

SITE-SPECIFICITY IN THE BAEYER-VILLIGER OXIDATION OF 2-ALKYL-9-AZABICYCLO[3.3.1]NONANE-3,7-DIONES: EXCLUSIVE CLEAVAGE OF THE ALKYLATED HALF OF THE TWIN-PIPERIDONE SYSTEM

Takefumi Momose* and Shohgo Atarashi

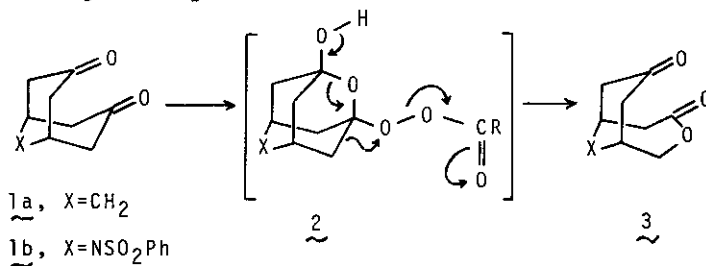
Faculty of Pharmaceutical Sciences, Osaka University
Yamada-kami, Suita, Osaka 565, Japan.

Conrad Hans Eugster

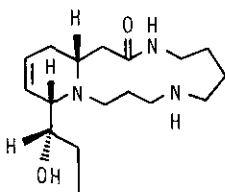
Organisch-chemisches Institut der Universität Zürich
Rämistrasse 76, CH-8001 Zürich, Schweiz

Abstract — The Baeyer-Villiger oxidation of 2-alkyl-N-methoxycarbonyl-9-azabicyclo[3.3.1]nonane-3,7-diones (9a and 9b) proceeded site-specifically to afford the keto lactones (11a and 11b) which were transformed into the cis-2,6-disubstituted piperidines related to palustramic acid.

In the previous papers,¹ there was reported that the Baeyer-Villiger oxidation of bicyclo[3.3.1]nonane-3,7-dione (1a) or its analogue (1b) gave the keto lactone (3) as a single product via the intermediate (2) resulting from through-space participation of the facing carbonyls.

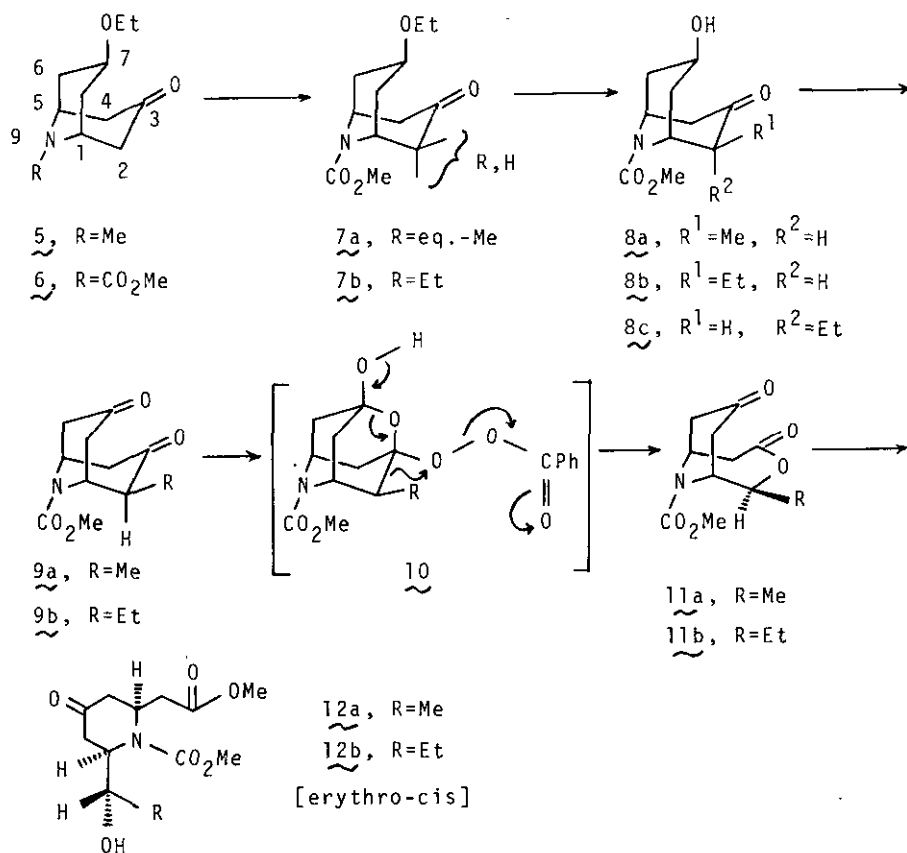


This communication describes a site-specific Baeyer-Villiger oxidation of 2-alkyl-9-azabicyclo[3.3.1]nonane-3,7-diones and an approach to the stereoselective synthetic design of palustramic acid, the piperideine fragment of the Equisetum alkaloid palustrine (4).²



