Ring Expansion of Bicyclo[2.1.1.]hexan-2-one and Related Compounds

THOMAS GIBSON

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

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The diazomethane ring-expansion reaction of bicyclo[2.1.1]hexan-2-one and related compounds has been investigated as a method for the synthesis of bicyclo[3.1.1]heptanones. The reaction, while sluggish, provides a convenient procedure for the synthesis of bicycloheptanones **6–14** from the bicyclohexanones **1–5**. The lack of epoxide formation, the preference for C_2–C_3 over C_1–C_2 bond migration, and the lack of reactivity of the products **6–14** is discussed in terms of the influence of ring strain and steric effects on the zwitterionic intermediate in the reaction.

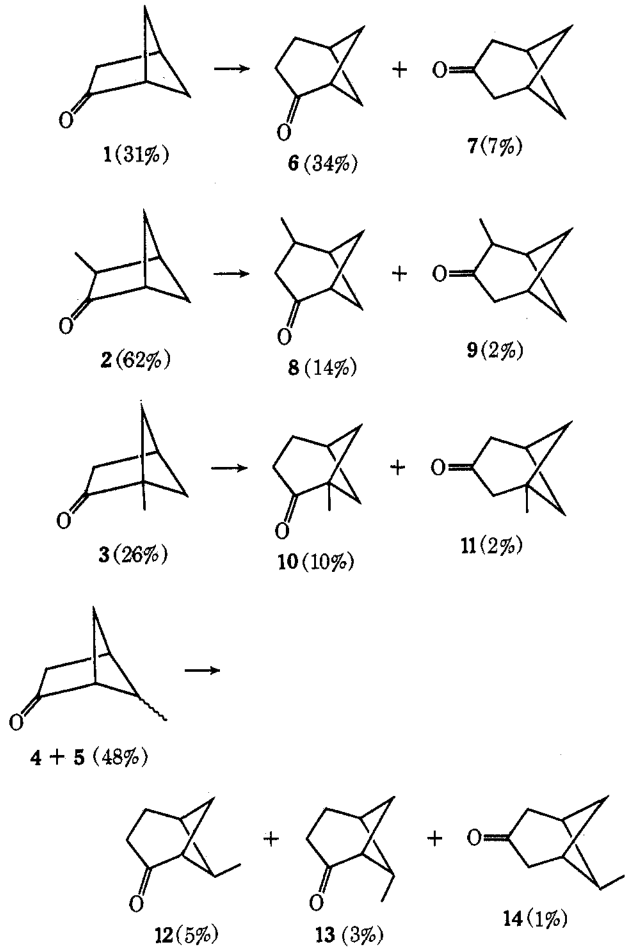
Various approaches to the construction of compounds of the bicyclo[3.1.1]heptane series are possible. Four of these, involving ring formation in 1,3-disubstituted cyclobutanes, ring closure of 2-tosyloxymethylcyclohexanones,[1] photocycloaddition of 1,6-heptadienes, and ring contraction of bicyclo[3.2.1]octanes, have been discussed at some length by Musso, *et al.*[2] For some time we have been engaged in attempts to utilize the photocycloaddition method for this purpose.[3] Since it appears from this work that direct cycloaddition to the bicyclo[3.1.1]heptane system from acyclic dienone precursors is not feasible, we have examined a variation of this approach. This involves initial cycloaddition to the bicyclo[2.1.1]hexan-2-one system,[4] followed by a ring-expansion reaction. The availability of compounds **1–5** by the photocycloaddition process[4] provided a source of materials suitable for a thorough study of the ring expansion reaction, the results of which are presented in this paper.

Results

Synthesis of Bicyclo[2.1.1]hexanones.—Compounds **1–5** (Chart I) were prepared by the method previously described.[4] The isomers **4** and **5** were used as the 1:3 *exo–endo* mixture obtained from the irradiation of *trans*-1,5-heptadien-3-one.[4b]

Ring-Expansion Reactions.—The ring expansion reactions were carried out in methanol by generation *in situ* of diazomethane from *N*-methyl-*N*-nitrosourethane.[5,6] The results shown in Chart I, which gives yields of products and recovery of starting material as determined by gas–liquid partition chromatography (glpc), were obtained with the use of approximately 2 molar equiv of urethane per mol of ketone. The use of a larger excess of diazomethane did not lead to an improvement in yields, although a thorough study of this point has not been carried out. All reactions gave varying amounts of *N*-methylurethane, which interfered with analysis and isolation of products on polar glpc columns. The most convenient isolation procedure found involved basic hydrolysis to remove urethane followed by preparative glpc using a nonpolar liquid phase such as SE-30.

