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Bicyclo[3.3.1]nonanes as Synthetic Intermediates. III.[1] The Baeyer-Villiger Oxidation of Some Bicycloalkyl Phenyl Ketones

Takefumi Momose and Osamu Muraoka

Faculty of Pharmaceutical Sciences, Osaka University[2]

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The Baeyer–Villiger oxidation of 3β-benzoylbicyclo[3.3.1]nonane (**1**), 8β-benzoylbicyclo[4.3.1]decane (**2**), and 3β-benzoylbicyclo[3.2.1]octane (**3**) is described. The ratio of the main product bicycloalkyl benzoate to its isomeric product phenyl bicycloalkanecarboxylate was determined to be *ca.* 10: 1 by the ^{1}H-NMR measurement of the crude mixture. The Baeyer–Villiger reaction of cyclohexyl phenyl ketone (**11**) was also carried out and was found to give a similar result in its isomer ratio of the products. The high selectivity in this oxidation enabled the practicable preparation of bicyclo[3.*n*.1]alkan-3-ones *via* bicyclo[3.*n*.1]alk-3β-yl phenyl ketones to be achieved.

Keywords——Baeyer–Villiger oxidation; bicyclo[3.*n*.1]alk-3β-yl phenyl ketone; cyclohexyl phenyl ketone; migratory aptitude; bicyclo[3.*n*.1]alkan-3β-ol; bicyclo-[4.3.1]decan-8β-ol; synthetic route to bicyclo[3.*n*.1]alkan-3-one; ^{1}H-NMR; ^{13}C-NMR

There is continued interest in application of the Baeyer–Villiger reaction to the stereospecific and regiospecific synthesis[3] of specifically substituted molecules, and much has been investigated of its mechanism[4] as well as migratory aptitude.[4b,c,h–j,5] From a study of a series of alkyl aryl ketones[4c,i,j,5a] as well as from other studies,[4b,h,5b] the relative ease of migration (*i.e.* the migratory aptitude) of various groups in the Baeyer–Villiger reaction has been found to follow the order *t*-alkyl>cyclohexyl~*sec*-alkyl~benzyl~phenyl>primary alkyl >cyclopropyl>methyl. But, as for the behavior of the α-ketonic moieties in bicycloalkyl phenyl ketones, little is known owing, in part, to the relative inaccessibility of the simple derivatives suitable for the investigation. In connection with our recent interest[6] in the bicyclo[3.*n*.1]alkane system, we had occasion to synthesize 3β-benzoylbicyclo[3.3.1]nonane (**1**), 8β-benzoylbicyclo[4.3.1]decane (**2**), and 3β-benzoylbicyclo[3.2.1]octane (**3**) which would provide an interesting vehicle for the study of this problem. We report now some results which serve to delineate the course of the reaction of these bicycloalkyl phenyl ketones, and also re-examination of the literature result[4c] concerning the Baeyer–Villiger reaction of cyclohexyl phenyl ketone.

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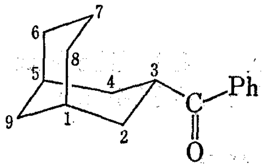
2) Location: *133-1, Yamada-kami, Suita, Osaka 565, Japan.*
3) See, for example, P.A. Grieco, Y. Yokoyama, S. Gilman, and Y. Ohfune, *J. C. S. Chem. Commun.*, **1977**, 870; G. Mehta, P.N. Pandey, and T.-L. Ho, *J. Org. Chem.*, **41**, 953 (1976); A.J. Playtis and J.D. Fissekis, *J. Org. Chem.*, **40**, 2488 (1975); E.J. Corey, N.M. Weinshenker T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker, and N.M. Weinshenker, *ibid.*, **92**, 397 (1970); E.J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).
4) *a*) S.L. Friess, *J. Am. Chem. Soc.*, **71**, 2571 (1949); *b*) W. von E. Doering and L. Speers, *ibid.*, **72**, 5515 (1950); *c*) S.L. Friess and N. Franham, *ibid.*, **72**, 5518 (1950); *d*) S.L. Friess and R. Pinson, Jr., *ibid.*, **74**, 1302 (1952); *e*) S.L. Friess and P.E. Frankenburg., *ibid.*, **74**, 2679 (1952); *f*) W. von E. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953); *g*) M.F. Hawthorne and W.D. Emmons, *ibid.*, **80**, 6398 (1958); *h*) J.C. Robertson and A. Swelim, *Tetrahedron Lett.*, **1967**, 2871; *i*) A. Nishihara and I. Kubota, *J. Org. Chem.*, **33**, 2525 (1968); *j*) E.E. Smissman, J.P. Li, and Z.H. Israili, *ibid.*, **33**, 4231 (1968); *k*) Y. Ogata and Y. Sawaki, *ibid.*, **34**, 3985 (1969); *l*) B.W. Palmer and A. Fry, *J. Am. Chem. Soc.*, **92**, 2580 (1970); *m*) R.D. Chambers and M. Clark, *Tetrahedron Lett.*, **1970**, 2741.
5) *a*) S.L. Friess and A.H. Soloway, *J. Am. Chem. Soc.*, **73**, 3968 (1951); *b*) R.R. Sauers and R.W. Ubersax, *J. Org. Chem.*, **30**, 3939 (1965).
6) T. Momose and O. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **26**, 288 (1978), and ref. 1.



