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THE SYNTHESIS OF
5,5-DIMETHYLBICYCLO[2.1.1]HEXANE-1-CARBOXALDEHYDE

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF THE
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THE SYNTHESIS OF
5,5-DIMETHYLBICYCLO[2.1.1]HEXANE-1-CARBOXALDEHYDE

By Kikuye Ebisu

A thesis submitted to the Graduate School of the University
of Hawaii in partial fulfillment of the requirements
for the degree of Doctor of Philosophy.

ABSTRACT

The highly strained bicyclo[2.1.1]hexane system has been of considerable interest to chemists especially in connection with bond angle deformation studies. Previous synthetic routes to the bicyclo[2.1.1]hexane system have largely involved photolytic ring contraction of the bicyclo[2.2.1]heptane system.

The nitrous acid deamination of a bridgehead amino alcohol, 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (I), was studied with the hope that ring contraction would occur. The product of the reaction was an aldehyde, which was readily oxidized by air. N.m.r. data indicated that the product was 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (II), m.p. 84.5-88°; $[\alpha]_D^{23}$ -6.8° (benzene);

semicarbazone, m.p. 192-193.2° dec. The yield of aldehyde based on the semicarbazone was 76%. The aldehyde was oxidized with hydrogen peroxide to 5,5-dimethylbicyclo-[2.1.1]hexane-1-carboxylic acid, m.p. 120.2-122.2°; $[\alpha]_D^{23} +11.2^\circ$ (benzene).

Synthesis of the bridgehead amino alcohol I involved rearrangement of 2-bromo-2-nitrobornane with silver nitrate to 1-nitrocamphene (III). Evidence is presented in support

III

of structure III. Ozonization of 1-nitrocamphene and reduction of the resulting nitro ketone yielded the bridgehead amino alcohol I, m.p. 100-102°; $[\alpha]_D^{23} -10.3^\circ$ (ethanol).

Attempts to prepare another bridgehead amino alcohol, 1-amino-4-bromo-5,5-dimethylbicyclo[2.2.1]heptan-2-ol, were unsuccessful. Treatment of 4-bromo-5,5-dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-carboxamide with sodium hypobromite in excess base yielded the 2-oxazolidone IV, which

IV

decomposed at 212-222°.

The 2-oxazolidone was converted with sulfuric acid to a neutral ketone, m.p. 169.4-170.4°. Structure V is proposed for the compound on the basis of elemental analyses and spectral data.

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I. INTRODUCTION

A. Statement of the Problem

The nitrous acid deamination of bicyclic 2-amino alcohols has not, as yet, been studied. The deamination of acyclic amino alcohols has been studied extensively using, in some instances, carbon-14-labeled compounds.¹ The mechanism for the reactions studied has been postulated to involve largely open or "classical" carbonium ion intermediates rather than the bridged ion species. Ring contraction and hydride shift have been observed in the deamination of monocyclic amino alcohols.^{2,3}

The deamination of the bridgehead amino alcohol, 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (1), was studied with the hope that ring contraction to the bicyclo[2.1.1]hexane system 2 would occur. The reaction of this

bicyclic compound, if successful, would provide a non-photochemical route to the bicyclo[2.1.1]hexane system.

B. Survey of the Literature

Over the years workers in several laboratories have shown considerable interest in the synthesis of the highly strained bicyclo[2.1.1]hexane system. Previous synthetic approaches have largely involved the use of radiant energy to effect ring contraction of the bicyclo[2.2.1]heptane system to the bicyclo[2.1.1]hexane system.

Calculations of the internal bond angles of the two ring systems were made by Wilcox.⁴

The photochemical conversion of carvone (3) to carvonecamphor (4) by Ciamician and Silber⁵ in 1908 was the first reported synthesis of a compound containing the bicyclo[2.1.1]hexane system. Carvonecamphor was subsequently oxidized to a dicarboxylic acid 5 and a keto carboxylic acid 6.⁶ The correct structures for carvone-

camphor and the two carboxylic acids were firmly established in 1957 by Buchi and Goldman.⁷

In 1955 Horner and Spietschka⁸ found that the photolysis of α -diazocamphor (7) brought about a Wolff rearrangement which yielded the ring-contracted acid, 1,6,6-trimethylbicyclo[2.1.1]hexane-5-carboxylic acid (8). The carboxyl group was assigned the exo configuration by Meinwald and co-workers.⁹

Meinwald and Gassman¹⁰ in 1960 prepared a series of racemic and optically active bicyclo[2.1.1]hexane derivatives with functional groups of known configuration

on the two-carbon bridge. The important intermediate in their work was also an α -diazo ketone, 3-diazonopinone (9), which was irradiated to produce 5,5-dimethylbicyclo[2.1.1]hexane-2 β -carboxylic acid (10) in 65-68% yield.

In 1961 Wiberg and co-workers¹¹ synthesized several bicyclo[2.1.1]hexane derivatives without methyl substituents. The photolysis of diazonorcamphor in methanol gave methyl bicyclo[2.1.1]hexane-5-carboxylate in 54% yield. Wiberg and his group also prepared bridgehead bicyclo[2.1.1]hexane derivatives by irradiating 1-chloro-diazonorcamphor.^{11,12}

Srinivasan¹³ obtained bicyclo[2.1.1]hexane in low yield from the mercury photosensitized decomposition of norcamphor. The mercury photosensitized isomerization of 1,5-hexadiene gave the same compound also in low yield.¹⁴

In 1963 Cookson and co-workers¹⁵ irradiated citral (11) and obtained 1,6,6-trimethylbicyclo[2.1.1]hexane-5 α -carboxaldehyde (12) in small amounts.

Liu and Hammond¹⁶ synthesized 5,5-dimethyl-1-vinylbicyclo[2.1.1]hexane (14) by irradiating myrcene (13).

The only nonphotochemical synthesis of a bicyclo[2.1.1]hexane has been reported as a private communication by Stork to Meinwald.¹⁷ No physical data has been given for the reaction, which involved an internal alkylation.

The first known synthesis of a bicyclo[2.1.1]hexene was reported recently by Crowley.¹⁸ The irradiation of α -phellandrene (15) gave 5-isopropyl-2-methylbicyclo[2.1.1]hex-2-ene (16) in 45% yield.

