

for water acting as a proton transfer agent. Addition of 3–5 units of ω to our observed value in perchloric acid of 0.65 yields a derived $\omega = 3.6$ –5.7, well within the range suggested for water acting as a proton transfer agent. Thus we conclude that water is involved as a proton transfer agent in the rate-limiting step for acid hydrolysis of γ -hydroxybutyramide.

In a discussion of the results of Zörn,^{1a} Witkop¹¹ suggested a nucleophilic attack of hydroxy oxygen on the carbonyl carbon of the protonated amide and direct

(11) B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961).

transfer of hydroxy hydrogen proton to nitrogen. In order to accommodate a role for water as a proton transfer agent as indicated in this study, we suggest that the proton transfer from oxygen to nitrogen is mediated by one or more water molecules. Water removes the proton from the hydroxy oxygen and donates another proton to the nitrogen atom.

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The Chemistry of 7-Substituted Norbornenes. The Reaction of Bicyclo[2.2.1]hept-2-en-7-one with Peracid^{1,2}

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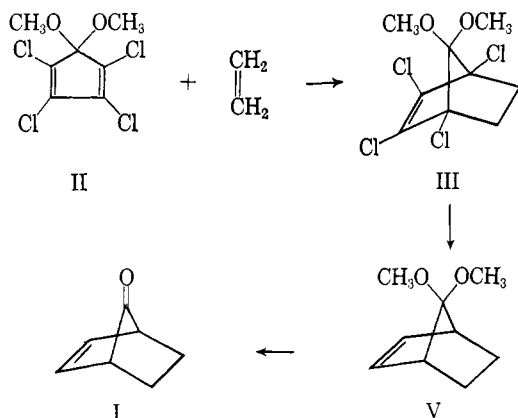
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A short synthetic route to 7-substituted bicyclo[2.2.1]hept-2-enes has been developed. Bicyclo[2.2.1]hept-2-en-7-one has been prepared and was found to react with perbenzoic acid to give the epoxide (XI) rather than the Baeyer–Villiger product, indicating that there is very little interaction between the carbonyl and the non-conjugated double bond.

Although much is known about the chemistry of norbornenes, a relatively small amount of this recorded knowledge deals with the reactions of 7-substituted bicyclo[2.2.1]hept-2-enes. This paucity of information is due to the lack of a simple synthetic route to these relatively unknown compounds. We describe herein a simple four-step synthesis of bicyclo[2.2.1]hept-2-en-7-one (I). Certain reactions of I are discussed. Of particular interest is the reaction of this unsaturated ketone with perbenzoic acid.

Ethylene reacts with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (II) in an inert atmosphere at 180° to yield the expected Diels–Alder adduct (III).⁴ Dechlorination of III according to the procedure of Winstein⁵ gave partial reduction of the double bond



(1) (a) Presented in part before the Division of Organic Chemistry, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, p. 53M; (b) a preliminary communication of part of this work has appeared: P. G. Gassman and P. G. Pape, *Tetrahedron Letters*, **No. 1**, 9 (1963).

(2) We are indebted to the National Science Foundation, Grant 25221, for partial support of this research.

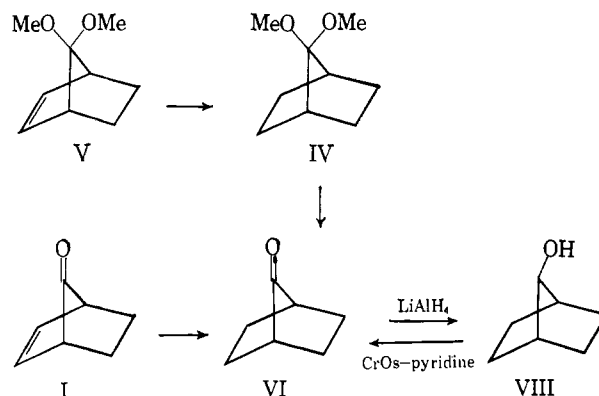
(3) National Science Foundation Summer Fellow, 1962.

(4) P. E. Hoch, *J. Org. Chem.*, **26**, 2066 (1961).