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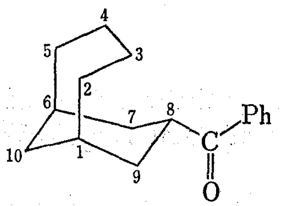

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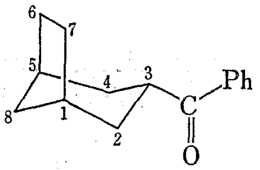

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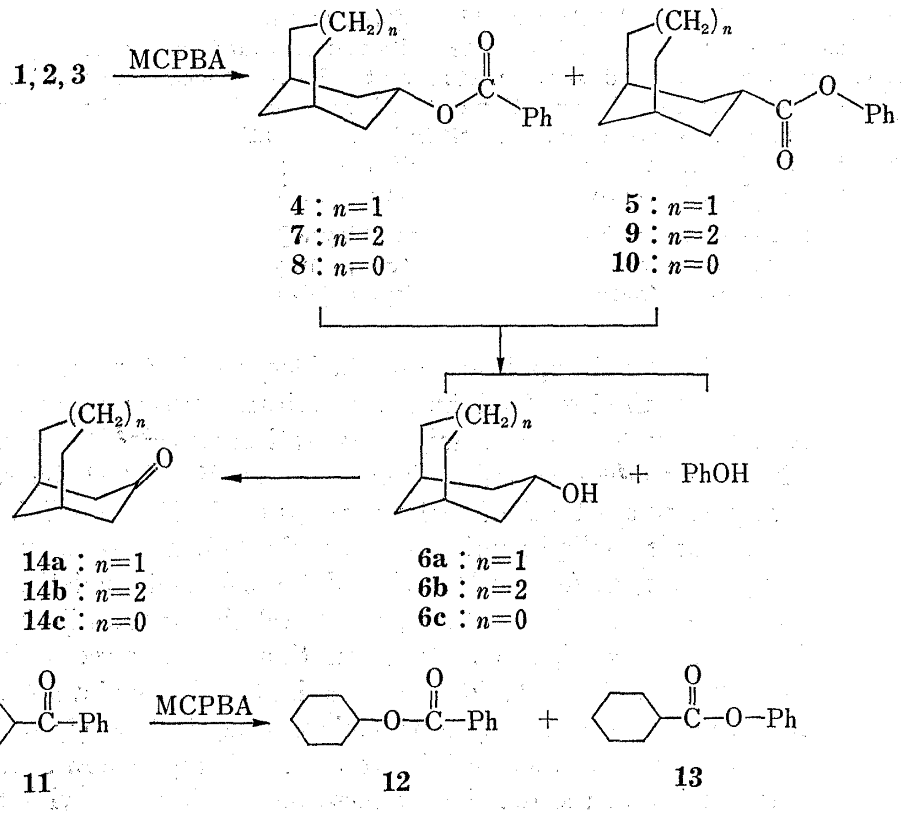

