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ABSOLUTE CONFIGURATION OF THE SUBSTITUENT AT C-7 IN GUAIOL

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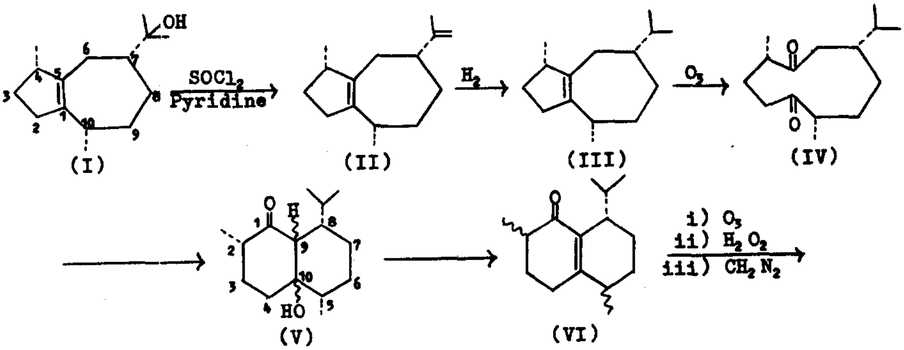
IN the preceding papers,[1] it was established that both the C-4 and the C-10 methyl groups in guaiol (I) possess the α-configuration. Now the question remains as to whether the substituent at C-7 in guaiol is α- or β-oriented.

In this experiment, an attempt was made to determine the absolute configuration of the hydroxyisopropyl group at C-7 in guaiol by degradation of 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (V) which was reported in the previous paper.[2]



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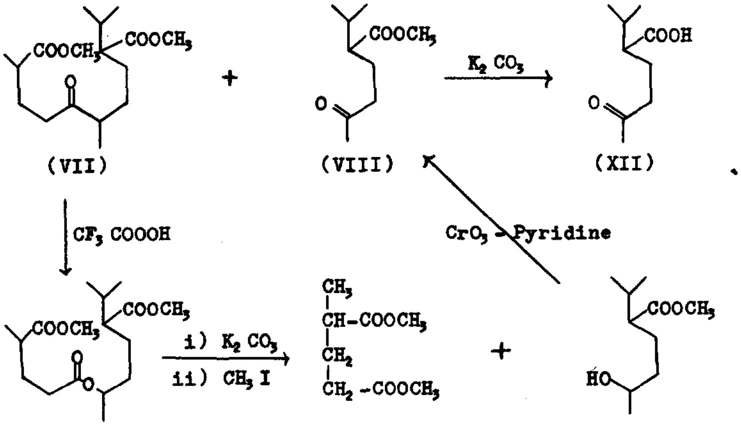
[1] **K. Takeda and H. Minato, Tetrahedron Letters No. 22, 33 (1960); K. Takeda and H. Minato, Chem. Pharm. Bull. (Japan) 9 (1961), in press; H. Minato, Ibid. 9 (1961), in press.**

[2] **K. Takeda, H. Minato and S. Nosaka, Tetrahedron (1961), in press.**



(VII) (VIII) (XII)

(IX) (X) (XI)

The ten-membered ring diketone (IV) was produced through II and III and possesses a bulky isopropyl group. This fact suggests that the conformation possessing the thermodynamically more stable equatorial-like isopropyl group at C-7 is preferred in IV.

When IV was heated at 190-200° without a solvent, or treated with acetic acid under reflux for 1 hr, or with 0.1 N solution of sodium methoxide in methanol under reflux for 1 hr, the result in each case was that the same product, V, was obtained. It would therefore be expected that the isopropyl group in V also possesses the more stable equatorial configuration. This assumption was established by observation of the NMR spectrum of V in chloroform. The spectrum at 56.4 Mc/sec shows a doublet signal (4.97 p.p.m. referred to chloroform) of a proton attached to a carbon atom which is α to a carbonyl group. The fact that the signal is split into a doublet with a 10.5 c.p.s. spin coupling constant indicates the existence of one proton on the adjacent carbon atom. This interpretation of the NMR spectrum leads to the conclusion that the hydrogen atoms at C-8 and C-9 are oriented trans-diaxially[3] to one another and that the isopropyl group at C-8 is equatorial in V.

In view of the course of production of V, the C-4 and C-10 methyl groups and the C-7 hydroxyisopropyl group in guaiol are considered to have maintained these original configurations in V.

Treatment of V with 1 mole sodium hydride in absolute toluene followed by mesylation with mesyl chloride and then chromatography on neutral alumina gave VI and two stereoisomers of V, m.p. 112-112.5°, $[\alpha]_D$ +24.5° and m.p. 130-131.5°, $[\alpha]_D$ -31.4°, as by-products. During the course of this reaction, it is obvious that epimerisation of the quasi-equatorial isopropyl group at C-8 in VI does not occur, although its racemisation may occur to some extent.