(5) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

resulting in a mixture of saturated and unsaturated ketals, IV and V, respectively. Although this mixture could be separated by extraction of the unsaturated ketal (V) with aqueous silver nitrate solution, this extra purification step was undesirable. Substitution of sodium for lithium in the dechlorination reaction gave pure 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), which on hydrolysis under acidic conditions gave bicyclo[2.2.1]hept-2-en-7-one (I). The over-all yield of I from II was 45%.

The conversion of bicyclo[2.2.1]hept-2-en-7-one to well characterized compounds was considered to be an essential part of establishing the structure of I. Catalytic hydrogenation of I gave a 92% yield of bicyclo[2.2.1]heptan-7-one (VI), a compound described in the literature as an oil⁶ and as a solid.⁷ Although our sample of the saturated ketone corresponded in melting point to that given in the literature,⁷ the melting point of its 2,4-dinitrophenylhydrazone (VII) did not agree with the literature values.^{6,7} Whereas both Walborsky and Norton list a melting point in the range 133–135°



(6) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).

(7) C. Norton, thesis, Harvard University, 1955.

(8) Norton (ref. 7) reports 134–135° while we have found 137.2–137.8° for the melting point of the 2,4-dinitrophenylhydrazone of I.

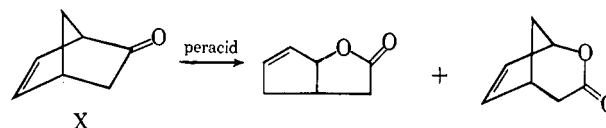
for VII, we found a melting point of 158.2–158.8°. This was a confusing factor, especially since the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]hept-2-en-7-one melts in the 134–138° range.⁸ Since the literature preparation of bicyclo[2.2.1]heptan-2-one made use of the oxidation of bicyclo[2.2.1]heptan-7-ol (VIII), we wondered if this oxidative approach was giving a mixture of ketones from which the 2,4-dinitrophenylhydrazone of something other than VI was being isolated. This idea was tested by preparing the well characterized bicyclo[2.2.1]heptan-7-ol and subjecting this alcohol to Sarett oxidation. The ketone formed in this reaction gave a crude 2,4-dinitrophenylhydrazone, m.p. 155–157° (157–158° after recrystallization), thus demonstrating that the oxidation of pure VIII was uncomplicated.⁹

One of the more interesting facets of bicyclo[2.2.1]hept-2-en-7-one chemistry is the possible interaction of the carbonyl group and the nonconjugated double bond. In view of the large interaction between the carbonyl function and the nonconjugated olefinic linkage in dehydronorcamphor (X), as indicated by its ultraviolet charge transfer band at 225 m μ (ϵ 2800)¹⁰ and by its behavior in its reaction with peracid,¹¹ we investigated the possible existence of nonconjugated interactions in I.

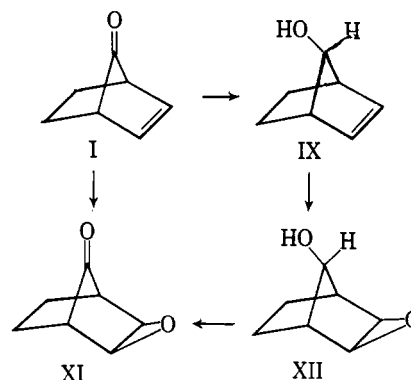
The ultraviolet spectrum of bicyclo[2.2.1]hept-2-en-7-one obtained under standard conditions showed no strong charge transfer band. This is in conflict with the much quoted spectrum of I described by Norton.⁷ Whereas Norton reports $\lambda_{\text{max}}^{\text{ethanol}}$ 233 m μ (ϵ 1300), we found only strong end absorption in the 205-m μ region. Our observation of the absence of spectral evidence for a strong transannular interaction is strengthened by the recent report of Hurst and Whitham,¹² who obtained spectral data similar to ours for 1,5,5-trimethylbicyclo[2.2.1]hept-2-en-7-one, *i.e.*, absorption rising to ϵ 3000 at *ca.* 200 m μ . Thus from a spectroscopic point of view there is little, if any, nonconjugated interaction of the two π -systems.¹³

A second indication that there is very little interaction between the carbonyl and the nonconjugated double bond resulted from the reaction of I with perbenzoic acid. As is commonly known, conjugated ketones

react with peracid to give the Baeyer–Villiger product, whereas systems in which there is no interaction between the carbonyl and the double bond yield epoxides. Baeyer–Villiger reactions also occur in systems where there is no formal conjugation but where a strong nonconjugated interaction exists between the carbonyl and olefinic functions.^{11,14} Dehydronorcamphor (X) has been shown by Meinwald and co-workers¹¹ to undergo only the Baeyer–Villiger reaction. They also have shown that this reaction is accompanied by skeletal rearrangement.



