boric acid and 1.4 g. of alloxan in 20 ml. of glacial acetic acid. The flavin synthesis began immediately and the mixture was shaken at 40–50° for thirty minutes. The product was allowed to stand at room temperature for forty-eight hours and then evaporated to dryness as above. The crude product was suspended in 250 ml. of 5% acetic acid, heated to boiling and filtered. On cooling, 0.82 g. of fine orange needles are deposited which is 33% of the theoretical amount. The flavin melts with decomposition at 255–256°, darkening at 245°. The product was recrystallized from water for analytical purposes. The purified material resembles riboflavin in crystalline form but the color is yellow-orange.

*Anal.* Calcd. for $C_{19}H_{24}N_4O_6$: C, 56.34; H, 5.98; N, 13.85. Found: C, 55.9; H, 5.9; N, 14.0.

**Physical Data.**—The ultraviolet absorption spectra were measured on solutions containing 10.3 micrograms of riboflavin[25] and 11.1 micrograms of the diethyl analog per milliliter, or $2.74 \times 10^{-5}$ mole per liter made up in ordinary distilled water. The optical density was read directly from the spectrophotometer and plotted as extinction coefficients.

The rotation was determined on a solution containing the equivalent of 0.826 g. per 100 ml. in tenth normal sodium hydroxide and found to be $[\alpha]^{24}D$ −26.3°.

Fluorescence measurements were made at 4360 Å.[26] on solutions containing 0.0773 microgram of riboflavin and 0.0833 microgram of the diethyl analog per milliliter, or $2.055 \times 10^{-7}$ mole per liter.

**Biological Data.**—The biological activity of the diethyl analog was determined by the use of *Lactobacillus casei* 7469. Growth curves were compared to those obtained by the use of riboflavin at equimolecular levels. The curves for the diethyl analog and riboflavin were superimposable within the limits of error of the method, throughout the range from zero to $8.22 \times 10^{-10}$ mole per milliliter.

(25) U. S. P. Riboflavin which had been recrystallized from water was used.

(26) This filter is provided with the Model 12-A Coleman Electronic Photofluorometer for riboflavin determinations.

**Acknowledgment.**—I am happy to acknowledge the help given me by Drs. V. Boekelheide and D. S. Tarbell of the Department of Chemistry, by making available the high pressure hydrogenator and for their interest and discussion. I also want to thank Dr. K. Altman of the Atomic Energy Commission for permitting me to use the ultraviolet spectrophotometer and advising me in its use.

## Summary

1. The complete synthesis of 6,7-diethyl-9-(D-1′-ribityl)-isoalloxazine has been described.

2. The steps involved begin with *o*-diethylbenzene and proceed through 4-bromo-*o*-diethylbenzene, 3,4-diethylaniline, 3,4-diethylacetanilide, 4,5-diethyl-2-nitroacetanilide, 4,5-diethyl-2-nitroaniline, 4,5-diethyl-2-nitroaniline-N-D-ribopyranoside to 6,7-diethyl-9-(D-1′-ribityl)-isoalloxazine.

3. Comparisons are made to riboflavin with regard to rotation, fluorescence and ultraviolet spectra.

4. The new riboflavin analog, 6,7-diethyl-9-(D-1′-ribityl)-isoalloxazine has been found capable of serving as the sole source of flavin in the growth of *Lactobacillus casei*.

