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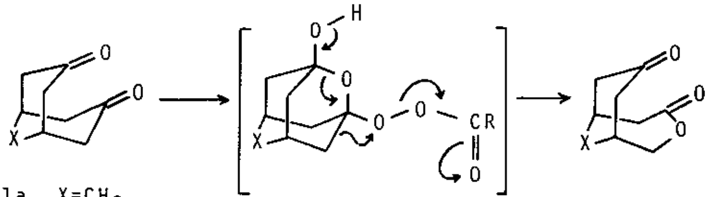
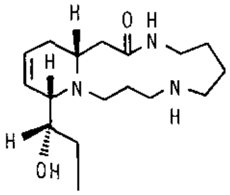
Abstract —— The Baeyer-Villiger oxidation of 2-alkyl-N-methoxycarbonyl-9-azabicyclo[3.3.1]nonane-3,7-diones (9a and 9b) proceeded site-specifically to afford the keto lactones (11a and 11b) which were transformed into the *cis*-2,6-disubstituted piperidines related to palustramic acid.

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.



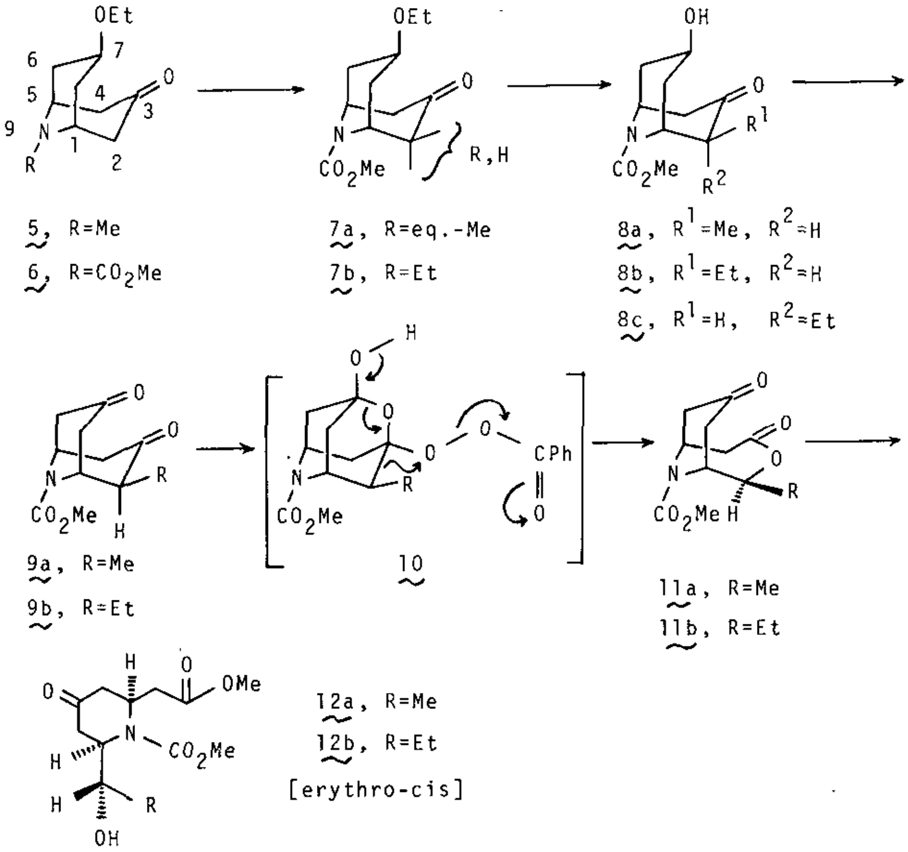
1a, X=CH$_2$
1b, X=NSO$_2$Ph
2
3

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]



4

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 configuration[4] by decoupling experiment on the pmr spectrum[5] 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 evidences[6] on their oximes. The equatorial isomers 8a and 8b were oxidized with chromium trioxide-pyridine to give the diketones 9a [78% yield; IR(CCl_4): 1730(sh), 1715cm^{-1}] and 9b [78% yield; IR(CCl_4): 1730(sh), 1710cm^{-1}]. The Baeyer-Villiger oxidation of 9a and 9b with m-chloroperbenzoic acid in boiling methylene chloride[7] gave the keto lactones 11a [93% yield; IR($CHCl_3$): 1747, 1720(sh), 1705cm^{-1}; MS: m/e 241(M^+, 4.5%)] and 11b [94% yield; IR($CHCl_3$): 1750, 1720(sh), 1708cm^{-1}; MS: m/e 255(M^+, 7%)], respectively. In the pmr spectrum of 11a, the C_2-H signal at δ 4.71 was changed from a quartet (J=7Hz) to a singlet[8] by decoupling of the doublet (J=7Hz) for methyl group at δ 1.38. In 11b, the double-doublet (J=7,6Hz) for the C_2-H at δ 4.37 was changed to a singlet[8] 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 C_2-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(CCl_4): 3450, 1740(sh), 1725(sh), 1708cm^{-1}; MS: m/e 273(M^+, 0.5%); PMR($CDCl_3$): δ 1.13(d, J=7Hz),



5, R=Me
6, R=CO_2Me

7a, R=eq.-Me
7b, R=Et

8a, R^1=Me, R^2=H
8b, R^1=Et, R^2=H
8c, R^1=H, R^2=Et

9a, R=Me
9b, R=Et

10

11a, R=Me
11b, R=Et

12a, R=Me
12b, R=Et
[erythro-cis]

3.69, 3.73 (s, $OCH_3\times2$), 4.22(m, carbinol H)] and 12b [43% yield; IR(CCl_4): 3450, 1740(sh), 1725(sh), 1708cm^{-1}; MS: *m/e* 287(M^+, 0.6%); PMR($CDCl_3$): δ 0.99(t, *J*=7Hz), 1.41(quintet-like, $-C\underline{H}_2CH_3$), 3.7, 3.72(s, $OCH_3\times2$), 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

1. (a) T. Momose, S. Atarashi, and O. Muraoka, Tetrahedron Lett., 1974, 3697;
(b) T. Momose and S. Atarashi, Heterocycles, 1978, 9, 631.

2. (a) C.H. Eugster, Heterocycles, 1976, 4, 51; (b) Eugster et al. recently reported the synthesis of threo- and erythro-cis/trans-dihydropalusrine: 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 C_2-H at δ 2.64 was changed to a doublet (*J*=5Hz) by decoupling of the methyl signal at δ 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 $CDCl_3$ 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 δ 2.4 was changed to a triplet (*J*=7Hz), and the signal of the C_4-axial H appeared as a doublet (*J*=16Hz) at δ 2.05, but in the oxime of **8c** the C_4-axial H signal appeared as a doublet (*J*=16Hz) at δ 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-diaxial 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°.

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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