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Bicyclo[3.3.1]nonanes as Synthetic Intermediates. V.[1] The Baeyer-Villiger Oxidation of Bicyclo[3.3.1]nonane-3,7-dione and Its Congeners[2]

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The Baeyer-Villiger oxidation, which is known to be unsuccessful with the bicyclo-[3.3.1]nonan-3-one system, was shown to proceed smoothly with the 3,7-dioxo compounds **1** and **6**. The particular steric factors affecting the reaction of these and related systems are discussed.

Keywords——Baeyer-Villiger reaction; bicyclo[3.3.1]nonane-3,7-dione; N-benzenesulfonyl-9-azabicyclo[3.3.1]nonane-3,7-dione; 3-oxabicyclo[4.3.1]decane-4,8-dione; oxa-adamantanol intermediate; α,α-dicyanomethylene as ketone equivalents; backside steric hindrance; *m*-chloroperbenzoic acid; Robinson-Schöpf condensation

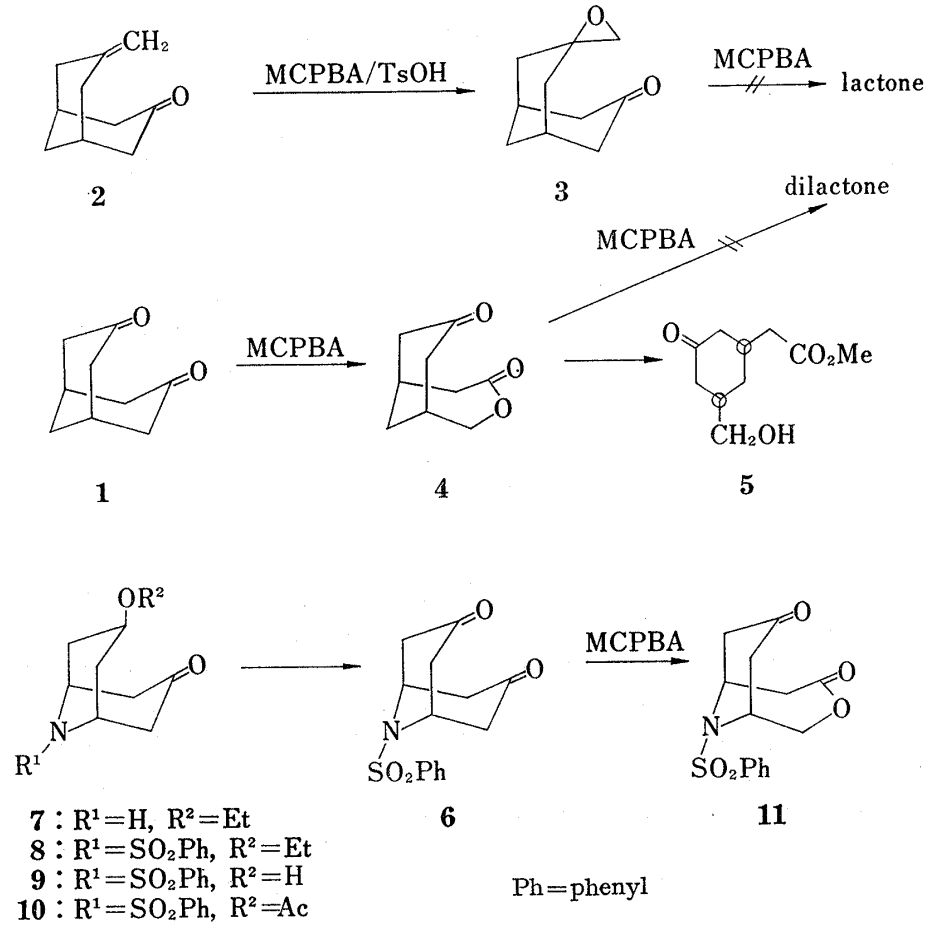
In the previous paper,[1] there was reported the unusual inactivity of the bicyclo[3.3.1]-nonan-3-one system against soft nucleophiles such as peracids. The failure of the reaction was explained in terms of the backside steric hindrance by the axial (*endo*) hydrogen at C-7 in this ketone. Then, we examined the peracid oxidation of the systems bearing an sp^2 structure at C-7, and found[2] bicyclo[3.3.1]nonane-3,7-dione (**1**)[4] to be reactive. This paper describes a full account of the experiments for the peracid oxidation of **1** and related systems.