C. Objectives of this Research

The characterization by chemical and physical methods of the product(s) of the deamination of 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (18) was the primary objective of this research. However, before this objective could be met, the previously unknown amino alcohol 18 had to be synthesized. Synthesis of the compound by reduction of the known nitro ketone, 3,3-dimethyl-1-nitrobicyclo[2.2.1]heptan-2-one (17),^{19,20} was undertaken.

Synthesis of the bridgehead amino alcohol 20 from the known hydroxy amide, 4-bromo-5,5-dimethyl-2-hydroxybicyclo-[2.2.1]heptane-1-carboxamide (19),²¹ was attempted during the course of this research.

D. Acknowledgement

I would like to thank the Department of Health, Education, and Welfare for a grant (Title IV National Defense Graduate Fellowship) in support of this research.

II. EXPERIMENTAL

Elemental analyses were done by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim(Ruhr), Germany and by the Berkeley Analytical Laboratory, Berkeley, California.

All melting points are corrected and were taken with an Anschütz total immersion thermometer.

Optical rotations were taken in a two decimeter polarimeter tube with an O. C. Rudolph and Sons polarimeter.

Infrared spectra were recorded with a Beckman IR5 Infrared Spectrophotometer. Solvents used were reagent grade chloroform and carbon tetrachloride. Potassium bromide powder for infrared spectroscopy (Matheson Coleman and Bell) was used for spectral determinations in the solid phase.

Intensities of the infrared absorption maxima are designated as strong(s), medium(m) and weak(w); shoulder(sh).

Nuclear magnetic resonance (n.m.r.) spectra were obtained with a Varian Associates Model A-60 Analytical NMR Spectrometer. Reagent grade carbon tetrachloride and deuteriochloroform (Merck Sharp and Dohme) were used as solvents. The chemical shifts are given in parts per million (p.p.m. = δ) downfield from tetramethylsilane as

the internal reference.

A. Synthesis of 2-Bromo-2-nitrobornane (I)²²

A solution of potassium hydroxide (600 g., 10.7 m.) in 1 l. of water was cooled in an ice bath. Bromine (400 g., 2.50 m.) was added to the solution with stirring. D-Camphor oxime (100 g., 0.599 m.) was added to a cold solution of 200 g. of potassium hydroxide in 700 ml. of water. The alkaline mixture of the oxime was cooled in an ice bath and crushed ice (150 g.) was added. The mixture containing the oxime was added to the cold hypobromite solution with stirring. The temperature was kept below 50°. The resulting mixture was stirred for 10 hr. and was then allowed to stand at room temperature for 12-24 hr. The green nitroso compound was removed by filtration and converted to compound I by air oxidation for about one week. The yield after two recrystallizations from ethanol was 32%, m.p. 193-198° dec. (lit.²² m.p. 220°).

B. Preparation of 1-Nitrocamphene (II)²³

A solution of 2-bromo-2-nitrobornane (30 g., 0.114 m.) in 200 ml. of ethanol was heated to reflux temperature. Silver nitrate (50 g., 0.294 m.) was added in small amounts. The mixture was protected from light and was refluxed vigorously with stirring for 27 hr. The silver bromide and excess silver nitrate were removed by filtration. The ethanol in the filtrate was removed using

a vacuum evaporator. The residue was steam distilled and approximately 700 ml. of distillate was collected.

The distillate was extracted with ether and the ether extract was dried over anhydrous magnesium sulfate. The oil obtained after removal of the solvent was dissolved in the minimum amount of ethanol. It was necessary to seed the ethanolic solution with a crystal of 1-nitrocamphene.

The product (9.11 g., m.p. 50-54°) was obtained in 44% yield (lit.²³ 50%). After one recrystallization, compound II melted at 54.2-55.6° (lit.²³ m.p. 56°).

Proton resonance signals in the n.m.r. spectrum (deuteriochloroform) appeared at δ 1.17 (singlet, 6 H); 1.70-2.65 (multiplets, 7 H); 4.80 (doublet, $J = \underline{\text{ca.}}$ 1 c.p.s., 1 H) and 4.85 (doublet, $J = \underline{\text{ca.}}$ 1 c.p.s., 1 H). The n.m.r. spectrum of 1-nitrocamphene is shown in Fig. 1.

C. Ozonization of 1-Nitrocamphene

With slight modifications, 3,3-dimethyl-1-nitro-bicyclo[2.2.1]heptan-2-one (III) was prepared according to the procedure by Higaki.²⁰ A Welsbach T-23 ozonator was used. Ozone (ca. 0.12 m. per hr.) was introduced into a solution containing 1-nitrocamphene (14.8 g., 0.0814 m.) and chloroform (150 ml.). The solution was treated with ozone for 2 hr. at ice bath temperature and 1 hr. at room temperature. An additional 500 ml. of chloroform was added during the reaction.

Water (100 ml.) was added and the resulting mixture

Fig. 1. N.M.R. Spectrum of 1-Nitrocamphene

was refluxed for 40 min. The product was isolated by extraction with chloroform, removal of the solvent and crystallization of the resulting oil from ethanol.

The nitro ketone III (13.5 g., m.p. 90-94°) was obtained in 91% yield (lit.²⁰ 81%). After further recrystallization from ethanol, the melting point was raised to 96-97.2° (lit.²⁰ m.p. 94-95.5°).

Signals in the n.m.r. spectrum (deuteriochloroform) appeared at δ 1.16 (singlet, 3 H); 1.22 (singlet, 3 H) and 1.70-2.90 (multiplets, 7 H). The n.m.r. spectrum of the nitro ketone is shown in Fig. 2.

D. Baeyer-Villiger Oxidation of 3,3-Dimethyl-1-nitro-bicyclo[2.2.1]heptan-2-one (III) to 4,4-Dimethyl-1-nitro-3-oxabicyclo[3.2.1]octan-2-one (V)

The method of Meinwald and Frauenglass²⁴ was used. Hydrogen peroxide (10 ml. of a 30% soln., 0.098 m.) was cooled in an ice bath. Glacial acetic acid (10 ml.) was slowly added. A solution of the nitro ketone III (3.00 g., 0.0164 m.) in 30 ml. of acetic acid was added to the peroxide solution with swirling. An additional 35 ml. of acetic acid and anhydrous sodium acetate (1.50 g., 0.0183 m.) were added. The resulting solution was kept in the dark for 9 days.

