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NOVEL STERIC FACTORS OPERATING ON THE BAEYER-VILLIGER OXIDATION OF BICYCLO[3,3,1]NONAN-3-ONE SYSTEM

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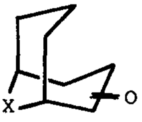
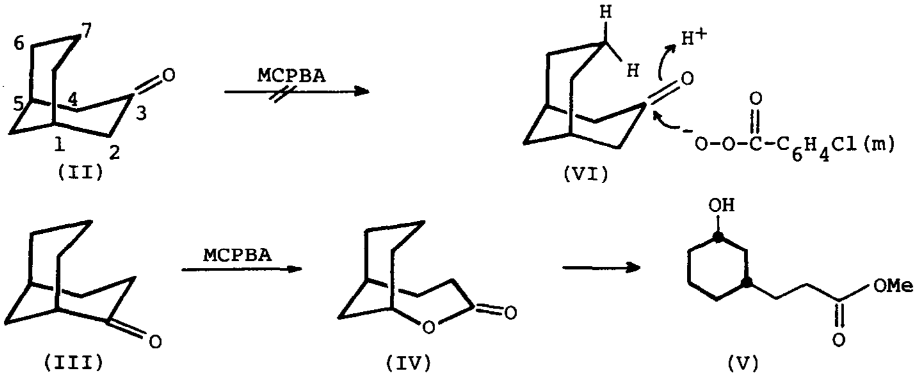
In the course of the exploratory study on applicability of bicyclo[3,3,1]-nonanone system (I) to natural product synthesis, one of us previously examined the Baeyer-Villiger oxidation of I and found out an anomalous inactivity of 3-oxo system (I, $X=\rangle NSO_2Ph)^1$. In order to reveal the behavior of carbocyclic 3-oxo system (I, $X=\rangle CH_2$) toward Baeyer-Villiger oxidation, we examined various 3-oxobicyclo[3,3,1]nonanones functionalized at C-7 by trigonal structure, and succeeded in the oxidative cleavage of 3-oxo system by introduction of 7-oxo function.



(I)

Oxidation[2] of bicyclo[3,3,1]nonan-3-one (II)[3] with m-chloroperbenzoic acid (MCPBA) was found unsuccessful with complete recovery of II, whereas the 2-oxo compound (III)[4] was easily oxidized to the expected lactone (IV), which was readily converted to the hydroxy ester (V) on treatment with p-toluenesulfonic acid in methanol. This anomalous inactivity can be explained by assuming the backside steric hindrance by axial (endo) hydrogen on C-7 which operates on the stage of the Baeyer-Villiger intermediate formation as depicted in VI.

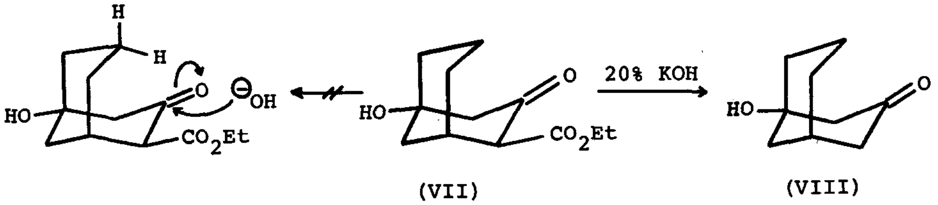


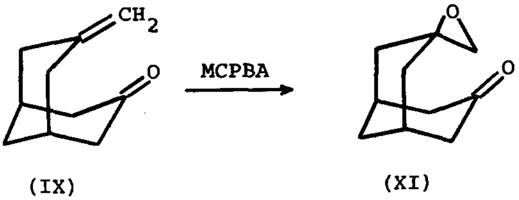
This concept can also explain the fact that an attempted acid cleavage[5] of the β-keto ester (VII) using 20% pottasium hydroxide in hot ethanol resulted exclusively in the ketonic cleavage to give the hydroxy ketone (VIII)[6] instead of a dicarboxylic acid.

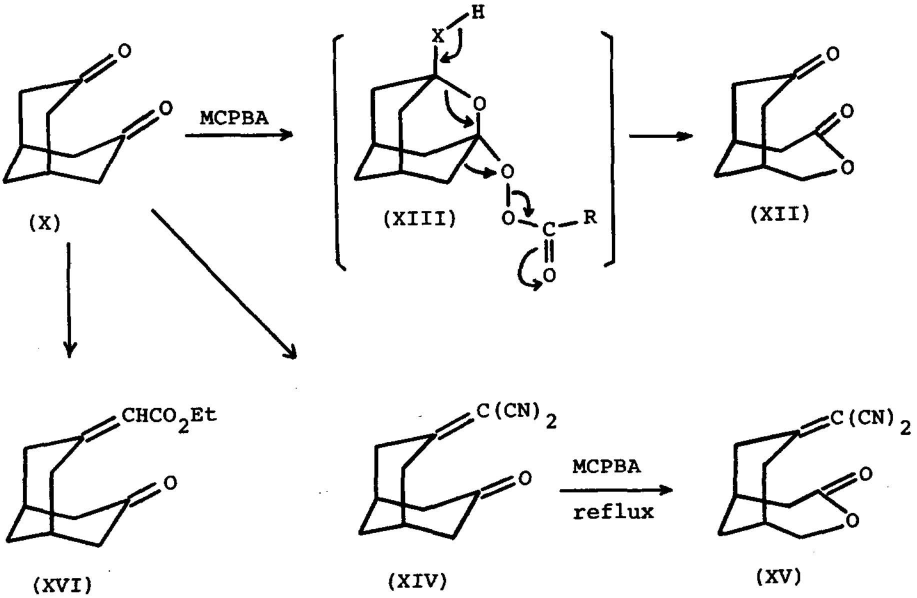
Then, we examined the oxidation of the 7-methylene ketone (IX)[7] and the 7-oxo ketone (X)[8] in which the C-7 position possessed sp^2 structure. Even in detailed experiment on IX was obtained no carboxylic product but the epoxy ketone (XI) as reported by previous workers[9]. On the contrary, X was easily oxidized, in 79% yield, to the keto lactone (XII), m.p. 173-175°, IR (KBr): 1732, 1720 cm^{-1}; NMR ($CDCl_3$): δ 4.34(1H, d × d, J=13Hz, 2Hz, -CH-OCO-), 4.24 (1H, d × d, J=13Hz, 4.3Hz, -CH-OCO-); MS: m/e 168(M^+, 16%).