Oxidation of 7-Methylene- and 7-Oxo-bicyclo[3.3.1]nonan-3-ones

Although the oxidation of 7-methylenebicyclo[3.3.1]nonan-3-one (**2**)[5] was reexamined[6] by use of *m*-chloroperbenzoic acid (MCPBA) in the presence of *p*-toluenesulfonic acid (TsOH), no lactone products were obtained, the epoxide **3** being the only product. Treatment of **2** with 30% hydrogen peroxide in a hot alkaline solution[7] was also found unsuccessful with complete recovery of the starting material. On the contrary, the diketone **1** was readily oxidized in 79% yield to a keto lactone (**4**). Its proton magnetic resonance (PMR) spectrum displays an ABX signal pattern due to the acyloxylated methylene protons at δ 4.24 and 4.34. Further treatment of **4** with MCPBA gave no dilactone, but resulted in complete recovery of **4**. The methanolysis of **4** by use of TsOH in methanol gave the hydroxy keto ester **5** in 88% yield.

A 9-aza analogue of **1** was next examined.[8] *N*-Benzenesulfonyl-9-azabicyclo[3.3.1]-nonane-3,7-dione (**6**) was prepared as follows. The Robinson-Schöpf condensation of β-ethoxyglutaraldehyde with ammonium chloride and acetonedicarboxylic acid gave an amino

1) Part IV: T. Momose, O. Muraoka, S. Atarashi, and T. Horita, *Chem. Pharm. Bull.* (Tokyo), **27**, 222 (1979).
2) Presented in part as a communication: T. Momose, S. Atarashi, and O. Muraoka, *Tetrahedron Lett.*, **1974**, 3697.
3) Location: *133-1, Yamada-kami, Suita, Osaka 565, Japan.*
4) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963); T. Momose and O. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **26**, 288 (1978).
5) H. Hamill, A. Karim, and M.A. McKervey, *Tetrahedron*, **27**, 4317 (1971).
6) Stepanov and co-workers described the perphthalic acid oxidation of **2** into the epoxy ketone **3**; F.N. Stepanov, T.N. Utochka, and A.G. Yurchenko, *Zh. Org. Khim.*, **8**, 1183 (1972) [*C.A.*, **77**, 88263*m* (1972)].
7) Under this condition, cyclohexanone was reported to be oxidized to ε-hydroxycaproic acid in good yield: see S.W. Fox, E.H. Polak, M.W. Bullock, and Y. Kobayashi, *J. Am. Chem. Soc.*, **73**, 4979 (1951).
8) Reported in brief in a preliminary form: see T. Momose and S. Atarashi, *Heterocycles*, **9**, 631 (1978).



2 3 1 4 5 6 11

7 : R^1=H, R^2=Et
8 : R^1=SO_2Ph, R^2=Et
9 : R^1=SO_2Ph, R^2=H
10 : R^1=SO_2Ph, R^2=Ac

Ph=phenyl

Chart 1

ketone (**7**),[9] which was converted into its sulfonamide (**8**). Treatment of **8** with boron tribromide afforded a ketol (**9**) in 78% yield. Its acetate (**10**) displays a PMR signal due to the C-7 proton at δ 4.91 with a half width ($W_{1/2}$) of 22 Hz as a nine-line multiplet characteristic of an axial hydrogen at C-3 of the bicyclo[3.3.1]nonan-3β-ol system,[10] the feature of which suggests an equatorial orientation for the C-7 substituent in **7**—**10**. Oxidation of **9** with chromium trioxide–pyridine gave the diketone **6** in 80% yield. Peracid oxidation of **6** with MCPBA in boiling methylene chloride gave a keto lactone (**11**) in 68% yield. The PMR spectrum displays an ABX signal pattern at δ 4.23 and 4.47 due to the methylene protons adjacent to the acyloxyl oxygen of the lactone formed.

Oxidation of 7-Oxobicyclo[3.3.1]non-3-ylidene Compounds

The results of the oxidation of both diketones **1** and **6** suggest that a polarized unsaturated bond on C-7 is essential for achievement of the peracid oxidation of the bicyclo[3.3.1]nonan-3-one system. In order to verify this concept, two compounds bearing a polarized *exo* double bond at C-7 were prepared and examined upon the peracid oxidation. The Witting reaction of **1** with triethyl phosphonoacetate gave the bicycloalkylideneacetate **12** in 89% yield. The bicycloalkylidenemalononitrile **13** was prepared in 61% yield by reaction of **1** with malononitrile in the presence of piperidinium acetate. Oxidation of **12** and **13** at room temperature

9) The N-methyl derivative of **7** was prepared by Stetter *et al.*; H. Stetter and R. Mehren, *Liebigs Ann. Chem.*, **709**, 170 (1967).

