Baeyer–Villiger Oxidation of *syn*-7-Chloronorcamphor and *syn*-7-Bromonorcamphor

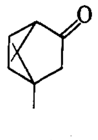
R. R. SAUERS AND J. A. BEISLER

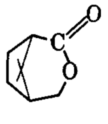
School of Chemistry, Rutgers, The State University, New Brunswick, New Jersey

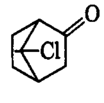
Received August 7, 1963

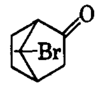
Baeyer–Villiger oxidation of *syn*-7-chloronorcamphor and *syn*-7-bromonorcamphor has been investigated. The major products are those formed by methylene migration.

The recent finding that epicamphor (I) is oxidized by peracetic acid to form only β-campholide (II),[1] contrary to predictions based on electronic considerations,[2] has excited our interest in extending the scope of "anomalous" Baeyer–Villiger oxidations. In this communication we describe the results of the reaction of peracetic acid with *syn*-7-chloronorcamphor[3] (III) and *syn*-7-bromonorcamphor[4] (IV) with the expectation that these two ketones would also lead to substantial amounts of lactones *via* nonelectronically controlled transition states.



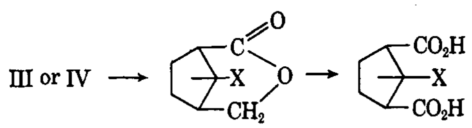






Results

In both bases, the major product was that lactone which arises from migration of the methylene carbon as opposed to the methine carbon at the bridgehead.

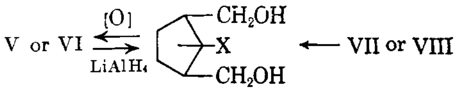


V, X = Cl
VI, X = Br

VII, X = Cl
VIII, X = Br

The structures of these new lactones are assigned as shown on the basis of several lines of evidence. First, they could both be oxidized with nitric acid to the dicarboxylic acids (VII and VIII). Mixture melting points with samples prepared by nitric acid oxidation of the starting ketones were undepressed.

In addition, the lactones were reduced by lithium hydride to the diols (IX and X), both of which were independently synthesized from the dimethyl esters of the acids (VII and VIII). The relatively high yields and close correspondence of physical properties are suggestive of relatively homogeneous lactones initially.



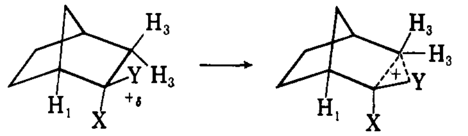
IX, X = Cl
X, X = Br

As a final check on the structure and homogeneity of the lactones, the authentic diols (IX and X) were subjected to mild oxidation.[5] Lactones were formed whose physical properties were very similar, but not quite identical, with those of the Baeyer–Villiger products. Assuming that the Baeyer–Villiger reactions produce only the two possible isomeric pairs of lactones, it is possible to make an estimate of the compositions of the products using the integrated n.m.r. curves since the isomers have different numbers of low-field protons. On this basis, the Baeyer–Villiger lactones are calculated to contain 53% and 71% V and VI, respectively. The figures are probably minimal, considering the other experimental evidence.

Discussion

In addition to what has already been said[1,6] concerning these oxidations with respect to electronic effects *vs.* chair–boat forms in the transition states, we would like to point out a third factor which we believe influences these reactions.

First, we would like to call attention to the results of several rather different kinds of ring-expansion reactions of norbornyl systems of this same general type, *i.e.*, alkyl migrations toward incipient positive centers (eq. 1).



(1)

In addition to Baeyer–Villiger oxidation of norcamphor[6c] (migration toward oxygen), there are five other similar transformations recorded in the literature: reaction of norcamphor with hydrazoic acid[7] (migration to nitrogen), decomposition of norbornyl azide[8] (migration to nitrogen), reaction of norcamphor with diazomethane[9] (migration to carbon), deamination of *exo*-norbornylmethylamine[10] (migration to carbon), and solvolysis of *exo*-norbornylmethyl tosylate[9] (migration to carbon). While these reactions represent a broad spectrum of reaction types, it is intriguing that in the last five cases methylene migration is favored over methine migration despite the generation of boat forms in the transition states. Thus, it appears that it is the Baeyer–Villiger reaction of norcamphor which is exceptional in that it alone is controlled by electronic factors.[11]

---

[1] R. R. Sauers and G. P. Ahearn, *J. Am. Chem. Soc.*, **83**, 2759 (1961).

[2] M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *ibid.*, **80**, 6393 (1958).

[3] J. D. Roberts, F. O. Johnson, and R. A. Carboni, *ibid.*, **76**, 5692 (1954).

[4] V. A. Rolleri, Ph.D. thesis, University of Delaware, 1958.

