[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY, ITHACA, N. Y.]

Highly Strained Bicyclic Systems. VI.[1] Reactions of 1,5,5-Trimethylbicyclo[2.1.1]hexane-6-carboxylic Acid and the Synthesis of Bicyclo[2.1.1]hexyl Analogs of Borneol and Isoborneol[2]

BY JERROLD MEINWALD, ARTHUR LEWIS AND PAUL G. GASSMAN

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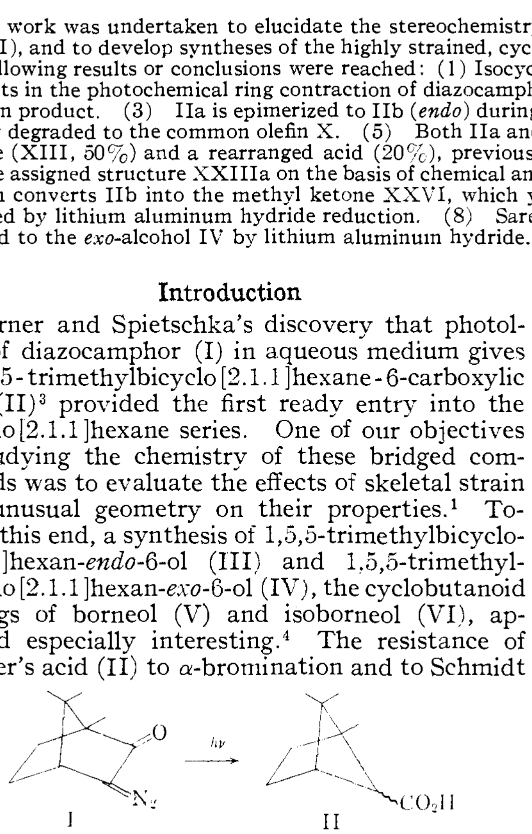
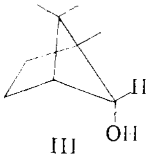
This work was undertaken to elucidate the stereochemistry of Horner's 1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (II), and to develop syntheses of the highly strained, cyclobutanoid analogs (III, IV) of borneol and isoborneol (V, VI). The following results or conclusions were reached: (1) Isocyclenone (VII) and camphoric anhydride (VIII) are neutral by-products in the photochemical ring contraction of diazocamphor (I) to II. (2) This photolysis yields IIa (*exo*) as the chief reaction product. (3) IIa is epimerized to IIb (*endo*) during hydrolysis of its methyl ester. (4) Both IIa and IIb can be readily degraded to the common olefin X. (5) Both IIa and IIb are isomerized by sulfuric acid to dihydro-β-campholenolactone (XIII, 50%) and a rearranged acid (20%), previously considered an "epimer" of II. (6) This rearranged acid may be assigned structure XXIIIa on the basis of chemical and physical evidence and independent synthesis. (7) Methyllithium converts IIb into the methyl ketone XXVI, which yields the *endo*-alcohol III on trifluoroperacetic acid oxidation followed by lithium aluminum hydride reduction. (8) Sarett oxidation of III yields the cyclobutanone XXVII, which is reduced to the *exo*-alcohol IV by lithium aluminum hydride.

Introduction

Horner and Spietschka's discovery that photolysis of diazocamphor (I) in aqueous medium gives a 1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (II)[3] provided the first ready entry into the bicyclo[2.1.1]hexane series. One of our objectives in studying the chemistry of these bridged compounds was to evaluate the effects of skeletal strain and unusual geometry on their properties.[1] Toward this end, a synthesis of 1,5,5-trimethylbicyclo-[2.1.1]hexan-*endo*-6-ol (III) and 1,5,5-trimethylbicyclo[2.1.1]hexan-*exo*-6-ol (IV), the cyclobutanoid analogs of borneol (V) and isoborneol (VI), appeared especially interesting.[4] The resistance of Horner's acid (II) to α-bromination and to Schmidt degradation has been reported; both reactions gave an isomeric acid, regarded as the C_6-epimer of II, in place of the anticipated products.[3] We wish to describe the results of a more extensive study of the chemistry of Horner's acid, undertaken with the aims of clarifying its stereochemistry and of developing paths to III and IV.



I II



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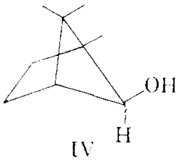

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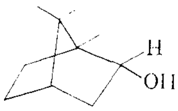

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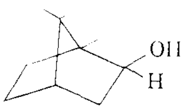
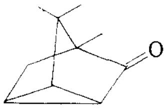


VI

Discussion

The photochemical ring contraction of I was carried out as described previously to give II (m.p. 100–101°, $[\alpha]_D + 13.8°$) in about 60% yield. In addition, about 20% of a neutral fraction was isolated. Vapor phase chromatography of this fraction showed the presence of at least two major constituents, which were separated by fractional sublimation and crystallization. The more volatile component proved to be isocyclenone (VII), formed by a typical carbene insertion reaction. The less volatile component was found to be camphoric anhydride (VIII), apparently resulting from reaction of I or the corresponding carbene with dissolved oxygen.



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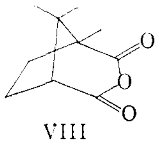
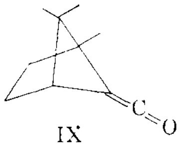


VIII



IX

In considering the problem of the stereochemistry of Horner's acid, we anticipated from work in a related series that the intermediate ketene IX would suffer hydration from the less hindered side giving predominantly the unstable epimer of II.[5] To test this point, the corresponding methyl ester was prepared and heated for a prolonged period with sodium methoxide in methanol.[6] Although the product recovered from this treatment was only unchanged ester, saponification using excess base in aqueous ethanol gave a new acid (m.p. 43.0–43.5°, $[\alpha]_D + 68.7°$) in excellent yield. Apparently under these conditions the desired epimerization proceeded rapidly, competing favorably with ester hydrolysis.[7]

The properties of our new acid were markedly different from those of Horner's "epimer" (m.p.

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[1] For Parts IV and V of this series see J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961), and J. Meinwald, *Rec. Chem. Prog.*, **22**, 39 (1961).