Chart 1

Treatment of **1** with *m*-chloroperbenzoic acid (MCPBA) gave a poorly separable mixture of esters, the benzoate (**4**) and the phenyl ester (**5**), in 93% yield. The main component of the mixture was identified as **4** on the basis of its spectral properties and of its behavior toward alkaline hydrolysis. The infrared (IR) spectrum of the mixture showed a strong absorption due to a benzoate carbonyl at 1718 cm^{-1} accompanied by a weak band due to an alkanoate carbonyl of **5** at 1760 cm^{-1}. The carbon-13 nuclear magnetic resonance (^{13}C–NMR) spectrum showed distinctly strong eleven peaks attributing to **4** accompanied by some trace peaks due to **5** (Table II). The proportion of **4** and **5** was determined directly by the proton magnetic resonance (^{1}H–NMR) spectrum of the crude mixture which showed two complex multiplets in the region of δ 6.90—8.20, one centered at 8.02 ppm due to the aromatic protons *ortho* to the benzoate carbonyl in **4** and the other centered at 7.42 ppm due to those at the *meta* and the *para* position in **4** and to the five aromatic protons of **5**. The ratio of the integrated area of this region (δ 6.90—7.60) to that of the remainder (δ 7.90—8.20) was *ca.* 1.7. Assuming that the products are the two isomeric esters, it can be calculated that ester **4** constitutes *ca.* 92% of the products. Alkaline hydrolysis of the mixture gave bicyclo[3.3.1]nonan-3β-ol

(**6a**),[7] and a small amount of phenol was obtained on neutralization of the aqueous phase with carbon dioxide. The molar ratio of this alcohol (**6a**) and phenol was *ca.* 11:1.

TABLE I. Some Physical and Spectral Properties of the Baeyer–Villiger Products

Compound No.	Appearance bp(°C/mmHg)	Yield (%)	Analysis (%) Calcd. (Found) C	H	IR $\nu_{\max}^{CCl_4}$ cm⁻¹:	NMR (in CCl_4) δ:
4	Solid (mp 31—34) 140—141/2.0	85	78.63 (78.55	8.25 8.31)	2920, 1718, 1276 1110, 708	7.92—8.11(2H, m), 7.25—7.65 (3H, m), 5.31(1H, m, $W_{1/2}$: 22 Hz), 1.10—2.50(14H, m)
7	Oil 161—162/1.0	82	79.03 (78.78	8.58 8.66)	2925, 1720, 1277 1114, 710	7.88—8.10(2H, m), 7.20—7.55 (3H, m), 5.30(1H, m, $W_{1/2}$: 20 Hz), 1.10—2.50(16H, m)
8	Solid (mp 36—40) 128—129/2.5	81	78.23 (77.92	7.88 8.96)	2950, 1725, 1278 1118, 710	7.88—8.07(2H, m), 7.20—7.60 (3H, m), 5.16(1H, m, $W_{1/2}$: 21 Hz), 1.10—2.50(12H, m)
12[a]	——	78	74.97 (74.62	8.39 8.41)	2946, 1722, 1278 1112, 710	7.74—8.10(2H, m), 7.20—7.55 (3H, m), 4.94(1H, br, $W_{1/2}$: 18 Hz), 1.10—2.20(10H, m)
13[b]	——	—	74.97 (74.66	8.39 8.42)	2943, 1760, 1195 1162, 1150, 1120	6.75—7.50(5H, m), 2.44(1H, br, $W_{1/2}$: 20Hz), 1.05—2.20(10 H, m)

a) *Cf*, T. Kudo and A. Nose, *Yakugaku Zasshi*, **95**, 1411(1975).
b) See ref. 8.

TABLE II. ^{13}C-NMR Chemical Shifts for the Baeyer–Villiger Products[a]

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Ester ketone	Aromatic carbons α	*ortho*	*metha*	*para*
4	29.47	37.36	71.02	37.36	29.47	30.82	22.53	30.82	34.46		165.50	131.04	129.49	128.21	132.53
7	34.39	31.49	27.71	27.71	31.49	34.39	38.10	68.75	38.10	30.81	164.60	130.89	129.27	127.65	131.83
8	34.80	38.24	70.27	38.24	34.80	28.66	28.66	39.05			165.91	130.91	129.42	128.14	132.52
12	72.10	31.57	23.54	25.50	23.54	31.57					164.50	131.11	129.36	127.87	132.06
13	42.96	28.80	25.22	25.70	25.22	28.80					172.39	151.01	121.33	128.75	124.91

a) Chemical shifts in ppm for TMS, in CCl_4.

Application of this reaction to the homologous ketones, **2** and **3**, led to similar results to give the corresponding esters, **7** and **8**, as main products, respectively, along with a slight amount of their isomers, **9** and **10**. The isomer ratio of the products from these systems were also determined by their ^{1}H-NMR properties to be *ca.* 9—11:1.