ROCHESTER, NEW YORK RECEIVED MAY 5, 1950

---

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

# Cyclic Polyolefins. XI. Carbonyl-bridged Compounds Derived from the Adduct of α-Carbethoxycyclohexanone and Acrolein

BY ARTHUR C. COPE AND MARTIN E. SYNERHOLM

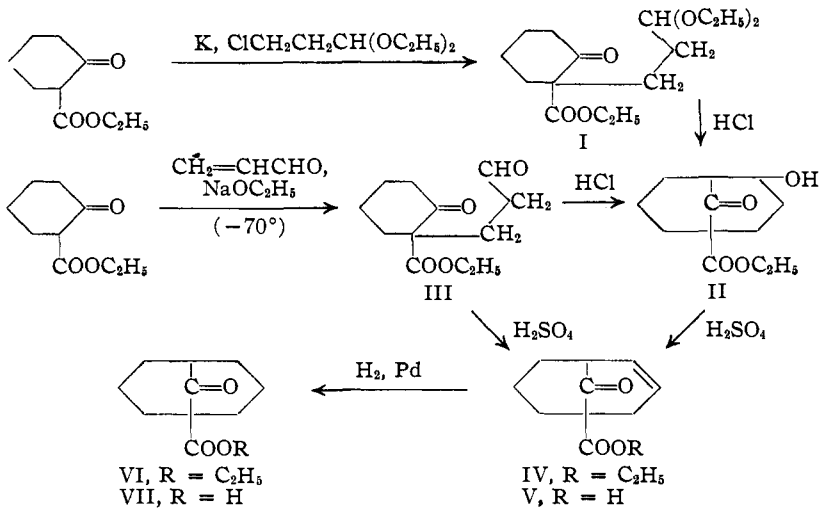
The success of syntheses of phenyl-substituted cyclooctadienes from carbonyl-bridged intermediates[1,2] has led us to investigate similar methods for the preparation of eight-membered ring compounds substituted by carboxyl groups.

The first route which was found to yield an intermediate useful in the projected synthesis was alkylation of the potassium enolate of α-carbethoxycyclohexanone with β-chloropropionaldehyde diethyl acetal in hydrocarbon solvents. This reaction produced β-(1-carbethoxy-2-ketocyclohexyl)-propionaldehyde diethyl acetal (I) in 31% yield. Mild acid hydrolysis of I yielded a viscous liquid which proved to be isomeric with the expected aldehyde, but boiled higher than the acetal from which it was prepared. This product is believed to be the cyclic aldol, II, formed by intramolecular condensation of the aldehyde III. Evidence in favor of this interpretation was obtained by development of a direct synthesis of the aldehyde III by the Michael addition of α-carbethoxycyclohexanone to acrolein. This reaction yielded only polymeric products under usual conditions for the Michael reaction, but it was possible to isolate the aldehyde III in 65–70% yield when the addition was conducted at −70° in the presence of a small amount of sodium ethoxide in ethanol. The product obtained in this manner was fluid rather than viscous, and boiled lower than the diethyl acetal I. The structure of this product (the aldehyde III) was established by oxidation with silver oxide, which yielded β-(1-carbethoxy-2-ketocyclohexyl)-propionic acid, identified by comparison with an authentic sample. When the aldehyde III was treated with acids under conditions similar to those used for hydrolysis of the acetal I, a viscous liquid was formed which appeared to be identical with the cyclic aldol II prepared from the acetal. Both II and III yielded 1-carbethoxybicyclo[3.3.1]non-3-en-9-one (IV) on treatment with concentrated sulfuric acid. Less drastic

(1) Cope, Fawcett and Munn, THIS JOURNAL, **72**, 3399 (1950).

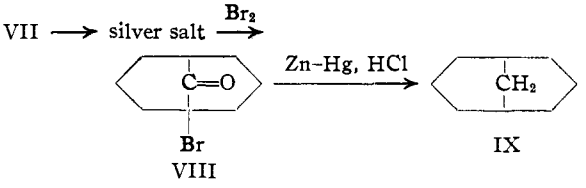
(2) Cope and Hermann, *ibid.*, **72**, 3405 (1950).

conditions were required to effect a similar condensation and dehydration in the series previously investigated,[1,2] in which the intermediate would be a more easily dehydrated tertiary alcohol compared to the secondary alcohol intermediate (II) in the present case.

