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THE SYNTHESIS OF (±)-ROYLEANONE

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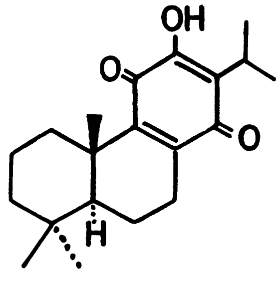
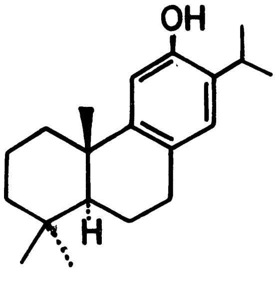
(±)-Royleanone (I) has been synthesized from 5,7,8-trimethoxy-1-tetralone (III) via (±)-11,12,14-trimethoxypodocarpa-8,11,13-triene (XIII). The synthetic (±)-I was shown to be identical with natural royleanone by their spectral comparisons.

Royleanone, a diterpenoid quinone, was isolated from the roots of Inula royleana D. C. by Edwards et al.1) and they assigned its structure to be I. Recently, during the course of search for tumor inhibitors of plant origin, Kupchan et al.2) also isolated royleanone from Taxodium distichum Rich (Taxodiaceae) and reported on its cytotoxicity against Eagle's KB strain of human carcinoma of the nasopharynx. Although royleanone was synthesized in a 7% yield1) by the oxidation of ferruginol (II) with hydrogen peroxide, because of its cytotoxicity the present authors also attempted the total synthesis of I.