The solution of the lactone was cooled in an ice bath. A cold solution of sodium carbonate (70 g. in 300 ml. of water) was added. The lactone was isolated by extraction

Fig. 2. N.M.R. Spectrum of 3,3-Dimethyl-1-nitrobicyclo[2.2.1]heptan-2-one

with chloroform (three 100-ml. portions). The chloroform extract was washed with a dilute sodium bisulfite solution and then with water. The extract was dried over anhydrous magnesium sulfate. The white solid obtained after removal of the solvent was recrystallized from ethanol. The lactone V (1.29 g., 39%) melted at 140-145°. After further recrystallization from ethanol, the lactone melted at 147.2-149.2°; $[\alpha]_D^{23} +92.5^\circ$ (c 5.13 g./100 ml., chloroform).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03; O, 32.13. Found: C, 54.48, 54.47; H, 6.66, 6.59; N, 7.20, 7.14; O, 32.03, 31.95.

The infrared spectrum of the lactone (chloroform) contained absorption bands at 3.35(w), 5.72(s), 6.45(s), 6.83(w), 7.19(w), 7.28(m), 7.55(m), 7.65(m), 7.91(w), 8.10(w), 8.51(s), 8.72(w), 9.06(s), 9.28(w), 9.51(m), 10.52(m), 10.79(w), 11.10(w) and 12.11μ (m). The infrared spectrum is shown in Fig. 3.

Signals in the n.m.r. spectrum (deuteriochloroform) appeared at δ 1.46 (singlet, 3 H); 1.53 (singlet, 3 H) and 1.95-3.10 (multiplets, 7 H). The n.m.r. spectrum of the lactone is shown in Fig. 4.

E. Reduction of 3,3-Dimethyl-1-nitrobicyclo[2.2.1]heptan-2-one (III) to 1-Amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (IV)

The bridgehead amino alcohol IV was prepared by the

Fig. 3. Infrared Spectrum of 4,4-Dimethyl-1-nitro-3-oxabicyclo[3.2.1]octan-2-one

Fig. 4. N.M.R. Spectrum of 4,4-Dimethyl-1-nitro-3-oxabicyclo[3.2.1]octan-2-one

method of Kornblum and co-workers.²⁵ The nitro ketone III (9.30 g.) was dissolved in 52 ml. of glacial acetic acid. Platinum dioxide (1.78 g.) was added to the solution. A Parr pressure reaction apparatus was used and the pressure of hydrogen was maintained at 45 p.s.i. for 42 hr. The mixture was filtered to remove platinum. Most of the acetic acid was removed by freeze-drying the filtrate. The resulting solution was made basic with sodium carbonate and then strongly basic with 20% sodium hydroxide.

The basic solution was extracted twice with chloroform (100, 75 ml.). The aqueous extract was saturated with sodium chloride and extracted with chloroform (three 75-ml. portions). The combined chloroform extracts were washed with water (three 10-ml. portions) and dried over anhydrous magnesium sulfate. The chloroform was removed using a vacuum evaporator. The resulting oil was dissolved in hexane and a white crystalline solid appeared within a few minutes. The product was soluble in water and sublimed readily.

The amino alcohol (5.40 g., m.p. 91-97°) was obtained in 68% yield. After one recrystallization, the compound (4.85 g., 61%) melted at 98-100.5°. An analytical sample was prepared after five recrystallizations from hexane, m.p. 100-102°; $[\alpha]_D^{23}$ -10.3° (c 5.07, ethanol).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.69, 69.81; H, 10.92, 11.12;

N, 9.22, 9.12.

Absorption bands in the infrared spectrum (carbon tetrachloride) appeared at 3.04(s, broad), 3.40(s), 3.49(s), 6.32(m), 6.85(s), 7.22(m), 7.33(m), 7.53(m), 8.12(m), 8.26(m), 8.55(w), 8.72(w), 9.00(s), 9.27(s), 10.00(m), 10.42(m), 10.67(m), 10.86(m), 11.20(m) and 11.60 μ (m). The infrared spectrum of the amino alcohol is shown in Fig. 5.

F. Preparation of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (VII)

The method of McCasland² was followed. A 4 molal sodium nitrite solution (7.5 ml., 8.54 g. of soln., 0.0267 m.) was added dropwise with stirring to a solution containing 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (0.805 g., 0.00518 m.) and acetic acid (20 ml. of a 50% soln.). The reaction mixture was stirred under nitrogen at room temperature for 55 min. The mixture was neutralized with sodium carbonate in the cold, saturated with sodium chloride and filtered. The crude aldehyde VII was mixed with anhydrous magnesium sulfate and the resulting mixture was sublimed under reduced pressure at room temperature for 1 hr. Cold water (ca. 5°) was introduced into the cold finger of the sublimator.

The sublimed aldehyde (0.228 g., 32%) was a colorless, waxy solid which melted at 84.5-88°; $[\alpha]_D^{23}$ -6.8° (c 5.08, benzene). A sample of the sublimed material in carbon

Fig. 5. Infrared Spectrum of 1-Amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol

tetrachloride was injected into a gas chromatograph (Aerograph A-90-P, Wilkens Instrument and Research, Inc., 5-ft. column packed with 20% silicone Ge-SF-96 on 60/80 mesh firebrick). The sample was temperature programmed from 125 to 250°. The sublimed material was found to be homogeneous. The crude material was also found to be homogeneous by gas chromatography. The aldehyde was readily oxidized by air and disappeared upon standing.

The infrared spectrum of the aldehyde (carbon tetrachloride) showed absorption bands at 3.38(s), 3.46(m), 3.58(w), 3.70(w), 5.85(s), 6.81(w), 6.87(w), 7.21(w), 7.30(w), 7.66(w), 7.80(w), 7.94(w), 8.02(w), 8.83(w) and 11.31 μ (w). The infrared spectrum is shown in Fig. 6.

Signals in the n.m.r. spectrum (carbon tetrachloride) appeared at δ 0.92 (singlet, 3 H); 1.06 (doublet, $J = 7.5$ c.p.s., 1 H); 1.28 (singlet, 3 H); 1.77 (multiplet, 4 H); 2.08 (multiplet, 1 H); 2.33 (broad, 1 H) and 9.67 (singlet, 1 H). The n.m.r. spectrum of the aldehyde is shown in Fig. 7.