[5] V. I. Stenberg and R. J. Perkins, *J. Org. Chem.*, **28**, 323 (1963).

[6] (a) W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950); (b) M. F. Murray, B. A. Johnson, R. R. Pederson, and A. C. Ott, *ibid.*, **78**, 981 (1956); (c) J. Meinwald and E. Frauenglass, *ibid.*, **82**, 5235 (1960).

[7] R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961).

[8] C. L. Arcus, R. E. Marks, and R. Vitterlain, *Chem. Ind.* (London), 1193 (1960).

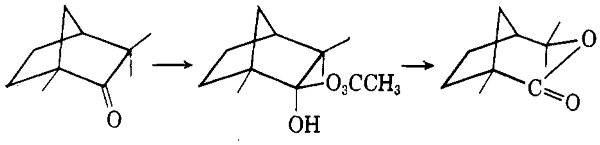
[9] R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963).

[10] J. Berson and D. Willner, *J. Am. Chem. Soc.*, **84**, 675 (1962).

[11] J. A. Berson and S. Suzuki, *ibid.*, **81**, 4088 (1959), have cogently discussed the relative importance of electronic effects in migrations toward oxygen, nitrogen, and carbon and have concluded that migrations to oxygen should be the most sensitive to electronic differences in the migrating groups.

It seems necessary to consider forces which might work in opposition to both electronic and boat-form interactions in the transition states. The conformation of the leaving residue does not appear to be important since it can readily attain *trans* coplanarity with either of the migrating groups.[2] We believe that the extra factor involved in these reactions is associated with the torsional strain caused by the eclipsed nonbonded interactions between the substituents on C-2 and the hydrogens on C-3.[12] On the other hand, nonbonded interactions between substituents on C-2 and the bridgehead are much less severe since the dihedral angles involved are approximately 44° (H_1 with X) and 79° (H_1 with Y).[13] Thus, migration of the C-2–C-3 bond proceeds with considerable relief of eclipsing strain whereas migration of the C-1–C-2 bond would be expected to involve much less strain relief.

Applied to Baeyer–Villiger reactions of bicyclic ketones, these arguments lead to the conclusion that migration of the C-2–C-3 bond will always be favored regardless of substitution or orientation of the hydroxy-perester functions. The results of fenchone oxidation (eq. 2) can now be understood more clearly using these considerations. The electronic effects are essentially equal and the competition is between formation of the boat form and relief of torsional strain. The major product (*ca.* 60%) was the one predicted on the latter basis.



(2)

In those cases where a *syn*-7-substituent is present, these two steric effects operate in the same direction; *i.e.*, chair forms are formed by migration of the C-2–C-3 bond since the hydroxy perester has the opposite configuration from that of the fenchone case.[6c]

Finally, there appears to be a rough correlation between the amount of the "wrong" lactone and the size of the 7-substituent. Assuming that the order of increasing bulk is chlorine < bromine < methyl,[14] one sees an increase in the per cent of methylene migration $< \sim 53\% < \sim 71\% < \sim 100\%$. Presumably, this series also represents the order of increasing importance of boat-form interactions in the transition states.

Experimental

Melting points are uncorrected and were determined on a Mel-Temp apparatus. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer. N.m.r. spectra were recorded with a Varian, Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard.

***syn*-7-Chloronorcamphor.**—*syn*-7-Chloro-*exo*-2-norbornanol was prepared by the procedure of Roberts and co-workers[3] and was oxidized to *syn*-7-chloronorcamphor by the procedure of Brown and Garg.[15] From 27.9 g. (0.19 mole) of alcohol there was obtained 20.6 g. (75%) of a waxy solid, b.p. 67–71° (0.4 mm.), lit.[3] b.p. 105–112° (13 mm.). The 2,4-dinitrophenylhydrazone melted at 191–192, lit.[3] m.p. 192.5–193.5°; the semicarbazone melted at 184–185°, lit.[3] m.p. 183.5–185°. The ketone used in the next step was purified by regeneration from the semicarbazone.[16]

Oxidation of *syn*-7-Chloronorcamphor with Peracetic Acid.—The ketone (10.5 g., 0.073 mole) was dissolved in 100 ml. of glacial acetic acid containing 3.0 g. of sodium acetate. Thirty-five milliliters (*ca.* 0.21 mole) of 40% peracetic acid in acetic acid was added and the solution was kept for 2 weeks in the dark at room temperature. The products were isolated by addition of 500 ml. of water followed by ether extraction. After washing the combined extracts with sodium carbonate and water they were dried over sodium sulfate and evaporated to give 9.2 g. (77%) of crude lactones. All of the starting ketone had been consumed as shown by gas chromatography.

