

THE SYNTHESIS OF dl-SANDARACOPIMARADIENE, dl-PIMARADIENE
AND SOME OBSERVATIONS ON THE STRUCTURE OF RIMUENE¹

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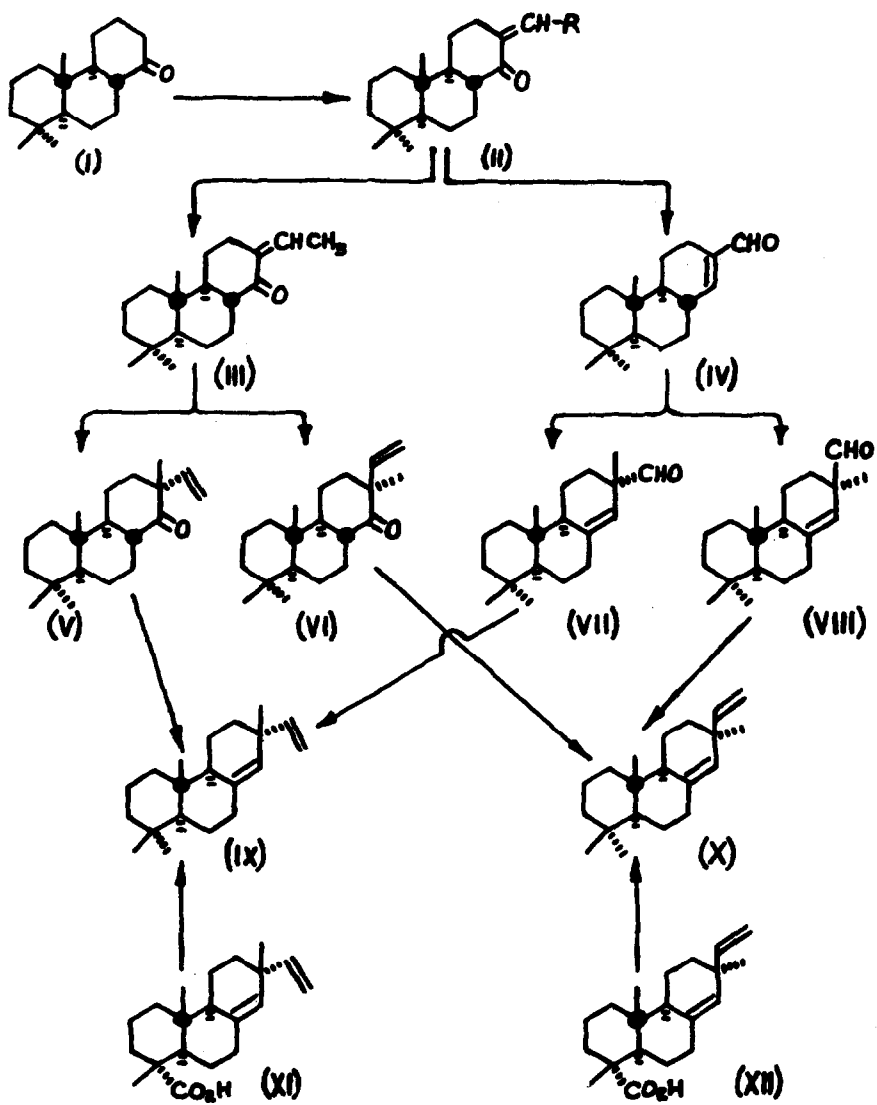
In the field of total synthesis of the diterpenoid resin acids, efforts reported to date have concerned themselves with construction of the appropriate A and B rings². We now wish to report the results of a program directed toward the elaboration of the ring C substitution pattern present in the pimaric acids.

When the tricyclic ketone(I), prepared independently in substantially the same fashion as that reported by Turner and co-workers³, was condensed with ethyl formate in the presence of sodium methoxide and then with pyrrolidine, there resulted an 83% yield of the pyrrolidinomethylene ketone(II, R=C₄H₈N)

¹ A portion of this work was presented at the International Symposium on The Chemistry of Natural Products, Sydney, Australia, August, 1960.