An attempt to prepare the p-nitrobenzoate of any alcoholic product in the filtrate from the crude aldehyde yielded negative results. The only product isolated was p-nitrobenzoic acid.²⁶

G. Oxidation of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde²⁷

Nine milliliters of a 4 molal sodium nitrite solution

Fig. 6. Infrared Spectrum of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde

Fig. 7. N.M.R. Spectrum of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde

(10.4 g. of soln., 0.0325 m.) was added dropwise to a solution containing 1-amino-3,3-dimethylbicyclo[2.2.1]-heptan-2-ol (1.00 g., 0.00645 m.) and acetic acid (25 ml. of a 50% soln.). The mixture was stirred at room temperature for 1 hr. The mixture was cooled and neutralized with sodium carbonate. The crude aldehyde was filtered and washed with cold water.

The aldehyde was added gradually to a solution containing sodium hydroxide (8 ml. of a 5% soln.) and hydrogen peroxide (4 ml. of a 30% soln.) which had been heated to 65-70° in a water bath. The mixture was shaken periodically and kept at 65-70° for 20 min. Another 3 ml. of 30% hydrogen peroxide was added during the reaction. The solution was acidified to Congo red. The white solid which precipitated was removed by filtration.

The acid VIII (0.287 g., m.p. 115-119°) was obtained in 29% yield, based on the amino alcohol. The acid was purified by sublimation under reduced pressure at 50-60°, m.p. 118-120.2°, 120.2-122.2° (variable m.p.); $[\alpha]_D^{23} +11.2'$ (c 5.03, benzene).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.15, 70.27; H, 9.07, 9.20; O, 20.65, 20.72.

Absorption bands in the infrared spectrum (carbon tetrachloride) were present at 3.38(s), 3.70(m), 3.81(m), 5.90(s), 7.03(m), 7.21(w), 7.29(w), 7.58(m), 7.81(m),

8.11(m), 8.31(m), 8.79(w), 9.06(w), 9.39(w), 10.57(m, broad) and 10.36_{μ} (w). The infrared spectrum of the acid is shown in Fig. 8.

The n.m.r. spectrum of the acid (carbon tetrachloride) contained peaks at δ 0.91 (singlet, 3 H); 1.14 (doublet, $J = 7.5$ c.p.s., 1 H); 1.28 (singlet, 3 H); 1.80 (multiplet, 4 H); 2.02 (multiplet, 1 H); 2.29 (broad, 1 H) and 12.15 (singlet, 1 H). The n.m.r. spectrum is shown in Fig. 9.

The neutralization equivalent (N.E.)²⁷ of the acid was found to be 155. The acid was dried at 60° for 2 hr. It was dissolved in a mixture of water and the minimum amount of ethanol. The titrant was a 1/10 N sodium hydroxide solution. One drop of phenolphthalein was used as the indicator.

<u>Wt. of Acid</u>	<u>Water:Ethanol</u>	<u>1/10 N NaOH</u> (Corr. Vol.)	<u>N.E.</u>
0.1153 g.	25 ml.:17 ml.	7.400 ml.	155.6
0.1080	25 :17	6.960	155.0
		Average	155
		Mol. Wt.	154.2

H. Preparation of the Semicarbazone of 5,5-Dimethyl-bicyclo[2.1.1]hexane-1-carboxaldehyde²⁷

Five milliliters of a 4 molal sodium nitrite solution

Fig. 8. Infrared Spectrum of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxylic acid

Fig. 9. N.M.R. Spectrum of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxylic acid

(5.77 g. of soln., 0.0181 m.) was added dropwise with stirring to a solution containing 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (0.500 g., 0.00322 m.) and acetic acid (15 ml. of a 50% soln.). The reaction was carried out at room temperature. After 50 min. the mixture was cooled and neutralized with sodium carbonate.

Fifteen milliliters of ethanol was added to dissolve the aldehyde which had precipitated during the reaction. Semicarbazide hydrochloride (0.520 g., 0.00465 m.) and sodium acetate trihydrate (0.800 g., 0.00588 m.) were added. The solution was shaken vigorously. A white powdery solid was formed within 2 min. after the addition of the two reagents. The mixture was kept in the cold and filtered.

The semicarbazone (0.480 g., m.p. 189-191° dec.) was obtained in 76% yield, based on the amino alcohol. An analytical sample was prepared after three recrystallizations from ethanol-water, colorless needles, m.p. 192-193.2° dec.

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.69, 61.72; H, 8.66, 8.80; N, 21.58, 21.41.

I. Preparation of the Dimedone Derivative IX of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde²⁷

The aldehyde was prepared as was described previously in Part H using sodium nitrite (5 ml. of a 4 molal soln.,

0.0181 m.), 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (0.500 g., 0.00322 m.) and acetic acid (15 ml. of a 50% soln.). The crude aldehyde was dissolved in 10 ml. of 70% ethanol. The solution of the aldehyde was added gradually to a hot solution containing dimedone (0.398 g., 0.00284 m.), ethanol (15 ml. of a 70% soln.) and piperidine (2 drops). The resulting solution was heated in a water bath at about 75° for 8 min. One ml. of water was added and the solution was left to stand at room temperature overnight. The product was recovered by filtration.

The dimedone derivative IX (0.198 g., m.p. 170-173.5°) was obtained in 15% yield, based on the amino alcohol. An analytical sample was prepared after four recrystallizations from 70% ethanol, white crystals, m.p. 176-178°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06; O, 15.98. Found: C, 74.91, 75.08; H, 9.03, 9.16; O, 16.01, 15.92.

Absorption maxima in the infrared spectrum (KBr disc) appeared at 3.39(s), 3.48(sh), 3.85(m, broad), 6.31(s), 6.89(m), 7.05(m), 7.23(s), 7.34(s), 7.51(m), 7.70(m), 7.98(m), 8.34(w), 8.56(m), 8.65(m), 9.24(w), 9.49(w), 9.62(w), 9.81(w), 10.39(w), 10.76(m), 11.17(m), 11.60(m), 12.02(m), 12.28(w), 13.71(w) and 15.16 μ (w). The infrared spectrum of the dimedone derivative is shown in Fig. 10.