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The 2-methyl- and 2-ethyl-N-methoxycarbonyl-9-azabicyclo[3.3.1]nonane-3,7-diones (9a and 9b) were prepared as follows. 7-Ethoxy-pseudopelletierine (5)³ was converted to the carbamate (6) in 66% yield by treatment with methyl chlorocarbonate, and monoalkylated by successive treatments with dimethyl carbonate in the presence of sodium hydride and with alkyl iodides followed by saponification and decarboxylation. The yields of α -monoalkyl ketones (7a and 7b) from 6 were 49 and 56%, respectively. The methyl group in 7a was assigned equatorial configuration⁴ by decoupling experiment on the pmr spectrum⁵ of its oxime. Treatment of 7a with boron tribromide in methylene chloride at -78° afforded a single ketol (8a) in 84% yield, but with 7b two stereoisomeric ketols (8b and 8c) were obtained in a ratio of ca. 5.7:1 in 88% sum yield. The main and minor products were assigned to an equatorial and an axial isomer, respectively, on the basis of the pmr evidences⁶ on their oximes. The equatorial isomers 8a and 8b were oxidized with chromium trioxide-pyridine to give the diketones 9a [78% yield; IR(CCl₄): 1730 (sh), 1715cm⁻¹] and 9b [78% yield; IR(CCl₄): 1730 (sh), 1710cm⁻¹]. The Baeyer-Villiger oxidation of 9a and 9b with m-chloroperbenzoic acid in boiling methylene chloride⁷ gave the keto lactones 11a [93% yield; IR(CHCl₃): 1747, 1720 (sh), 1705cm⁻¹; MS: m/e 241 (M⁺, 4.5%)] and 11b [94% yield; IR(CHCl₃): 1750, 1720 (sh), 1708cm⁻¹; MS: m/e 255 (M⁺, 7%)], respectively. In the pmr spectrum of 11a, the C₂-H signal at δ 4.71 was changed from a quartet ($J=7\text{Hz}$) to a singlet⁸ by decoupling of the doublet ($J=7\text{Hz}$) for methyl group at δ 1.38. In 11b, the double-doublet ($J=7,6\text{Hz}$) for the C₂-H at δ 4.37 was changed to a singlet⁸ by decoupling of the methylene signal due to the ethyl group. These results indicate that in the Baeyer-Villiger oxidation of these diketones the peracid attacked site-specifically the alkylated piperidone ring and that the C₂-carbon rearranged selectively via the intermediate such as 10. Methanolysis of 11a and 11b in methylene chloride-methanol in the presence of alumina performed the ring cleavage to afford the erythro-cis products 12a [70% yield; IR(CCl₄): 3450, 1740 (sh), 1725 (sh), 1708cm⁻¹; MS: m/e 273 (M⁺, 0.5%); PMR(CDCl₃): δ 1.13 (d, $J=7\text{Hz}$),



3.69, 3.73 (s, OCH₃×2), 4.22(m, carbinol H) and 12b [43% yield; IR(CCl₄): 3450, 1740(sh), 1725(sh), 1708cm⁻¹; MS: m/e 287(M⁺, 0.6%); PMR(CDCl₃): δ 0.99(t, J=7Hz), 1.41(quintet-like, -CH₂CH₃), 3.7, 3.72(s, OCH₃×2), 3.92(m, carbinol H)].

The ester 12b has the piperidine skeleton bearing all of the asymmetric centers of palustrine (4, threo-cis) though epimeric with respect to the hydroxyl configuration. Inversion of the hydroxyl configuration in 12b and stereoselective synthesis of 4 are now under investigation.

REFERENCES AND FOOTNOTES

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 (b) T. Momose and S. Atarashi, *Heterocycles*, 1978, 9, 631.
- (a) C.H. Eugster, *Heterocycles*, 1976, 4, 51; (b) Eugster et al. recently reported the synthesis of threo- and erythro-cis/trans-dihydropalustrine: see E. Wälchli-Schaer and C.H. Eugster, *Helv. Chim. Acta*, 1978, 61, 928.

3. H. Stetter and R. Mehren, Liebigs Ann. Chem., 1967, 709, 170.
4. In the pmr spectrum of the only stable oxime of 7a, the quintet-like signal for the anti C₂-H at δ 2.64 was changed to a doublet (\underline{J} =5Hz) by decoupling of the methyl signal at δ 1.19, the feature of which suggests an axial orientation for the C₂-hydrogen; cf. ref. 1b.
5. PMR spectra were measured for the CDCl₃ solution with TMS as an internal standard on a Hitachi R-22 spectrometer operating at 90MHz.
6. In the decoupling experiment of the bridgehead hydrogens in the oxime of 8b, the multiplet signal for the anti C₂-H at δ 2.4 was changed to a triplet (\underline{J} =7Hz), and the signal of the C₄-axial H appeared as a doublet (\underline{J} =16Hz) at δ 2.05, but in the oxime of 8c the C₄-axial H signal appeared as a doublet (\underline{J} =16Hz) at δ 2.16. This downfield shift⁹ of the C₄-axial H in the oxime of 8c could be explained in terms of a deshielding effect due to a 1,3-diaxial relationship of the axial ethyl group at C₂. The feature also suggests an equatorial orientation for the C₂-ethyl group in 8b.
7. 4,4'-Thiobis(6-tert-butyl-m-cresol) was catalytically used as a radical inhibitor: see Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, and T. Goto, Chem. Commun., 1972, 64.
8. Inspection of the Dreiding model indicates the dihedral angle between the C₂ and bridgehead C₁-hydrogen to be ca. 90°.
9. See, for example, (a) D. Tavernier and M. Anteunis, Tetrahedron, 1971, 27, 1677; (b) T.A. Grabb and E.R. Jones, ibid., 1970, 26, 1217; (c) T. Masamune, S. Numata, H. Matsue, A. Matsuyuki, T. Sato, and H. Murase, Bull. Chem. Soc. Japan, 1975, 48, 2294.

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