Correction of the Absolute Configuration of Nuphar Alkaloids

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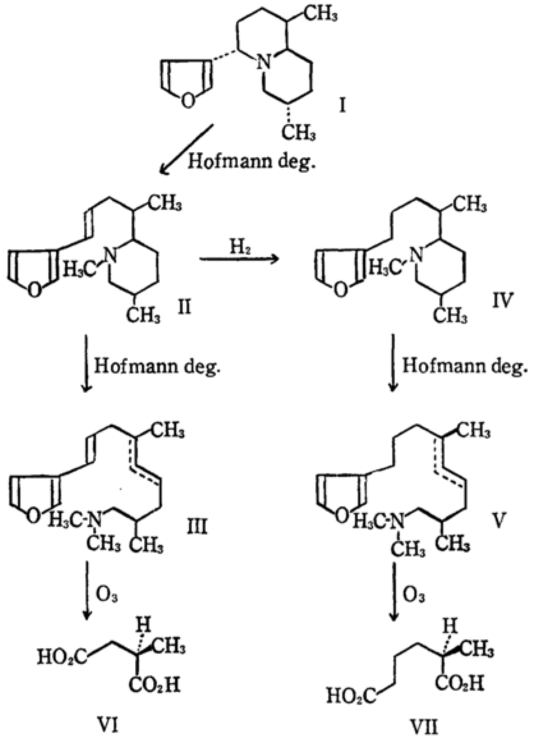
Previously, we reported the determination of the absolute configuration of *Nuphar* alkaloids[1] on the basis of (−)-α-methyladipic acid (VII), an oxidation product from anhydrodihydrodes-*N*-methyldeoxynupharidine (V), having the S-configuration. This configurational assignment of (−)-α-methyladipic acid was derived from the basis of its synthesis from (−)-α-methyl-γ-butyrolactone which was correlated with S(−)-methylsuccinic acid.[2],[*1]

Recently Turner *et al.* obtained R(−)-α-methylglutaric acid, R(+)-β-methyladipic acid and (−)-α-methyladipic acid from the oxidation of cytochalasins A and B,[3] metabolites of *Helminthosporium dematioideum*, and they suggested that (−)-α-methyladipic acid is shown to have the R-configuration.[4]



Now we reinvestigated the oxidation of the second Hofmann degradation product of deoxynupharidine (I) and found that the oxidation of anhydrodes-*N*-methyldeoxynupharidine (III) gave R(+)-methylsuccinic acid (VI).

Therefore (−)-α-methyladipic acid should have R-confuguration as was suggested by Turner and the stereostructures of nuphar alkaloids are shown to have the antipodal configuration of the previously presented formulae[5-7] (*e.g.* formula I is given to the stereostructure of the main alkaloid deoxynupharidine.).

Experimental

Anhydrodes-*N*-methyldeoxynupharidine (III). Deoxynupharidine (I) methoiodide (40 g) was dissolved in methanol (300 m*l*) and shaken with silver oxide (prepared from 50 g of silver nitrate) for 1 hr and then filtered. The filtrate was evaporated and heated on the water bath for 2 hr. The reaction mixture was extracted with ether and the ethereal solution was washed with water. The solvent was evaporated and the residue was distilled at 113—115°C/10^{-3} mmHg to give 20.5 g of des-*N*-methyldeoxynupharidine.

To the above oil (20.5 g) was added methyl iodide (25 g) and then the methoiodide obtained was subjected to Hofmann degradation in the same manner mentioned above to give 14.6 g of anhydro base, bp 125°C/10^{-3} mmHg.

Oxidation of the Anhydro Base. The above anhydro base was dissolved in chloroform (200 m*l*) and treated with a stream of oxygen containing ozone under ice-salt cooling. To the reaction mixture was added water (600 m*l*) and heated on the water bath under removing the chloroform by evaporation, then 30% hydrogen peroxide (600 m*l*) was added to the solution and heated for an additional 4 hr. The resulting mixture was extracted continuously with ether for 36 hr and water was added to the ether extract, then the solvent removed. The residual aqueous solution, after decomposition of a remaining hydrogen peroxide by the addition of sodium bisulfite, was reextracted with ether and the dried ether extract was methylated with ethereal diazomethane. The obtained methyl esters were separated by fractional distillation. An ester distilled at 100—103°C/21 mmHg gave dimethyl methylsuccinate which was identical with an authentic specimen in IR spectra. The ester was boiled

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[1] M. Kotake, I. Kawasaki, T. Okamoto, S. Matsutani, S. Kusumoto and T. Kaneko, This Bulletin, **35**, 1335 (1962).

[2] T. Kaneko, K. Wakabayashi and H. Katsura, *ibid.*, **35**, 1149 (1962).

[*1] This conclusion was uncertain, owing to the very small optical rotation of α-methyladipic acid. Experiments on the confirmation of this acid by an unequivocal process are now in progress.

[3] D. C. Aldridge, J. J. Armstrong, R. N. Speake and W. B. Turner, *Chem. Commn.*, **1967**, 26.

[4] W. B. Turner's personal communication and D. C. Aldridge, J. J. Armstrong, R. N. Speake and W. B. Turner, *J. Chem. Soc.*, (*C*), **1967**, 1667.

[5] I. Kawasaki, S. Matsutani and T. Kaneko, This Bulletin, **36**, 1474 (1963).

[6] Y. Arata, *Chem. Pharm. Bull.*, **13**, 907 (1965).

[7] Y. Arata and T. Ohashi, *ibid.*, **13**, 1247 (1965).

for 3 hr with 6 N hydrochloric acid and then evaporated to dryness. The residue was recrystallized three times from benzene to give 400 mg of methylsuccinic acid, mp 106—108°C, $[\alpha]_D^{16}$ +7.74 (*c* 20, abs. ethanol).

Found: C, 45.57; H, 6.10%. Calcd for $C_5H_8O_4$: C, 45.45; H, 6.10%.

TLC on silica gel G afforde done spot at R_f, 0.30. ($EtOH:H_2O:NH_4OH$, 51:6:7).