J. Cyclization of the Dimedone Derivative IX to the
Octahydroxanthene Derivative X²⁷

The dimedone derivative IX of 5,5-dimethylbicyclo-[2.1.1]hexane-1-carboxaldehyde (0.157 g.) was dissolved in 13 ml. of 80% ethanol. Concentrated hydrochloric acid (2 drops) was added and the solution was heated at about 80° for 10 min. One milliliter of 80% ethanol and an additional drop of hydrochloric acid were added during the reaction. Water was added to the cloud point and the mixture was kept in the cold. The white product was recovered by filtration.

The octahydroxanthene derivative X (0.125 g., m.p. 222.4-223.2° dec.) was obtained in 83% yield. An analytical sample was prepared after four recrystallizations from methanol-water, white powder, m.p. 224.7-225.7° dec.

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96; O, 12.55. Found: C, 78.87, 78.75; H, 8.98, 8.86; O, 12.52, 12.43.

The infrared spectrum (KBr disc) showed peaks at 3.40(s), 3.47(m), 6.04(s), 6.19(m), 6.82(m), 7.00(w), 7.24(m), 7.34(s), 7.50(w), 7.61(w), 7.72(w), 8.11(m), 8.32(s), 8.57(s), 8.76(s), 9.02(w), 9.77(w), 9.99(m), 10.56(w), 10.69(w), 10.90(w), 11.21(w), 11.50(w), 12.35(w), 13.02(w), 14.77(w) and 15.20μ (w). The infrared spectrum of the octahydroxanthene derivative is shown in Fig. 11.

Fig. 10. Infrared Spectrum of the Dimedone Derivative
of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde

Fig. 11. Infrared Spectrum of the Octahydroxanthene Derivative
of 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde

K. Rearrangement of 2-Bromo-2-nitrobornane (I) to
Isoxazoline XI with Sulfuric Acid²⁸

A mixture of concentrated sulfuric acid (163 ml.) and 30-60° petroleum ether (50 ml.) was cooled to -5°. A solution of 2-bromo-2-nitrobornane (43.0 g.) in 30-60° petroleum ether (100 ml.) was added dropwise to the vigorously stirred mixture of the acid and petroleum ether. The temperature was held at -5 to 0°. The mixture was stirred an additional 0.5 hr. at -5° and was poured on ice. After filtration the product was washed with dilute ammonia and with water.

The isoxazoline XI (14.6-17.2 g.) was obtained in 37-43% yield after three recrystallizations from ethanol (lit.²⁸ 46-60%). The compound decomposed at 200° (lit.²⁸ dec. 210-220°).

L. Isomerization of Isoxazoline XI to 4-Bromo-5,5-dimethyl-
2-hydroxybicyclo[2.2.1]heptane-1-carbonitrile (XII)²⁸

The isoxazoline XI (9.12 g., 0.0374 m.) was added to a solution of ethanol (27 ml. of a 95% soln.) and hydrochloric acid (4.5 ml. of a 12 N soln., 0.054 m.). The mixture was refluxed for 15 min., poured on ice and filtered.

The crude hydroxy nitrile XII (9.04 g., 99%) melted at 242-244.5°. The compound melted at 243-245° after one recrystallization from ethanol-water (lit.²⁸ quantitative yield, m.p. 244-245°).

M. Preparation of 4-Bromo-5,5-dimethyl-2-hydroxybicyclo-[2.2.1]heptane-1-carboxamide (XIII)

The amide XIII was synthesized from 4-bromo-5,5-dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-carbonitrile (XII) according to the method of Noller.²⁹ The hydroxy nitrile (4.40 g., 0.0180 m.) was dissolved in 50 ml. of ethanol. Hydrogen peroxide (50 ml. of a 30% soln., ca. 0.5 m.) and sodium hydroxide (7.7 ml. of a 20% soln.) were added. The temperature of the reaction mixture was kept at 40-50° by external cooling (45 min.). The temperature was maintained at 50° by external heating for an additional 1.25 hr. Water (120 ml.) was added and the resulting mixture was cooled in ice.

The product (shiny white flakes) was filtered and was washed with water. The amide (4.17 g., 88%) melted at 222-226°. The melting point was raised to 227-229° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{16}NO_2Br$: C, 45.80; H, 6.15; N, 5.34. Found: C, 45.78, 45.78; H, 6.11, 6.09; N, 5.16, 5.26.

Absorption maxima in the infrared spectrum (KBr disc) appeared at 2.95(s), 3.02(s), 3.38(m), 3.42(m), 6.03(s), 6.12(s), 6.46(m), 6.82(m), 7.20(s), 7.28(sh), 7.75(m), 8.03(m), 8.25(w), 8.75(w), 9.04(m), 9.28(w), 9.49(m), 10.17(m), 10.53(w), 11.00(w), 11.22(s), 11.50(m), 12.40(w) and 15.01μ (m). The infrared spectrum of the amide is

shown in Fig. 12.

N. Rearrangement of 4-Bromo-5,5-dimethyl-2-hydroxybicyclo-[2.2.1]heptane-1-carboxamide to the 2-Oxazolidone XVI³⁰

A solution of sodium hydroxide (3.50 g., 0.0875 m.) in 30 ml. of water was cooled to 0°. Sodium hypobromite was prepared by adding bromine (0.80 ml., ca. 0.015 m.) to the basic solution with stirring. The finely divided amide (3.01 g., 0.0115 m.) was added to the hypobromite solution. The resulting mixture was stirred in the cold until the amide had dissolved (1-2 hr.). The solution was warmed gently until the white product appeared. The mixture was heated for another 5 min. The product was filtered and washed with water.

The 2-oxazolidone XVI was obtained in 70-78% yield after one recrystallization from ethanol, dec. 207-226°. An analytically pure sample decomposed at 212-222°.

Anal. Calcd. for $C_{10}H_{14}NO_2Br$: C, 46.16; H, 5.42; N, 5.38; Br, 30.71. Found: C, 46.06, 46.36; H, 5.41, 5.45; N, 5.54, 5.52; Br, 30.79, 30.74.