In 1950, Friess and Farnham[4c] reported the perbenzoic acid oxidation of cyclohexyl phenyl ketone (**11**) leading to the formation of cyclohexyl benzoate (**12**) and phenyl cyclohexanecarboxylate (**13**) in a ratio of 5:1. A marked contrast in the selectivity between their (**11**) and our related systems (**1**—**3**) made us re-examine the literature results. In our experiment using MCPBA as oxidant, the Baeyer–Villiger reaction of **11** gave **12** and **13** in a ratio of *ca.* 10:1, which was in good agreement with the results obtained from the reaction of **1**, **2**, and **3**. The compound (**13**)[8] was alternatively prepared by the condensation of

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[7] J.P. Schaefer, J.C. Lark, C.A. Flegal, and L.M. Honig, *J. Org. Chem.*, 32, 1372 (1967).
[8] Preparative methods for **13** have been reported using cyclohexanecarbonyl chloride as a starting material: see, for example, *a*) S.S. Bhargava, S.K. Jain, and G.S. Saharia, *Indian J. Chem.*, 5, 543 (1967); *b*) A.G. Ismailov and B.A. Salimova, *Zh. Org. Khim.*, 4, 85 (1968).

cyclohexanecarboxylic acid with phenol in the presence of trifluoroacetic anhydride and used as an authentic specimen in the product analysis by ^{1}H–NMR measurement.

Consequently, the ease of migration of cyclohexyl group in the Baeyer–Villiger reaction is about ten times as much as that of aryl group, and di-, tri-, and tetramethylene moieties bridging at the β,β' position exert no significant effects to this migratory aptitude. And in addition, this high selectivity of oxidation was found to realize the practicable preparation of bicyclo[3.*n*.1]alkan-3-ones *via* bicyclo[3.*n*.1]alk-3β-yl phenyl ketones. Bicycloalkanols **6a**, **6b** and **6c** which were obtained as the only non-acidic product by saponification of the Baeyer–Villiger products were oxidized with chromic trioxide to give the corresponding bicyclic ketones (**14a**, **14b** and **14c**) in good yields, respectively.

Experimental[9]

Materials——The bicycloalkyl phenyl ketones employed in this study were prepared by the method described in a preceding paper.[1] Cyclohexyl phenyl ketone was commercially available from Aldrich Chemical Company, Inc. and was purified by distillation before use.

A typical reaction of the series was carried as follows:

The Baeyer–Villiger Reaction——To a solution of ketone (**1**, 2.28 g, 0.01 mol) in absolute CH_2Cl_2 (30 ml) was added MCPBA (*ca.* 0.013 mol), and the reaction mixture was swirled at intervals and set aside in the dark. On completion of the reaction (8 days), the reaction mixture was washed with a 5% sodium thiosulfate–$NaHCO_3$ solution (10 ml × 3) to remove *m*-chlorobenzoic acid and excess peracid. The washings were combined and extracted with CH_2Cl_2 (10 ml × 2), and the combined CH_2Cl_2 layer was washed with water. Removal of the solvent gave 2.27 g of a colorless oil, which gave two close spots on TLC but one peak on GLC and was used on the next reaction without further purification. A sample for analysis of the main product was obtained by preparative TLC with $CHCl_3$ as an eluent, and detailed data were listed in Tables I and II. The ^{1}H–NMR spectrum of the crude product [δ 7.90—8.20 (2H, m, arom H of the *ortho* position for **4**), 6.90—7.60 (3.4H, m, arom H of the *meta* and the *para* position for **4** and the five aromatic protons for **5**)] indicated a 12 : 1 mixture of **4** and **5**.

Saponification of the Oxidation Products——The crude ester mixture was saponified by heating with 30% sodium hydroxide, and a sublimate trapped in the condenser was collected and taken up in ether (30 ml). The ethereal solution was washed with brine (5 ml × 2), and careful removal of the solvent from the solution gave 1.0 g (0.0072 mol) of purified bicyclo[3.3.1]nonan-3β-ol (**6a**) as colorless crystals, mp 101—101.5° (lit.,[7] 100—101°).