² For example, see G. Stork and J. W. Schulenberg, J. Am. Chem. Soc. 78, 250 (1956); E. Wenkert and A. Tahara, J. Am. Chem. Soc. 82, 3229 (1960); J. A. Barltrop and A. C. Day, Chemistry and Industry 1450 (1959); V. R. Ghatak, D. K. Datta and S. C. Ray, J. Am. Chem. Soc. 82, 1728 (1960).

³ R. B. Turner and P. E. Shaw, Tetrahedron Letters No. 18, 24 (1960).



m.p. 154-156° (C,80.17%; H,10.65%; N,4.20%). Treatment of this derivative with methyl magnesium bromide⁴ and then 2N aqueous hydrochloric acid afforded a 90% yield of the corresponding ethylidene ketone(III) m.p. 76-76.5° ($\lambda_{\max}^{\text{alc}}$ 292 m μ (7070); C,82.99%; H,10.96%).

Completion of the substitution at C13⁵ was accomplished by methylation of the ethylidene ketone(III) with methyl iodide in the presence of potassium t-butoxide in t-butyl alcohol. Chromatography of the resulting mixture of C13 epimers on Florisil afforded first a 5% yield of the ketone(VI) m.p. 78-80°(C,83.33%; H,11.18%) and then a 30% yield of its epimer (V) m.p. 69-70°(C,83.14%; H,11.08%). The assignment of this stereochemistry to these ketones is based on their chromatographic behaviour and their ultraviolet spectra. On both column and gas-liquid chromatography, the higher melting ketone is eluted first, a result expected of the compound containing an axially oriented vinyl group. The homoconjugation⁶ expected of the axially oriented α -vinyl ketone is observed in the ultraviolet spectrum of the higher melting ketone - $\lambda_{\max}^{\text{alc}}$ 294m μ (104)- and the lack of significant conjugation between the vinyl grouping and the carbonyl in the lower melting

⁴ C. Jutz, Ber. 91, 1867 (1958).

⁵ Steroid numbering is used throughout, and although formulas of only one enantiomer are drawn, they are taken to represent a racemate except where indicated.

⁶ R. C. Cookson and N. S. Wariyar, J. Chem. Soc. 2302 (1956); H. Labhart and G. Wagniere, Helv. Chim. Acta 42, 2219 (1959).

ketone $-\lambda_{\max}^{\text{alc}}$ 292m μ (50)- attests to the equatorial conformation of its vinyl grouping.

The final stages of the synthesis were accomplished by reducing each ketone with sodium in alcohol, followed by benzylation and pyrolytic elimination of benzoic acid. Thus the higher melting ketone(VI) led to the diene(X)(C,88.26%; H,11.84%; 90% homogeneous by gas-liquid chromatography) as an oil through the corresponding 14 β -benzoate, m.p. 82-84°C, 82.15%; H,9.81%) in 61% yield. Similarly the lower melting ketone(V) was converted to the diene(IX)(C,88.21%; H,11.81%; 95% homogeneous by gas-liquid chromatography) also an oil via its 14 β -benzoate, m.p. 125-126°C, 82.01%; H,9.76%) in 70% yield.

Despite the success attained in the above synthesis, the final pyrolytic decomposition was considered a weak point in the synthetic scheme. In order to circumvent this step the ketone(I) was converted in 72% yield to the cyclohexyl enol ether (II, R=C₆H₁₁O) m.p. 119-120°C, 80.21%; H,10.80%) by etherification⁷ of the above mentioned hydroxymethylene derivative with cyclohexanol. Reduction⁸ with sodium borohydride in methanol and subsequent treatment with aqueous mineral acid afforded the aldehyde(IV) m.p. 81-83°C, 83.18%; H,10.83%) in 66% yield. This aldehyde was readily methylated with methyl iodide in the presence of potassium t-butoxide in t-butyl alcohol. When the resulting mixture of epimeric β -unsaturated

⁷ A. Eschenmoser, J. Schreiber and S. A. Julia, Helv. Chim. Acta 36, 482 (1953).