In the case of bicyclo[2.2.1]hept-2-en-7-one, we have been able to isolate only the epoxidation product, *exo*-2,3-epoxybicyclo[2.2.1]heptan-7-one (XI). This structural assignment was substantiated by infrared data (typical bicyclo[2.2.1]heptan-7-one carbonyl triplet at 5.39, 5.60, and 5.68; epoxide band at 11.92 μ) and by independent synthesis as follows. Lithium aluminum hydride reduction of I gave bicyclo[2.2.1]hept-2-en-anti-7-ol (IX). Treatment of IX with perbenzoic acid gave *exo*-2,3-epoxybicyclo[2.2.1]heptan-anti-7-ol (XII). On Sarett oxidation XII was converted to XI, identical in all respects to the product of the reaction of I with perbenzoic acid. Since the reaction of perbenzoic acid with I and IX yielded epoxides of similar stereochemistry it is assumed that the epoxidation occurred from the least hindered or *exo* side of the double bond.



Experimental¹⁵

Hexachlorocyclopentadiene.—The Hooker Chemical Company product was used without purification.¹⁶

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (II).—Hexachlorocyclopentadiene was converted to II with methanolic potassium hydroxide according to the procedure of McBee.¹⁷

(9) An alternate explanation of the low melting points recorded by earlier workers is that the bicyclo[2.2.1]heptan-7-ol being oxidized was contaminated with a small amount of bicyclo[2.2.1]hept-2-en-7-ol (IX) resulting in a mixture of VI and I. Although this possibility could not be rigorously checked it was found that when I was mixed with VI and the mixture treated with 2,4-dinitrophenylhydrazine reagent, a derivative was obtained, m.p. 133–134°, after recrystallization from ethanol.

(10) (a) See S. Winstein, L. De Vries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1961), for a leading reference; (b) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962); (c) R. C. Cookson and N. S. Wariyar, *ibid.*, 2302 (1956); (d) P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956).

(11) J. Meinwald, M. C. Seidel, and B. C. Cadoff, *ibid.*, **80**, 6303 (1958).
(12) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 710 (1963).

(13) We have recently learned that Δ^8 -dihydro-dicyclopentadien-8-one, a substituted bicyclo[2.2.1]hept-2-en-7-one, shows $\lambda_{\text{max}}^{\text{acetone}}$ 187.5 m μ (ϵ 6200) with shoulders at 190.0, 195.5, 203.0, and 215 m μ . This is reported to be in excellent agreement with a spectrum of bicyclo[2.2.1]hept-2-en-7-one determined by S. Winstein. This data indicates the possible existence of a weak charge transfer $\pi \rightarrow \pi^*$ transition. We wish to thank Dr. Kirby V. Scherer for making this information available prior to publication. See also K. V. Scherer, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 61M. R. K. Bly and R. S. Bly recently have reported an ultraviolet spectrum for bicyclo[2.2.1]hept-2-en-7-one similar to that which we found. See R. K. Bly and R. S. Bly, abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 25M; also, R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

(14) S. Mori and F. Mukawa, *Bull. Chem. Soc. Japan*, **27**, 479 (1954).

(15) All melting points and boiling points are uncorrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herley, Denmark, or by Dr. Alfred Berhardt, in the Max-Planck Institute, Mulheim (Ruhr) Hohenweg, Germany. Vapor phase chromatographic analyses were performed on an Aerograph Hy-Fi gas chromatograph. Preparative chromatography in the case of 7-ketonorborene was carried out on an Aerograph Auto-Prep Model 700. Ultraviolet absorption spectra were run on a Cary Model 14 spectrophotometer. Infrared spectra were performed on a Perkin-Elmer Infracord except in the cases of 7-ketonorborene and 7-ketonorborene which were determined on a Perkin-Elmer Model 237 spectrophotometer.

