[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Reactions of 1-Bromobicyclo[3.3.1]nonan-9-one

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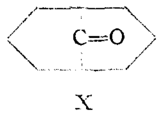
Some improvements in the recently reported synthesis of 1-bromobicyclo[3.3.1]nonan-9-one (I) have been made, and additional evidence has been obtained supporting the structures assigned to I and intermediates in its preparation. The structure of the product formed from I and sodium or sodamide in liquid ammonia has been proved to be bicyclo[3.3.0]-octane-1-carboxylic acid amide (IV), formed in a reaction analogous to the Favorskii rearrangement.

The bromoketone I precipitated silver bromide immediately on treatment with silver nitrate in ethanol, and formed a mixture of bicyclo[3.3.0]octane-1-carboxylic acid (V) and the corresponding ethyl ester (VI). The same rearrangement occurred when I was treated with mercuric acetate in ethanol. These reactions appear to be analogous to the Favorskii reaction of α-bromoketones with bases; I and potassium hydroxide in ether also formed the acid V under the usual conditions of the Favorskii rearrangement. Investigation of α-bromoisobutyrophenone as a model compound showed that it reacted with silver nitrate in aqueous ethanol, although heating was required, forming silver bromide and α,α,α-dimethylphenylacetic acid. These reactions are interpreted as being similar in mechanism to the pinacol rearrangement.

The synthesis of 1-bromobicyclo[3.3.1]nonan-9-one (I) was described recently,[2] and it was reported that I reacted with sodium or sodamide in liquid ammonia forming a compound $C_9H_{15}NO$ for which structure IV was proposed. The bromoketone also was reported to react immediately with silver nitrate in aqueous ethanol, precipitating silver bromide, but the nature of the organic product was not investigated. This paper describes some improvements in the synthesis of the bromoketone I, additional evidence supporting the structures assigned to I and intermediates in its preparation, proof of the structure of IV, and an investigation of the reaction of I with silver nitrate and certain other reagents.

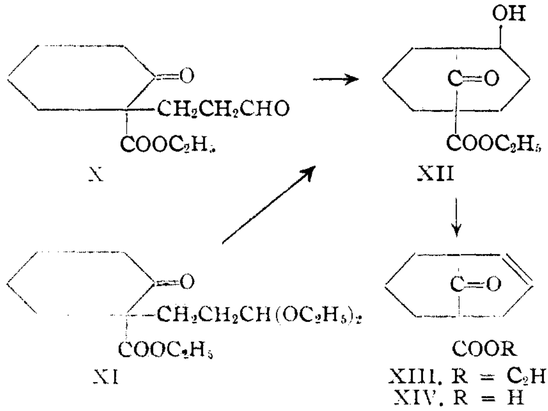


I, X = Br
II, X = COOH
III, X = $COOC_2H_5$

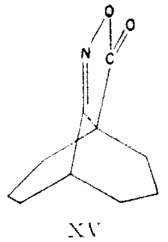
IV, X = $CONH_2$
V, X = COOH
VI, X = $COOC_2H_5$
VII, X = H
VIII, X = NO_2
IX, X = NH_2

One of the intermediates in the synthesis of I is β-(1-carbethoxy-2-ketocyclohexyl)-propionaldehyde (X), which on treatment with cold concentrated sulfuric acid forms 1-carbethoxybicyclo-[3.3.1]non-3-en-9-one (XIII).[2] Both X and its diethyl acetal XI on treatment with hydrochloric acid in aqueous acetic acid gave what appeared to be identical products which were assigned the cyclic aldol structure XII. Evidence for this structure now has been obtained by isolation of XII from both of these sources and determination of the infrared spectra of the two samples (Fig. 1). The spectra were identical within experimental error and contained a moderately strong band at 2.8μ indicating the presence of a hydroxyl group.

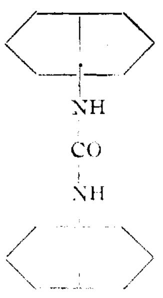
The synthesis leading to I was improved by reducing the unsaturated ester XIII to the saturated ester III in 94% yield in the presence of a palladium-on-barium sulfate catalyst. The ester III was hydrolyzed to the acid II in 89% yield. (The final step in the synthesis of I is the reaction of the silver salt of II with bromine.) The oximes of the acids XIV and II were prepared, and like many of the pairs of saturated and unsaturated compounds with this ring system prepared in the earlier work,[2] appeared to be isomorphous, since both had the same melting point and a mixed melting point was not depressed. Treatment of the oxime of II with *p*-toluenesulfonyl chloride in an attempt to prepare a lactam by a Beckmann rearrangement caused the loss of water instead and the formation of an isoxazolone (XV). Evidence for this structure was obtained from its infrared spectrum (Fig. 1), for no band was present in the region 2.0–3.1μ, indicating the absence of a hydroxyl group. Other bands in the spectrum of XV which are in accord with the isoxazolone structure are the carbonyl band at 5.59μ and a band at 6.08μ in the region in which carbon–nitrogen double bonds cause absorption. Formation of an isoxazolone structure from the oxime of II provides supporting evidence for the β-ketoacid structure assigned to that compound.