Absorption bands in the infrared spectrum (KBr disc) were present at 3.10(m), 3.20(sh), 3.40(m), 5.75(s), 6.75(w), 6.87(w), 7.03(w), 7.28(m), 7.65(m), 7.73(m), 8.00(m), 8.20(m), 8.39(m), 8.99(m), 9.31(w), 9.50(m), 9.78(w), 10.38(s), 11.08(m), 12.17(m), 12.51(w), 12.90(m), 13.80(w), 14.30(w), 14.90(w) and 15.78μ (w). The infrared spectrum of the 2-oxazolidone is shown in Fig. 13.

Fig. 12. Infrared Spectrum of 4-Bromo-5,5-dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-carboxamide

O. Nitrosation of the 2-Oxazolidone XVI

The method of White³¹ was followed with the only modification that the reaction was conducted at room temperature instead of at 0°. The 2-oxazolidone XVI (1.00 g., 0.00384 m.) was dissolved in a mixture of glacial acetic acid (4 ml., 0.0697 m.) and acetic anhydride (19 ml.). Sodium nitrite (5.91 g., 0.0857 m.) was added in small amounts with stirring. The mixture was protected from light and stirred for 1.5 hr.

Water (150 ml.) was added and the greenish-yellow N-nitroso compound XVII was recovered by filtration. The compound (1.07 g., 96%) was sensitive to light. The N-nitroso compound was recrystallized from ethyl acetate-hexane at room temperature. The crude material and the recrystallized material decomposed at 188-194°.

Anal. Calcd. for $C_{10}H_{13}N_2O_3Br$: C, 41.53; H, 4.53; N, 9.69. Found: C, 41.07, 41.18; H, 4.33, 4.42; N, 9.63, 9.79.

Absorption maxima in the infrared spectrum (KBr disc) appeared at 3.38(m), 5.49(s), 6.55(s), 6.73(w), 6.84(m), 7.18(m), 7.29(m), 7.52(m), 7.72(m), 7.85(s), 8.01(m), 8.14(m), 8.28(m), 8.50(s), 8.67(s), 8.92(s), 9.14(m), 9.32(s), 9.47(m), 9.75(m), 10.12(s), 10.42(m), 10.70(m), 11.05(s), 11.20(m), 13.21(s), 13.66(m), 14.32(m) and 15.33μ (m). The infrared spectrum of the N-nitroso compound is shown in Fig. 14.

Fig. 13. Infrared Spectrum of the 2-Oxazolidone XVI

Fig. 14. Infrared Spectrum of the N-Nitroso Derivative of XVI

P. Rearrangement of the 2-Oxazolidone XVI to Ketone XVIII

Water (10 ml.) and concentrated sulfuric acid (10 ml.) were added to the 2-oxazolidone XVI (1.00 g.). The mixture was refluxed gently for 30 min. and poured on ice. The material which had collected on the condenser was removed with a small amount of ethanol. The mixture was filtered and the neutral ketonic product XVIII was washed with cold water. The crude material (0.614 g., 74%) melted at 168-170.2°. The ketone melted at 169.4-170.4° after recrystallization from hexane.

Anal. Calcd. for $C_9H_{13}OBr$: C, 49.78; H, 6.03; Br, 36.81. Found: C, 49.85, 49.98; H, 6.11, 6.03; Br, 37.14, 37.28.

Absorption bands were present in the infrared spectrum (carbon tetrachloride) at 3.35(s), 3.48(sh), 5.70(s), 6.73(m), 6.85(s), 7.22(m), 7.33(m), 7.80(s), 8.09(w), 8.21(m), 8.43(w), 8.60(m), 8.78(w), 9.49(s), 9.63(m), 10.08(s), 10.24(m), 10.58(m), 10.69(m), 11.03(m) and 11.76 μ (s). The infrared spectrum of the ketone is shown in Fig. 15.

Proton resonance signals in the n.m.r. spectrum (deuteriochloroform) appeared at δ 1.05 (singlet, 3 H); 1.14 (singlet, 3 H) and 1.33-2.70 (multiplets, 7 H). The n.m.r. spectrum of the ketone is shown in Fig. 16.

Fig. 15. Infrared Spectrum of Ketone XVIII

Fig. 16. N.M.R. Spectrum of Ketone XVIII

III. DISCUSSION OF RESULTS

A. Synthesis of 1-Amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (IV)

The synthesis of the bridgehead amino alcohol IV required five major steps beginning with the conversion of d-camphor to d-camphor oxime. The procedure by Forster²²

was used to prepare 2-bromo-2-nitrobornane (I), which was isolated in 32% yield. A Wagner-Meerwein rearrangement³² occurred when 2-bromo-2-nitrobornane was treated with silver nitrate. The product was a bridgehead nitro compound, 1-nitrocamphene (II), which was obtained in 44%

infrared spectrum (Fig. 3): 5.72 (C=O str.* of δ -lactone),^{37,38} 6.45 (NO₂ str.) and 8.51 μ (C-O str.). Two singlets due to the protons of the gem-dimethyl group (δ 1.46, 3 H; 1.53, 3 H) were present in the n.m.r. spectrum of the lactone (Fig. 4). The large downfield shift, about 0.3 p.p.m., relative to the methyl proton resonance signals of the nitro ketone indicated that the gem-dimethyl group of the lactone is adjacent to an oxygen atom.

Catalytic reduction of nitro ketone III in glacial acetic acid yielded the bridgehead amino alcohol IV in 61% yield, m.p. 100-102°; $[\alpha]_D^{23}$ -10.3°. The infrared spectrum (Fig. 5) showed absorption in the 3μ region attributable to the O-H and N-H stretching vibrations. An absorption band at 6.32μ (N-H def.) was also present. The hydroxyl group is tentatively assigned the endo configuration. It is assumed that the hydrogen adsorbed on platinum would approach the bicyclic system III predominantly from the less hindered exo side.

* The bond vibration modes are abbreviated as str.
(stretching vibration) and def. (deformation vibration).

The reduction of camphenilone (VI) was studied recently by Hueckel and co-workers.⁴⁰ Reduction with lithium aluminum hydride (steric-approach-controlled) gave endo-camphenilol. Raney nickel catalyzed hydrogenation yielded a mixture containing about 85% of the endo alcohol.