(16) We wish to thank the Hooker Chemical Co. for a generous gift of this compound.

(17) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 946 (1949).

7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).⁴—A mixture of nitrogen and ethylene was bubbled into 200 g. of II which had been preheated to 185°. After maintaining these conditions for 6 hr. the reaction mixture was cooled and vacuum distilled to give 173.4 g. (78.5%) of III, b.p. 72–81° (0.10 mm.) [lit.⁴ b.p. 56° (0.05 mm.)].

Lithium Dechlorination of 7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).—To a stirred solution of 30 g. (0.102 mole) of III and 100 g. (1.35 moles) of *t*-butyl alcohol in 525 ml. of tetrahydrofuran under a nitrogen atmosphere was added 15 g. (2.55 g.-atoms) of finely chopped lithium wire. After 20 min. a vigorous exothermic reaction began which was controllable by attentive cooling with an ice bath. This exothermic reaction was maintained at steady reflux for 1 hr. As the exothermic reaction subsided the reaction mixture was heated externally to steady reflux for 1 hr. and then stirred at room temperature for an additional hour. The mixture was poured onto 3 l. of ice and extracted with three 250-ml. portions of ether. The ethereal solution was washed with three 500-ml. portions of water and one 200-ml. portion of saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the drying agent was removed by filtration. The solution was concentrated by distillation through a Vigreux column and then distilled *in vacuo* to give 10.10 g. (64%) of a colorless liquid, b.p. 70–81° (30 mm.). This product was shown by v.p.c., catalytic hydrogenation, and n.m.r. to be a mixture of ca. 65% 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V) and ca. 35% 7,7-dimethoxybicyclo[2.2.1]heptane (IV).

7,7-Dimethoxybicyclo[2.2.1]hept-2-ene (V). Method A. By Separation from the Mixture of 7,7-Dimethoxybicyclo[2.2.1]hept-2-ene (V) and 7,7-Dimethoxybicyclo[2.2.1]heptane (IV) with Aqueous Silver Ion.¹⁸—A solution of 20.24 g. of a mixture of V and IV in 50 ml. of pentane was extracted with ten 25-ml. portions of a 20% aqueous silver nitrate solution. The reaction was followed by v.p.c., which showed a very pronounced decrease in the relative height of the unsaturated ketal peak in the mixture after each extraction. The combined silver nitrate extracts were poured into 100 ml. of concentrated ammonium hydroxide containing chipped ice. The ammonium hydroxide solution was extracted with pentane. The pentane extract was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The solution was concentrated by distillation and distilled *in vacuo* to give 10.26 g. (50.7% of the original mixture) of pure 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), as shown by v.p.c., b.p. 74–78° (30 mm.). The clear liquid product was redistilled to give an analytical sample, b.p. 78° (30 mm.), n_{D}^{25} 1.4584; infrared spectrum (neat), strong *cis* olefin absorption at 14.12 μ .

Anal. Calcd. for C₉H₁₄O₂: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.10; H, 9.13; O, 20.91.

A 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]hept-2-en-7-one was prepared from 0.22 g. (0.0014 mole) of 7,7-dimethoxybicyclo[2.2.1]hept-2-ene by treating it with standard reagent¹⁹ to give 0.35 g. (86%) of orange crystals, m.p. 133–134°. This derivative was recrystallized five times from 95% ethanol to give an analytical sample, m.p. 137.2–137.8°; ultraviolet absorption, $\lambda_{\max}^{\text{ethanol}}$ 358 m μ (ϵ 22,800), 224 (18,700); $\lambda_{\max}^{\text{CHCl}_3}$ 362 m μ (ϵ 23,800), [lit.⁷ m.p. 134–135°, $\lambda_{\max}^{\text{CHCl}_3}$ 360 m μ (ϵ 26,300)].

Anal. Calcd. for C₁₃H₁₂N₄O₄: C, 54.16; H, 4.20; N, 19.44. Found: C, 54.23; H, 4.36; N, 19.38.