XIII, R = C_2H_5
XIV, R = H



XV



XVI

The structure of the neutral compound $C_{19}H_{15}NO$ formed from the bromoketone I by reaction with sodium or sodamide in liquid ammonia was estab-

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[1] U. S. Rubber Co. Fellow, 1949–50.

[2] A. C. Cope and M. E. Synerholm, THIS JOURNAL, **72**, 5228 (1950).

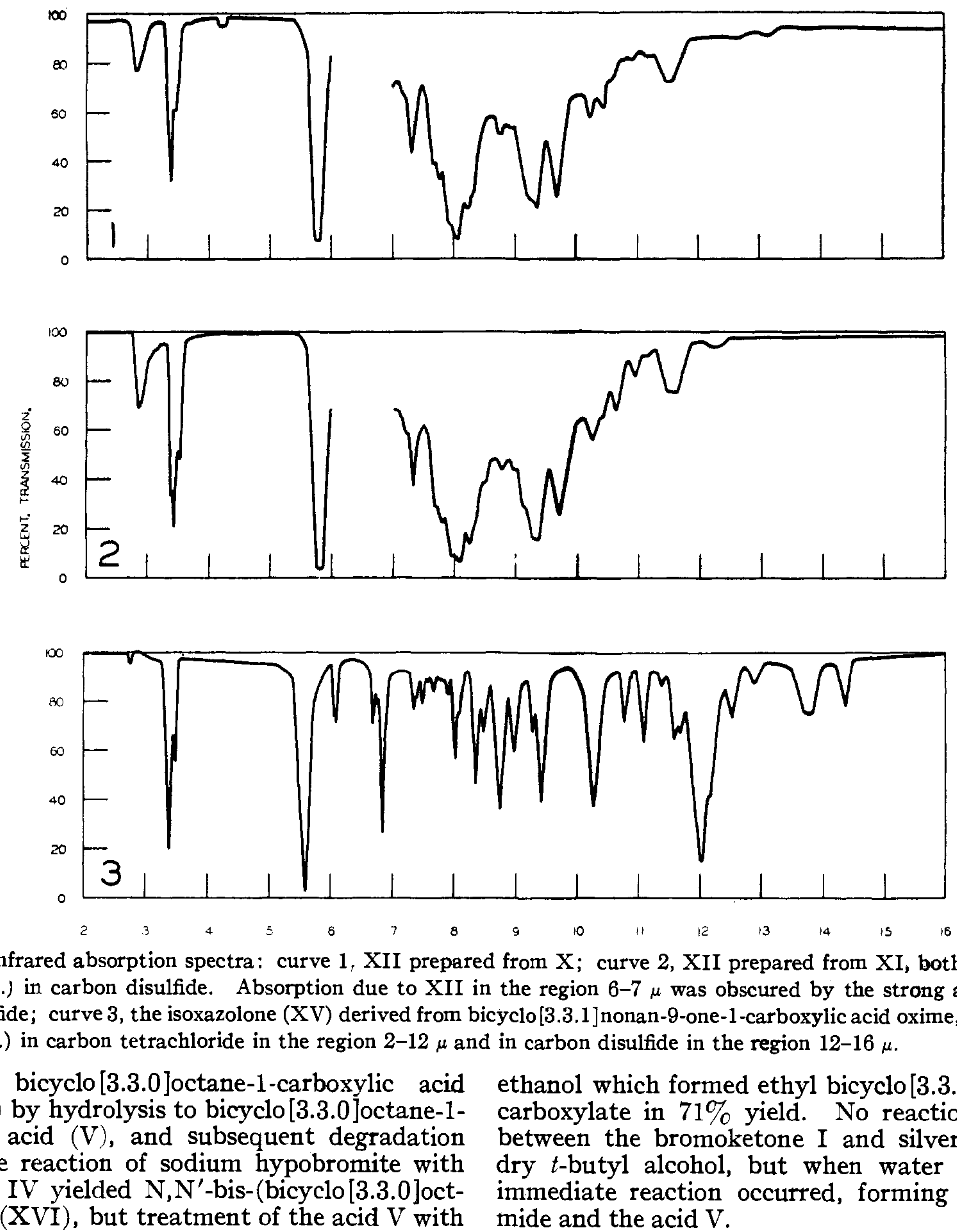

Fig. 1.—Infrared absorption spectra: curve 1, XII prepared from X; curve 2, XII prepared from XI, both as solutions (100 mg./ml.) in carbon disulfide. Absorption due to XII in the region 6–7 μ was obscured by the strong absorption of carbon disulfide; curve 3, the isoxazolone (XV) derived from bicyclo[3.3.1]nonan-9-one-1-carboxylic acid oxime, as a solution (100 mg./ml.) in carbon tetrachloride in the region 2–12 μ and in carbon disulfide in the region 12–16 μ.