[2] Presented before the Division of Organic Chemistry of the American Chemical Society at the 139th National Meeting in St. Louis, Mo., March 21–30, 1961 (abstract page 39-O). See also J. Meinwald, A. Lewis and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 2549 (1960), for a preliminary account of part of this work.

[3] L. Horner and E. Spietschka, *Chem. Ber.*, **88**, 934 (1955).

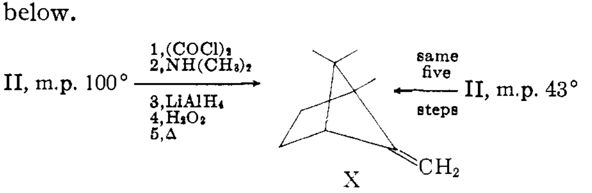
[4] Independent work aimed at a study of the analogs of *exo*- and -norborneol has been carried out by K. B. Wiberg, B. R. Lowry T. H. Colby, *J. Am. Chem. Soc.*, **83**, 3998 (1961).

[5] J. Meinwald and P. G. Gassman, *ibid.*, **82**, 2857 (1960).

[6] For a recent example of the use of this type of procedure, see G. W. Eigenmann and R. T. Arnold, *ibid.*, **81**, 3440 (1959).

[7] A closely related pattern of behavior was described by J. Meinwald and P. G. Gassman, *ibid.*, **82**, 5445 (1960).

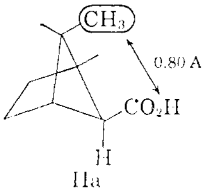
80–81°, $[\alpha]_D$ −26.9°), requiring that one of these two acids be a rearrangement product. The treatment with concentrated sulfuric acid (or with hot bromine and phosphorus) seemed more suspect, and evidence to show that the original 100° acid and its new 43° isomer share a common carbon skeleton was successfully obtained as outlined below.



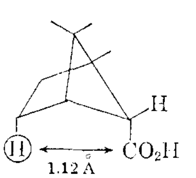
X

Each acid was converted into its acid chloride, dimethylamide, *t*-amine and amine oxide. Cope pyrolysis[8] of both amine oxides proceeded very readily, and both gave rise to the highly volatile, crystalline olefin X. Structure X, once assigned to camphene,[9] was supported by analytical data and infrared evidence (maxima at 3.29, 5.96 and 11.56 μ, which vanish on treatment with bromine).

In deciding which of these two acids should be assigned the *exo* configuration IIa and which the *endo* configuration IIb, use was made of invaluable tables published by Wilcox.[10] From these, the distances between the center of the carboxyl carbon and the edge of the nearest neighbor from which an unfavorable non-bonded interaction would be expected are found to be 0.80 Å. for IIa and 1.12 Å. for IIb. Thus, IIa appears significantly destabilized by non-bonded repulsions. Since Horner's 100° acid is efficiently isomerized to its 43° epimer, this isomerization can be confidently formulated as IIa → IIb, and the stereochemical problem is solved.

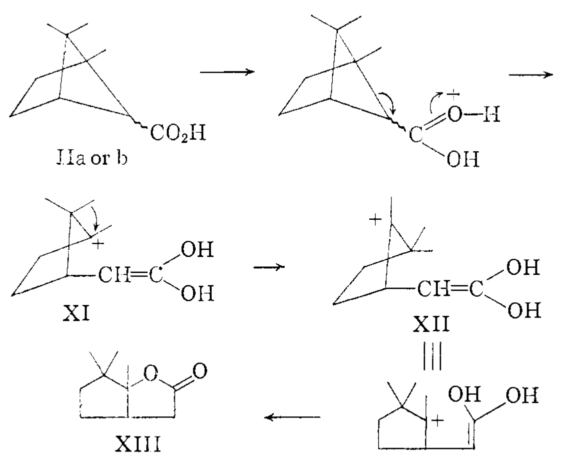


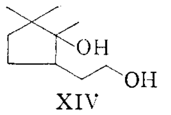
IIa



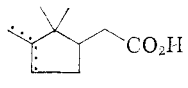
IIb

Before turning to the work on degradative reactions, it is appropriate to consider the previously misinterpreted rearrangement of IIa to an isomeric acid. Treatment of IIa (or IIb) with sulfuric acid was found to give 20% of the reported *acid* (m.p. 80–81°, $[\alpha]_D$ −26.9°), along with 50% of an unnoticed *neutral* isomer (m.p. 36–37°, $[\alpha]_D$ + 3.9°). A strong 5.64 μ infrared maximum suggested formulation of the neutral product as a γ-lactone, and the reaction sequence outlined below led to the hypothesis that it was dihydro-β-campholenolactone (XIII).[11] Direct comparison of this lactone with an authentic sample of XIII revealed their identity; confirmation was provided by the fact that both samples gave the same diol (XIV) upon lithium aluminum hydride reduction.[12]

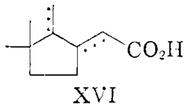




XIV



XV



XVI

Driving force for this rearrangement is probably provided by the relief of strain accompanying rupture of the folded cyclobutane ring, although we have shown in other work that this cleavage is not general for bicyclo[2.1.1]hexanes.[1]

Turning now to the acid formed along with XIII, possible deprotonation of intermediates XI or XII leads to consideration of composite formulas XV and XVI. The failure of the acid to react with tetranitromethane, bromine, potassium permanganate and ozone, however, immediately excludes these possibilities and requires a bicyclic structure. The close similarity between the isomerization conditions and those of the cinenic acid rearrangement (XVII → XVIII), known to involve decarbonylation, rearrangement and recarbonylation,[13] suggested analogous paths leading to two bicyclo[3.1.0]hexanes (XIX, XX) or two bicyclo[2.2.0]hexanes (XXI, XXII). Although n.m.r. investigation of the 80° acid failed to yield any helpful information, end-absorption in the ultraviolet spectrum of the acid suggested conjugation between the carboxyl group and a cyclopropane ring. To bring the suspected chromophore into a less ambiguous spectral region, the acid was converted to the corresponding methyl ketone with methyllithium. This ketone showed clear spectral indications (λ_{max} 5.90 μ[14a]; $\lambda\lambda_{max}^{EtOH}$ 206 mμ (ϵ 5,700), 278 mμ (ϵ 67)[14b]) of cyclopropyl carbonyl conjugation. Its 2,4-dinitrophenylhydrazone had its long wave length maximum at 370 mμ, in accordance with expectations for this chromophore.[15] The only readily derivable structure

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(8) For a recent reference to the use of this technique, see A. C. Cope, E. Ciganek, C. F. Howell and E. E. Schweizer, *J. Am. Chem. Soc.*, **82**, 4663 (1960).

