.p. 192–193°.

Anal.—Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.66; H, 11.44.

Purification of Dihydroterebinthol (VI).—This compound, previously prepared (1), was purified as described for terebinthol (V) until a fraction m.p. 160-161° was obtained.

Anal.—Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.14; H, 11.69.

Reduction of Dihydroschinol (VII) to VI.—Dihydroschinol (VII) was reduced with lithium aluminum hydride in ether by the same procedure previously described (1). Purification on a Celite-magnesium trisilicate (1:1) column gave a crystalline product which did not depress the mixed melting point with dihydroterebinthol (VI) and the infrared spectra were identical.

Ultraviolet Analysis of Dihydroterebinthol (VI).—The ultraviolet spectrum of dihydroterebinthol (VI) was obtained in the region 205–225 mμ and compared with the spectra of Δ^8-lanostanol and Δ^7-ergostene. See Fig. 1.

Retropinacol Rearrangement of Dihydroschinol (VII).—A solution of 1.5 Gm. of dihydroschinol (VII) in 150 ml. of methylene chloride was treated with 0.75 Gm. of phosphorus pentachloride. This solution was stirred for 2 hours then refluxed for 1 hour. The reaction mixture was then added to 50 ml. of water and steam distilled to remove the solvent and hydrolyse the phosphorus pentachloride. The residue remaining weighed about 1 Gm. and could not be purified.

Ozonolysis of Crude Retropinacol Products (XI).—One gram of the crude retropinacol product (XI) in 30 ml. of carbon tetrachloride at 0° was treated with a stream of 3% ozonized oxygen for 30 minutes. Water and a few pieces of zinc were then added and the mixture steam distilled into an aqueous acid solution of 2,4-dinitrophenylhydrazine. From this solution was isolated the corresponding acetone derivative, confirmed by a mixed melting point with the authentic compound.

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