Method B. By Direct Sodium Dechlorination of 7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).—To a vigorously stirred solution of 31.92 g. (0.109 mole) of III, 90 g. (1.22 moles) of *t*-butyl alcohol, and 525 ml. of tetrahydrofuran under a nitrogen atmosphere was added 59 g. (2.57 g.-atoms) of finely chopped sodium metal. The mixture was heated to initiate the reaction, and a small amount of heat was applied during the reaction in order to maintain a steady reflux. No cooling was necessary in this reaction. After refluxing for 8 hr. the heating was stopped. The excess sodium reacted by slowly adding methanol (about 500 ml.) to the reaction mixture.

The reaction mixture was poured over 2 l. of ice and the reaction flask washed with about 700 ml. of water. The solution was extracted with four 250-ml. portions of ether. The combined

ethereal solution was washed with three 500-ml. portions of water and one 250-ml. portion of a saturated sodium chloride solution. The ethereal solution was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. After concentration by distillation the solution was distilled *in vacuo* to give 10.55 g. (62.8%) of 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), b.p. 70–77° (30 mm.). Its infrared spectrum and v.p.c. retention time were identical with those with the analytical sample of V. The latter instrumental method showed that V was uncontaminated by IV.

Bicyclo[2.2.1]hept-2-en-7-one (I).—7,7-Dimethoxybicyclo[2.2.1]hept-2-ene (19.80 g.) was stirred vigorously with 25 ml. of 5% sulfuric acid for 20 hr. at 35° followed by extraction with two 10-ml. portions of pentane. The pentane solution was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The solution was concentrated by distillation at atmospheric pressure and the residue was distilled *in vacuo* to give 12.59 g. (91%) of bicyclo[2.2.1]hept-2-en-7-one (I), b.p. 66–70° (34 mm.). Redistillation gave an analytical sample, b.p. 63° (30 mm.), n_{D}^{25} 1.4775. Infrared carbonyl absorption (neat) was 5.37 (medium), 5.58 (strong), 5.62 μ (medium); ultraviolet absorption, $\lambda_{\max}^{\text{ethanol}}$ 273 m μ (ϵ 43), $\lambda_{\max}^{\text{CHCl}_3}$ 273 m μ (ϵ 41), $\lambda_{\max}^{\text{acetone}}$ 274 m μ (ϵ 31) [lit.⁷ b.p. 46–55° (13 mm.), n_{D}^{25} 1.4780, infrared carbonyl absorption, 5.62 μ (strong)].

Anal. Calcd. for C₇H₈O: C, 77.75; H, 7.46. Found: C, 77.56; H, 7.69.

A 2,4-dinitrophenylhydrazone was prepared from 0.20 g. (0.00185 mole) of the unsaturated ketone (I) to give 0.52 g. (97%) of orange crystals, m.p. 123–130°. The product was recrystallized twice from 95% ethanol to give pure needles, m.p. 136–137°.

7,7-Dimethoxybicyclo[2.2.1]heptane (IV).—In a hydrogenation flask 10.91 g. of a mixture of V and IV and 0.200 g. of 5% palladium on carbon were stirred under hydrogen at room temperature and atmospheric pressure. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The filtrate was vacuum distilled to give 9.53 g. (87%) of 7,7-dimethoxybicyclo[2.2.1]heptane (IV), b.p. 78–80° (30 mm.). The product was redistilled twice to give an analytical sample, b.p. 80° (30 mm.), n_{D}^{25} 1.4533.

Anal. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.32; O, 20.49. Found: C, 69.46; H, 10.28; O, 20.45.

A 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]heptan-7-one was prepared directly from 0.20 g. (0.0013 mole) of 7,7-dimethoxybicyclo[2.2.1]heptane to give 0.34 g. (91%) of crude orange crystals (VII), m.p. 152–153°. This derivative was recrystallized five times from 95% ethanol to give an analytical sample as orange needles, m.p. 158.2–158.8°. Ultraviolet absorption was $\lambda_{\max}^{\text{ethanol}}$ 358 m μ (ϵ 20,400), 227 (16,700); $\lambda_{\max}^{\text{CHCl}_3}$ 362 m μ (ϵ 22,500) [lit.⁷ $\lambda_{\max}^{\text{CHCl}_3}$ 367 m μ (ϵ 19,100)].

Anal. Calcd. for C₁₃H₁₄N₄O₄: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.79; H, 4.87; N, 19.38.