Failure of the oxidative cleavage of methylene ketone IX with 30% hydrogen peroxide in a hot alkaline solution[10] or of the second oxidation of lactonic ketone XII with MCPBA in boiling methylene chloride suggests that an intermediate (XIII, $X={>}O$) resulted from the through-space interaction[11] between the C-3 carbonyl and the polarized unsaturated bond on C-7 would be essential for this oxidation. The prediction was evidently realized by the successful oxidation of the α,α-dicyanomethylene ketone (XIV) which was prepared, in 61% yield, by reaction of X with malononitrile. The lactone (XV), m.p. 134-136°, IR (KBr): 2240, 1730, 1588 cm^{-1}; NMR ($CDCl_3$): δ 4.34, 4.31(2H, main peak of $-CH_2-OCO-$); MS: m/e 216(M^+, 15%), was obtained in 15% yield, probably via intermediate XIII ($X={>}C(CN)_2$), by refluxing XIV with MCPBA in methylene chloride. The fact that the oxidation of XIV did not proceed at room temperature or that the ethoxycarbonyl analog (XVI)[12] was recovered unchanged even after refluxing with MCPBA in methylene chloride suggests that even near-planar groups on C-7 also exert the significant steric hindrance on the Baeyer-Villiger reaction of 3-oxo group by a backside constraint.

This is the first example where the Baeyer-Villiger oxidation of bicyclo[3,3,1]nonan-3-one system is successful, and would provide a stereoselective synthetic pathway to several alicyclic compounds.


H
H
O
OH
HO
CO2Et
HO
O
CO2Et
(VII)
20% KOH
HO
O
(VIII)


CH2
O
MCPBA
O
O
(IX)
(XI)


O
O
MCPBA
(X)
X
H
O
O
O
C
R
O
(XIII)
O
O
O
(XII)
CHCO2Et
O
(XVI)
C(CN)2
O
(XIV)
MCPBA
reflux
C(CN)2
O
O
(XV)

NOTES AND REFERENCES

1. T. Momose and C. H. Eugster: unpublished work.
2. Peracid oxidation of 9-oxo system was reported to afford the corresponding lactones$^{a-c)}$, but that of 2-oxo or 3-oxo system has not been reported.
   a) A. C. Cope and D. M. Gale, J. Am. Chem. Soc., 85, 3743 (1963); b) H. M. Hellman, R. A. Jerussi and J. Lancaster, J. Org. Chem., 32, 2148 (1967); c) R. A. Appleton, K. H. Baggaley, S. C. Egan, J. M. Davies, S. H. Graham and D. O. Lewis, J. Chem. Soc.(C), 1968, 2032.
3. J. P. Schaefer, J. C. Lark, C. A. Flegal and L. M. Honig, J. Org. Chem., 32, 1372 (1967).
4. M. Hartmann, Z. Chem., 6, 182 (1966).
5. *2-Carbethoxycyclohexanone, on heating with 30% sodium hydroxide in methanol,* gave pimelic acid in 80-88% yield: H. R. Snyder, L. A. Brooks and S. H. Shapiro, Org. Synth., Coll. Vol. II, 531 (1943).
6. M. A. Eakin, J. Martin and W. Parker, Chem. Commun., 1968, 298.
7. H. Hamill, A. Karim and M. A. McKervey, Tetrahedron, 27, 4317 (1971).
8. H. Stetter and P. Tacke, Chem. Ber., 96, 694 (1963).
9. a) T. Mori, K. H. Yang, K. Kimoto and H. Nozaki, Tetrahedron Letters, 1970, 2419; b) F. N. Stepanov, T. N. Utochka and A. G. Yurchenco, Zh. Org. Khim., 8, 1183 (1972) [C. A., 77, 88263m (1972)]
10. Under this condition, cyclohexanone was reported to be oxidized to afford ε-hydroxycaproic acid in good yield: S. W. Fox, E. H. Polak, M. W. Bullock and Y. Kobayashi, J. Am. Chem. Soc., 73, 4979 (1951).
11. Some examples of such an interaction can be found in the reduction of diketone X by Raney Nickel (13) or in the Grignard reaction of X (14) or in the protonation of methylene ketone IX (15).
12. Prepared from diketone X by reaction with triethyl phosphonoacetate.
13. H. Stetter, P. Tacke and J. Gärtner, Chem. Ber., 97, 3480 (1964).
14. Idem., ibid., 99, 1435 (1966).
15. Idem., ibid., 98, 3888 (1965).