An analytical sample was obtained by gas chromatography on a 5 ft. × 0.25 in. column of silicone (SE-30) at 200° and had m.p. 77–85°, $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.68 μ.

Anal. Calcd. for $C_7H_9ClO_2$: C, 52.33; H, 5.60; Cl, 22.11. Found: C, 52.35; H, 5.69; Cl, 21.86.

The n.m.r. spectrum of this material showed a complex multiplet centered at 5.5 τ which included protons on chlorine- and oxygen-bearing carbons. The ratio of the integrated area of this region to the area of the remainder of the spectrum (between 7 and 8 τ) was 0.39. Assuming that the only two products present are the two isomeric lactones, it can be calculated that lactone V constitutes 53% of the product.

Diacid VII.—Oxidation of the lactonic product was effected by heating 0.978 g. of lactone with 15 ml. of a 70:30 mixture of concentrated nitric acid and water for several minutes. The process was repeated with 10 ml. of the nitric acid solution followed by dilution with water and ether extraction. The acidic products were removed from the combined ether extracts with sodium carbonate solution which was subsequently acidified to liberate the acid fraction. The product was extracted into ether which was dried and evaporated to give 0.14 g. (12%) of *cis*-2-chloro-*cis*-cyclopentane-1,3-dicarboxylic acid after trituration with chloroform. The melting point was 186–189° dec., lit.[3] m.p. 186–187° dec., and was undepressed on admixture with an authentic sample, m.p. 189–191°, prepared similarly in 27% yield by oxidation of *syn*-7-chloronorcamphor.

The **dimethyl ester** of the diacid VII was prepared in 94% yield by heating with BF_3–methanol reagent[17] and had m.p. 108.5–109.5° (needles from cyclohexane), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.80 μ.

Anal. Calcd. for $C_9H_{13}ClO_4$: C, 48.98; H, 5.89; Cl, 16.10. Found: C, 49.24; H, 6.14; Cl, 16.27.

The n.m.r. spectrum showed a sharp singlet at 6.27 τ for the methyl protons and a triplet (J = 4 c.p.s.) at 5.17 τ for the proton on the chlorine-bearing carbon. The relative areas under these peaks was 6:1.

***cis*-1,3-Bis(hydroxymethyl)-*cis*-2-chlorocyclopentane. A. From Diester.**—The diol IX was prepared in 96% yield by reduction of the above diester with lithium aluminum hydride in ether. The melting point of the crude product was 77–80° and was raised to 80–81° by crystallization from benzene, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.92, 9.65 (sh), and 9.80 μ.

Anal. Calcd. for $C_7H_{13}ClO_2$: C, 51.06; H, 7.90; Cl, 21.58. Found: C, 51.29; H, 8.01; Cl, 21.75.

B. From Lactone V.—Lithium aluminum hydride reduction of the Baeyer–Villiger product gave an 81% yield of crude diols whose infrared spectrum was essentially identical with that of the pure diol prepared by procedure A. From a 40-mg. sample of crude diol there was obtained 35 mg. of crystals with m.p. 77–78.5°. The mixture melting point was 78–79°.

Oxidation of Diol IX to Lactone V.[5]—The diol (0.91 g., 5.53 mmoles) was dissolved in 15 ml. of ether and treated with 3.58 g. (12 mmoles) of sodium dichromate dihydrate in 10 ml. of distilled water containing 2.5 ml. of 96% sulfuric acid. After 1 hr. at room temperature, 50 ml. of water was added and the layers were separated. The aqueous phase was extracted further with ether and the combined extracts were washed with sodium carbonate solution. After drying over magnesium sulfate, the ether was evaporated to give 0.27 g. (30%) of lactone V, m.p. 81–92° (sealed capillary). A sample purified by gas chromatography had m.p. 92–99°. Strong absorptions appeared in the infrared

---

[12] The magnitude of this strain is probably on the order of 2 to 3 kcal./mole. See W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. I.

[13] F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

[14] See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 236.

[15] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

[16] W. G. Woods and J. D. Roberts, *J. Org. Chem.*, **22**, 1124 (1957).

[17] Obtained from Applied Science Laboratories, Inc., State College, Pa. For procedure, see L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

spectrum (CCl_4) at 5.70, 8.32, 8.67, and 9.43 μ. The Baeyer–Villiger lactone had some medium intensity bands not found in this spectrum.