The alkaline solution was shaken with ether and then saturated with carbon dioxide to liberate the free phenol. The phenol was extracted with ether (10 ml × 3) and the extract was washed with brine. Removal of the solvent gave 0.061 g (0.00065 mol) of phenol.

In this run, total yield of the ROH product amounted to 0.00785 mol, or 78.5% of the theoretical. The molar ratio of bicycloalkanol to phenol was *ca.* 11 : 1.

Bicyclo[4.3.1]decan-8β-ol (6b)——The alcohol (**6b**) was obtained by saponification of the corresponding Baeyer–Villiger products in 70% yield as highly sublimable crystals, mp 80—81°. IR ν_{max}^{KBr} cm^{-1}: 3275, 2905, 2848, 1460, 1030. ^{1}H–NMR ($CDCl_3$) δ: 3.96 (1H, m, C_8–H), 2.00—2.45 (2H, br, C_1–, C_6–H), 2.12 (1H, s, OH), 1.00—2.00 (14H, m, ring methylene). ^{13}C–NMR ($CDCl_3$) δ: 65.28 (C_8), 42.49 (C_7, C_9), 34.71 (C_1, C_6), 31.87 (C_2, C_5), 30.84 (C_{10}), 27.96 (C_3, C_4). *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.51; H, 11.83.

Biocyclo[3.3.1]nonan-3-one (14a)——Following the method described by Schaefer *et al.*,[7] **6a** was converted into **14a** in 93% yield. This product was homogeneous on GLC and identical with an authentic specimen obtained by an alternative method.[1]

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[9] Melting points and boiling points are uncorrected. IR spectra were taken on a Hitachi EPI–G3 grating spectrophotometer. ^{1}H–NMR spectra (90 MHz) were measured for the 10% solution in CCl_4 with a Hitachi R-22 spectrometer with tetramethylsilane as an internal standard. Coupling constants (*J*) are given in Hz, and the following abbreviations are used; br=broad, m=muitiplet, arom=aromatic. The 22.63 MHz ^{13}C–NMR spectra were measured for the solution in CCl_4 with a Hitachi R–22CFT spectrometer, in conjunction with a HITAC 10-II computer, with tetramethylsilane as an internal standard. Gas–liquid partition chromatography (GLC) was carried out on a Perkin-Elmer 800 gas chromatograph, equipped with a stainless column (2 mm × 1.8 m) packed with 1.5% SE-52 on chromosorb W (60—80 mesh) with N_2 carrier gas: flow rate of 30 ml/min. Thin-layer chromatography was performed on Merck TLC and PLC Plates Silica Gel 60 F_{254}. All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

Bicyclo[4.3.1]decan-8-one (14b)——To a stirred solution of **6b** (0.308 g) in purified acetone (5 ml) was added dropwise a slight excess of Jones reagent (1.2 ml), followed by stirring at room temperature for 15 min. After decomposing the excess oxidant with iso-PrOH and making alkaline with anhyd. K_2CO_3, the mixture was extracted with ether (10 ml × 3). The extract was washed with brine and evaporated to give a solid, which on sublimation gave **14b** (0.283 g, 93.0%) as colorless crystals. This product was homogeneous on GLC and identical with an authentic specimen obtained *via* an alternative route.$^{1)}$

Bicyclo[3.2.1]octan-3-one (14c)——The alcohol (**6c**) was obtained by the saponification of the corresponding Baeyer–Villiger products in 70% yield and was oxidized into **14c** in 92% yield following the method described by Kraus.$^{10)}$ This product was homogeneous on GLC and identical with an authentic specimen obtained *via* an alternative route.$^{1)}$

Phenyl Cyclohexanecarboxylate (13)——A mixture of cyclohexanecarboxylic acid (3.2 g, 0.025 mol), phenol (3.0 g, 0.032 mol), trifluoroacetic anhydride (0.3 ml), and dry toluene (50 ml) was heated under reflux by use of a Dean–Stark water separator for 18 hr. The cooled solution was washed with satd. $NaHCO_3$ (15 ml × 2) and then with water (10 ml × 3). Removal of the solvent gave a pale yellow oil, which on distillation gave **13** (4.25 g, 84.2%) as a colorless oil, bp 105—106°/1.0 mmHg (lit., 119—120°/1.5 mmHg,$^{8a)}$ 133—134°/7 mmHg$^{8b)}$).

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10) W. Kraus, *Chem. Ber.*, **97**, 2719 (1964).