(9) O. Aschan, "Die Constitution des Kamphers und Seiner Wichtigsten Derivate," Friedrich Vieweg und Sohn, Braunschweig, 1903, offers a very interesting account of the status of this area of terpene chemistry at the turn of the century.

(10) C. F. Wilcox, Jr., *J. Am. Chem. Soc.*, **82**, 414 (1960).

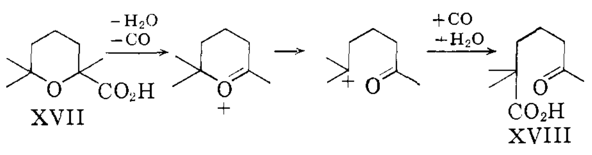
(11) J. D. Connolly and K. H. Overton, *Proc. Chem. Soc.*, 188 (1959).

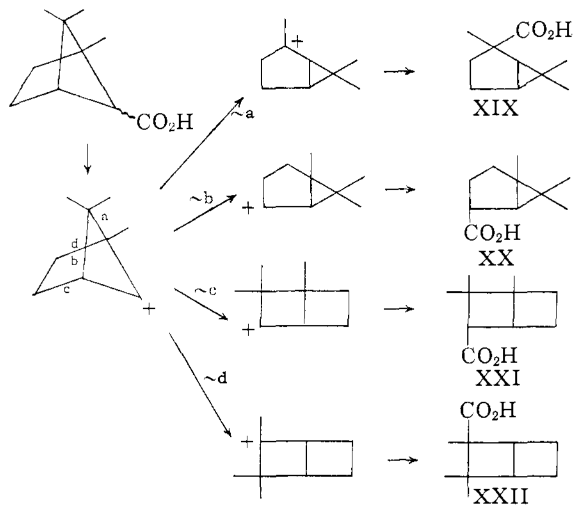
(12) We are grateful to Dr. Overton for supplying authentic samples of XIII and XIV.

(13) J. Meinwald, H. C. Hwang, A. P. Wolf and D. Christman, *J. Am. Chem. Soc.*, **82**, 483 (1960).

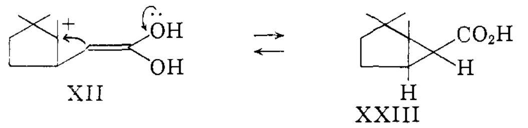
(14) (a) G. W. Cannon, A. A. Santilli and P. Shenian, *ibid.*, **81**, 1660 (1959). (b) For a recent example and leading reference, see D. H. R. Barton and P. T. Gilham, *J. Chem. Soc.*, 4596 (1960).

(15) J. D. Roberts and C. Green, *ibid.*, **68**, 214 (1946).





fitting these requirements is XXIII, arising from ion XII by C-alkylation (rather than the O-alkylation process which yields XIII). Further treatment of XXIII with sulfuric acid converts



it into XIII, a process which is readily interpreted as an acid-catalyzed opening of the cyclopropane ring, followed by normal lactonization.

Additional physical evidence supporting structure XXIII was derived from examination of its near-infrared spectrum, a technique which has much to contribute to structural problems,[16] although it has not yet become one of the standard tools in structural investigations. It is known that cyclopropyl methylene groups show characteristic first overtones in the 1.64 μ region,[16,17] but data for tertiary cyclopropyl hydrogens do not seem to be available. We find that XXIII shows a characteristic peak at 1.679 μ at significantly shorter wave length than any saturated CH absorptions other than those of three-membered rings. A variety of bicyclo[2.1.1]hexanes do not show absorption in this region, so that this band cannot be attributed to the CH of a strained cyclobutyl ring. Since the intensity of this band is related to the number of cyclopropyl hydrogens,[16] the model compound XXIV was synthesized as shown. Equimolar solutions of XXIII and XXIV revealed well-resolved peaks at 1.679 μ of equal intensity

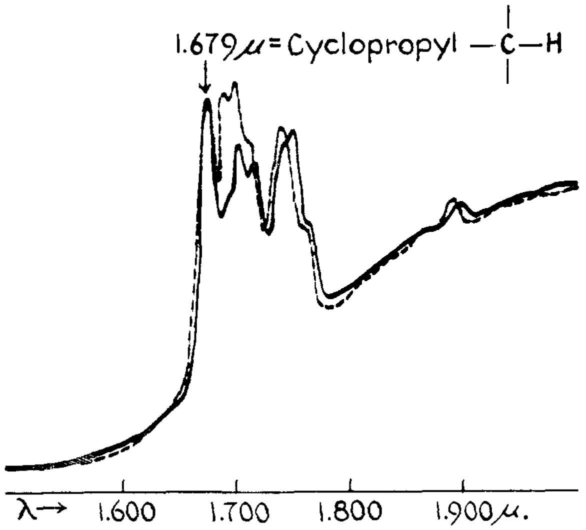
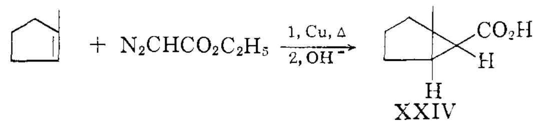
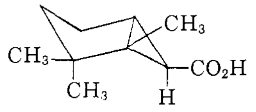


Fig. 1.—Near infrared spectra of XXIII (dotted line; 250 mg. in 34 ml. of CCl_4) and XXIV (solid line; 208 mg. in 34 ml. of CCl_4) as recorded on a Cary model 14 spectrophotometer.

(Fig. 1), providing strong evidence for the presence of two cyclopropyl hydrogens in XXIII. It is noteworthy that in this instance, near-infrared spectroscopy serves where n.m.r. fails, since a tertiary cyclopropyl proton does not appear at the unusually high field characteristic of the cyclopropyl methylene protons.[18]



Finally, definitive chemical evidence for the structure of Horner's rearrangement product was provided by an independent synthesis of (±)-XXIII, carried out by employing (±)-1,5,5-trimethylcyclopentene in place of 1-methylcyclopentene in the diazoacetic ester reaction used earlier to obtain the model XXIV.[19] The reported melting point for Horner's racemic product (125°) agrees with that found for (±)-XXIII (123–124°), and the solution infrared spectra of the synthetic acid and methyl ester are superimposable on those obtained from the levorotatory rearrangement product. Although the question of the stereochemistry of XXIII has not been studied explicity, the conditions involved in its formation from II and in its independent synthesis permit the assignment of the less crowded 6-*exo* configuration XXIIIa with some confidence.