CHART I



Some difficulty was encountered in isolation of products from the reaction of **4** and **5**, and therefore complete characterization was not possible. Compounds **6** and **7** were identified by direct comparison of their infrared spectra and glpc behavior with those of authentic samples.[7] Ketones **6–14** displayed the expected infrared carbonyl maxima for this system, as well as nmr spectra consistent with the assigned structures. The details of these spectra are recorded in the Experimental Section.

We found high-resolution mass spectrometry to be a most useful tool for the purpose of establishing the position of the carbonyl group in the isomers formed in a reaction. Thus, the ketone **6**, in which the carbonyl group is adjacent to the bridgehead position, showed a base peak at *m/e* 67, corresponding to a composition of

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(1) E. Wenkert and D. P. Strike, *J. Org. Chem.*, **27**, 1883 (1962); F. Nerdel, D. Frank, and H. Marschall, *Angew. Chem.*, **74**, 587 (1962); K. B. Wiberg and G. W. Klein, *Tetrahedron Lett.*, 1043 (1963).

(2) H. Musso, K. Naumann, and K. Grychtol, *Chem. Ber.*, **100**, 3614 (1967).

(3) T. W. Gibson and W. F. Erman, unpublished results.

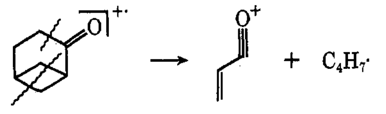
(4) (a) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965); (b) T. W. Gibson and W. F. Erman, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(5) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

(6) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Amer. Chem. Soc.*, **61**, 1057 (1939).

(7) We express our thanks to Professor H. Musso for kindly providing us with samples of these two compounds.

C_5H_7. The most abundant oxygen-containing fragment appeared at m/e 55, corresponding to a composition of C_3H_3O. The process leading to this fragment can be rationalized as shown and is supported by the observation of the analogous fragmentation in nopinone (**15**) which generates the ion C_5H_7O as the most abundant oxygen-containing fragment, along with the C_3H_3O ion at lower intensity.



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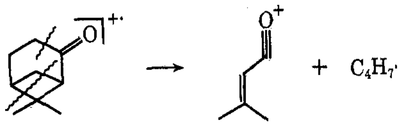

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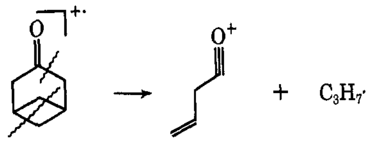
Ketone **7**, on the other hand, shows as the base peak an oxygen-containing fragment corresponding to a composition of C_4H_5O, probably arising from the process shown.



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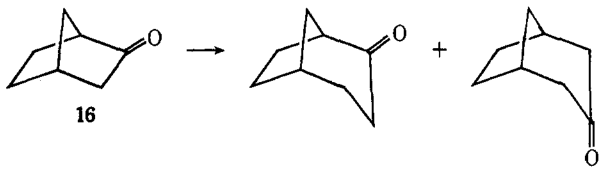
The observation of analogous data from the other product sets allowed unambiguous assignment of structures (*cf.* Experimental Section).

Discussion

In addition to the synthetic utility of this process, there are a number of mechanistic questions of interest. We wished to know what effect placing the carbonyl group in a rigid bicyclic framework would have on three relationships: competition between ring expansion and epoxide formation, the relative migratory aptitudes of bridgehead *vs.* bridge carbon atoms, and the relative reactivities toward ring expansion of bicyclo[2.1.1]hexanones and bicyclo[3.1.1]heptanones. It has been generally accepted that the reaction involves nucleophilic addition of diazomethane to the carbonyl group, generating a zwitterionic intermediate, which is then partitioned between epoxide formation and alkyl shift.[8] The following discussion will be based on the assumption that this mechanism is operating.

Epoxide Formation.—The non-Lewis acid catalyzed reaction of diazomethane with alicyclic ketones generally results in some epoxide formation.[8] We were unable however, to isolate any epoxides from the reactions of **1–5** with diazomethane, nor did we obtain any evidence for their presence in crude reaction products by examination of ir and nmr spectra. This parallels the behavior shown by norcamphor (**16**) in the ring-expansion reaction[9] in which no epoxide formation was observed. The absence of epoxide formation in that system was rationalized on the basis of ring strain in the zwitterionic intermediate, which would favor partition toward ring expansion rather than closure to spiro epoxide. This effect would be expected to be even more pronounced in the more highly strained bicyclohexane system, and it is therefore not surprising that epoxide formation was not observed.