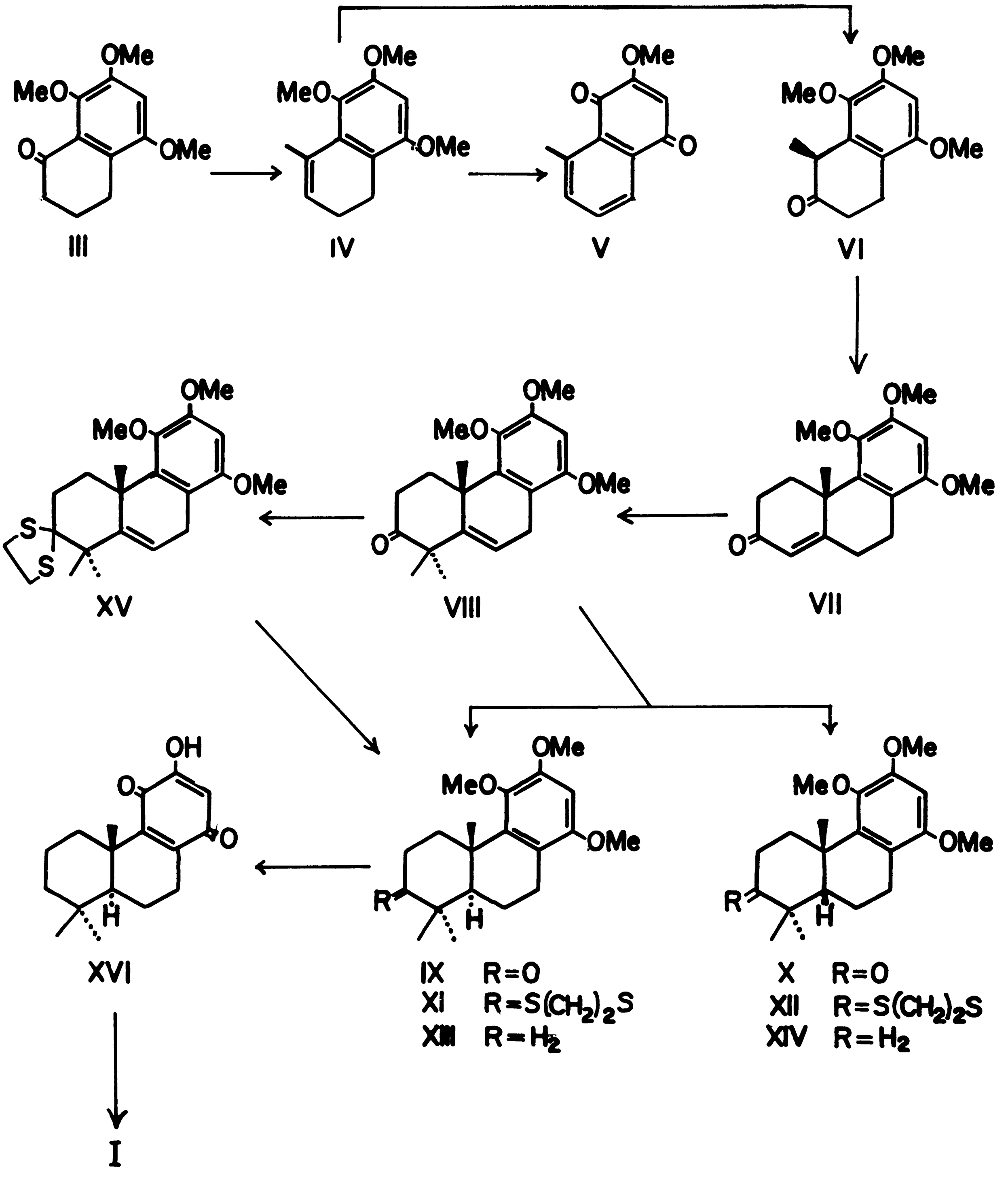


I



II

In this communication we wish to report on the new synthesis of (±)-I starting from 5,7,8-trimethoxy-1-tetralone (III).3,4) The Grignard reaction of III with methylmagnesium iodide afforded the corresponding alcohol, which was then dehydrated with dilute sulfuric acid to give 3,4-dihydro-5,7,8-trimethoxy-1-methylnaphthalene (IV);5) NMR in CCl_4 (δ)6): 2.14 (methyl group), 3.61, 3.70, 3.76 (three methoxyl groups), 5.77 (vinyl proton), 6.30 ppm (aromatic proton). In order to obtain (±)-1-methyl-5,7,8-trimethoxy-2-tetralone (VI), the dihydronaphthalene derivative (IV) was treated with lead tetraacetate in acetic acid to give yellow crystals (V), mp 151.5-152.5°C; IR in $CHCl_3$: 1676, 1645, 1618, 1588 cm^{-1}; UV in EtOH: λ_{max} 243 (ε 15700), 248.5 (ε 16000), 276 (ε 14700), 345 nm (ε 3700). Since the NMR spectrum of V in $CDCl_3$ showed signals at δ 2.73 and 3.87 ppm (methyl and methoxyl groups) and at δ 6.10 and 7.4-8.1 ppm (four protons), the structure of V was deduced to be 2-methoxy-8-methyl-1,4-naphthoquinone. Therefore, IV was oxidized with perbenzoic acid in chloroform and the product was then refluxed with methanol containing dilute sulfuric acid to give VI, mp 90-91°C; the NMR spectrum ($CDCl_3$) of which showed signals at δ 1.36 ppm (methyl group), at δ 3.77, 3.81, 3.87 ppm (three methoxyl groups), and at δ 6.44 ppm (aromatic proton). The condensation of VI with methyl vinyl ketone in the presence of sodium ethoxide afforded (±)-2,3,4,9,10,12-hexahydro-12-methyl-5,6,8-trimethoxy-2-oxophenanthrene (VII), mp 134.5-135.5°C; IR in $CHCl_3$: 1660 cm^{-1}; UV in EtOH: λ_{max} 236 (ε 24200), 290.5 nm (ε 4500). Subsequently, VII was methylated with methyl iodide in t-butanol in the presence of potassium t-butoxide to give (±)-11,12,14-trimethoxypodocarpa-5,8,11,13-tetraene-3-one (VIII), mp 153-154°C, NMR in $CDCl_3$ (δ): 1.32 (6H), 1.35 (3H) (three methyl groups), 3.81, 3.83, 3.87 (three methoxyl groups), 5.83 (vinyl proton), 6.48 ppm (aromatic proton). The hydrogenation of VIII over platinum oxide in acetic acid afforded a mixture of the dihydro derivatives which were separated by means of column chromatography on silica gel to give a minor product (IX), mp 156-158°C, NMR in CCl_4 (δ): 1.08 (three methyl groups), 3.74 (6H), 3.78 (3H) (three methoxyl groups), 6.28 ppm (aromatic proton), and a major product (X), mp 141.5-142.5°C, NMR in CCl_4 (δ): 0.95, 1.08, 1.31 (three methyl groups), 3.74 (6H), 3.79 (3H) (three methoxyl groups), 6.28 ppm (aromatic proton). These minor (IX) and major (X) products were converted with ethanedithiol in benzene in the presence of boron trifluoride etherate into the corresponding thioketals (XI and XII) which were further treated with Raney nickel in boiling ethanol to give (±)-11,12,14-trimethoxypodocarpa-8,11,13-trienes, XIII and XIV (mp 69-72°C), respectively. In the NMR spectrum (CCl_4) XIII showed signals at δ 0.89, 0.92, and 1.23 ppm due to the three methyl groups, while XIV showed the corresponding signals at δ 0.51, 0.92, and 1.24 ppm. These spectral data suggest that the configurations of the A/B ring junction in XIII and XIV are trans7) and cis respectively. Since it is known that the natural royleanone possesses a trans A/B ring junction, the above procedure for the preparation of the intermediate XIII was not effective because of its low yield. Thus, VIII was converted into the corresponding thioketal (XV), mp 143-144°C. The treatment of XV with Raney nickel followed by the catalytic reduction over 10% palladium-charcoal in acetic acid afforded XIII containing a small amount of XIV. Subsequently, XIII was demethylated with boron tribromide in dichloromethane to the corresponding hydroxyl derivative,



which was then heated with benzene under bubbling of oxygen gas to give a hydroxyquinone (XVI), mp 195.5-197°C dec.; IR (KBr): 3235, 1655, 1625, 1595 cm^{-1}; UV in EtOH: λ_{max} 276.5 (ε 15400), 418 nm (ε 600). The NMR spectrum of XVI in $CDCl_3$ showed signals at δ 0.89, 0.92, and 1.24 ppm (three methyl groups), at δ 5.95 ppm (vinyl proton), and at δ 7.19 ppm (hydroxyl proton). Our final step in the total synthesis of (±)-I was achieved by the introduction of an isopropyl group at the C-13 position. The alkylation[8] of XVI with isobutyryl peroxide[9] in acetic acid gave (±)-I, mp 153-154°C; IR in $CHCl_3$: 3355, 1672, 1632, 1600 cm^{-1}; UV in CCl_4: λ_{max} 277 (ε 13800), 283sh (ε 13500), 403 nm (ε 430); NMR in $CDCl_3$ (δ): 0.91, 0.94, 1.27 (three methyl groups), 1.16, 1.27 (isopropyl methyls), 7.28 ppm (hydroxyl proton); Mass: m/e 316 (M^+). The IR spectrum of the synthetic (±)-I in chloroform was identical in every respect with that of natural royleanone and the other spectral data were also in good accordance with those published.[1,10]

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