The n.m.r. spectrum of this product was slightly simpler than the Baeyer–Villiger product and the ratio of areas of high-field to low-field protons was almost exactly 9:3.

syn-**7-Bromonorcamphor.**—*syn*-7-Bromo-*exo*-2-acetoxynorbornane was prepared by the procedure of Krieger[18] and had b.p. 117–122° (2.5 mm.), lit.[18] b.p. 124–125° (13 mm.), lit.[4] 94–95° (1 mm). Lithium aluminum hydride reduction of this substance in ether gave the corresponding alcohol as a viscous liquid. Oxidation of the crude alcohol by the method of Brown and Garg[15] gave *syn*-7-bromonorcamphor in 70% yield, b.p. 101–106° (1.25 mm.), n^{20}_{D} 1.5349 [lit.[4] b.p. 126–127° (1 mm.), n^{22}_{D} 1.5123]. The 2,4-dinitrophenylhydrazone melted at 202–203°, lit.[4] m.p. 193–194°.

The semicarbazone was prepared in the usual manner, m.p. 187–188°.

Anal. Calcd. for $C_8H_{12}N_3OBr$: C, 39.05; H, 4.92; N, 17.08. Found: C, 38.94; H, 4.89; N, 17.37.

Oxidation of *syn*-**7-Bromonorcamphor with Peracetic Acid.**—To a solution of 1.52 g. (8.05 mmoles) of ketone (purified by regeneration of the semicarbazone[16]) in 30 ml. of glacial acetic acid containing 0.5 g. of sodium acetate was added 15 ml. (*ca.* 0.09 mole) of 40% peracetic acid. After standing at room temperature in the dark for 15 days, the reaction mixture was diluted with water and extracted with ether. Further processing, as before, gave 1.2 g. (73%) of a viscous oil which was shown to contain no starting material by gas chromatography. This product discolored on attempted molecular distillation and the corresponding n.m.r. spectrum showed two main regions of absorption. One region was centered at 5.5 and the other extended from 7 to 8 τ. The relative areas of these two regions was 0.43 from which it can be calculated that the mixture of lactones is at least 71% VI. The carbonyl stretching frequency appeared at 5.75 μ ($CHCl_3$) and the spectrum in general showed a few weak bands not found in the spectrum of VI prepared later from the diol.

A small sample (0.129 g.) was purified for analysis by crystallization from pentane at −70° to give 0.089 g. of crystalline material which melted at 59.5–61° after sublimation.

Anal. Calcd. for $C_7H_9BrO_2$: C, 40.97; H, 4.39. Found: C, 41.07; H, 4.66.

Diacid VIII.—Oxidation of the bromolactone (0.86 g.) with nitric acid gave 0.2 g. (21%) of crystalline material, m.p. 170–172° dec. The melting point was undepressed on admixture with a sample, m.p. 176.5–177° dec., prepared similarly in 25% yield by nitric acid oxidation of *syn*-7-bromonorcamphor. The diacids were somewhat unstable and did not give good carbon-hydrogen analyses. The dimethyl ester was prepared with BF_3–methanol reagent[17] and could be readily purified by crystallization from pentane, m.p. 86–87°, $\lambda_{\max}^{CHCl_3}$ 5.86 μ.

Anal. Calcd. for $C_9H_{13}BrO_4$: C, 40.75; H, 4.91; Br, 30.19. Found: C, 40.78; H, 5.03; Br, 30.10.

The n.m.r. spectrum showed a triplet (J = 4 c.p.s.) at 5.17 and a sharp singlet at 6.22 τ. The relative areas of these two peaks was 1:6.

cis-**1,3-Bis(hydroxymethyl)**-*cis*-**2-bromocyclopentane. A. From Diester.**—The previous diester was reduced with lithium aluminum hydride in ether to give a 78% yield of diol X, m.p. 92–93.5°. The infrared spectrum was identical with that of the sample prepared in procedure B.

B. From Lactone VI.—Lithium aluminum hydride reduction of the lactone (1.55 g.) in ether gave 0.87 g. (55%) of crystalline diol X, m.p. 93–93.5°. The infrared spectrum in chloroform showed O–H absorption at 2.78 (sharp) and 2.92 μ (weak, broad) and C–O absorption at 9.6 and 9.75 μ (strong).

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.19; H, 6.22; Br, 38.28. Found: C, 39.97; H, 6.19; Br, 38.52.

Oxidation of Diol X.—Oxidation of diol X (0.17 g.) dichromate as before gave 0.050 g. of an oil which solidified on sublimation at 25 μ, m.p. 61.5–62.5° (sealed capillary). Strong infrared peaks appeared at 5.73, 8.68, 9.22, 9.43, and 9.63 μ (CCl_4).

Acknowledgment.—We wish to thank the National Science Foundation for financial support (G-19143) and for funds toward the purchase of the n.m.r. spectrometer. J. A. B. wishes to acknowledge the National Institutes of Health for a predoctoral fellowship.

---

[18] H. Krieger, *Suomen Kemistilehti*, **34B**, 24 (1961).