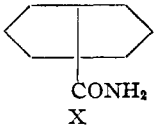



The unsaturated ketoester IV was purified by distillation and characterized by preparation of its 2,4-dinitrophenylhydrazone and semicarbazone, and by saponification to the corresponding ketoacid (V). When the acid V was the desired product, it could be obtained conveniently by saponification of the crude, undistilled ester IV as it was obtained from the cyclization. By this procedure, V was obtained from III in an over-all yield of 69%. The acid V was characterized by analysis, neutral equivalent, and preparation of the 2,4-dinitrophenylhydrazone and amide. The acid was not decarboxylated by heating alone or in the presence of quinoline and copper. Such stability of a β-ketoacid with the carboxyl group at a bridgehead position is a consequence of the steric factors summarized in Bredt's rule, and has been observed for other acids with structures of that kind.[3]

Hydrogenation of the acid V in the presence of a palladium catalyst resulted in the absorption of approximately 140% of one molar equivalent of hydrogen, caused by partial reduction of the ketone carbonyl group as well as the double bond. The saturated ketoacid VII was isolated in 50–60% yield after the crude reduction product was treated with potassium dichromate and sulfuric acid in aqueous acetic acid to oxidize the hydroxy acid present as an impurity to VII. The saturated acid VII appeared to be isomorphous with V, both melting at approximately the same temperature and giving no depression in mixed melting point. The same was true of the amides and the 2,4-dinitrophenylhydrazones of the two acids. The 2,4-dinitrophenylhydrazones of the corresponding esters IV and VI also had approximately the same melting points and a mixed melting point of the two was not depressed. Like the unsaturated acid V, the saturated acid VII could not be decarboxylated by heating. The acid VII was decarboxylated by conversion to the silver salt followed by treatment with bromine, which formed 1-bromobicyclo[3.3.1]nonan-9-one (VIII) in 74% yield. The bromoketone VIII was characterized by analysis and by preparation of the 2,4-dinitrophenylhydrazone derivative. Its carbon skeleton was established by reduction with amalgamated zinc and hydrochloric acid to the solid hydrocarbon, bicyclo[3.3.1]nonane (IX), which was proved by mixed m. p. and comparison of infrared spectra to be identical to a sample of IX prepared by reduction of bicyclo[3.3.1]nonan-2,6-dione.[4]




In an attempt to reduce VIII by treatment with sodium in liquid ammonia immediate reaction was observed. Instead of a reduction product a nitrogen-containing compound $C_9H_{15}NO$ was formed, which failed to yield a hydrochloride either in aqueous solution or in ether. The same compound was obtained by treating the bromoketone VIII with sodamide in liquid ammonia. It failed to react with semicarbazide or 2,4-dinitrophenylhydrazine under the usual conditions for the preparation of ketone derivatives, and formed ammonia on treatment with boiling sodium hydroxide. A possible structure for this compound is X, which would be the product of a Favorskii type of rearrangement of VIII. The structure of this compound is under investigation, as are other reactions of the bromo-




(3) Bredt, *J. prakt. Chem.*, **148**, 221 (1937). Prelog, Barman and Zimmermann, *Helv. Chim. Acta*, **32**, 1291 (1949), have observed that acids corresponding in structure to V and VII with a methyl substituent in the 4-position were not decarboxylated on heating with quinoline at 250°.

(4) Meerwein and Schürmann, *Ann.*, **398**, 225 (1913); Meerwein, Kiel and Klösgen, *J. prakt. Chem.*, **104**, 184 (1922).

ketone VIII. VIII reacts immediately with silver nitrate in aqueous ethanol, precipitating silver bromide, in contrast to other compounds containing a halogen located at a bridgehead position in which the halogen is inert. Examples of such inert halogen compounds are 1-chloroapocamphane,[5] the maleic anhydride adduct of 9-bromoanthracene[6] and 1-bromotriptycene.[7] The reactivity of the bromine in VIII may be a consequence of the fact that rearrangement of the carbon skeleton occurs in its reactions, as would be the case in the formation of X from VIII.