XXIIIa

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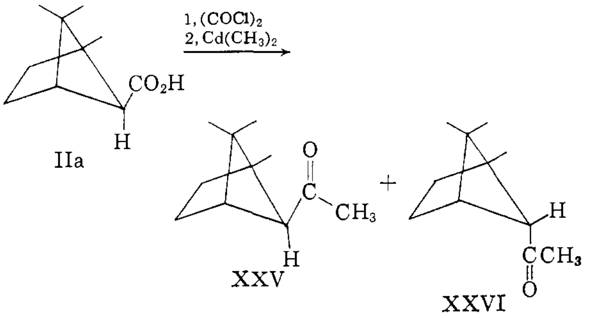
[16] An intriguing account of the present status of near-infrared spectroscopy is presented by R. F. Goddu in C. N. Reilley's "Advances in Analytical Chemistry and Instrumentation," Interscience Publishers, Inc., New York, N. Y., Vol. 1, 1960, pp. 347–424.

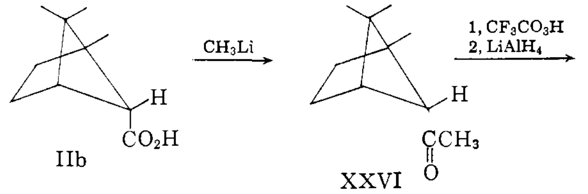
[17] W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958). Recent results of Mr. S. S. Labana indicate that a variety of newly synthesized bicyclo[3.1.0]hexanes all show characteristic absorption in the 1.68 μ region, attributable to cyclopropyl CH bonds.

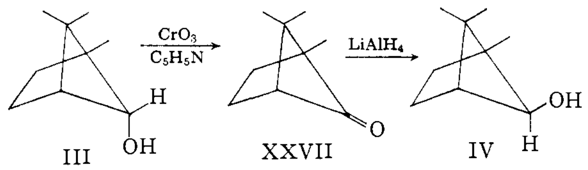
[18] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 52.

[19] This synthesis was carried out by Professor A. W. Burgstahler and Robert Sticker, and will be described by them elsewhere. We are most grateful to the University of Kansas group for providing us with a sample of (±)-XXIII.

With the stereochemical and rearrangement problems disposed of, we may turn to the preparation of the borneol and isoborneol analogs III and IV. Ozonolysis of the exocyclic olefin X, even under the conditions appropriate for the cleavage of camphene to camphenilone,[20] gave a mixture of at least three products, and was therefore not studied further. Osmylation of X gave only a low yield of crude diol, and appeared unpromising. Application of the Baeyer–Villiger reaction, however, gave the desired results. The highly hindered acid IIa proved inert to methyllithium in ethyl ether and in refluxing tetrahydrofuran. However, the acid chloride derived from IIa reacted smoothly with dimethylcadmium to give the *exo*-ketone XXV accompanied by a small amount of the more stable *endo* isomer XXVI, which was synthesized independently as described below. Rather than use this inhomogeneous ketone for further work, the *endo*-acid IIb was converted into the *endo*-ketone XXVI, a reaction which proceeded readily with ethereal methyllithium. Trifluoroperacetic acid oxidation[21] of XXVI followed by lithium aluminum hydride reduction gave a good yield of III as an optically active, crystalline solid.







Sarett reagent[22] converted III into the rather unstable cyclobutanone XXVII (λ_{max} 5.61 μ), which was reduced by lithium aluminum hydride to the isoborneol analog IV. The ketones XXVI and XXVII, as well as the alcohols III and IV, gave good evidence of homogeneity upon gas chromatographic analysis. Both of the epimeric alcohols III and IV have similar and very easily depressed melting points, as well as surprisingly similar retention times. However, their distinctive specific rotations (+15.1° for III and −17.4° for IV) and their infrared spectra, which reveal striking differences in the "finger-print" region, leave no doubt that they are different substances.

A further study of the chemistry of these compounds is now in progress.

Acknowledgments.—The support of this research by the Alfred P. Sloan Foundation and the National Science Foundation is acknowledged with pleasure. The senior author would like to thank the John Simon Guggenheim Foundation for a Fellowship during the academic year 1960–1961, and the Department of Chemistry, Stanford University, for its cordial hospitality in the Winter and Spring 1961 Quarters.

Experimental

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*exo*-6-carboxylic Acid (IIa).—The photochemical ring contraction of I was carried out as described by Horner and Spietschka to give the acid II, m.p. 100–101°, $[\alpha]_D$ +13.8° ($CHCl_3$), in about 60% yield.[3] In addition to the acidic product, 3.16 g. of neutral material was obtained from the irradiation of 13.0 g. of I. Vapor phase chromatography (using 0.5% polyethylene glycol on glass beads at 85°, with helium as carrier) showed that at least two compounds (retention times, 3.00, 3.90 min.) were present in the neutral material. A volatile solid with a strong camphor-like odor was collected by sublimation, and purified by repeated sublimation, m.p. 165–167°; infrared spectrum (KBr), 5.70 μ. The melting point of isocyclenone is 168–170°.[23]

A semicarbazone was prepared in the usual way. Two recrystallizations from ethanol gave an analytical sample, m.p. 242.5–243° (isocyclenone semicarbazone m.p. 243–244°).[23]

Anal. Calcd. for $C_{11}H_{17}ON_3$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.57; H, 8.35; N, 19.90.