Bicyclo[2.2.1]heptan-7-one (VI).—In a 25-ml. flask with distillation head, 2.06 g. (0.015 mole) of 7,7-dimethoxybicyclo[2.2.1]heptane and 15 ml. (0.25 mole) of glacial acetic acid were heated to 115° for 10 hr. After cooling the solution was transferred to a separatory funnel with 30 ml. of petroleum ether (b.p. 35–45°). A solution of 12 g. (0.30 mole) of sodium hydroxide in 40 ml. of water was carefully added dropwise with cooling. An additional 40 ml. of water was added to dissolve the sodium acetate that had formed. The water layer was separated and washed twice more with 25-ml. portions of petroleum ether. The combined petroleum ether extracts were dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The filtrate was concentrated to 15 ml. and transferred to a low temperature recrystallization apparatus in which a nitrogen atmosphere was maintained. The temperature was lowered slowly to Dry Ice temperature. At –20° a white crystalline solid began to precipitate. After crystallization was complete, the solvent was removed and the precipitate dried by passing nitrogen over the crystals to give 0.93 g. (64%) of extremely volatile bicyclo[2.2.1]heptan-7-one (VI), m.p. 77–79°.

Sublimation at 40° (7 mm.), two purifications by preparative v.p.c. (3/8 in. \times 20 ft. aluminum column packed with 20% Dow 710 on 42/60 firebrick, helium as the carrier gas) and one further sublimation gave an analytical sample of VI as a clear waxy solid, m.p. 79.5–80.5°; infrared carbonyl absorption (Nujol), 5.42 (weak), 5.61 (strong), 5.73 μ (medium); ultraviolet absorption, $\lambda_{\max}^{\text{CHCl}_3}$ 292 m μ (ϵ 22), $\lambda_{\max}^{\text{acetone}}$ 293 m μ (ϵ 18) [lit.⁷ m.p. 80.2–

(18) S. Winstein and H. L. Lucas, *J. Am. Chem. Soc.*, **60**, 836 (1938).

(19) R. L. Shriner, R. C. Fuson, and D. Y. Custin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

81.6°; infrared carbonyl absorption, 5.70 (strong), 5.62 μ (weak); ultraviolet absorption, $\lambda_{\max}^{\text{ethanol}}$ 287 m μ (ϵ 32).

Anal. Calcd. for C₇H₁₀O: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.36.

A 2,4-dinitrophenylhydrazone derivative (VII) was prepared from 0.21 g. (0.0019 mole) of VI to give 0.50 g. (90%) of orange needles, m.p. 157.2–157.5°.

Hydrogenation of Bicyclo[2.2.1]hept-2-en-7-one (I).—In a hydrogenation flask 0.119 g. (0.00184 mole) of I with ca. 5 ml. of 95% ethanol and 50 mg. of 5% palladium on carbon was stirred under hydrogen at room temperature and atmospheric pressure. After 40 min. the ketone had taken up 98% of the theoretical volume of hydrogen. The catalyst was removed by filtration and the resulting filtrate was treated with 2,4-dinitrophenylhydrazone reagent to give 0.480 g. (92%) of the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]heptan-7-one, m.p. 152–154°. After recrystallization from ethanol, the orange needles melted at 156–157.5°.

Bicyclo[2.2.1]heptan-7-ol (VIII).—To a solution of 0.1029 g. (0.00093 mole) of bicyclo[2.2.1]heptan-7-one in 10 ml. of anhydrous ether was added dropwise with stirring a solution of 0.7412 g. (0.019 mole) of lithium aluminum hydride in 4 ml. of ether at 0°. After addition was complete the solution was stirred for 2 hr. whereupon 2.96 ml. of water was added dropwise to the stirring solution. The resulting slurry was stirred for 0.5 hr., filtered, and the precipitate washed with ether. The filtrate was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The ether was removed by flash evaporation to give 0.0897 g. (86%) of VIII, m.p. 151.5–153°. The white crystalline solid was recrystallized twice from petroleum ether (b.p. 65–75°) to give pure VIII, m.p. 152.4–153.6° (lit.²⁰ m.p. 152–153°).