## Experimental[8]

**β-(1-Carbethoxy-2-ketocyclohexyl)-propionaldehyde Diethyl Acetal (I).**—Dry xylene (200 ml.) and 12 g. of clean potassium were placed in a dry 500-ml. three-necked flask equipped with a stirrer, reflux condenser, dropping funnel and an electric heating mantle. Air in the system was displaced with nitrogen, the mixture was heated to melt the potassium, and a solution of 51 g. of α-carbethoxycyclohexanone[9] in 50 ml. of xylene was added dropwise with stirring. The potassium enolate dissolved when the mixture was heated, and after all of the potassium had reacted a solution of 51 g. of β-chloropropionaldehyde diethyl acetal[10] in 50 ml. of xylene was added rapidly. The mixture was stirred and heated under reflux for fifteen hours, at which time acidimetric titration of an aliquot showed that 83% of the base had been neutralized. The mixture was cooled, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Rapid distillation of the residue at 2 mm. to separate high-boiling material followed by distillation through a Vigreux column yielded 18.4 g. (31%) of I, b. p. 150–160° (2 mm.). An analytical sample distilled through a 30 × 0.7 cm. semimicro column[11] had b. p. 130–135° (0.6 mm.); $n^{25}D$ 1.4562; $d_4^{25}$ 1.0307; $MD$ calcd. 78.95; found 78.9.

*Anal.* Calcd. for $C_{16}H_{28}O_5$: C, 64.05; H, 9.40. Found: C, 64.42; H, 9.32.

Similar results were obtained when the alkylation was conducted in cumene and in *p*-cymene, except that the reaction proceeded more rapidly in the higher boiling solvents.

**1-Carbethoxy-4-hydroxybicyclo[3.3.1]nonan-9-one (II)** was obtained by treating 1 g. of I with 4 ml. of acetic acid, 2 ml. of water and 1 ml. of concentrated hydrochloric acid. The mixture was warmed for a few minutes and allowed to stand at room temperature for eighteen hours, after which it was neutralized with aqueous sodium bicarbonate and extracted with ether. The extracts were dried over magnesium sulfate, concentrated, and the residue was distilled in a molecular type still at 0.3 mm. and a heating block temperature of 170–200°. The colorless, viscous distillate (0.5 g.) had $n^{25}D$ 1.4930.

*Anal.* Calcd. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.01. Found: C, 63.88; H, 8.01.

**β-(1-Carbethoxy-2-ketocyclohexyl)-propionaldehyde (III).**—Sodium (0.17 g.) was dissolved in 50 ml. of absolute ethanol (dried by treatment with sodium and diethyl phthalate) in a dry 500 ml. three-necked flask fitted with a Hershberg stirrer and a dropping funnel. Hydroquinone (0.2 g.) was added and the solution was cooled to −70° in a bath of acetone and Dry-Ice. A mixture of 25 g. of α-carbethoxycyclohexanone[9] and 10 g. of redistilled acrolein was added dropwise with stirring during a period of one hour at −70° to −60°. The cooling bath was removed and the mixture was stirred for another thirty minutes, after which it was brought to a *p*H of approximately 7 (Hydrion paper) by adding glacial acetic acid or hydrogen chloride in ethanol. The solvent was removed under reduced pressure and the viscous residue was dissolved in 100 ml. of ether and washed with water and dilute sodium bicarbonate solution. The ether solution was dried over sodium sulfate and concentrated under reduced pressure. After a rapid preliminary distillation to separate the product from high-boiling material, fractionation through a 16-cm. Vigreux column gave III in 65–75% yield. The product from a similar preparation obtained in a yield of 21 g. (63%) had b. p. 140–143° (1.5 mm.), $n^{25}D$ 1.4718; $d^{25}_4$ 1.094; $MD$ calcd. 57.12, found 57.6.

