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CORRELATION OF VALEROIDINE WITH S(-)METHOXYSUCCINIC ACID AND OF MONO- AND DITIGLOYL-TROPANE-3.6-DIOL WITH ITS R(+)ANTIMER

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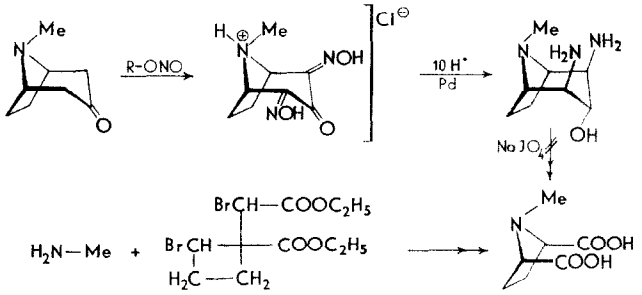
Valeroidine (1) is derived from (-)tropane-3α.6β-diol while its antimer is the alkamine of 6β-tigloyloxy-3α-hydroxy tropane (2) and of 3α.6β-ditigloyloxytropane (3).

The relative configurations of the hydroxyl groups in valeroidine were established by chemical methods (4,5,6), the absolute configuration has been deduced from the strong rightwards shift of the $/\alpha/_D$ value during the cyclization of (-)N-ethoxycarbonylmethyl-3α.6β-dihydroxytropanium iodide to the (+) lactone and by adopting (7) Hudson's lactone rule (8,9). In consequence, the 3R:6R configuration was ascribed (7) to the (-) derivative and hence the 3S:6S structure to the (+) antimer.

Despite the general validity of this empirical rule - except for a single case (10) - it seemed desirable to check the correctness of this deduction by unequivocal chemical interconversions.

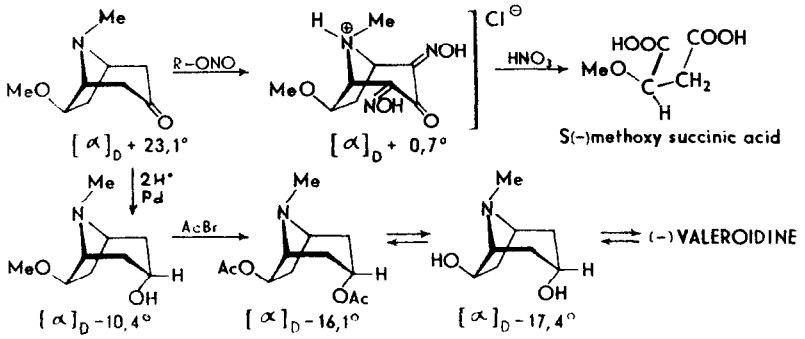
First, destruction of the 6-membered ring, without affecting the 5-membered one, leading to 4-oxo proline of known configuration (11) appeared to be the most simple

approach. Direct oxidation of either tropan-3-one or its 6-substituted derivatives with a variety of agents, e.g. selenium dioxide, lead tetraacetate, Fenton's reagent, wet silver oxide, potassium hypobromite failed to give any identifiable products, e.g. N-methyl-succinimide or N-methyl-pyrrolidine-2.5-dicarboxylic acid. Accordingly, we attempted to carry out a more systematic degradation of that ring by converting tropane-3-one via the bis-isonitroso derivative into 2.4-diamino-tropan-3α-ol followed by cleavage with sodium periodate. Consumption of 2.0 moles of periodate and formation of 2.1 moles of ammonium chloride has been observed, however, neither the expected dialdehyde, nor its oxidation product, i.e. N-methyl-pyrrolidine-2.5-dicarboxylic acid could be detected, although the latter was synthesized for sake of comparison, following the lines given by Willstätter (12). The compound showed a very characteristic UV absorption at 264 mμ permitting easy identification.

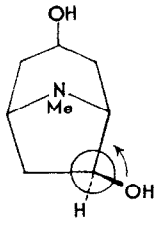


As a second alternative, 6-methoxytropane-3-one (13) was converted into the 2.4-dioximino derivative and this refluxed with 65% nitric acid. Methoxysuccinic acid contaminated with some oxalic acid was obtained in 20% yield, m.p. 104° - 106° alone and mixed with a specimen prepared by

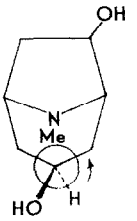
methylation from (±) malic acid with subsequent hydrolysis of the ester. Based upon this success, 6-methoxytropane-3-one was resolved by (+) tartaric acid (tartrate, m.p. 132°; $/\alpha/_D$ + 23.9° (H_2O); found: C, 48.82, 48.95; H, 6.67, 6.65; N, 4.65, 4.72%. Calcd. for $C_{13}H_{21}NO_8$: C, 48.90; H, 6.63; N, 4.39%.), and the dextrorotatory derivative (Found: N, 8.61%. Calcd. for $C_9H_{15}NO_2$: N, 8.26%; $/\alpha/_D$ + 23.1° (H_2O)) converted into the dioximino ketone hydrochloride (Found: N, 16.28; Cl^-, 13.50, 13.65%. Calcd. for $C_9H_{14}N_3O_4Cl$: N, 15.94 Cl^-, 13.45%; $/\alpha/_D$ + 0,7° (H_2O)), and this, in turn, oxidised by nitric acid to give S(-)methoxysuccinic acid identical with a specimen obtained from S(-)malic acid by methylation (14). The (+) ketone was hydrogenated catalytically to 6(-)methoxytropine ($/\alpha/_D$ - 10.4° (H_2O)). Correlation of the same with (-)tropane-3α.6β-diol was achieved in two steps: (i) acetobromolysis of this methoxy compound gave methyl bromide and (-)3α.6β-diacetoxy-tropane ($/\alpha/_D$ - 16.1° (ethanol)); picrate m.p. 193°) without affecting the C-O bond at the asymmetric centre at C_6. This (-)3.6-diacetoxy-tropane proved to be identical in every respect with the product we obtained by acetylation from the alkamine of natural valeroidine. (ii) Furthermore, deacetylation of the diacetate gave pure (-)3α.6β-tropane-diol (m.p. 207.5° - 211°; $/\alpha/_D$ - 17.4° (ethanol)).



This provides unequivocal evidence that the relative configuration of the methoxy group in (+)6-methoxytropane-3-one is β and has the absolute configuration S. Consequently, (-)tropane-3.6-diol from Javanese Coca leaves and also valeroidine have S configuration at C_6. Hence, all these



6S



3S

compounds possess 3S:6S configuration, quite opposite those deduced in previous investigations (7) by adopting Hudson's lactone rule. Thus, the 3R:6R configuration is valid for the dextrorotatory alkamine both of 6β-tigloyloxytropane-3α-ol from leaves of Datura cornigera and of 3α.6β-ditigloyloxytropane from Datura ferox, innoxia and stramonium.

The reason for the failure of Hudson's lactone rule as observed above, still calls for further investigation. Full details of this work will be published in the Journal of the Chemical Society, London.

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