The residue after sublimation was recrystallized five times from pentane to give a white solid, m.p. 220°. A mixed melting point with camphoric anhydride (m.p. 220°)[24] gave no depression. The infrared spectrum (KBr), 5.57, 5.70 μ, was identical with that of camphoric anhydride.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*exo*-6-carboxylic Acid Methyl Ester.—An ethereal solution of diazomethane was added dropwise to an ethereal solution of 10.00 g. of IIa until the color of the diazomethane persisted. The reaction mixture was dried over anhydrous magnesium sulfate, filtered, and the solvent removed on a flash evaporator. The residue was fractionally distilled to give 9.96 g. (92%) of ester, b.p. 98–100° (18 mm.), n^{28}_D 1.4570, $[\alpha]_D$ +29° (EtOH). This material showed a 2.52 min. retention time on a 0.5% polyethylene glycol 400 on glass bead column (3′ × 1/4″) at a temperature of 119°, using helium as carrier gas. No impurity was detectable.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*endo*-6-carboxylic Acid (IIb).—To a solution of 6.00 g. of sodium hydroxide in 80 ml. of ethanol and 20 ml. of water was added 9.10 g. of the methyl ester of IIa. This solution was refluxed for 2 hr., diluted with 100 ml. of water and extracted thoroughly with ether. The aqueous solution was acidified with dilute hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was sublimed to give 7.25 g. (86%) of IIb, m.p. 43–43.5°, $[\alpha]_D$ + 68.7° ($CHCl_3$).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.61; H, 9.52.

An anilide was prepared *via* the acid chloride. Two recrystallizations from aqueous ethanol gave an analytical sample as silky, white needles, m.p. 128–128.5°.

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[20] P. S. Bailey, *Chem. Ber.*, **88**, 795 (1955).

[21] W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

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

[23] Elsevier's "Encyclopedia of Organic Chemistry," Elsevier Publishing Co., Inc., New York, N. Y., Vol. 13, Sec. III, 1946, p. 1051.

[24] J. L. Simonsen, "The Terpenes." Cambridge University Press, Cambridge, England, Vol. II, 1949, p. 480.

Anal. Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.13; H, 8.74; N, 5.88.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*endo*-6-carboxylic acid methyl ester was prepared by treatment of 1.00 g. of the acid IIb with diazomethane as described for the *exo*-methyl ester to give 0.97 g. (90%) of product, b.p. 97–99° (19 mm.), n^{28}D 1.4545, [α]D +64.4° (EtOH). This product showed a 2.20 min. retention time using v.p.c. under the same conditions used for the epimeric ester; no impurity was detectable. Using a 6′ column of the same type, at 85°, a retention time of 19.9 min. (*cf.* 21.8 min. for the epimeric ester) was observed.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.53; H, 9.96.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*exo*-6-dimethylcarboxamide.—A solution of 5.00 g. of IIa and 4.50 g. of oxalyl chloride in 50 ml. of dry benzene was allowed to stand at room temperature for 18 hr. The benzene–oxalyl chloride was removed under reduced pressure. The residual acid chloride was diluted to 50 ml. with dry ether, and dimethylamine was bubbled into the solution. The dimethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure to give 5.45 g. (94%) of amide, b.p. 86–88° (1 mm.), n^{28}D 1.4861, [α]D +22.3° (EtOH).

Anal. Calcd. for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.45; H, 10.75; N, 7.28.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexane-*endo*-6-dimethylcarboxamide was prepared *via* the acid chloride as described for the *exo*-dimethylcarboxamide. A 4.60-g. portion of the acid IIb gave 4.40 g. (82%) of product, b.p. 105–107° (3 mm.), n^{28}D 1.4818, [α]D +19.7° (EtOH).

Anal. Calcd. for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.47; H, 10.80; N, 7.28.

(+)-*exo*-6-Dimethylaminomethyl-1,5,5-trimethylbicyclo-[2.1.1]hexane.—A solution of 5.00 g. of *exo*-amide in 50 ml. of anhydrous ether was added dropwise to a stirred suspension of 3.50 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The reaction mixture was stirred at room temperature for 12 hr., cooled to 0° and quenched by dropwise addition of 14.0 g. of water. The resultant mixture was stirred vigorously for 2 hr. and then filtered. The precipitated salts were washed thoroughly with ether, and the combined ether extract was dried over anhydrous magnesium sulfate. Evaporation of the ether followed by fractional distillation of the residue gave 4.28 g. (90%) of amine, b.p. 88–90° (18 mm.), n^{28}D 1.4640, [α]D +8.7° (EtOH).

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.60; H, 13.09; N, 7.23.

A picrate of this amine was prepared in 95% ethanol. Three recrystallizations from 95% ethanol gave an analytical sample as yellow needles, m.p. 132–132.5°.

Anal. Calcd. for $C_{18}H_{26}O_7N_4$: C, 52.67; H, 6.39; N, 13.65. Found: C, 52.79; H, 6.43; N, 13.86.

(+)-*endo*-6-Dimethylaminomethyl-1,5,5-trimethylbicyclo-[2.2.1]hexane.—The *endo*-amine was prepared by lithium aluminum hydride reduction as described for the *exo*-dimethylamine. Reduction of 3.60 g. of the *endo*-amide gave 3.16 g. (94%) of amine, b.p. 86–87° (19 mm.), n^{28}D 1.4588, [α]D +27.6° (EtOH).

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.67; H, 12.82; N, 8.06.

A picrate was prepared in 95% ethanol. Three recrystallizations from 95% ethanol gave an analytical sample as yellow needles, m.p. 126–127°.

Anal. Calcd. for $C_{18}H_{26}O_7N_4$: C, 52.67; H, 6.39; N, 13.65. Found: C, 52.69; H, 6.46; N, 13.51.

***exo*-6-Dimethylaminomethyl-1,5,5-trimethylbicyclo-[2.1.1]hexane N-oxide.**—To a solution of 3.05 g. of *exo*-amine in 7 ml. of methyl alcohol was added, with stirring and cooling, 8 ml. of 30% hydrogen peroxide. After stirring for an additional 12 hr., a small amount of platinum black was added, and the mixture was stirred for 24 hr. to destroy the excess hydrogen peroxide. The solution was then filtered and the solvent evaporated in a stream of dry air.

A picrate of the residual N-oxide was prepared in 95% ethanol. Two recrystallizations from 95% ethanol gave an analytical sample as yellow needles, m.p. 136–137°.

Anal. Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15; N, 13.14. Found: C, 50.96; H, 6.18; N, 13.29.

***endo*-6-Dimethylaminomethyl-1,5,5-trimethylbicyclo-[2.1.1]hexane N-oxide** was prepared by treatment of 2.15 g, of the *endo*-amine with 30% hydrogen peroxide as described for the *exo* epimer.