lished as bicyclo[3.3.0]octane-1-carboxylic acid amide (IV) by hydrolysis to bicyclo[3.3.0]octane-1-carboxylic acid (V), and subsequent degradation of V. The reaction of sodium hypobromite with the amide IV yielded N,N′-bis-(bicyclo[3.3.0]oct-1-yl)-urea (XVI), but treatment of the acid V with hydrazoic acid formed 1-aminobicyclo[3.3.0]octane (IX), which was characterized as the picrate. An authentic sample of IX was prepared by the reduction of 1-nitrobicyclo[3.3.0]octane (VIII), which was obtained by nitration of *cis*-bicyclo[3.3.0]-octane.[3] Picrates of IX prepared by the two routes had the same melting point and mixed melting point.

It was of interest to determine the nature of the organic product formed in the very rapid reaction of the bromoketone I with silver nitrate. Not only are bromine atoms situated at bridgehead positions usually inert (see references cited in ref. 2); even the simple α-bromoketone, ω-bromoacetophenone, fails to react with alcoholic silver nitrate at room temperature. The organic product obtained from I and silver nitrate in ethanol proved to be a mixture of the acid V and its ethyl ester, VI. A rapid reaction also occurred between the bromoketone I and mercuric acetate in absolute ethanol which formed ethyl bicyclo[3.3.0]octane-1-carboxylate in 71% yield. No reaction occurred between the bromoketone I and silver nitrate in dry *t*-butyl alcohol, but when water was added immediate reaction occurred, forming silver bromide and the acid V.

The rearrangement of the carbon skeleton of the bromoketone I in its transformation to the acid V or ester VI by reaction with silver nitrate or mercuric acetate is analogous to the rearrangement which occurs in the Favorskii reaction of α-bromoketones with basic reagents. The bromoketone I was treated with dry potassium hydroxide in ether, and under these conditions commonly used for the Favorskii reaction was partially transformed to the acid V. The ability of silver nitrate and mercuric acetate to catalyze the rearrangement of I to V or VI can be interpreted in terms of a "push-pull" mechanism for the transformation, suggested by the work of Swain[4] concerning the termolecular kinetics of S_N1 and S_N2 displacements. According to this interpretation, ethanol or water first adds to the carbonyl group of I, and a shift of electrons forming the carbonyl group and establishing the C_5–C_1 bond supply the "push." The electron pair

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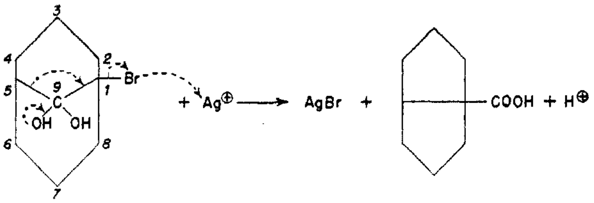
(3) A. C. Cope and W. R. Schmitz, THIS JOURNAL, 72, 3056 (1950).

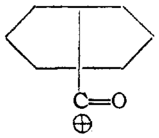
(4) C. G. Swain, *ibid.*, 70, 1119 (1948); C. G. Swain and R. W. Eddy, *ibid.*, 70, 2989 (1948).

of the C_5–C_9 bond is in a sterically favorable position to attack the C_1 carbon atom from the back side as the bromine is displaced, aided by a "pull" by the silver or mercuric ion.

Such a process is similar to the commonly accepted mechanism of the pinacol rearrangement. The formation of an intermediate cyclopropanone in the rearrangement of I by establishment of a bond between C_5 and C_1 with the elimination of hydrogen bromide, postulated for certain Favorskii rearrangements,[5] is unlikely. Formation of such an intermediate would require loss of a proton from C_5 to produce an anion that would not be stabilized by resonance, for the C_5–C_9 bond could not have partial double bond character without violating Bredt's rule.[6]



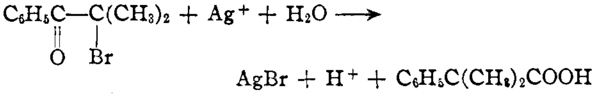
The reaction of I with sodamide leading to IV can be represented in a similar manner. The failure of I to react with silver nitrate in dry *t*-butyl alcohol could be attributed to steric hindrance interfering with the addition of *t*-butyl alcohol to the carbonyl group, to the insolubility of silver nitrate in *t*-butyl alcohol, or to the non-polar character of *t*-butyl alcohol as a reaction medium. The reaction in *t*-butyl alcohol was conducted as a test for the carbonium ion XVII, which would be expected to react with *t*-butyl alcohol forming the *t*-butyl ester of the acid V if it were formed as an intermediate.



