The Absolute Structure of Actinidine

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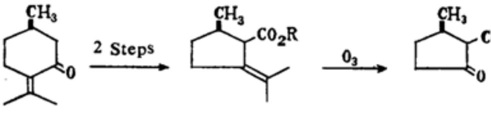
(+)-Actinidine, the enantiomeric from of the levorotatory natural product, has been synthesized from (+)-pulegone through methyl pulegenate (Ib).

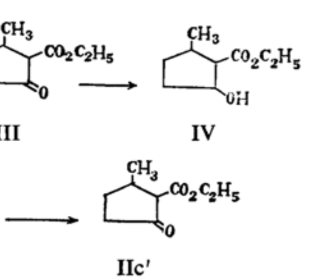
The synthesis was preceded by the scrupulous confirmation of the plane structure of pulegenic acid (Ia), presented by H. Rupe and K. Schäfer¹⁾ to be 2-isopropyliden-5-methyl-cyclopentanecarboxylic acid. The ethyl ester (Ic) of Ia was ozonolyzed to ethyl 2-methyl-5-oxocyclopentanecarboxylate (IIc), b. p. 95~96°C/10 mmHg (Found: C, 63.31; H, 8.35. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29 %), and the racemic form of the latter was synthesized.



I II

a : R=H; b : R=CH_3; c : R=C_2H_5

The half ethylene dithio-ketal (III), m. p. 63°C (Found: C, 50.53: H, 6.23; S, 24.59. Calcd. for $C_{11}H_{16}O_3S_2$; C, 50.77; H, 6.20; S, 24.62 %) of ethyl 2-methyl-4, 5-dioxocyclopentanecarboxylate²⁾ was reduced on treatment with Raney nickel to the hydroxy ester (IV) (ν_{OH} 2.89 μ in infrared absorption spectrum), which was converted into the corresponding keto ester (IIc′) by the successive oxidation with the complex of chromic oxide-pyridine. IIc and IIc′ were proved to be identical through the mixed fusion test and the comparison of the infrared absorption spectra of their semicarbazones.



III IV

IIc′

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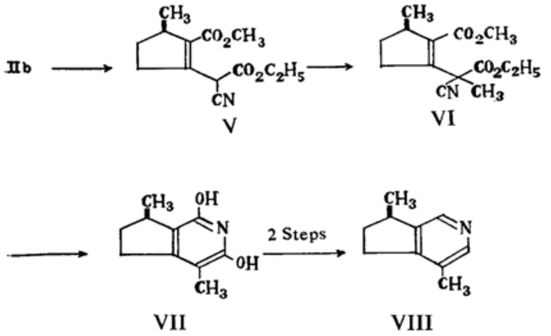
[1] H. Rupe and K. Schafer, *Helv. Chim. Acta*, **11**, 466 (1928).

[2] H. Staudinger and L. Ruzicka, ibid., 7, 381 (1924).

The attempts to hydroxylate the isopropyliden group in Ib with selenium dioxide under the various conditions were so all in failure that the authors were impelled to take a rather circuitous route for the purpose. The satisfactory result was achieved when the methyl ester (IIb), b. p. 90~92°C/12 mmHg (Found: C, 61.29; H, 7.91. Calcd. for $C_8H_{12}O_3$: 61.52; H, 7.75 %), was chosen as a key compound and the necessary C_3-moiety was re-introduced into IIb as shown below.



The condensation product (V) of IIb with ethyl cyanoacetate was treated with methyl iodide in the ethoxide solution and the methylated diester (VI) was hydrolyzed with acid or alkali to the dihydroxypyridine derivative (VII), m. p. 172~173°C (Found: C, 67.15; H, 7.51; N, 7.98. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%). The chlorination of VII and the successive catalytic hydrogenation of the dichloro-compound, similar to those reported in the synthesis of DL-actinidine[3], yielded the base (VIII), the purified picrate (Found: C, 50.95; H, 4.36; N, 14.91. Calcd. for $C_{16}H_{16}O_7N_4$; C, 51.06; H, 4.29; N, 14.89 %) of which melted at 146~147°C. The regenerated base, b. p. 88~90°C/5 mmHg, from the latter gave the value of $[\alpha]^{15}_{D}+16.1^\circ$ (c 5.52 chloroform) and the identical infrared absorption chart with the natural alkaloid. Although the absolute values of rotatory power were not equal between these two actinidines obtained, the synthesized one was likely to be in a more purified state.

As the asymmetric center of (+)-pulegone had already been correlated in the stereochemical analysis to D-series[4], the absolute configuration of $C_{(7)}$-carbon atom in natural actinidine (6, 7-dihydro-4, 7-dimethyl-5(*H*)-2-pyrindine) has now been established.

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[3] T. Sakan, A. Fujino, F. Murai, A. Suzui and Y. Butsugan, This Bulletin, 32, 1155 (1959).

[4] K. Freudenberg and W. Hohmann, *Ann.*, 584, 54 (1953).