Sarett Oxidation of Bicyclo[2.2.1]heptan-7-ol (VIII).—A solution of 0.73 g. of VIII in 20 ml. of pyridine was added to the complex formed from 2.0 g. of chromium trioxide and 20 ml. of pyridine.²¹ After standing for 24 hr. the reaction mixture was poured into water and extracted with three portions of benzene-ether. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. Treatment of the concentrate with 2,4-dinitrophenylhydrazine reagent gave 0.70 g. (37%) of VII, m.p. 155–157°, without purification.

exo-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI).—Bicyclo[2.2.1]hept-2-en-7-one (1.50 g., 0.0139 mole) was added to 44.5

(20) S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 422 (1953).

ml. of benzene containing 2.35 g. (0.0170 mole) of perbenzoic acid. The reaction mixture was kept at 2° for 64 hr. at which time iodometric titration indicated the reaction of 0.0129 mole of perbenzoic acid. The reaction mixture was extracted with two 25-ml. portions of a 10% sodium hydroxide solution followed by 25 ml. of water, and dried over anhydrous magnesium sulfate. Removal of the drying agent, followed by concentration of the solvent and dilution with pentane gave 0.99 g. (0.008 mole, 62%) of white crystalline XI. A combination of recrystallization from petroleum ether (b.p. 60–70°) and sublimation gave an analytical sample, m.p. 144–145°.

Anal. Calcd. for C₇H₈O₂: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.46.

Bicyclo[2.2.1]hept-2-en-anti-7-ol (IX).—Bicyclo[2.2.1]hept-2-en-7-one (2.16 g.) was treated with excess lithium aluminum hydride in anhydrous ether at 0°. Hydrolysis with water, followed by filtration and removal of the solvent, gave an oily solid, which, after recrystallization from hexane and sublimation, yielded 1.20 g. (52%) of pure IX, m.p. 117.5–119.5° (lit. m.p. 117–118°).^{7,22}

exo-2,3-Epoxybicyclo[2.2.1]heptan-anti-7-ol (XII).—Bicyclo[2.2.1]hept-2-en-7-ol (0.55 g.) was added to a solution of 0.975 g. of perbenzoic acid in 25 ml. of methylene chloride. The reaction mixture was allowed to stand for 72 hr. at 2°, washed twice with 25 ml. of saturated sodium carbonate solution, washed once with 10 ml. of water, and dried over anhydrous magnesium sulfate. The solvent was stripped to yield 0.51 g. (82%) of white crystalline product, m.p. 150–155°. Two recrystallizations from hexane-benzene followed by sublimation gave an analytical sample of XII, m.p. 195.6–196.4°.

Anal. Calcd. for C₇H₁₀O₂: C, 66.64; H, 7.99. Found: C, 67.00; H, 8.19.

exo-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI) via Oxidation of XII.—A solution of 0.50 g. of pure XII in 15 ml. of pyridine was added to a stirred solution of the complex formed from 1.50 g. of chromium trioxide in 15 ml. of pyridine.²¹ The reaction was stirred overnight, diluted with water, and extracted with ether. The ethereal solution was washed thoroughly with water, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated to give 0.15 g. of semicrystalline keto epoxide. One recrystallization from petroleum ether (b.p. 60–70°) followed by sublimation gave pure XI, m.p. 142.5–143.5°. The infrared spectrum of this product was identical with XI obtained from the reaction of I with perbenzoic acid.

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The Synthesis of 1 α -Methylhydrocortisone and 1 α -Methylcortisone Acetate¹

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The synthesis of 1 α -methylhydrocortisone, 1 α -methylcortisone, and 1-methylprednisolone are described. The 1-methyl substituent is introduced by conjugate addition of methyl Grignard to the Δ^1 -3-keto steroid (I). The configuration of the 1-methyl is assigned by optical rotatory dispersion.

The introduction of methyl groups into the hydrocortisone molecule at positions 2,^{2a} 6,^{2b} 15,³ and 16⁴ has led to an enhancement of anti-inflammatory activity of the parent corticoid. Methylation at virtually all other positions in the hydrocortisone molecule, to give 4-⁵ 5-⁶ 7-⁷ 9-^{8,10} 11-⁹ 12-¹⁰ 14-, and 21-¹¹methyl-

hydrocortisones, has been reported to lead to diminution of anti-inflammatory activity. For the cases of enhanced cortical activity in which the substituent clearly can be designated as axial or equatorial (*i.e.*, exclusive of 15- and 16-methyl), methyl group orientation has been both α and equatorial. In order to

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