XVII

In contrast to its reactivity with silver nitrate, the bromoketone I failed to react appreciably with sodium iodide in acetone, as would be expected from the location of the bromine at a bridgehead position. The bromoketone I also failed to react with bromine in acetic acid, presumably because enolization of the ketone would require the formation of a double bond at a bridgehead position, which is not possible for steric reasons (Bredt's rule).

In order to determine whether the ability of silver nitrate to induce a rearrangement of the carbon skeleton of an α-bromoketone like that occurring in I was unique for that case or more general in character, α-bromoisobutyrophenone was treated with silver nitrate in aqueous ethanol. Silver bromide was precipitated when the mixture was heated, and the rearrangement product, α,α,α-dimethylphenylacetic acid, was isolated in 40% yield.



$$\underset{\substack{\|\\ O}}{C_6H_5C}—\underset{\substack{|\\ Br}}{C}(CH_3)_2 + Ag^+ + H_2O \longrightarrow AgBr + H^+ + C_6H_5C(CH_3)_2COOH$$

The reaction of α-bromoisobutyrophenone with potassium hydroxide also was investigated, and found to result in displacement of the bromine by hydroxyl and the formation of α-hydroxyisobutyrophenone rather than a rearrangement product. The reaction of other α-halogen substituted ketones with silver nitrate, mercuric acetate and other heavy metal salts is being investigated.

Experimental[7]

1-Carbethoxy-4-hydroxybicyclo[3.3.1]nonan-9-one (XII) was prepared from β-(1-carbethoxy-2-ketocyclohexyl)-propionaldehyde (X) by the procedure previously described[2] and distilled in a molecular-type still at 0.14 mm. with a heating bath temperature of 112°. A fraction with $n^{25}\text{D}$ 1.4921 was analyzed and its infrared spectrum was determined (Fig. 1).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 64.25; H, 7.86.

Another sample of XII was prepared from β-(1-carbethoxy-2-ketocyclohexyl)-propionaldehyde diethyl acetal (XI) by the procedure previously described.[2] The infrared spectra of the samples of XII prepared by the two routes were identical within experimental error (Fig. 1).

1-Carbethoxybicyclo[3.3.1]nonan-9-one (III).—A solution of 5.0 g. of 1-carbethoxybicyclo[3.3.1]non-3-en-9-one (XIII)[2] in 130 ml. of 95% ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 2.5 g. of 5% palladium-on-barium sulfate catalyst.[8] The reduction stopped after 8 hours and absorption of 99% of one molar equivalent of hydrogen. The oil remaining after separation of the catalyst and concentration of the filtrate was purified by a short-path distillation at 0.3 mm. with a heating block temperature of 130°, and yielded 4.70 g. (94%) of III, m.p. 37–39°. Another sample of the ester III was prepared from 0.9 g. of bicyclo[3.3.1]nonan-9-one-1-carboxylic acid (II), which was dissolved in 20 ml. of methanol, neutralized with potassium hydroxide, and converted to the silver salt by addition of a solution of 1.03 g. of silver nitrate in 5 ml. of water. The silver salt was washed with a little water, dried at 70°, and heated with 15 ml. of ethyl iodide under reflux on a steam-bath for 2 hours. After separation of the silver iodide and concentration, the residue was distilled in a short-path still at 0.3 mm. with a heating block temperature of 100°. The yield of III was 0.96 g. (77%), m.p. 37.5–39°. An analytical sample which was distilled through a semi-micro column[9] had b.p. 98–100° (0.55 mm.), m.p. 38–39.5°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.77.

A mixed melting point of III with the unsaturated ester, 1-carbethoxybicyclo[3.3.1]non-3-en-9-one (XIII) (m.p. 48–50°), was depressed to 33.5–38°.

Bicyclo[3.3.1]nonan-9-one-1-carboxylic Acid (II).—A solution of 50 g. of 1-carbethoxybicyclo[3.3.1]non-3-en-9-one (XIII)[2] in 550 ml. of 95% ethanol was shaken with hydrogen at room temperature and 28–12 p.s.i. in the presence of 5.0 g. of 5% palladium-on-barium sulfate catalyst.[8] The reduction stopped after 8 hours and the absorption of 96% of one molar equivalent of hydrogen. The catalyst was separated by filtration, and the filtrate was concentrated under reduced pressure. A solution of 20 g. of sodium hydroxide in 150 ml. of water was added to the residue,

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[5] R. B. Loftfield, THIS JOURNAL, **72**, 632 (1950); **73**, 4707 (1951).