10) See, for example, *a*) J.P. Schaefer, J.C. Lark, C.A. Flegal, and L.M. Honig, *J. Org. Chem.*, **32**, 1372 (1967); *b*) W.D.K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, **1965**, 2589; *c*) C.-Y. Chen and R.J.W. Le Fèvre, *J. Chem. Soc.*, **1965**, 3473.

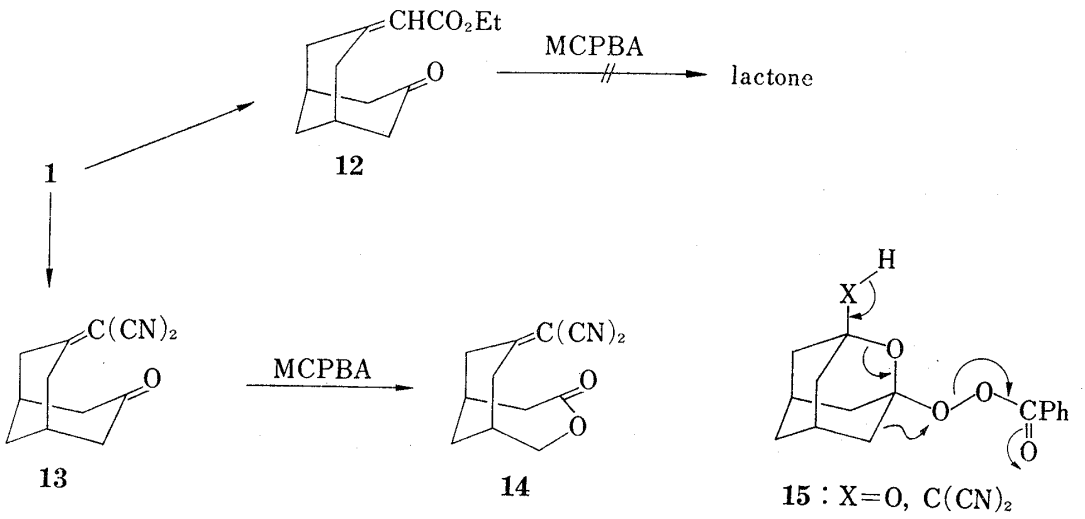


Chart 2

was unsuccessful, and resulted in recovery of the starting material. Under the condition of gentle reflux, **13** was converted into the lactone **14** in 15% yield after a long reaction period while **12** was not oxidized. From these results, it is concluded that an oxaadamantanol intermediate (**15**) or its substitute plays a significant role in the successful conduction of the reaction between the diketonic system and peracids, and also that the significant steric hindrance on the Baeyer-Villiger oxidation of the 3-oxo system is derived not only from the axial (*endo*) hydrogen but also from near-planar groups at C-7 by way of "backside constraint." The concept also interprets the reaction of 7-methylbicyclo[3.3.1]non-6-en-3-one with perphthalic acid to afford an oxaadamantane instead of a lactonic product.[11]

Experimental

All melting points and boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-G3 grating spectrophotometer. PMR spectra were measured for the solution in $CDCl_3$ or in CCl_4 with a Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard. Coupling constants (J) and half widths ($W_{1/2}$) are given in Hz, and the following abbreviations are used; s=singlet, bs=broad singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra (MS) were taken on a Hitachi RMU-6E mass spectrometer. All organic extracts were dried over anhydrous sodium sulfate before evaporation. Column chromatography was performed on Merck Aluminiumoxid (Aktivitätsstufe II-III). Preparative thin-layer chromotography (TLC) was performed on Merck Kieselgel 60 PF_{254} or Merck Aluminiumoxid PF_{254} (Typ T).