Migratory Aptitudes.—The results shown in Chart I reveal that there is a ratio of approximately 5–7:1 in favor of bridge migration (C_3) over bridgehead migration (C_1). This behavior is similar to that shown by both norcamphor (**16**) and bicyclo[3.2.1]octan-2-one (**17**), which are reported to give 2:1 ratios in favor of bridge migration in the presence of 0.1 equiv of diazomethane.[9] This preference for 2,3- over 1,2-bond shift was attributed to nonbonded interactions in the zwitterion intermediate, in which eclipsing with the hydrogens in the 3 position occurs, weakening the 2,3 bond. The same would be true in the bicyclo[2.1.1]-hexanones, and, in fact, studies of molecular models show that this effect should be somewhat accentuated in this system. In the bicyclo[2.1.1]hexane system, the bridgehead hydrogen is situated in a perfectly staggered orientation to the two C_2 substituents, while appreciable eclipsing occurs at this position in the bicyclo[2.2.1]heptane system. Thus the difference in relief of strain brought about by stretching of the C_2–C_3 bond in preference to stretching of the C_1–C_2 bond would be greater in the bicyclohexane system, leading to the larger ratio observed.



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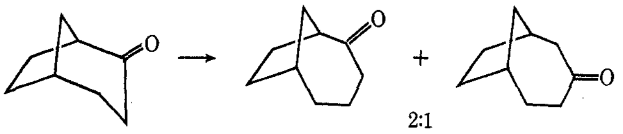

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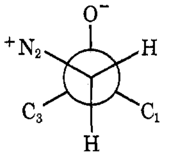
The steric situation around C_2 in the zwitterion intermediate should also have an effect on the relative energies of the rotational conformers (**18** and **19**)



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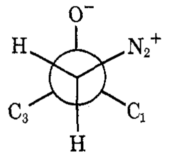

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[8] C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, pp 81–99.

[9] G. Fachinetti, F. Pietra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971).

leading to the transition states for bond migration. Turro and Gagosian,[10] attempting to explain migration preferences in the reaction of diazoethane with substituted cyclopropanes, considered energy differences in the rotational conformers leading to products to be an important factor. Comparison of Dreiding models of the rotational conformers **18** and **19** reveals a decidedly greater interaction between the diazo group (which with its accompanying solvent shell should be of considerably greater steric bulk than a hydrogen atom) and the syn C_3 hydrogen in **18** than with the bridgehead hydrogen in **19**. This occurs as a result of the eclipsed arrangement of the tetrahedral C_2 substituents with the C_3 hydrogens, in contrast to their staggered relationship with the C_1 hydrogen, as mentioned above. This would favor somewhat conformer **19**, which leads to C_2–C_3 bond migration. This effect does not appear to be significantly altered by the presence of a methyl group at C_1. In **2**, with a methyl group at C_3, which would presumably lead to trans approach of nucleophile, the effect is slightly accentuated, leading to a slightly greater preference for C_2–C_3 bond migration. The data obtained for **4** and **5** are not sufficiently accurate to use with any confidence, but it would not be expected that the methyl group at C_5 would have any significant effect on rotational energy differences. Thus, steric effects in the intermediate zwitterion provide two arguments for rationalizing the preference for C_2–C_3 bond shift in the bicyclohexane system.

Relative Reactivities.—In view of the known greater reactivity of cyclohexanone over cyclopentanone toward ring expansion,[8] we anticipated some difficulty in stopping the reaction of the bicyclohexanones at the bicycloheptanone stage. In fact, this situation exists in the norcamphor series, in which reactivity of the bicyclo[3.2.1]octanone **17** is much greater than that of **16**.[9] To get some information on this point, we carried out the attempted ring expansion of nopinone (**15**) under the same conditions used for the bicyclohexanones. Reaction with diazomethane produced from 2 equiv of urethane was carried out for 2 days, after which time glpc analysis revealed no loss of starting material and no detectable ring-expansion products. This result appeared promising with respect to the planned use of the ring-expansion reaction for synthesis of the bicyclo[3.1.1]heptanone system, but we felt that the unreactivity of nopinone might be due to the presence of the *gem*-dimethyl group. This grouping would be expected to hinder formation of a tetrahedral center at the carbonyl carbon, irrespective of the route of approach of the nucleophile to the carbonyl group. However, this unreactive behavior appears to be characteristic of the bicyclo[3.1.1]heptanone system, since in no instance could we obtain any glpc evidence for the formation of bicyclo[4.1.1]octanones in the ring-expansion reactions shown in Chart I, even in the presence of a large excess of diazomethane. Study of models of the three ring systems does not provide any ready explanation for the low reactivity of the bicyclo[3.1.1]heptanones. However, their stability to diazomethane serves to make the ring expansion reaction convenient for their synthesis.