[6] See P. D. Bartlett and G. F. Woods, *ibid.*, **62**, 2935 (1940), for a similar case in which enolization of hydrogen at a bridgehead of bicyclo[2.2.2]octane-2,6-dione is inhibited.

[7] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates for analyses and for the infrared spectra, which were determined with a Baird Double Beam Infrared Recording Spectrometer, Model B, fitted with a sodium chloride prism.

[8] *Org. Syntheses*, **26**, 77 (1946).

[9] C. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

and the mixture was heated under reflux until the ester layer disappeared and a solution was formed (3 hours). The solution was cooled, treated with Norit, filtered, and acidified with concentrated hydrochloric acid. The acid II separated as white crystals in a yield of 35.5 g. (82% from XIII), m.p. 135–136.5°. The acid II also was prepared in 89% yield by saponification of the ester III by heating under reflux with an excess of 10% aqueous potassium hydroxide for 2 hours.

Bicyclo[3.3.1]nonan-9-one-1-carboxylic Acid Oxime.—The acid II (0.9 g.) and 1.0 g. of hydroxylamine hydrochloride were dissolved in 20 ml. of 95% ethanol. Potassium hydroxide (4.0 g.) was added, followed by enough water to give a clear solution, which was heated under reflux for 2 hours. The mixture was cooled, poured into 50 ml. of cold water, and acidified with concentrated hydrochloric acid. Glistening white plates of the oxime precipitated and were collected on a filter; the yield was 0.80 g. (83%), m.p. 169–170° (dec.). An analytical sample melting at 169.2–169.9° (dec., sample inserted at 160° and the temperature raised 1° per minute) was prepared by recrystallization from 50% ethanol.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.78; H, 7.76; N, 7.08.

Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic Acid Oxime.—By a procedure similar to the one described above 1.0 g. of the unsaturated acid XIV yielded 0.80 g. (85%) of the oxime. An analytical sample melting at 169.5–170.2° (dec., sample inserted at 160° and the temperature raised 1° per minute) was prepared by recrystallization from 50% ethanol. This oxime appeared to be isomorphous with the corresponding saturated oxime described above, for a mixture of the two melted at 168.4–168.8° (dec.).

Anal. Calcd. for $C_{10}H_{12}NO_3$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.83; H, 6.83; N, 6.94.

Isoxazolone (XV) Derived from Bicyclo[3.3.1]nonan-9-one-1-carboxylic Acid Oxime.—A solution of 1.0 g. of bicyclo[3.3.1]nonan-9-one-1-carboxylic acid oxime in 10 ml. of dry pyridine was treated with 1.0 g. of *p*-toluenesulfonyl chloride, added in one portion. The mixture was allowed to stand at room temperature overnight, and then was poured into 10 ml. of concentrated hydrochloric acid with cooling. The mixture was cooled to 0° and the white crystals of XV which formed were collected on a filter and washed with water; yield 0.65 g. (63%), m.p. 103–106°. Sublimation at 0.3 mm. with a heating block temperature of 110° yielded XV as shining white crystals melting at 104–105°. Recrystallization from water did not change the melting point.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 66.99; H, 7.31; N, 7.82. Found: C, 67.02; H, 7.24; N, 7.68.

Structure of Bicyclo[3.3.0]octane-1-carboxylic Acid Amide (IV) (a) Hydrolysis.—A mixture of 0.35 g. of the amide IV (prepared from the bromoketone I and sodamide in liquid ammonia[2]) and 20 ml. of 10% potassium hydroxide was heated under reflux for 4 hours, at which time the evolution of ammonia had ceased and the amide had dissolved. The solution was cooled and acidified with concentrated hydrochloric acid. The white, crystalline acid which separated was collected on a filter and purified by a short-path distillation at 0.15 mm. with a heating block temperature of 90°. The colorless liquid distillate crystallized and amounted to 0.30 g. (86%) of bicyclo[3.3.0]octane-1-carboxylic acid (V), m.p. 46–47°, which gave a negative unsaturation test with bromine in carbon tetrachloride.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.23; H, 9.12.