Attempted Oxidation of 7-Methylenebicyclo[3.3.1]nonan-3-one (2)——To a solution of 1.45 g (9.7 mmol) of **2** in 50 ml of dry CH_2Cl_2 were added 3.0 g of MCPBA and a catalytic amount of TsOH, and the solution was allowed to stand at room temperature for 2 hr. The reaction mixture was washed with satd. $NaHCO_3$[12] and brine. Removal of the solvent gave a colorless solid homogeneous on TLC, which was recrystallized from benzene to give 1.2 g (75%) of colorless needles, mp 257—259.° The product was identical with the epoxy ketone (**3**) reported by the previous workers.[13]

3-Oxabicyclo[4.3.1]decane-4,8-dione (4)——To a solution of 50 mg (0.33 mmol) of bicyclo[3.3.1]nonane-3,7-dione (**1**)[4] in 5 ml of dry CH_2Cl_2 was added 460 mg of MCPBA, and the solution was allowed to stand at room temperature overnight. The mixture was washed with satd. $NaHCO_3$[12] and brine. Removal of the solvent gave a colorless solid, which was sublimed at 90—95° (0.015 mmHg) to afford 44 mg (79%) of **4** as a colorless solid, mp 173—175.° IR ν_{max}^{KBr} cm^{-1}: 1732 (lactone), 1720 (CO). PMR ($CDCl_3$) δ: 4.24 (1H, dd, J=13, 4.3, 1H of -CH_2OCO-), 4.34 (1H, dd, J=13, 2, 1H of -CH_2OCO-). MS m/e: 168 (M^+, 16%). *Anal.* Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.16.

11) F.N. Stepanov, T.N. Utochka, A.G. Yurchenko, and S.D. Isaev, *Zh. Org. Khim.*, **10**, 59 (1974) [*C.A.*, **80**, 108298*u* (1974)].
12) The saturated $NaHCO_3$ solution used after the peracid oxidation contains 2% $Na_2S_2O_3$ in order to remove the excess MCPBA.
13) T. Mori, K.H. Yang, K. Kimoto, and H. Nozaki, *Tetrahedron Lett.*, **1970**, 2419.

Methyl *cis*-3-Hydroxymethyl-5-oxocyclohexaneacetate (5)——A solution of 70 mg (0.42 mmol) of **4** and a catalytic amount of TsOH in 7 ml of dry MeOH was heated under reflux for 5 hr. After removal of MeOH under reduced pressure, 10 ml of $CHCl_3$ was added to the residue, and the organic layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give an oily residue ,which was distilled to afford 74 mg (88%) of **5** as a colorless oil, bp 150—155° (0.22 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1740—1710 (CO). PMR ($CDCl_3$) δ: 2.03 (1H, bs, OH), 3.59 (2H, d, J=8, -C<u>H</u>$_2$OH), 3.69 (3H, s, -OCH_3). MS *m/e*: 200 (M^+, 3%). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.98; H, 8.14.

N-Benzenesulfonyl-7β-ethoxy-9-azabicyclo[3.3.1]nonan-3-one (8)——A mixture of 64 g of β-ethoxyglutaraldehyde tetraethyl acetal[14] and 150 ml of 0.1 N HCl was stirred at 40—45° for 20 min. To this was added an aqueous solution (1000 ml) containing 15 g of NH_4Cl, 40 g of acetonedicarboxylic acid and 120 g of AcONA (trihydrate), and the solution was adjusted to pH 3.5—4 by addition of 6N HCl, and stirred for 7 days at room temperature. The solution was shaken with CH_2Cl_2 to remove neutral and acidic substances. The acidic solution was made alkaline (pH 9) with K_2CO_3, saturated with NaCl and extracted with CH_2Cl_2 repeatedly. The combined extract was evaporated to afford 11 g of a dark brown oil, which was taken in 70 ml of benzene followed by addition of 7 ml of pyridine and of benzenesulfonyl chloride (8.5 g). The mixture was stirred overnight, washed with 2N HCl, satd. $NaHCO_3$ and brine and evaporated to give a semi-solid, which was washed with hexane and chromatographed on alumina. Elution with $CHCl_3$ gave 5.1 g (7.2%) of **8** as colorless needles (from isopropyl ether), mp 131—133.° IR ν_{max}^{KCl} cm^{-1}: 1715, 1350, 1165, 1120—1065. PMR ($CDCl_3$) δ: 1.09 (3H, t, J=7, -CH_2<u>C</u>H_3), 2.40 (2H, d, J=17, C_2-, C_4-eq.H), 2.76 (2H, dd, J=17, 7, C_2-, C_4-ax.H), 3.39 (2H, q, J=7, -C<u>H</u>$_2$$CH_3$), 3.24—3.75 (1H, m, $W_{1/2}$=16, C_7-H). *Anal.* Calcd. for $C_{16}H_{21}O_4NS$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.52; H, 6.61; N, 4.46.

