

STUDIES IN TERPENOIDS - XXXIII.
SYNTHESIS OF 3-METHOXY-7-HYDROXYCADALENAL

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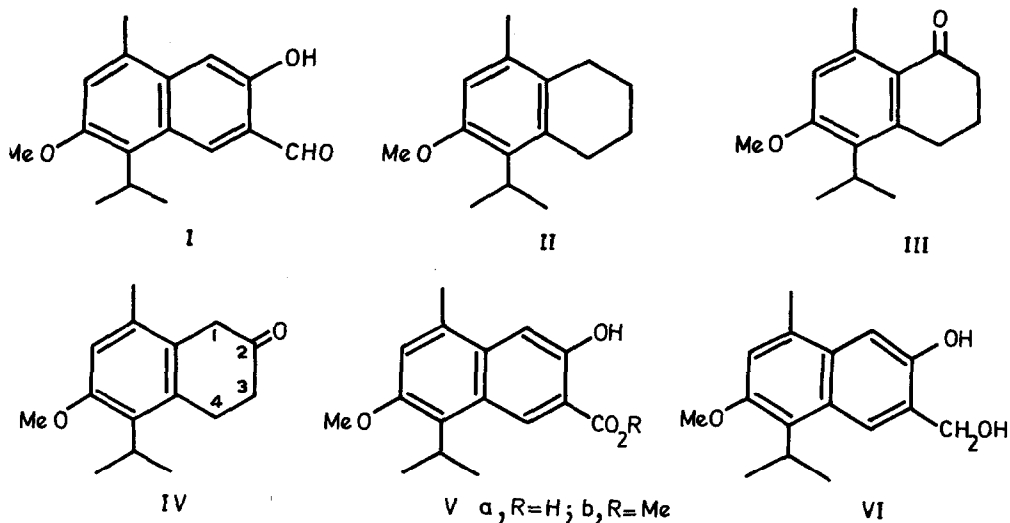
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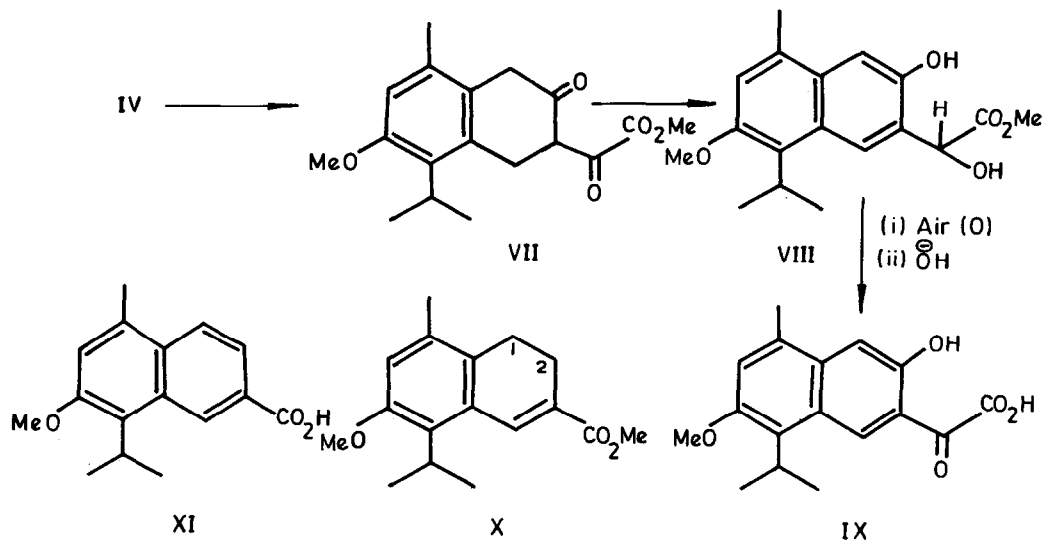
Rowe and co-workers¹ isolated several phenolic sesquiterpenoids of the cadalene family from the elm (Ulmus) heartwoods. The syntheses of four of these have been reported in 1971 from these laboratories². We now report the synthesis of the fifth member of this group, viz., 3-methoxy-7-hydroxy-cadalenal (I) which was first isolated from Ulmus rubra Muhl.^{1a,b} and later from other Ulmus species^{1c}.