(b) **Reaction with Sodium Hypobromite.**—To a solution of sodium hypobromite prepared from 2.0 g. of bromine and 2.0 g. of sodium hydroxide in 20 ml. of water at 0° was added bicyclo[3.3.0]octane-1-carboxylic acid amide (IV) (1.82 g.), and the suspension was stirred at −3 to −5° for 80 minutes. Not all of the solid dissolved, and the mixture was heated at 80° with stirring for 1 hour and allowed to stand overnight at room temperature. The mixture was saturated with sodium chloride, and extracted with five 50-ml. portions of ether. The combined extracts were dried over magnesium sulfate, concentrated, and the crystalline residue was sublimed at 0.3 mm. with a heating block temperature of 130° for 1 hour. The small amount of sublimate, m.p. 111–180°, was recrystallized repeatedly from methylcyclohexane and resublimed; 20 mg. of an unidentified, white, crystalline compound that did not contain nitrogen was obtained, m.p. 206–208°. The major portion of the product was sublimed by raising the heating block temperature to 220°. N,N′-Bis-(bicyclo[3.3.0]oct-1-yl)-urea (XVI) was collected in a yield of 0.58 g. (32%), m.p. 272°. Two recrystallizations from 95% ethanol gave pure XVI melting at 277–277.5°.

Anal. Calcd. for $C_{17}H_{28}N_2O$: C, 73.86; H, 10.21; N, 10.14. Found: C, 74.10; H, 10.37; N, 10.07.

(c) **Conversion of Bicyclo[3.3.0]octane-1-carboxylic Acid (V) to 1-Aminobicyclo[3.3.0]octane (IX).**—Concentrated sulfuric acid (1.5 ml.) was added to a solution of 0.7 g. of the acid V in 5 ml. of benzene, and 0.4 g. of sodium azide was added slowly during a period of 20 minutes, with stirring and cooling so that the temperature remained at 15–20°. The mixture was allowed to stand at room temperature overnight and then 15 ml. of water was added, followed by an excess of sodium hydroxide (with cooling). The amine IX was extracted with four 20-ml. portions of ether, and the extracts were dried over magnesium sulfate and concentrated (carefully to avoid distillation of IX with the ether). A saturated solution of picric acid in ether was added to the residue until no more precipitate was formed. Three crystallizations from water yielded the picrate of IX as flat yellow needles, m.p. and mixed m.p. with an authentic sample described below, 212–213.8°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.52; H, 5.17; N, 16.01.

1-Nitrobicyclo[3.3.0]octane (VIII) was prepared from 2.37 g. of *cis*-bicyclo[3.3.0]octane (VII)[8] and a solution of 3.3 ml. of concentrated nitric acid (sp. gr. 1.42) in 6.7 ml. of water, which were heated in a sealed tube at 120° for 6 hours. The mixture was allowed to cool to room temperature overnight. The tube was opened, and the mixture was diluted with 100 ml. of water and extracted with 25 ml. of ether. The ether extract was washed with three 40-ml. portions of 20% sodium hydroxide to remove any secondary nitro compounds, and the basic washings were added to the original nitric acid solution. The resulting basic solution was extracted with 25 ml. of ether and the combined ethereal extracts were washed with two 30-ml. portions of water and dried over magnesium sulfate. The ether was distilled and the residue was fractionated twice through a semi-micro column. The fractionation separated 0.9 g. (38%) of recovered *cis*-bicyclo[3.3.0]octane, b.p. 61–63° (59 mm.), and 0.593 g. (18%) of 1-nitrobicyclo[3.3.0]octane (VIII), b.p. 78.5–79° (3.35 mm.), $n^{25}\text{D}$ 1.4807.

Anal. Calcd. for $C_8H_{18}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.89; H, 8.64; N, 8.92.

1-Aminobicyclo[3.3.0]octane (IX) was prepared by the hydrogenation of a solution of 154 mg. of 1-nitrobicyclo-[3.3.0]octane in 5 ml. of methanol in the presence of 0.3 g. of W-7 Raney nickel catalyst.[10] The reduction stopped after 50 minutes and the absorption of 93% of three molar equivalents of hydrogen. The catalyst was separated by filtering and centrifuging, and 0.19 g. of picric acid was added to the clear methanol solution. The picrate of IX was isolated by evaporating the methanol and recrystallizing the residue from water. Several crystallizations yielded the pure picrate as flat yellow needles, m.p. 211.8–213.6°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.40; H, 5.18; N, 15.75.

Reactions of 1-Bromobicyclo[3.3.1]nonan-9-one (I).—The bromoketone I was prepared by the method previously described from bromine and the silver salt of bicyclo[3.3.1]-nonan-9-one-1-carboxylic acid[2]; m.p. 59–60°. It failed to react with the following reagents: (1) bromine in acetic acid; (2) liquid ammonia at the boiling point (2 hours, 92% recovery of I); (3) piperidine in ether under reflux (2 hours 93% recovery of I); (4) sodium iodide in acetone under reflux (14 days, 50% recovery of I and 10% of sodium bromide).