A picrate of the N-oxide was prepared in 95% ethanol. Two recrystallizations from 95% ethanol gave an analytical sample as yellow needles, m.p. 134–135°.

Anal. Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15; N, 13.14. Found: C, 50.81; H, 6.23; N, 13.32.

6-Methylene-1,5,5-trimethylbicyclo[2.1.1]hexane (X). A.—The N-oxide prepared from 2.70 g. of *exo*-amine was pyrolyzed at 130–135° under a vacuum of 50 mm. The pyrolysis products were condensed in a trap which had been cooled in a Dry Ice–acetone-bath to −50°. The trapped material was diluted with ether, and washed with water until the aqueous solution showed no signs of basicity. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether removed by distillation. The residue was sublimed to give 1.18 g. (69%) of X, m.p. 60–61°; infrared spectrum (neat): 3.29, 5.96, 11.56 μ. These peaks vanish when X is allowed to react with bromine in carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.37; H, 11.96.

B.—The N-oxide prepared from 2.70 g. of *endo*-amine on pyrolysis under the same conditions gave 1.08 g. (63%) of X, m.p. 60–61°; infrared spectrum (neat) identical with that of the olefin obtained from the *exo* isomer.

Rearrangement of the 1,5,5-Trimethylbicyclo[2.1.1]-hexane-6-carboxylic Acids.—Six grams of finely ground IIa was added slowly to 20 ml. of vigorously stirred concentrated sulfuric acid. After the addition was complete, the reaction mixture was stirred at 45–50° for 0.5 hr., cooled, and poured onto 250 g. of ice. The solution was neutralized with dilute aqueous sodium hydroxide solution and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether evaporated under reduced pressure. The residue (3.42 g.) was fractionally distilled to give 2.94 g. (49%) of XIII, b.p. 94–96° (2 mm.). The distillate crystallized immediately to give a waxy solid, m.p. 35–37°; infrared (neat): 5.64 μ. Sublimation gave an analytical sample, m.p. 36–37°, [α]D +3.9° (*c* 1.5). The infrared spectrum of this product was superimposable on that of an authentic sample of XIII.[12]

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.53; mol. wt., 168. Found: C, 71.43; H, 9.44; mol. wt., 169.

The basic aqueous solution was acidified with dilute hydrochloric acid. The precipitate which formed was collected by filtration and air-dried to give 1.16 g. (19%) of XXIII; recrystallization from dilute acetic acid and subsequent sublimation gave an analytical sample, m.p. 80–81°, [α]D −26.9° (*c* 1.3) (chloroform); ultraviolet spectrum: at 210 mμ ε = 600. This acid gave no color with tetranitromethane, and failed to react with bromine, potassium permanganate and ozone.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.53. Found: C, 71.32; H, 9.63.

The infrared spectrum of this material was identical to that of the synthetic sample of ±-XXIII provided by Burgstahler and Sticker.[19]

The same two products were formed in comparable amounts when IIb was used in place of IIa.

Lithium Aluminum Hydride Reduction of XIII.—A solution of 0.30 g. of XIII in 15 ml. of anhydrous ether was added dropwise to a stirred suspension of 0.30 g. of lithium aluminum hydride in 5 ml. of anhydrous ether. Stirring was continued for 6 hr. at room temperature. Water (1.20 g.) was added dropwise and the resulting inorganic salts were removed by filtration and washed thoroughly with ether. The solution was dried over anhydrous magnesium sulfate, filtered and the solvent was removed to yield 0.22 g. (72%) of XIV. Recrystallization from 60–70° petroleum ether gave a sample of the diol, m.p. 145–145.5°, m.m.p. (with authentic sample of XIV[12]) 145–145.5°.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.90; H, 11.88.

1,2,2-Trimethylbicyclo[3.1.0]hexane-6-carboxylic Acid Methyl Ester.—An ethereal solution containing 45 mg. of

XXIII was treated with an excess of ethereal diazomethane. The solvent was allowed to evaporate and an analytical sample, n^{22}_{D} 1.4608, was prepared by gas chromatography. Infrared analysis showed no olefinic carbon–hydrogen absorption, and the spectrum was identical to that of the ester prepared from Burgstahler and Sticker's (±)-XXIII.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.35; H, 9.89. Found: C, 72.24; H, 10.17.

Dihydro-β-campholenolacetone from XXIII.—Sixty milligrams of XXIII and 2 ml. of concentrated sulfuric acid were carefully mixed and stirred at 45–50° for 45 min. The reaction mixture was poured onto ice, made basic with dilute potassium hydroxide solution and extracted with ether. The ethereal solution was dried and then ether distilled off to give 30 mg. of XIII.

1,2,2-Trimethyl-6-acetylbicyclo[3.1.0]hexane.—The methyllithium prepared from 0.70 g. of methyl iodide, 0.10 g. of lithium and 15 ml. of anhydrous ether was added dropwise to a stirred solution of 300 mg. of XXIII in 10 ml. of anhydrous ether. After stirring for 1 hr., the reaction mixture was diluted with water and ether, and the layers were separated. Acidification of the basic aqueous layer gave 166 mg. of unreacted starting acid XXIII. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether removed under reduced pressure to give 106 mg. (80% based on unrecovered XXIII) of the desired methyl ketone; infrared spectrum (neat): 5.90 μ; ultraviolet spectrum (ethanol): $\lambda\lambda_{\max}$ 206 mμ (ε 5,700), 278 mμ (ε 67).

A 2,4-dinitrophenylhydrazone was prepared in the usual way. Four recrystallizations from ethanol gave bright orange needles, m.p. 156–157°; ultraviolet spectrum (ethanol): $\lambda\lambda_{\max}$ 235 mμ (ε 11,800), 370 mμ (ε 17,600).

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 58.98; H, 6.53; N, 16.32.

1-Methylbicyclo[3.1.0]hexane-6-carboxylic Acid (XXIV).—A mixture of 4.10 g. of 1-methylcyclopentene,[25] 2.85 g. of ethyl diazoacetate and 0.28 g. of powdered copper was heated on a steam-bath for about 4 min., at which time a vigorous exothermic reaction started. The reaction mixture was cooled to room temperature where the rate of nitrogen evolution continued to be extremely rapid. When the gas evolution ceased, the reaction mixture was immersed in an ice-bath and an additional 2.85 g. of ethyl diazoacetate was added. Vigorous evolution of gas occurred for about 30 min. The reaction mixture was filtered and fractionally distilled to give 3.07 g. (36%) of crude ester, b.p. 94–101° (15 mm.). This material could not be obtained analytically pure, but was hydrolyzed directly to the acid.