Experimental Section[11]

Attempted Ring Expansion of Nopinone (15).—To an ice-cooled solution of 0.50 g (3.6 mmol) of nopinone[12] in 16 ml of methanol was added 0.25 g of anhydrous Na_2CO_3. A solution of 0.97 g (7.4 mmol) of *N*-methyl-*N*-nitrosourethane in 9 ml of methanol was then added over 25 min. After addition was complete, the ice bath was removed and the solution was allowed to warm to ambient temperature and stirred for 2 days. Filtration followed by distillation gave an oily residue composed mainly of nopinone and *N*-methylurethane. The latter impurity was removed by treatment with 10 ml of 1 *N* NaOH at 60° for 4 hr. The 0.530 g of neutral material recovered showed an infrared spectrum and glc analysis nearly identical with those of starting material. No peaks were observed in the glpc analysis in the area in which ring expansion products would be expected to appear.

Ring Expansion of 1.—To a solution of 0.30 g of **1** in 20 ml of methanol over 0.40 g of Na_2CO_3 was added 1.20 g of nitrosomethylurethane in methanol solution.[6] The solution was stirred overnight at room temperature, the excess diazomethane was destroyed with 1 ml of 3% HCl, the solution was neutralized with NaOH, and the solvent was removed by distillation. The residue was taken up in water, the aqueous solution was extracted with ether, and the ether solution was dried over $MgSO_4$. Distillation gave 0.457 g of colorless oil, bp 85–95° (20 mm). A glpc analysis on two columns[11] showed four major peaks in the ratio of 31:5:38:25, which were collected and identified spectroscopically. Yields were calculated on the basis of the areas under the glpc peaks, assuming equivalent response of the TC detector to the different compounds.

Peak 1 (31%) was identified as recovered **1**.

Peak 2 (**7**, 7% yield) had sublimed, mp 60–62° (lit.[2] 59°). The ir spectrum was identical with that of an authentic sample, as was the glpc retention time on an SE-30 column.[7] The nmr spectrum showed signals at τ 8.65 (2 H, dd, J = 7 and 2 Hz), 7.7 (2 H, m), and 7.55 (6 H, s). The high-resolution mass spectrum showed a moleclar ion at m/e 110 ($C_7H_{10}O$) and a base peak at m/e 69 (C_4H_5O).

Peak 3 was identified by spectroscopic means as *N*-methylurethane.

Peak 4 (**6**, 34% yield) was semicrystalline. The ir spectrum and glpc retention time on an SE-30 column were identical with those of an authentic sample.[7] The nmr spectrum showed signals at τ 8.41 (2 H, dd, J = 7 and 3 Hz), 8.00 (2 H, m), 7.46 (4 H, m), and 7.20 (2 H, q, J = 5 Hz). The high resolution mass spectrum showed a molecular ion at m/e 110 ($C_7H_{10}O$), the base peak at m/e 67 (C_5H_7), and the most intense oxygen-containing fragment at m/e 55 (C_3H_3O).

The *p*-toluenesulfonylhydrazone had mp 209–210° (lit.[2] 206–208°).

The reaction was repeated using 8 equiv of urethane added in two batches over a 4-day period. The *N*-methylurethane was removed by hydrolysis and the neutral product was distilled to give a 40% yield of a mixture composed mainly of **6** and **7**, with some starting material and other impurities present. No evidence was seen for further ring-expanded materials.[13]

Ring Expansion of 2.—A solution of 0.502 g of **2** in methanol

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(10) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970).