B. Deamination of 1-Amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (IV)

Nitrous acid deamination of amino alcohol IV with sodium nitrite in acetic acid solution yielded 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (VII),

m.p. 84.5-88°; $[\alpha]_D^{23}$ -6.8°; infrared spectrum (Fig. 6): 3.58, 3.70 (C-H str. of formyl group), 5.85 (C=O str.) and 7.21, 7.30 μ (C-H def. of gem-dimethyl group).

The product of the reaction was found to be homogeneous by vapor phase chromatography on a silicone column. The possibility that traces of other products were formed is not excluded.

The n.m.r. spectrum of the aldehyde (Fig. 7) was similar to the spectra of other bicyclo[2.1.1]hexane derivatives reported in the literature:^{13,16,41} C₅-CH₃, δ 0.92 (singlet); C₆-endo-H, 1.06 (doublet, J=7.5 c.p.s.); C₅-CH₃, 1.28 (singlet); C₂- and C₃-H₂, 1.77 (multiplet); C₆-exo-H, 2.08 (multiplet); C₄-H, 2.33 (broad) and C₁-CHO, 9.67 (singlet). The distinguishing feature of the spectrum was the high-field doublet equivalent to one proton centered at δ 1.06. The doublet (J=7.5 c.p.s.) was due to coupling of the C₆-endo proton with the C₆-exo proton.⁴¹ The singlet at δ 9.67 indicated that the formyl group is adjacent to a tertiary carbon atom.

The aldehyde VII was oxidized with 30% hydrogen peroxide to 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid (VIII) in 29% yield based on the amino alcohol IV,

VIII

m.p. 120.2-122.2°; $[\alpha]_D^{23} +11.2^\circ$; infrared spectrum (Fig. 8): 3.0-4.2 (broad, O-H str.), 5.90 (C=O str.) and 7.21, 7.29 μ (C-H def. of gem-dimethyl group). The neutral equivalent of the acid was found to be 155.

The n.m.r. spectrum of the acid VIII (Fig. 9) was similar to that of its precursor, aldehyde VII: C₅-CH₃, δ 0.91 (singlet); C₆-endo-H, 1.14 (doublet, J = 7.5 c.p.s.); C₅-CH₃, 1.28 (singlet); C₂- and C₃-H₂, 1.80 (multiplet); C₆-exo-H, 2.02 (multiplet); C₄-H, 2.29 (broad) and C₁-COOH, 12.15 (singlet). The assignments for the C₆-exo and C₄ protons of the aldehyde and the acid are tentative, although one would expect the C₄ proton to resonate further downfield than the C₆-exo proton.⁴¹

The semicarbazone of aldehyde VII was prepared directly from the deamination reaction medium to determine the extent of ring contraction. The yield of semicarbazone (m.p. 192-193.2° dec.) based on the amino alcohol IV was 76%. An estimation of the yield of aldehyde in the deamination reaction would then be about 85-90%.

Condensation of the aldehyde with 5,5-dimethylcyclohexane-1,3-dione (dimedone) yielded the dimedone derivative IX, m.p. 176-178°, in 15% yield based on the amino alcohol. The dimedone derivative IX was converted in hydrochloric acid to the corresponding octahydro-xanthene X, m.p. 224-225.7° dec., in 83% yield.

The nitrous acid deamination of amino alcohol IV could have led to the formation of several possible products. The commonly accepted mechanism for the

deamination reaction involves the formation of a diazonium ion.^{42,43} The two unrearranged products, the diol and the acetate, would be formed by the attack of water and acetic acid, respectively, at the C₁ bridgehead position. A 1,2-hydride shift to the C₁ bridgehead position would result in the formation of the known ketone, camphenilone. Migration of the C₂-C₃ electron pair to the C₁ bridgehead position would lead to the formation of the ring-contracted aldehyde VII.

The diol, acetate and ketone would be formed with retention of configuration at the C₁ bridgehead atom.⁴⁴ The ring-contracted aldehyde would be formed with inversion of configuration at the same asymmetric center. The C₂-C₃ electron pair must approach the C₁ bridgehead atom from the side opposite the position temporarily occupied by the diazonium group because no other direction of approach is geometrically possible.

The only product detected in the deamination reaction was the ring-contracted aldehyde, 5,5-dimethylbicyclo-[2.1.1]hexane-1-carboxaldehyde (VII). Migration of the C₂-C₃ electron pair to the C₁ bridgehead position probably occurred simultaneously with or immediately after elimination of nitrogen.⁴⁵ The former process is a concerted one and the latter probably involves the formation of a short-lived bridgehead carbonium ion.

The formation of the highly strained aldehyde VII is

reasonable in view of the fact that an anti or trans relationship exists between the C_2-C_3 bond and the C_1-N bond of the diazonium ion intermediate. McCasland² has studied the nitrous acid deamination of cis- and trans-2-aminocyclohexanols. He found that the deamination of the trans compound yielded almost exclusively the ring-contracted product, cyclopentylmethanal. It is the C_2-C_3

bond which is conformationally trans and coplanar with respect to the C_1-N bond of the diazonium ion intermediate.

The cis isomer gave both the ring-contracted product, cyclopentylmethanal, and the product of a 1,2-hydride shift, cyclohexanone. The C_2-C_3 bond is trans and

coplanar with respect to the C₁-N bond in the diazonium ion intermediate of the axial hydroxy conformer. With the equatorial hydroxy conformer, the C-H bond at the C₂ position is trans and coplanar with respect to the C₁-N bond.

The reaction of 2-bromo-2-nitrobornane (I) with silver nitrate was conclusively shown to yield 1-nitrocamphene (II). Ozonization of 1-nitrocamphene resulted in the formation of 3,3-dimethyl-1-nitrobicyclo[2.2.1]heptan-2-one (III). Baeyer-Villiger oxidation of the nitro ketone yielded the lactone 4,4-dimethyl-1-nitro-3-oxabicyclo[3.2.1]octan-2-one (V).

The deamination of 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (IV) resulted in ring contraction to 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (VII) in 76% yield based on the semicarbazone. The over-all yield of the aldehyde from 2-bromo-2-nitrobornane was 19%.

C. Attempted Synthesis of 1-Amino-4-bromo-5,5-dimethylbicyclo[2.2.1]heptan-2-ol (XIV)

The deamination of the bridgehead amino alcohol IV gave the ring-contracted aldehyde VII in good yield (based on the semicarbazone). The next objective of this research was the synthesis of another bridgehead amino alcohol, 1-amino-4-bromo-5,5-dimethylbicyclo[2.2.1]heptan-2-ol (XIV). A study of the deamination reaction would then follow if the synthesis succeeded.