(a) **Reaction of I with Silver Nitrate in Ethanol.**—A solution of 7.83 g. of silver nitrate in 180 ml. of 50% ethanol was added to a solution of 10.0 g. of I in 120 ml. of 95% ethanol. Silver bromide precipitated immediately. The mixture was allowed to stand for 5 minutes and then was filtered to separate silver bromide, which after drying weighed 7.88 g. (92 %). Most of the solvent was distilled from the filtrate

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(10) *Org. Syntheses*, **29**, 28 (1949).

under reduced pressure, leaving an oil suspended in water. The mixture was extracted with six 25-ml. portions of ether and the combined extracts were dried over magnesium sulfate, concentrated, and the residue was fractionated twice through a semi-micro column.[9] The fractionation separated 0.90 g. (11%) of ethyl bicyclo[3.3.0]octane-1-carboxylate (VI), b.p. 30° (0.40 mm.), identical with a sample of VI described under (b) below, and 4.31 g. (61%) of bicyclo-[3.3.0]octane-1-carboxylic acid (V), b.p. 90–95° (0.35 mm.), m.p. 43–45°, which did not depress the melting point of a sample of V prepared by hydrolysis of the amide.

Repetition of the reaction of I with silver nitrate in absolute ethanol yielded 41% of the ester VI and 39% of the acid V.

(b) **Reaction of I with Mercuric Acetate in Ethanol.**—A solution of 1.5 g. of mercuric acetate and 2.0 g. of the bromoketone I in 35 ml. of absolute ethanol (dried with sodium and diethyl phthalate) was heated under reflux protected from atmospheric moisture for 4 hours. The solution was cooled, poured into 150 ml. of water, and extracted with three 50-ml. portions of ether. The ether extracts were combined, washed with sodium bicarbonate solution and water, and dried over magnesium sulfate. No acid separated when the basic extracts were acidified. The ether solution was concentrated and the residue was purified by a short-path distillation at 0.3 mm. with a heating block temperature of 100°, followed by fractionation through a semi-micro column. The yield of ethyl bicyclo[3.3.0]octane-1-carboxylate (VI), b.p. 76–79° (4.8 mm.), was 1.19 g. (71%). A redistilled analytical sample had b.p. 79° (4.8 mm.), $n^{25}\text{D}$ 1.4571.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; sapn. equiv., 182.2. Found: C, 72.45; H, 10.07; sapn. equiv., 179.4.

Saponification of the ester VI with an excess of 0.5 *N* sodium hydroxide by heating under reflux for 24 hours yielded 86% of bicyclo[3.3.0]octane-1-carboxylic acid (V), m.p. and mixed m.p. with a sample obtained by hydrolysis of the amide IV, 43–44.5°.

(c) **Reaction of I with Silver Nitrate in *t*-Butyl Alcohol.**—Powdered silver nitrate (2.4 g.) was added to a solution of 3.0 g. of the bromoketone I in 35 ml. of dry *t*-butyl alcohol. The mixture was heated under reflux for 4.5 hours, during which time the insoluble silver nitrate became more bulky, but there was no evidence of silver bromide formation. The mixture was cooled and filtered and the solid on the filter was washed with a little water. Part of the solid dissolved and the remainder turned yellow, and a yellow precipitate of silver bromide formed as soon as the aqueous filtrate entered the *t*-butyl alcohol solution. The silver bromide precipitates were combined, washed with water and ether and then dried; they weighed 2.34 g. (91%). The filtrate was diluted with 125 ml. of water and the product was isolated by extraction with ether and distillation. A yield of 1.50 g. (71%) of bicyclo[3.3.0]octane-1-carboxylic acid (V) was obtained, identified by its melting point and infrared spectrum.

The treatment of I with silver nitrate in dry *t*-butyl alcohol by the procedure described above was repeated, except that water was not added after the period of reflux. Instead the *t*-butyl alcohol was distilled under reduced pressure and the organic portion of the residue was separated from the silver nitrate by sublimation at 0.5 mm. with a heating block temperature of 130°. The product was purified by resublimation, which yielded 0.23 g. (46%) of crude recovered I, m.p. 48–58°, which after recrystallization from petroleum ether melted at 55–58° and did not depress the melting point of a known sample.