(11) Melting points were determined on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 and 137 spectrophotometers as neat films or 5% solutions in CCl_4. Nuclear magnetic resonance spectra were obtained on a Varian Associates HA-100 spectrometer using TMS as an internal reference in $CDCl_3$. Nmr data are recorded in this order: chemical shift (integration, multiplicity where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constant in hertz). Mass spectra were determined with an Atlas CH-4 spectrometer, or, where noted, high-resolution spectra were obtained with an Atlas SM-1 spectrometer. Glpc analyses were carried out on a Varian Aerograph Model 202B instrument using thermal conductivity detectors. Columns used were 5 ft × 0.25 in. stainless steel packed with 15% FFAP polyester or 15% SE-30 silicone oil on HMDS-treated 60–80 mesh Chromosorb W support. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(12) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 5445 (1960).

(13) The low material balances observed in these reactions are partially due to loss of the starting bicyclohexanones by codistillation with solvent, a fact which led to some difficulty in their synthesis. Glpc examination of the methanol obtained from reaction of **1** with diazomethane showed the presence of considerable amounts of **1** with no evidence for **6** or **7**. The yields of bicycloheptanone products are based on starting bicyclohexanone, and are probably reasonably accurate.

over 0.20 g of Na_2CO_3 was treated with 1.359 g of nitrosomethylurethane,[6] and the resulting mixture was stirred overnight at room temperature. Work-up followed by distillation gave 0.569 g of colorless oil, bp 60–70° (20 mm), which showed four major peaks on glpc analysis. Isolation and analysis identified these as *N*-methylurethane (30%), starting material (62%), and two ring-expanded products in yields of 2 and 14%. Pure materials were isolated by preparative glpc on a 10-ft SE-30 column. The minor product, **9**, showed λ_{max} 5.84 μ and nmr signals at τ 8.87 (3 H, d, J = 7 Hz), 8.64 (2 H, m), 7.2–8.0 (5 H), and 7.47 (2 H, s). The high-resolution mass spectrum showed a molecular ion at *m/e* 124 ($C_8H_{12}O$), the base peak at *m/e* 67 (C_5H_7), and major oxygen-containing fragments at *m/e* 69 (C_4H_5O) (68% of base peak) and 83 (C_5H_7O), corresponding to the two modes of the fragmentation pattern observed for **7**.

The major product, **8**, showed λ_{max} 5.80 μ and nmr signals at τ 8.95 (3 H, d, J = 6.5 Hz), 8.42 (2 H, m), 7.3–8.1 (6 H), and 7.20 (1 H, m). The high-resolution mass spectrum showed a strong molecular ion at *m/e* 124 ($C_8H_{12}O$), the base peak at *m/e* 68 (C_5H_8), and the major oxygen-containing fragment at *m/e* 70 (C_4H_6O) (44% of base peak).

The *p*-toluenesulfonylhydrazone had mp 162–164°.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.59; H, 6.85; N, 9.62.

Ring Expansion of 3.—A solution of 0.284 g of **3** in methanol over 0.20 g of Na_2CO_3 was treated with 0.821 g of nitrosomethylurethane,[6] and stirred overnight at room temperature. Distillation gave a mixture which contained 26% of recovered starting material and two ring-expansion products in 2 and 10% yields, both of which were isolated by preparative glpc.

The minor product, **11**, showed λ_{max} 5.80 μ and nmr signals at τ 8.92 (3 H, s), 8.58 (2 H, dd, J = 8 and 2 Hz), 8.08 (2 H, m), 7.73 (2 H, s), 7.63 (2 H, s), and 7.6 (1 H, m). The high-resolution mass spectrum showed a molecular ion at *m/e* 124 ($C_8H_{12}O$), the base peak at *m/e* 55 (C_4H_7), and major oxygen-containing fragments at *m/e* 83 (C_5H_7O) (99% of base peak) and 69 (C_4H_5O) (83% of base peak) resulting from the two possible modes of fragmentation of **11** corresponding to that of **7**.

The major product, **10**, showed λ_{max} 5.82 μ and nmr signals at τ 8.93 (3 H, s), 8.29 (2 H, dd, J = 7.0 and 2.5 Hz), 7.96 (4 H, m), 7.52 (2 H, t, J = 7 Hz), and 7.5 (1 H, m). The high-resolution mass spectrum showed a molecular ion at *m/e* 124 ($C_8H_{12}O$), the base peak at *m/e* 81 (C_6H_9), and the major oxygen-containing fragment at *m/e* 69 (C_4H_5O) (94% of base peak), establishing the presence of the carbonyl group at the 2 position.

The *p*-toluenesulfonylhydrazone had mp 159–161°.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.64; H, 6.86; N, 9.60.

