The Absolute Configuration of Rotenone

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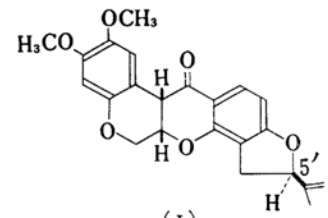
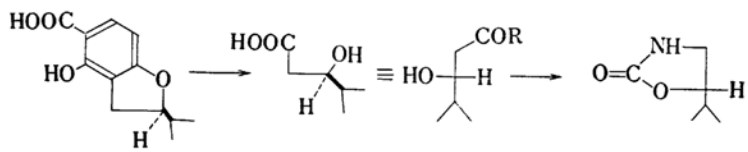
(Received December 22, 1960)

A recent short communication by Büchi et al.[1] on the absolute configuration of rotenone (I) prompts us to report our current work in this field. They submitted (−)dihydrotubaic acid (II) to exhaustive ozonolysis and obtained (+)3-hydroxy-4-methylpentanoic acid. In order to secure enough starting material, they synthesized (±)3-hydroxy-4-methylpentanoic acid and resolved it through the quinine salt to obtain the (−)acid (enantiomer of III, or IVa in Fischer projection), which they converted, via three steps into (−)2-methylpenta-3-ol with a known absolute configuration[2]. They thus established the (R) configuration[3] at position 5′ of rotenone. We also exhaustively ozonolysed (−)dihydrotubaic acid[4], m. p. 166°C, $[\alpha]_D^{25}-103.7°$ (methanol), then oxidized it with peracetic acid following our previous method[5]. The resulting hydroxy acid III was treated with diazomethane to afford the methyl ester IVb, b. p. 77∼86°C/18 mmHg $[\alpha]_D^{20}+19°$ (ethanol), which was converted into (−)3-hydroxy-4-methylpentanohydrazide IVc,



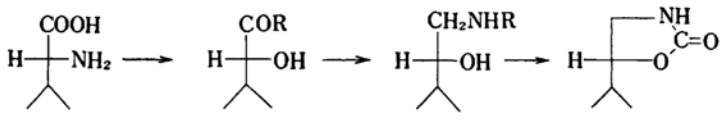
(I)



(II) (III) (IV) (V)

(a) R=OH
(b) R=OCH_3
(c) R=$NHNH_2$

1) G. Büchi, J. S. Kaltenbronn, L. Crombie, P. L. Godin and D. A. Whiting, *Proc. Chem. Soc.*, **1960**, 274.
2) See the footnote 4 and 5 of Büchi and Crombie's paper 1).
3) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 18 (1956).
4) S. Takei and M. Koide, *Ber.*, **62**, 3030 (1929).
5) H. Arakawa and M. Nakazaki, *Ann.*, **636**, 111 (1960).



(VI) (VII) (VIII) (IX)

(a) R=OH
(b) R=OCH_3
(c) R=NH_2

(a) R=H
(b) R=$COOC_2H_5$

m. p. 152~153°C, $[\alpha]_D^{19}$+43° (ethanol) with hydrazine. To relate this hydrazide IVc with D-valine, IVc was treated with nitrous acid[6] to afford (−)5-isopropyloxazolidone (V), m. p. 113~114°C, $[\alpha]_D^{18}$−44.5° (ethanol). Found: C, 55.93; H, 8.55; N, 10.98. Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.84%.

Racemic hydrazide IVc, m. p. 149~150°C, was prepared from ethyl 3-hydroxy-4-methylpentanoate which was prepared by the reduction of ethyl 3-oxo-4-methylpentanoate with sodium borohydride. Reaction with nitrous acid converted the racemic hydrazide IVc into the oxazolidone V, m. p. 87~88°C, the I. R. spectrum of which was found sound superimposable on that of the (−)oxazolidone V from rotenone.

(−)Methyl 2-hydroxy-3-methylbutanoate[7], b. p. 62~63°/15 mmHg, $[\alpha]_D^{17}$−1.4° (etahnol) prepared from D-valine[8], $[\alpha]_D^{16}$−27.6° (6 N hydrochloric acid), was treated with liquid ammonia to give the amide VIIc, m. p. 99~100°C, $[\alpha]_D^{15}$+65.1° (methanol) (racemic compound, m. p. 104~105°C), which in turn was reduced with lithium aluminumhydride to the aminoalcohol VIIIa.

Reaction of sodium methoxide with the ethyl carbamate drivative VIIIb, which was obtained from the aminoalcohol VIIIa by the action of ethyl chlorocarbonate in pyridine, gave (+)5-isopropyloxazolidone (IX), m. p. 113~114°C, $[\alpha]_D^{14}$+44.2° (ethanol). Found: C, 56.18; H, 8.68; N, 11.13%.

(−)5-Isopropyloxazolidone (V) derived from rotenone and (+)5-isopropyloxazolidone (IX) prepared from D-valine exhibited I. R. spectra which could be superimposed in every detail.

In order to make sure that they are enantiomorphic, an equal amount of (+) and (−) oxazolidone were mixed and recrystallized to give the racemic 5-isopropyloxazolidone which melted at 87~88°C, alone and admixed with the synthetic racemic oxazolidone from the racemic hydrazide.

Thus we could confirm Büchi and Crombie's result that rotenone has the (R) configuration at position 5'.

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6) Cf. C. Schöpf, G. Dummer and W. Wüst, ibid., **626**, 134 (1959); C. Schöpf and W. Wüst, ibid., **626**, 150 (1959).
7) E. Fischer and H. Scheibler, *Ber.*, **41**, 2891 (1908); P. D. Bartlett, M. Kuna and P. A. Leven, *J. Biol. Chem.*, **118**, 303 (1937); W. Klyne, "Progress in Stereochemistry", Vol. I, Butterworth, London (1950), p. 195.
8) We are indebted to Dr. Setsuji Sakurai, Ajinomoto Co., for his generous gift of D-valine.