A mixture of 1 g. of the distilled ester, 2 g. of potassium hydroxide, 10 ml. of water and 10 ml. of methanol was refluxed on a steam-bath for 3 hr. The methanol was removed on a flash evaporator, and the residual aqueous solution was acidified with dilute hydrochloric acid. The precipitate which formed was collected by filtration and air-dried to give 0.27 g. (32%) of crude XXIV, m.p. 50–53°. Recrystallization from nitromethane, followed by sublimation, gave an analytical sample, m.p. 62.5–63.0°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.56; H, 8.66.

Ozonolysis of 6-Methylene-1,5,5-trimethylbicyclo[2.1.1]-hexane.—A solution of 1.18 g. of X in 10 ml. of absolute methanol was exhaustively ozonized at −70 to −80°.[20] The ozonized solution was then added to a vigorously stirred mixture of 7.5 ml. of absolute methanol, 2.5 ml. of glacial acetic acid and 4.0 g. of sodium iodide, and stirred overnight. The mixture was diluted with 25 ml. of water, and sufficient sodium bicarbonate was added to make it basic. The reaction mixture was then extracted with ether, and the combined ethereal extracts dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent evaporated under reduced pressure to give 0.86 g. of an oil; infrared spectrum (neat): 2.90, 5.80 μ.

Vapor phase chromatography under the same conditions described for the two methyl esters showed the product to be a mixture of at least three components, retention times 4.30, 7.58 and 10.28 min.

Osmylation of 6-Methylene-1,5,5-trimethylbicyclo[2.1.1]-hexane.—A solution of 1.00 g. of osmium tetroxide in 10 ml. of dry dioxane was added to a solution of 0.50 g. of X in 10 ml. of dry dioxane. The stoppered reaction mixture was kept at room temperature for 4 days in the dark. The reaction mixture was saturated with hydrogen sulfide, filtered, and the precipitated salts washed with dioxane. The combined filtrates were taken to dryness under reduced pressure to give 0.20 g. of a semi-solid oil; infrared spectrum (neat): 3.00, 5.70–5.80 μ.

***exo*-6-Acetyl-1,5,5-trimethylbicyclo[2.1.1]hexane (XXV).** A.—The acid IIa was inert to prolonged treatment with excess methyllithium in both refluxing ether and refluxing tetrahydrofuran.

B.—To a solution of methylmagnesium iodide prepared in the usual way from 7.60 g. of methyl iodide and 1.28 g. of magnesium metal in 100 ml. of anhydrous ether was added 10.0 g. of anhydrous cadmium chloride during 10 min. The mixture was stirred and heated under reflux for 45 min. The ether was distilled from the reaction mixture and replaced by 100 ml. of dry benzene. About 10 mg. of anhydrous ferric chloride[26] was added, and the reaction mixture cooled in an ice-bath. The acid chloride prepared from 8.00 g. of IIa and oxalyl chloride, as described above, was added dropwise. After the addition was complete the mixture was stirred and refluxed for 2 hr. The reaction mixture was cooled in an ice-bath and 100 ml. of water was added cautiously. The aqueous phase was separated and extracted with ether. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was fractionally distilled to give 6.24 g. (78%) of an oil, b.p. 85–87° (11 mm.); infrared spectrum (neat): 5.88 μ, with no absorption in the hydroxyl region of the spectrum.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.65; H, 10.93.

A semicarbazone was prepared in the usual way. Three recrystallizations from ethanol gave an analytical sample, m.p. 209.5–210.5°.

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.52; H, 9.47; N, 19.02.

A 2,4-dinitrophenylhydrazone could not be formed in the normal way. The methyl ketone was heated with the reagent in ethanol at 70° for several minutes. On cooling, a derivative was obtained. Two recrystallizations from ethanol gave yellow crystals, m.p. 131–132°. The melting point was not depressed on mixing with the 2,4-dinitrophenylhydrazone obtained in the normal way from the epimeric *endo*-methyl ketone XXVI.

Although the ketonic product was analytically pure, vapor phase chromatography showed it to be a mixture of 80% of the desired methyl ketone XXV and 20% of the epimeric *endo*-methyl ketone XXVI (retention times 12.5 and 10.3 min., respectively, on a 6′ × 0.25″ column at 100°, packed with 0.3% polyethylene glycol 400 on glass beads, using helium as carrier).

(+)-*endo*-6-Acetyl-1,5,5-trimethylbicyclo[2.1.1]hexane (XXVI).—Methyllithium was prepared by adding a solution of 6.80 g. of methyl iodide in 35 ml. of anhydrous ether to a stirred suspension of 0.70 g. of lithium ribbon in 35 ml. of anhydrous ether at a rate necessary to maintain mild refluxing.

The resultant solution of methyllithium was added dropwise to a stirred solution of 3.36 g. of IIb in 50 ml. of anhydrous ether, during 1 hr. After stirring for an additional hour, the reaction mixture was poured onto 75 g. of crushed ice and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was fractionally distilled to give 2.75 g. (82%) of XXVI, b.p. 80–82° (12 mm.), n^{28}_{D} 1.4618, $[\alpha]_{\mathrm{D}}$ +34.6° (EtOH); infrared spectrum (neat): 5.88 μ, with no absorption in the hydroxyl region of the spectrum. Vapor phase chromatography, carried out as described for XXV, showed a single peak, 10.3 min. retention time.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.56; H, 11.00.

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(25) G. Chavanne and L. de Vogel, *Bull. soc. chim. Belg.*, **37**, 142 (1928).

(26) The authors are indebted to Professor James Cason for calling their attention to the catalytic effect of ferric chloride on the reaction of dimethylcadmium with acid chlorides.

A semicarbazone was formed in the usual way. Two recrystallizations from ethanol gave an analytical sample, m.p. 221–222°.

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.46; H, 9.45; N, 18.96.

A 2,4-dinitrophenylhydrazone was formed in the normal way. Three recrystallizations from ethanol gave an analytical sample, m.p. 131–132°.