(d) **Reaction of I with Mercuric Acetate in *t*-Butyl Alcohol.**—Mercuric acetate (1.5 g.) and 2.0 g. of the bromoketone I were added to 35 ml. of dry *t*-butyl alcohol. The mixture was heated at the reflux temperature (at which it formed a homogeneous solution) for 6 hours. A few milligrams of a solid which separated was removed, and the filtrate was poured into water and extracted with five 40-ml. portions of ether. The combined extracts were washed with saturated sodium carbonate solution and with water, and the alkaline extracts were acidified with concentrated hydrochloric acid and extracted with three 50-ml. portions of ether. The extracts of the acid solution were dried over magnesium sulfate and concentrated. A short-path distillation of the residue at 0.3 mm. with a heating block temperature of 120° yielded 1.05 g. (74%) of bicyclo[3.3.0]-octane-1-carboxylic acid (V), m.p. 40–43°.

(e) **Reaction of I with Potassium Hydroxide.**—Dry, powdered potassium hydroxide (0.27 g.) was added to a solution of 0.5 g. of I in 15 ml. of dry ether, and the mixture was heated under reflux protected from atmospheric moisture for 2.5 hours. Water was added, the layers were separated, and the aqueous layer was extracted with two 20-ml. portions of ether. The combined ether solutions were washed with water, dried over magnesium sulfate, and concentrated. Sublimation of the residue at 0.3 mm. with a heating block temperature of 110° yielded 0.32 g. (64%) of recovered I, m.p. 56–59°. The alkaline aqueous solution was acidified with concentrated hydrochloric acid and extracted with three 20-ml. portions of ether. The combined extracts were dried over magnesium sulfate, concentrated, and sublimed at 0.3 mm. with a heating block temperature of 100°, yielding 0.12 g. (34%) of bicyclo[3.3.0]octane-1-carboxylic acid (V), m.p. and mixed m.p. with an authentic sample, 41.5–44°.

Reaction of α-Bromoisobutyrophenone with Silver Nitrate.—α-Bromoisobutyrophenone[11] (2.41 g.) and silver nitrate (1.83 g.) in 25 ml. of ethanol and 10 ml. of water gave a solution which became faintly opalescent at room temperature, and formed a heavy precipitate of silver bromide within 15 minutes when heated on a steam-bath. The period of heating was continued for 30 minutes, and the mixture was filtered. The silver bromide was washed with a little ethanol and dried; it amounted to 1.92 g. (96%). The filtrate was poured into 150 ml. of water and the solution was extracted with four 40-ml. portions of ether. The extracts were washed with saturated sodium carbonate solution and water, dried over magnesium sulfate, and concentrated. Distillation of the residue gave 0.76 g. of an impure liquid, b.p. 55–84° (1.5 mm.), $n^{25}\text{D}$ 1.5109–1.5196, which on hydrolysis gave α,α,α-dimethylphenylacetic acid in 18% yield and was not further investigated. The sodium carbonate solution containing the acidic product of the reaction was acidified with concentrated hydrochloric acid and extracted with four 25-ml. portions of ether. Distillation of the ether left a yellow residue which crystallized. Sublimation at 0.2 mm. with a heating block temperature of 100° yielded 0.69 g. (40%) of white crystals of α,α,α-dimethylphenylacetic acid, m.p. and mixed m.p. with a known sample,[12] 77–78.5°.

Reaction of α-Bromoisobutyrophenone with Potassium Hydroxide.—Dry, powdered potassium hydroxide (0.5 g.) was added to a solution of 1.0 g. of α-bromoisobutyrophenone in 20 ml. of dry ether. A reaction occurred at once which caused the solution to turn yellow and a white precipitate to form. After heating under reflux protected from atmospheric moisture for 1 hour, the mixture was cooled, poured into 25 ml. of water, and the ether layer was separated. The alkaline aqueous layer was extracted with two 20-ml. portions of ether and the combined ether solutions were dried over magnesium sulfate. Acidification of the alkaline solution and extraction with ether failed to yield any acidic product. Concentration of the ether solution containing the neutral product left a residue which was purified by a short-path distillation at 0.3 mm. with a heating block temperature of 110°. The colorless liquid distillate contained 20 mg. of a solid, m.p. 181–184°, which was not investigated. Fractionation of the liquid through a semi-micro column yielded 0.41 g. (57%) of α-hydroxyisobutyrophenone, b.p. 101–106° (6 mm.), $n^{25}\text{D}$ 1.5282, which was identified by analysis and preparation of the semicarbazone.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.21; H, 7.55.

The semicarbazone, after recrystallization from 40% ethanol, melted at 187–188.2° (lit.[13] 184–185°).

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[11] A. Collet, *Bull. soc. chim. France*, [3] **17**, 78 (1897); b.p. 66° (0.40 mm.), $n^{25}\text{D}$ 1.5541.

[12] Prepared by the method of A. Haller and E. Bauer, *Ann. Chim.*, [9] **9**, 10 (1918).

[13] E. Blaize and E. Herzog, *Compt. rend.*, **184**, 1333 (1927).