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ABSOLUTE CONFIGURATION OF GUAIOL

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RECENTLY, Djerassi's group[*1] presented evidence on the absolute configuration of the methyl group at C-4 in guaiol (I) from the identity of bis-homonepetalinic acid and its derivative (III) having the known configurations at C-1, C-4 and C-5 in guaiol, with the degradation product of dextrorotatory dihydroguaiol (II). They also assumed tentatively the β[**] configuration of the C-10 methyl group in guaiol from the results of the rotatory dispersion curve of the indanone derivative (V) derived from the above-mentioned dibasic acid (III). Later, Šorm's group[2] reported on the absolute configuration of the C-10 position from

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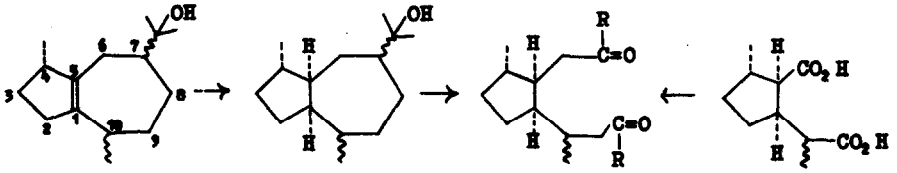
* We are very much indebted to Dr. Carl Djerassi (Stanford University) for sending us the manuscript of the paper "On the absolute configuration of guaiol. Correlation with Nepetalinic Acid" before publication.

1 E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Amer. Chem. Soc. 82 (1960), in press.

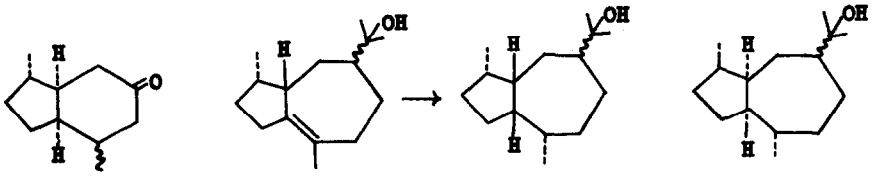
2 L. Dolejs, A. Mironov and F. Šorm, Tetrahedron Letters No. 11, 18 (1960).

** The terms "α" and "β" are used according to the steroidal convention.

the structural elucidation of levorotatory dihydroguaiol (VIIa) obtained from bulnesol (VI).



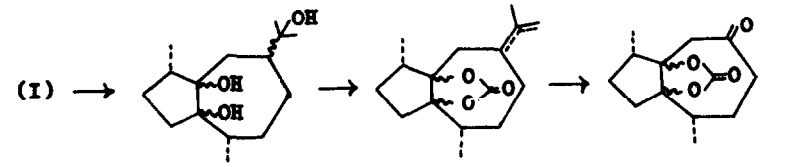
(I) (II) (III) R=OH or NH_2 (IV)



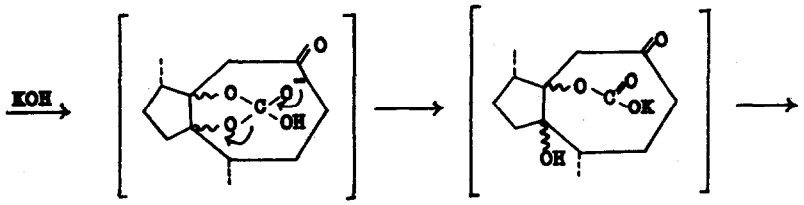
(V) (VI) (VIIa) (VIIb)

We now wish to report our results on the same problems by other routes.

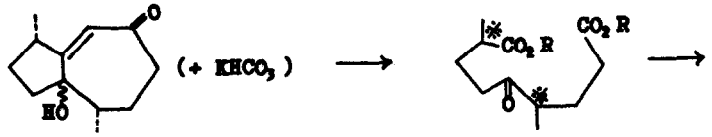
In the course of our attempted investigation on the synthesis of linderazulene[3] from guaiol, we obtained an α,β-unsaturated ketone (XI) by the following route:



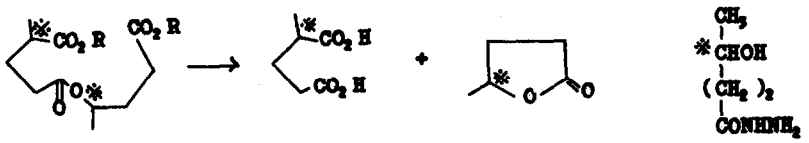
(VIII) (IX) (X)



[3] K. Takeda and W. Nagata, Pharm. Bull. 1, 164 (1953).