Anal. Calcd. for $C_{17}H_{22}O_4N_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 58.89; H, 6.25; N, 15.89.

(+)-1,5,5-Trimethylbicyclo[2.1.1]hexan-*endo*-6-ol(III).—A solution of trifluoroperacetic acid[21] was prepared by mixing 3.40 ml. of trifluoroacetic anhydride with 0.52 ml. of 90% hydrogen peroxide in 6.60 ml. of methylene chloride.

The resulting peracid solution was added dropwise to a stirred solution of 1.60 g. of XXVI, 3.90 g. of anhydrous dibasic sodium phosphate and 20 ml. of methylene chloride. The reaction mixture was stirred and refluxed for 8 hr., filtered, and the inorganic salts washed thoroughly with methylene chloride. The filtrate was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The infrared spectrum of the residue indicated some unchanged ketone was still present.

The total reaction product was, therefore, recycled by dissolving it in 20 ml. of methylene chloride to which 3.90 g. of anhydrous dibasic sodium phosphate had been added. The trifluoroperacetic acid obtained from 3.40 ml. of trifluoroacetic anhydride, 0.52 ml. of 90% hydrogen peroxide and 6.60 ml. of methylene chloride was added dropwise. Refluxing was maintained for 12 hr. The solution was cooled, filtered and the inorganic salts washed thoroughly with methylene chloride. The filtrate was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to give 1.83 g. of acetate (containing some trifluoroacetate, as indicated by infrared absorption at 5.60 as well as 5.78 μ).

The crude acetate was dissolved in 10 ml. of anhydrous ether and added dropwise to a stirred suspension of 1.00 g. of lithium aluminum hydride in 20 ml. of anhydrous ether. After stirring at room temperature for 8 hr., the reaction mixture was cooled to 0° and quenched by the dropwise addition of 4.0 ml. of water. The hydrolyzed mixture was stirred for 1 hr. and the precipitated salts were removed by filtration. The salts were washed thoroughly with ether, and the combined filtrates were dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was removed under reduced pressure. Sublimation of the crude product gave 1.01 g. (73% yield based on XXVI) of III, m.p. 95–97° with preliminary softening at 85°, $[\alpha]_D$ + 15.1° (EtOH). Preparative vapor phase chromatography gave an analytically pure sample, m.p. 121–122°. This material showed a 2.45 min. retention time on a column of the type used for the methyl esters, operated at 100°. No impurity was detectable.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.00; H, 11.39.

A *p*-nitrobenzoate was formed in the normal way. Two recrystallizations from aqueous ethanol gave an analytical sample, m.p. 98.5–99°.

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.65; H, 6.63; N, 5.06.

1,5,5-Trimethylbicyclo[2.1.1]hexan-6-one (XXVII).—To the complex formed from 2.70 g. of chromium trioxide in 40 ml. of dry pyridine[22] was added dropwise with stirring a solution of 1.50 g. of III in 20 ml. of dry pyridine. The resulting mixture was stirred at room temperature for 3 days, and then 160 ml. of water was added. The mixture was extracted with ether, and the ether washed repeatedly with water and then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure to give 0.76 g. (51%) of XXVII; infrared spectrum (neat): 5.61 μ, with no absorption in the hydroxyl region of the spectrum. This ketone showed a surprising tendency to decompose upon distillation.

(−)-1,5,5-Trimethylbicyclo[2.1.1]hexan-*exo*-6-ol (IV).—A solution of 0.75 g. of crude XXVII in 15 ml. of anhydrous ether was added dropwise to a stirred suspension of 0.50 g. of lithium aluminum hydride in 25 ml. of anhydrous ether at −5°. After stirring for 2 hr. at −5°, the mixture was hydrolyzed by the dropwise addition of 2.0 g. of water. The reaction mixture was filtered and the inorganic salts washed thoroughly with ether. The combined filtrates were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was sublimed under reduced pressure to give 0.56 g. (73%) of a waxy white solid. Preparative vapor phase chromatography gave an analytical sample, m.p. 124–125.5°, $[\alpha]_D$ −17.4°. This material showed a v.p.c. retention time of 2.55 min., with no detectable impurity, under the conditions used to examine its epimer III.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.15; H, 11.62.

An attempt to form a *p*-nitrobenzoate in the normal way was unsuccessful.

[Contribution from Avery Laboratory, University of Nebraska, Lincoln, Nebr.]

Elimination Reactions of α-Halogenated Ketones. VII.[1] Kinetics of Several Dehydrobromination Reactions of 4-Biphenylyl 1-Bromocyclohexyl Ketone

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The α-bromoketone 4-biphenylyl 1-bromocyclohexyl ketone (I) has been found to undergo elimination reaction in solvent acetonitrile and in solvent benzene to yield the α,β-unsaturated ketone 4-biphenylyl 1-cyclohexenyl ketone (II). The kinetics of the elimination reaction as promoted by piperidine, by morpholine, by tetraethylammonium bromide and by piperidine hydrobromide are reported. The kinetic results are discussed in terms of possible reaction mechanism. 4-Biphenylyl 2-piperidinocyclohexyl ketone (III) and 4-biphenylyl 2-bromocyclohexyl ketone (IV) have been prepared and characterized.

Introduction.—This communication reports upon the kinetics of several elimination reactions of 4-biphenylyl 1-bromocyclohexyl ketone (I) in solvent acetonitrile and in solvent benzene. Elimination from 4-biphenylyl 1-bromocyclohexyl ketone (I) produces the α,β-unsaturated ketone 4-biphenylyl 1-cyclohexenyl ketone (II).[2]

Previous communications in this series have reported upon the kinetics of elimination reactions of 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone (V) in solvent acetonitrile.[3,1] A merged substitution and elimination mechanism was proposed for these elimination reactions.

Discussion of Results

The decompositions of α-bromoketone I, of piperidine and of morpholine in both acetonitrile and in benzene were found, even at 90.6°, to be

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(1) For paper VI in this series see D. N. Kevill and N. H. Cromwell, *J. Am. Chem. Soc.*, **83**, 3815 (1961).

(2) N. H. Cromwell and P. H. Hess, *ibid.*, **82**, 136 (1960).

(3) D. N. Kevill and N. H. Cromwell, *ibid.*, **83**, 3812 (1961).