N-Benzenesulfonyl-7β-hydroxy-9-azabicyclo[3.3.1]nonan-3-one (9)——A solution of 970 mg of **8** and 30 ml of dry CH_2Cl_2 was cooled to −78° and treated with 6 g of BBr_3 in 10 ml of dry CH_2Cl_2. A precipitate was formed immediately, and the stirring was continued for 5 hr at −78.° The cold bath was removed, and the solution was allowed to warm up to room temperature, wherein the precipitate had mostly disappeared. The reaction mixture was quenched by the addition of 5 ml of ether and 20 ml of satd. $NaHCO_3$. The organic layer was separated, and the aqueous layer was made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The combined organic layer was evaporated to afford the crude material, which was purified by preparative TLC on alumina (developing solvent: $CHCl_3$) and crystallized from Me_2CO–isopropyl ether to give 641 mg (78%) of **9** as colorless crystals, mp 181—183.° IR ν_{max}^{KCl} cm^{-1}: 3400 (OH), 1712, 1692 (CO). *Anal.* Calcd. for $C_{14}H_{17}O_4NS$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.04; H, 5.88; N, 4.86.

N-Benzenesulfonyl-7β-acetoxy-9-azabicyclo[3.3.1]nonan-3-one (10)——A solution of 50 mg of **9**, 0.4 ml of Ac_2O and 0.4 ml of pyridine was heated at 60° for 2 hr. After cooling, AcOEt was added to the mixture, and the organic layer was washed with 1N HCl, satd. $NaHCO_3$ and brine, and evaporated. The resulting residue was purified by preparative TLC on alumina (developing solvent: $CHCl_3$) to give 43 mg (75%) of **10** as colorless plates (from Me_2CO–isopropyl ether), mp 136—137.° IR ν_{max}^{KCl} cm^{-1}: 1750 (COO), 1710 (CO). PMR ($CDCl_3$) δ: 1.96 (3H, s, -$COCH_3$), 2.42 (2H, d, J=17, C_2-, C_4-eq.H), 2.72 (2H, dd, J=17, 6, C_2-, C_4-ax.H), 4.91 (1H, m, $W_{1/2}$=22, C_7-H). *Anal.* Calcd. for $C_{16}H_{19}O_5NS$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.03; H, 5.71; N, 4.37.

N-Benzenesulfonyl-9-azabicyclo[3.3.1]nonane-3,7-dione (6)——To an ice-cooled solution of 10 ml of dry CH_2Cl_2 and 0.35 ml of pyridine was added 210 mg of CrO_3, and the mixture was stirred for 15 min. At the end of this period, a solution of 100 mg of **9** in a small volume of dry CH_2Cl_2 was added in one portion. A tarry, black deposit separated immediately. After stirring for an additional 2 hr at room temperature, the solution was decanted from the insoluble material, and the residue was washed with 20 ml of CH_2Cl_2. The combined organic layer was washed with 1N HCl, satd. $NaHCO_3$ and brine, and evaporated to give a glass-like solid, which was washed with hexane to afford 80 mg (80%) of **6** as colorless crystals (from Me_2CO–isopropyl ether), mp 161—162.° IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO). PMR ($CDCl_3$) δ: 2.38 (4H, d, J=16, C_2-, C_4-, C_6-, C_8- *eq.*H), 2.71 (4H, dd, J=16, 6, C_2-, C_4-, C_6-, C_8-*ax.*H), 4.93 (2H, pseudo-t, C_1-, C_5-H). MS *m/e*: 293 (M^+, 6%). *Anal.* Calcd. for $C_{14}H_{15}O_4NS$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.66; H, 5.39; N, 4.87.