⁸ P. Seifert and H. Schinz, Helv. Chim. Acta 34, 728 (1951).

aldehydes was separated by chromatography on Florisil, there was obtained first a 25% yield of the axial aldehyde(VIII) m.p. 58-60°(C,83.30%; H,11.15%) and then a 35% yield of the equatorial aldehyde(VII) m.p. 77-80°(C,83.22%; H,11.02%). Each aldehyde was shown to be homogeneous by gas-liquid chromatography and stereochemical assignment was tentatively made on the basis of their chromatographic behaviour. This assignment was confirmed by the conversion of each aldehyde into the corresponding diene by treatment with methylenetriphenylphosphorane⁹ in ether solution. Thus the axial aldehyde(VIII) afforded the diene(X), m.p. 28-31°(C,88.00%; H,11.75%; homogeneous on gas-liquid chromatography) in 83% yield, and the equatorial aldehyde(VII) afforded the diene(IX) m.p. 22-25°(C,88.21%; H,11.78%; homogeneous on gas-liquid chromatography) in 85% yield. The infrared spectra and the retention times on gas-liquid chromatography of the dienes prepared by the latter synthesis are identical to those obtained via the first route. This latter synthesis proves beyond doubt that no rearrangement had occurred during the pyrolytic elimination employed in the first approach and furthermore represents a more convenient and effective method for construction of the pimaric acid ring C substitution pattern.

Since we have been able to synthesize the dl-dienes(IX) and (X) of known stereochemistry, especially about C13, it

⁹ G. Wittig and V. Schöllkopf, Ber. 87, 1318 (1954).

became of interest to corroborate independently the stereochemical assignment¹⁰ of the resin acids - particularly, sandaracopimaric(XI) and pimaric(XII). Each acid was converted by standard methods¹¹ to its corresponding diene: sandaracopimaric acid(XI) afforded sandaracopimaradiene(IX), m.p. 41-42°, $[\alpha]_D -12^\circ$ (C,87.97%; H,11.68%) in 56% overall yield, and pimaric acid(XII) yielded pimaradiene(X) m.p. 24-26°, $[\alpha]_D +99^\circ$ (C,87.97%; H,11.83%) in 66% yield. The infrared spectrum of *l*-sandaracopimaradiene is identical to the dl-diene(IX), thus substantiating the quasi-equatorial nature of the vinyl group in sandaracopimaric acid(XI). The infrared spectrum of *l*-pimaradiene is identical to the dl-diene(X), thereby corroborating the quasi-axial conformation of the vinyl group in pimaric acid(XII). Further substantiation of the identity of the active dienes and their dl-counterparts is found in gas-liquid chromatography where *l*-sandaracopimaradiene has an identical retention time to that of the dl-diene(IX) and d-pimaradiene to that of the dl-diene(X).

¹⁰ E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.* 80, 2912 (1958); 81, 688 (1959); B. Green, A. Harris and W. B. Whalley, *J. Chem. Soc.* 4715 (1958); O. E. Edwards and R. Howe, *Can. J. Chem.* 37, 760 (1959); *Chemistry and Industry* 537 (1959); H. R. Bruun, *Acta Chem. Scand.* 13, 379 (1959); and J. C. W. Chien, *J. Am. Chem. Soc.* 82, 4762 (1960).

¹¹ These conversions were made by the sequence: R-CO₂H → R-CH₂OH → R-CHO → R-CH=NNHCONH₂ → R-CH₃. Although space does not permit further elaboration, each stage went in high yield and all intermediate products were characterized by infrared spectra and combustion analysis.

The structure represented here for sandaracopimaradiene(IX) has been proposed¹² for the hydrocarbon rimuene. A direct comparison of our synthetic diene(IX) - both active and dl - with a sample of rimuene has shown the two to be different, and we are therefore forced to the conclusion that the structure of rimuene is incorrect. The recently reported conversion of sandaracopimaric acid to rimuene in unstated yield by Petru and co-workers¹³ suffers from the use of a Raney nickel desulfurization at the final stage which could have isomerized the diene system. This point is under further scrutiny in these laboratories.

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¹² L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmhurst, Tetrahedron Letters No. 8, 13 (1959).

¹³ V. Galik, J. Kuthan and F. Petru, Chemistry and Industry 722 (1960).