Ozonolysis of this α,β-unsaturated ketone (VI) in ethyl acetate followed by hydrogen peroxide oxidation in a neutral medium afforded a mixture of carboxylic acids. The methyl ester obtained by the action of diazomethane was chromatographed on neutral alumina and fractionated to obtain the following fractions: Fraction no. 1, a colorless mobile oil, b.p. 70-84°/1 mm and Fraction no. 2, a pale yellow oil, b.p. 144-145°/1 mm. Fraction no. 2 was the dimethyl ester of the expected keto-dibasic acid (VII), $[\alpha]_D$ -9.8° (Found: C, 64.90; H, 9.47. $C_{17}H_{30}O_5$ requires: C, 64.94; H, 9.62. I.R. $_{\text{film}}$ 1738, 1713 cm^{-1}), which in turn was rearranged by the Baeyer-Villiger reaction with trifluoroperacetic acid to the ester (IX), b.p. 142-143°/1 mm, $[\alpha]_D$ -2.4° (Found: C, 62.25;

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[3] A. D. Cohen, N. Sheppard and J. J. Turner, Proc. Chem. Soc. 118 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, J. Amer. Chem. Soc. 79, 1005 (1957), 80, 6098 (1958); R. U. Lemieux, R. K. Kullnig and R. Y. Moir, Ibid. 80, 2237 (1958).

H, 9.31. $C_{17}H_{30}O_6$ requires: C, 61.79; H, 9.15. I.R.$_{\text{film}}$ 1740 cm^{-1}). Treatment of Fraction no. 1 with Girard's reagent T gave *levorotatory* methyl α-isopropyl-γ-acetobutyrate (VIII), b.p. 81-82°/3 mm, $[\alpha]_D$ -9.0° (Found: C, 64.19; H, 9.87. $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.74. I.R.$_{\text{film}}$ 1733, 1712 cm^{-1}). This ketoester gave a semicarbazone, colorless needles, m.p. 128-129.5°, $[\alpha]_D$ -1.2° (Found: C, 54.59; H, 8.82; N, 16.98. $C_{11}H_{21}O_3N_3$ requires: C, 54.30; H, 8.70; N, 17.27).

On the other hand, IX was saponified by potassium carbonate in methanol, and its potassium salt was refluxed with methyl iodide in absolute methanol to give a mixture of methyl esters. Chromatography of this mixture on neutral alumina afforded methyl α-methylglutarate (X) as well as methyl α-isopropyl-δ-hydroxy-caproate (XI), b.p. 110-111°/5 mm, $[\alpha]_D$ +1.3° (Found: C, 63.60; H, 10.83. $C_{10}H_{20}O_3$ requires: C, 63.79; H, 10.71. I.R.$_{\text{film}}$ 3421, 1733 cm^{-1}), which was oxidized to VIII with chromium trioxide-pyridine. Saponification of VIII with potassium carbonate in methanol gave *levorotatory* α-isopropyl-γ-acetobutyric acid (XII), b.p. 147-150°/2 mm (bath temp), $[\alpha]_D$ -5.0° (semicarbazone, colorless needles, m.p. 140-142°. Found: C, 52.38; H, 8.51; N, 18.08. $C_{10}H_{19}O_3N_3$ requires: C, 52.38; H, 8.35; N, 18.33). Wallach[4,5] obtained *levorotatory* α-isopropylglutaric acid, m.p. 92-93°, $[\alpha]_D$ -15.82°, by oxidation of *levorotatory* α-isopropyl-γ-acetobutyric acid, b.p. 175-180°/19 mm, $[\alpha]_D$ -6.18°, which was derived from *dextrorotatory* fenchone, with sodium hypobromite.

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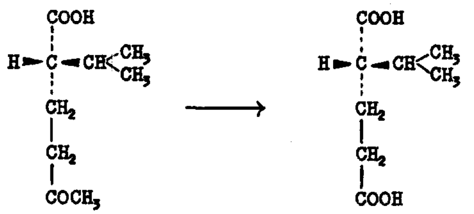
[4] O. Wallach, *Ann.* **369**, 63 (1909), **379**, 182 (1911).

[5] K. Frendenberg and W. Lwowski, *Ann.* **587**, 213 (1954).

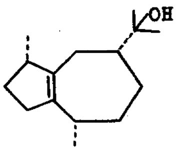
	Acid		Ester	
	$[\alpha]_D$	Semi-carbazone m.p.	$[\alpha]_D$	$[\alpha]_D$ of semi-carbazone
VIII	-5.0° (in dioxane)	140-142°	-9.0° (in dioxane)	-1.2° (in dioxane)
Wallach's VIII	-6.18° (without solvent)	138-140°	-5.58°*	----

* Ethyl ester (J. L. Simonsen, J. Chem. Soc. 119, 1646, 1653 (1921)).

Since Fredga[6] established that levorotatory α-isopropylglutaric acid has the S** (or D)-configuration, VIII should belong to the S-series.



(VIII) S-(-)-isopropylglutaric acid



(XIII)

Further, as the C-8 isopropyl group in 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (V) possesses the α-configuration, guaiol should be represented by XIII.

Acknowledgement —— The author expresses his gratitude to Mr. M. Tori for his aid in the determination and interpretation of the NMR spectra.

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[6] A. Fredga, Acta. chem. Scand. 1, 371 (1947).

** The configurational symbol S is based on the nomenclature sequence rule (R. S. Cahn, C. K. Ingold and V. Prelog, Experientia 12, 81 (1956)).