Ring Expansion of 4 and 5.—A solution of 0.250 g of a 3:1 endo:exo mixture of **4** and **5** in methanol over 0.20 g of Na_2CO_3 was treated with 0.692 g of nitrosomethylurethane,[6] and the mixture was stirred overnight at room temperature. Work-up followed by distillation gave 0.222 g of colorless oil, bp 60–80° (20 mm), which showed the presence of starting material (42%; 3:1), and two product peaks in yields of 1 and 9%. The minor product was identified as **14** on the basis of λ_{max} 5.82 μ, nmr signals at τ 8.72 (3 H, d, J = 6.8 Hz), 8.26 (1 H, br d, J = 7 Hz), 7.86 (2 H, m), 7.42 (4 H, s), and *ca.* 7.4 (2 H). The high-resolution mass spectrum showed a molecular ion at *m/e* 124 ($C_8H_{12}O$), the base peak at *m/e* 67 (C_5H_7), and the major oxygen-containing fragments in nearly equal intensity at *m/e* 83 (C_5H_7O) and 69 (C_4H_5O).

The nmr spectrum of the material corresponding to the major peak showed signals for two methyl groups at τ 9.15 (d, J = 6 Hz) and 8.67 (d, J = 6.8 Hz) in a ratio of 3:5. The high-resolution mass spectrum showed a molecular ion at *m/e* 124 ($C_8H_{12}O$) and a base peak at *m/e* 69 (C_4H_5O), while the ir spectrum showed a single carbonyl band at 5.82 μ. These data suggest the presence of a mixture of the two isomers **12** and **13** in a ratio of 5:3. The stereochemistry of the methyl groups in these compounds, as well as that of **14**, are assigned on the basis of their chemical shifts, in analogy with the chemical shift positions of methyl groups in other bicyclo[3.1.1]heptanes.[14]

Registry No.—**6**, 17159-87-4; **7**, 17159-75-0; **8**, 33122-17-7; **8** *p*-toluenesulfonylhydrazone, 33122-18-8; **9**, 33061-07-3; **10**, 33122-19-9; **10** *p*-toluenesulfonylhydrazone, 33122-20-2; **11**, 33061-08-4; **12**, 33066-01-2; **13**, 33066-02-3; **14**, 33061-09-5.

Acknowledgment.—The able technical assistance of R. L. Munyon, Sr., is gratefully acknowledged.

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(14) T. W. Gibson and W. F. Erman, *J. Amer. Chem. Soc.*, **91**, 4771 (1969).

The Crystal Structure of 1-(*p*-Bromophenyl)-1,2-epoxycyclohexane. Evidence for Three-Ring Phenyl Pseudoconjugation[1]

STEFANO MERLINO

Istituto di Mineralogia, Università di Pisa, 56100 Pisa, Italy

GIOVANNI LAMI, BRUNO MACCHIA,* FRANCO MACCHIA, AND LUIGI MONTI

Istituti di Chimica Farmaceutica e di Chimica Organica, Università di Pisa, 56100 Pisa, Italy

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1-(*p*-Bromophenyl)-1,2-epoxycyclohexane crystallizes in space group $P2_1/c$, with unit cell dimensions a = 9.91, b = 5.72, c = 19.41 Å; β = 102° 20 min. The structure was solved by single-crystal X-ray diffraction methods. Least-squares refinement led to a final agreement factor for the observed reflections, R = 0.072. In the molecular structure the cyclohexane ring has a half-chair conformation. The epoxydic ring (C–C bond length 1.48 Å with estimated standard deviation 0.02 Å, C–O bond lengths with mean value 1.47 Å, estimated standard deviation 0.02 Å) makes an angle of 83° with the phenyl ring, as the result of pseudoconjugative interaction. This interaction is also indirectly responsible for the particular conformation assumed by the cyclohexane ring.

The geometry of the variously substituted cyclohexane rings has been extensively studied by means of electron diffraction, X-ray, and microwave spectroscopy.[2] The structural determinations on 1,2-epoxycyclohexanes are largely limited[3,4] to the classical electron diffraction studies of Ottar[5] who measured the skeletal geometry and the various interatomic distances in this system. In particular, the 1,2-epoxycyclohexane

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(1) This work was supported by Consiglio Nazionale delle Ricerche, Roma.

(2) (a) C. Altona and M. Sundaralingam, *Tetrahedron*, **26**, 925 (1970); (b) H. Booth, *Progr. Nucl. Magn. Resonance Spectrosc.*, **5**, 231 (1969), and references cited therein.

(3) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(4) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p. 1.

(5) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).