The important intermediate in the amino alcohol synthesis was the hydroxy nitrile XII, which was first synthesized by Forster²² according to the following reaction scheme.

The above structures for the hydroxy nitrile XII and its isomer, the isoxazoline XI, were established by van Tamelen and Brenner in 1957.²⁸

The synthesis of the amino alcohol XIV would then require two additional steps: 1) conversion of the hydroxy nitrile to the corresponding amide XIII and 2) Hofmann rearrangement³⁰ of the amide to the amino alcohol.

Van Tamelen and Brenner²⁸ have observed that hydrolysis of hydroxy nitrile XII to the hydroxy amide XIII in acid or base does not occur. The reaction with concentrated sulfuric acid gave a $C_{10}H_{14}NOBr$ compound, presumably a tricyclic amide. Treatment of the hydroxy nitrile with 30% sodium hydroxide yielded an unsaturated nitrile.

The desired hydroxy amide XIII has been isolated, although in low yield, from the reactions of isoxazoline XI and hydroxy nitrile XII with hydroxylamine and sodium carbonate.²¹

Aliphatic and aromatic nitriles are known to react with hydrogen peroxide in a weakly basic medium.^{46,47,48} The corresponding amides are produced in 50-95% yield. Treatment of hydroxy nitrile XII with hydrogen peroxide

under the same conditions resulted in an 88% yield of the corresponding hydroxy amide XIII, m.p. 227-229°; infrared

spectrum (Fig. 12): 6.03 (C=O str.) and 6.12 μ (N-H def. and C-N str.).

The amino alcohol XIV was not formed in the reaction of the hydroxy amide XIII with sodium hypobromite and sodium hydroxide (Hofmann rearrangement). An intramolecular cyclization involving the isocyanate intermediate XV must have occurred as indicated by the elemental analysis and infrared spectral data of the product. The product of the reaction was the substituted

2-oxazolidone XVI, which decomposed at 212-222°; infrared spectrum (Fig. 13): 3.10, 3.20 (N-H str.) and 5.75 μ (C=O str.). The 2-oxazolidone was obtained in 70-78% yield.

The formation of the 2-oxazolidone XVI is plausible in view of the fact that 2-oxazolidones are also produced by the Curtius degradation of β -hydroxy acid azides.^{49,50} The Curtius degradation also involves the formation of an isocyanate intermediate.⁵¹

Results obtained from the Hofmann reaction of the hydroxy amide XIII -dihydropyran adduct were inconclusive. An oil was obtained, which was abandoned.

Nitrosation of the 2-oxazolidone XVI with sodium nitrite in acetic acid and acetic anhydride yielded the greenish-yellow N-nitroso oxazolidone XVII, which

XVII

decomposed at 188-194°; infrared spectrum (Fig. 14): 5.49 (C=O str.), 6.55 (N=O str.) and 7.18, 7.29 μ (C-H def. of gem-dimethyl group). The N-nitroso compound, obtained in 96% yield, was fairly sensitive to light but was stable in

the dark.

The N-nitroso compound was treated with sodium hydroxide at 0° , but no identifiable products were obtained. N-Nitroso alkyl urethanes have been found to decompose in base to the corresponding diazo alkanes.⁵²

D. Rearrangement of the 2-Oxazolidone XVI with Sulfuric Acid

The 2-oxazolidone ($C_{10}H_{14}NO_2Br$) was converted to a neutral $C_9H_{13}OBr$ compound in hot sulfuric acid solution. Hydrolysis of the 2-oxazolidone to the corresponding amino alcohol XIV had been expected. The product melted at $169.4-170.4^{\circ}$ and sublimed readily.

An absorption band at 5.70μ in the infrared spectrum of the compound (Fig. 15) indicated the presence of a five-membered ring ketone.³⁷ A doublet at 7.22 and 7.33μ due to a gem-dimethyl group was also present. The n.m.r. spectrum (Fig. 16) showed the bromine atom to be adjacent to a tertiary carbon atom because no proton resonance signals appeared beyond 2.7 p.p.m.⁵³ The methyl groups appeared as sharp three-proton singlets at δ 1.05 and 1.14.

Structure XVIII is proposed for the C_9 compound.

XVIII

A plausible mechanism would then involve 1)protonation of the carbonyl oxygen atom, 2)formation of a secondary carbonium ion, 3)rearrangement of the carbonium ion to an imine and 4)hydrolysis of the imine to the corresponding ketone.

Other attempts were made to hydrolyze the 2-oxazolidone XVI to the amino alcohol XIV. The 2-

XVI

XIV

oxazolidone was recovered unchanged in hot concentrated hydrochloric acid. Treatment of the 2-oxazolidone with 20% sodium hydroxide at reflux temperature yielded a small amount of an acid, m.p. 93-96°. The acid was not characterized. Further investigation of the reactions of the 2-oxazolidone is being continued in this laboratory.

IV. CONCLUSIONS AND SUMMARY

Four interesting molecular rearrangements were found to occur during the course of this research. The most significant of the four was the nitrous acid deamination (semipinacolic rearrangement) of the bridgehead amino alcohol IV,

The ring-contracted product, 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (VII), was formed in good yield (based on the semicarbazone). The product of a 1,2-hydride shift to the C₁ bridgehead atom was not detected although the resulting ketone would have been less strained than the ring-contracted product. The deamination reaction thus provides another synthetic route to the bicyclo[2.1.1]hexane system. The reaction may have general applicability in the synthesis of other highly strained cyclic systems.

Baeyer-Villiger rearrangement of the nitro ketone III

with peracetic acid yielded the lactone V.

Another rearrangement which was observed was the Hofmann rearrangement of the hydroxy amide XIII with sodium hypobromite. The 2-oxazolidone XVI was formed as a result of an intramolecular cyclization of the isocyanate intermediate.

A novel rearrangement occurred when the 2-oxazolidone XVI was treated with hot sulfuric acid solution. Structure XVIII is proposed for the product of the

rearrangement. The reaction provides a method for the removal of nitrogen at a bridgehead position.

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