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

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Abstract — The Baeyer-Villiger oxidation of 2-alkyl-N-methoxy-
carbonyl-9-azabicyclo[3.3.1]nonane-3,7-diones (9a and 9b) 
proceeded site-specifically to afford the keto lactones (1a
and 1b) which were transformed into the cis-2,6-disubstituted
piperidines related to palustramic acid.

In the previous papers, 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 partici-
pation of the facing carboxyls.

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 piperidine fragment of the Equisetum
alkaloid palustrine (4).2
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) 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 configuration by decoupling experiment on the pmr spectrum of its oxime. Treatment of 7a with boron tribromide in methylene chloride at -78°C 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 evidences 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), 1715 cm⁻¹] and 9b [78% yield; IR(CCl₄): 1730 (sh), 1710 cm⁻¹]. The Baeyer-Villiger oxidation of 9a and 9b with m-chloroperbenzoic acid in boiling methylene chloride gave the keto lactones 11a [93% yield: IR(CHCl₃): 1747, 1720 (sh), 1705 cm⁻¹; MS: m/e 241 (M⁺, 4.5%)] and 11b [94% yield; IR(CHCl₃): 1750, 1720 (sh), 1708 cm⁻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=7Hz) to a singlet by decoupling of the doublet (J=7Hz) for methyl group at δ 1.38. In 11b, the double-doublet (J=7,6Hz) for the C₂-H at δ 4.37 was changed to a singlet 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. Methanalysis 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), 1708 cm⁻¹; MS: m/e 273 (M⁺, 0.5%); PMR(CDC₁₃): δ 1.13 (d, J=7Hz),
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


4. In the pmr spectrum of the only stable oxime of \(7a\), the quintet-like signal for the anti \(C_2\)-H at \(\delta 2.64\) was changed to a doublet \((J=5\text{Hz})\) by decoupling of the methyl signal at \(\delta 1.19\), the feature of which suggests an axial orientation for the \(C_2\)-hydrogen; cf. ref. 1b.

5. PMR spectra were measured for the \(\text{CDCl}_3\) 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 \(C_2\)-H at \(\delta 2.4\) was changed to a triplet \((J=7\text{Hz})\), and the signal of the \(C_4\)-axial H appeared as a doublet \((J=16\text{Hz})\) at \(\delta 2.05\), but in the oxime of \(8c\), the \(C_4\)-axial H signal appeared as a doublet \((J=16\text{Hz})\) at \(\delta 2.16\). This downfield shift\(^9\) of the \(C_4\)-axial H in the oxime of \(8c\) could be explained in terms of a deshielding effect due to a 1,3-di-axial relationship of the axial ethyl group at \(C_2\). The feature also suggests an equatorial orientation for the \(C_2\)-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 \(C_2\) and bridgehead \(C_1\)-hydrogen to be ca. 90°.


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