(XI) (XII)



(XIII) (XIV) (XV) (XVI)

The identical triol (VIII), m.p. 106-107°, $[\alpha]_D^{24}$ -7°, I.R. ν_{max}^{Nujol} 3385 (OH), 1010 cm^{-1} (C-O), was obtained from guaiol either by the action of OsO_4 or by $KMnO_4$ oxidation. Treatment of this triol with phosgen easily afforded a mixture of unsaturated dioxycarbonyl compounds (IX), I.R. ν_{max}^{Nujol} 1796 (C=O), 1648 cm^{-1} (C=C), dehydration of the hydroxyl group in the side chain having occurred simultaneously. This mixture was converted without purification to a ketone (X), m.p. 113-114°, $[\alpha]_D^{21}$ +2.9°, I.R. ν_{max}^{Nujol} 1784, 1716 cm^{-1} (C=O), 2,4-dinitrophenylhydrazone, m.p. 241-243°, in ca 60% yield by ozonolysis. When this ketone was treated with 1 mol. KOH at room temperature for 3 hrs. in ethanol solution, filtration produced 94% of potassium hydrogencarbonate within 15 minutes, while the α,β-unsaturated ketone (XI), m.p. 47-49°, $[\alpha]_D^{28}$ +176.7°, U.V. $\lambda_{max}^{alcohol}$ 237.5 mμ (ε 9620), I.R. ν_{max}^{Nujol} 3445 (O-H), 1641 (C=O), 1603 cm^{-1} (C=C), was obtained from the filtrate in excellent yield. Although KOH was used in this case (the reaction proceeding most likely through the intermediates as shown in the flow-sheet), there probably occurred no epimerisation at C-4. Ozonolysis of the α,β-unsaturated ketone (XI) in ethyl acetate followed

by hydrogen peroxide oxidation in a neutral medium afforded an oily ketodibasic acid (XII R=H).

Its dimethyl ester (XII R=CH_3), b.p. 134°/1.5 mm., $[\alpha]_D^{24}$ +17.1°, I.R. ν_{max}^{Nujol} 1740, 1713 cm^{-1} (C=O), obtained by the action of CH_2N_2, was converted to the ester (XIII), b.p. 139°/2.5 mm., $[\alpha]_D^{21}$ +16.7°, I.R. ν_{max}^{Nujol} 1740 cm^{-1} (C=O), by the Baeyer-Villiger reaction.[4] As this reaction is accompanied by retention of cinfiguration of the migrating group[5] it was concluded that the C-10 methyl group kept its original configuration.

The thus obtained ester (XIII) was saponified by potassium carbonate in methanol to yield α-methylglutaric acid (XIV) as well as γ-methylbutyrolactone (XV).

α-Methylglutaric acid (XIV), m.p. 85-86°, obtained from this ester showed a positive rotatory power, $[\alpha]_D^{13}$ +17.9°, and was identical with the synthetic (+)-α-methylglutaric acid, m.p. 82-84°, $[\alpha]_D^{19}$ +15.4°.[6]

On the other hand, γ-methylbutyrolactone (XV) thus obtained showed b.p. 99-100°/23 mm., $[\alpha]_D^{23}$ -35.1°, and its infrared spectrum (film) was identical with that of synthetic (-)-γ-methylbutyrolactone,[7] b.p. 97-98°/22 mm., $[\alpha]_D^{23}$ -17.2°. Furthermore, the hydrazide (XVI) of this lactone derived from guaiol, m.p. 91.5-92.5°, $[\alpha]_D^{22}$ +16.6° was also identical in all respects (mixture melting point determination and infrared comparison) with the hydrazide of the synthetic (-)-lactone, m.p. 90-91°, $[\alpha]_D^{24}$ +19.0°.

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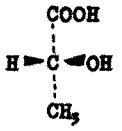
[4] W. D. Emmons and G. B. Lucas, J. Amer. Chem. Soc. 77, 2287 (1955).

[5] R. B. Turner, ibid. 72, 878 (1950).

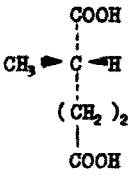
[6] E. Berner and R. Leonardsen, Liebigs Ann. 538, 1 (1939).

[7] P. A. Levene and H. L. Haller, J. Biol. Chem. 69, 165 (1926).

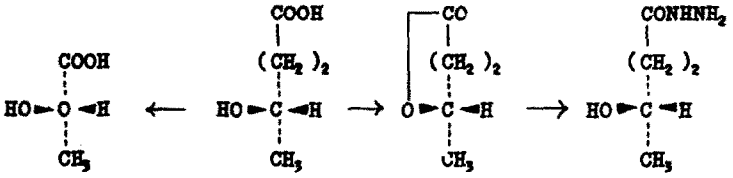
Since S-(+)-α-methylglutaric acid was correlated with R-(-)-lactic acid by A. Fredga[8] and S-(-)-γ-methylbutyrolactone with S-(+)-lactic acid by P. A. Levene[7,9] as shown in the chart, the C-4 and the C-10 methyl groups in guaiol both possess the α-configuration. Guaiol, levorotatory (m.p. 79°) and dextrorotatory dihydroguaiol (oil) should therefore be represented by XVII, VIIa and VIIb, respectively.



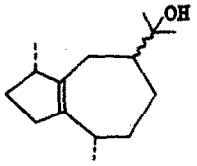
R-(-)-Lactic Acid



S-(+)-α-Methylglutaric Acid



S-(+)-Lactic Acid S-(-)-γ-Methylbutyrolactone



(XVII)

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[8] A. Fredga, Arkiv. Kemi. Mineral Geol. 24A, No. 32 (1947); E. J. Eisenbraun and S. M. McElvain, J. Amer. Chem. Soc. 77, 3383 (1955).

[9] P. A. Levene and H. L. Haller, J. Biol. Chem. 77, 555 (1928).