The known 5-methyl-7-methoxy-8-isopropyltetralin³ (II) was oxidized by chromic acid in acetic acid-propionic acid mixture⁴ to the 5-isopropyl-6-methoxy-8-methyl tetralone (III). The α -tetralone (III) was next converted to the β -tetralone (IV), the ketonic carbonyl of which is to become eventually the hydroxyl of the projected cadalenal (I). The transposition of the ketone (III \rightarrow IV) was effected by (i) NaBH₄ reduction of the tetralone (III) to the tetralol, (ii) dehydration, (iii) epoxidation of the 1,2-olefinic bond and (iv) acid catalysed rearrangement of the 1,2-epoxy-3,4-dihydronaphthalene.

Our next aim was to suitably functionalise C₃ of the β -tetralone (IV) for conversion to the natural product (I). Guided by the earlier findings of Soffer⁵ who could effect oxalylolation of simple β -tetralone at C₃ with dimethyl oxalate and dry sodium methoxide in benzene, and parallel observations



of others⁶ of preferential C_3 anion formation in β -tetralones in non-polar solvents, the β -tetralone (IV) was condensed with dimethyl oxalate under the conditions of Seffer⁵. Work-up of the reaction gave acidic and neutral material, consisting of the product esters and the unreacted β -tetralone (IV). While the gummy neutral material was too complex for separation and characterization, the acidic reaction product, m.p. 260–263°(dec.) (yellow crystals from aq. MeOH), isolated by extraction with bicarbonate, proved to be rewarding. It analysed for $C_{16}H_{18}O_4$, showed a strongly chelated carboxyl in the i.r. (1665 cm^{-1}) and exhibited almost identical absorption pattern in the u.v. as 2-hydroxy-3-naphthoic acids which have been unambiguously distinguished from 2-hydroxy-1-naphthoic acids⁷. The structure (Vb) assigned for its methyl ester, m.p. 122–123°, was fully supported by its n.m.r. spectrum which showed three aromatic proton singlets (C_1H at 7.24, C_4H at 8.63 and C_7H at 7.06 δ). The origin of Va from the β -tetralone (IV) is visualised as follows:



The isomerisation of the β -ketoexalate (VII) to the hydroxynaphthalene glycolate (VIII) finds precedent in the work of Soffer⁵ and Pelletier^{6d}. Aerial oxidation cum hydrolysis of the β -aryl- α -hydroxy ester (VIII) followed by acid promoted decarboxylation⁸ of the resulting naphthoylformic acid (IX) could give the 2-hydroxy-3-naphthoic acid (Va). The naphthol ester (Vb) was next reduced to the diol (VI), which on oxidation with Collins' reagent⁹ gave 3-methoxy-7-hydroxycadalenal (I), m.p. 129-131°. Recrystallisation of the synthetic compound with a seed of the authentic natural product raised its melting point to 137-138° (Rep.¹ for I, m.p. 138°), with no depression in the mixture melting point. The synthetic sample I compared in all respects (t.l.c., u.v., i.r. and n.m.r.) with the natural product. The naphthalene diol (VI) exhibited a facile tendency to undergo aerial oxidation to give the cadalenal (I), which is reminiscent of the postulated conversion, VIII \longrightarrow IX.

Attempted synthesis of the cadalenal (I) from the dihydronaphthoic ester (X), m.p.54.5-55.5°, by allylic oxidation followed by separation of the expected products of oxidation at C₁ and C₂, the latter yielding Vb, was infructuous, although this study gave some unusual results¹⁰. Attempted ortho hydroxylation of the naphthoic acid (XI), m.p.227.5-228.5°, by the thermal decomposition of its copper salts also did not succeed¹¹.

All new compounds gave correct elemental analyses and exhibited the expected spectral characteristics.

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