N-Benzenesulfonyl-10-aza-3-oxabicyclo[4.3.1]decane-4,8-dione (11)——To a solution of 75 mg of **6** in 10 ml of dry CH_2Cl_2 was added 175 mg of MCPBA, and the solution was heated under reflux for 44 hr. The mixture was washed with satd. $NaHCO_3$[12] and brine, and evaporated to give a glass-like material, which was washed with isopropyl ether to afford 54 mg (68%) of **11** as colorless crystals (from Me_2CO–isopropyl ether), mp 165—167.° IR ν_{max}^{KCl} cm^{-1}: 1750 (lactone), 1720 (CO). PMR ($CDCl_3$) δ: 4.23 (1H, dd, J=13, 4, 1H of -CH_2OCO-), 4.47 (1H, d, J=13, 1H of -CH_2OCO-). MS *m/e*: 309 (M^+, 2%). *Anal.* Calcd. for $C_{14}H_{15}O_5NS$: C, 54.37; H, 4.89; N, 4.53. Found: C, 53.84; H, 4.86; N, 4.48.

Ethyl 7-Oxobicyclo[3.3.1]non-3-ylideneacetate (12)——To a stirred suspension, flushed with N_2 and maintained at 35—40,° consisting of NaH (50% in oil) and 10 ml of dry benzene was added dropwise in 10 mins

14) T.V. Protopopova and A.P. Skoldinov, *Zh. Obshch. Khim.*, **27**, 57 (1957) [*J. Gen. Chem. USSR*, **27**, 65 (1957)].

a solution of 446 mg of triethyl phosphonoacetate[15] in 2 ml of dry benzene. The mixture was stirred for additional 30 mins followed by addition of a solution of 304 mg (2 mmol) of **1** in 10 ml of dry benzene at 20—30.° After the reaction was over, the resulting solution was decanted from a gummy precipitate, washed with brine, and evaporated under reduced pressure to afford an oily residue. Purification by preparative TLC on silica gel (developing solvent: ether–$CHCl_3$–MeOH=70: 60: 1) and distillation gave 393 mg (89%) of **12** as a colorless oil, bp 104—107° (0.07 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725—1710, 1650 (C=C). PMR (CCl_4) δ: 1.24 (3H, t, J=7, $-CH_2\underline{CH_3}$), 4.07 (2H, q, J=7, $-\underline{CH_2}CH_3$), 5.56 (1H, bs, -C=CH-). MS *m/e*: 222 (M^+, 3.5%). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.22.

7-Oxobicyclo[3.3.1]non-3-ylidenemalononitrile (13)——To a solution of 200 mg (1.31 mmol) of **1** and 90 mg of malononitrile in 20 ml of benzene were added 130 mg of piperidine and 0.5 ml of glacial AcOH, and the mixture was refluxed for 2 hr. After the reaction was over, the solution was washed with satd. $NaHCO_3$ and brine. Removal of the solvent gave a yellowish solid, which was purified by preparative TLC on silica gel (developing solvent: ether–benzene=4: 1) and recrystallized from benzene–hexane to afford 160 mg (61%) of **13** as colorless crystals, mp 128—129.° IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1705 (CO), 1590 (C=C). MS *m/e*: 200 (M^+, 51%). *Anal.* Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.12; H, 6.14; N, 14.14.

Attempted Oxidation of 12——A solution of 67 mg (0.3 mmol) of **12** and 100 mg of MCPBA in 7 ml of dry CH_2Cl_2 was heated under reflux for 8 hr. Usual work-up of the mixture gave 62 mg of the recovered **12**. No lactonic product was obtained.

4-Oxo-3-oxabicyclo[4.3.1]dec-8-ylidenemalononitrile (14)——To a solution of 120 mg (0.6 mmol) of **13** in 20 ml of dry CH_2Cl_2 was added 250 mg of MCPBA, and the solution was heated under reflux for 9 days. During the reaction, a total of 150 mg of MCPBA was added at intervals to the solution. The resulting mixture was washed with satd. $NaHCO_3$[12] and brine, and evaporated to give an oily residue. Separation of the fraction of a *Rf* value lower than that of the starting material on preparative TLC on silica gel (developing solvent: ether–benzene=5: 2) gave 25 mg of a semi-solid, which was triturated with ether to afford a colorless solid. After recrystallization from benzene–hexane was obtained 20 mg (15%) of **14** as colorless plates, mp 134—136.° IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1730 (lactone), 1588 (C=C). PMR ($CDCl_3$) δ: 4.33 (2H, d, J=3, $-CH_2OCO-$). MS *m/e*: 216 (M^+, 15%). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.67; H, 5.61; N, 12.63.

15) J. Wolinsky and K.L. Erickson, *J. Org. Chem.*, 30, 2208 (1965).