*Anal.* Calcd. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.01. Found: C, 63.77; H, 7.99.

A sample of III treated with a mixture of acetic acid, water and hydrochloric acid under the conditions described above for preparation of II from I gave a product which appeared to be identical with II, purified by a short-path distillation as a viscous, colorless liquid, $n^{25}D$ 1.4939; mol. wt. calcd. 226; found, 261 (Rast method in borneol).

**β-(1-Carbethoxy-2-ketocyclohexyl)-propionic acid** was prepared as a derivative from III (2 g.), which was added to the alkaline silver oxide mixture prepared from 2.5 g. of silver nitrate, 25 ml. of water, 1 g. of sodium hydroxide and 20 ml. of 95% ethanol. The mixture was stirred for one hour, filtered, and the filtrate was acidified with hydrochloric acid. The product was extracted with several portions of ether, and re-extracted from the ether with sodium bicarbonate solution. Acidification of the alkaline extracts and extraction with ether yielded 1 g. of β-(1-carbethoxy-2-ketocyclohexyl)-propionic acid, which crystallized on standing and after recrystallization from methylcyclohexane melted at 60–60.5° and did not depress the m. p. of a known sample.[12]

**1-Carbethoxybicyclo[3.3.1]non-3-en-9-one (IV). Preparation from II.**—A mixture of 5 g. of the acetal I, 20 ml. of glacial acetic acid, 10 ml. of water and 5 ml. of concentrated hydrochloric acid was allowed to stand overnight. The mixture was neutralized with sodium bicarbonate solution and extracted with ether; distillation of the ether left a residue of 3.3 g. of the viscous cyclic aldol II. The residue was dissolved in 15 ml. of concentrated sulfuric acid, with cooling in ice. The mixture was allowed to come to room temperature in a period of four hours, poured onto ice and extracted with several portions of ether. The extracts were washed with sodium bicarbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. Fractionation[11] of the residue yielded 1 g. (29%) of IV, b. p. 93° (0.45 mm.), $n^{25}D$ 1.4920, which crystallized on standing; m. p. 45–47° (a purer sample described below melted at 48.5–49.4°).

*Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.39; H, 7.45.

**1-Carbethoxybicyclo[3.3.1]non-3-en-9-one 2,4-dinitrophenylhydrazone** was prepared from IV by the general method described by Shriner and Fuson[13] and recrystallized from 95% ethanol as orange needles with a constant m. p. of 174–176°.

*Anal.* Calcd. for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19; N, 14.42; $OC_2H_5$, 11.6. Found: C, 55.62; H, 5.26; N, 14.62; $OC_2H_5$, 11.4.

**Preparation of IV from III.**—The aldehyde III (7.5 g.) was added in very fine drops with stirring to 15 ml. of concentrated sulfuric acid cooled in an ice-bath. The mixture was allowed to stand at room temperature for four hours and poured onto ice. The product separated as a brown

(5) Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939).

(6) Bartlett and Cohen, *ibid.*, **62**, 1183 (1940).

(7) Bartlett and Lewis, *ibid.*, **72**, 1005 (1950).

(8) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates for analyses.

(9) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 531.

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 137.

(11) Gould, Holzman and Niemann, *Anal. Chem.*, **20**, 361 (1948).

(12) Sheehan and Mumaw, to be published; Mumaw, Ph.D. thesis, Massachusetts Institute of Technology, 1949, p. 30.

(13) Shriner and Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, N. Y., 1948, p. 171.

solid (5.7 g.), which was washed with water and purified by a short-path distillation, which yielded 4.3 g. (62%) of IV as white needles, m. p. 48.5–49.4°.

**1-Carbethoxybicyclo[3.3.1]non-3-en-9-one semicarbazone**, prepared from IV, semicarbazide hydrochloride and sodium acetate in aqueous ethanol and recrystallized from 95% ethanol, had m. p. 206–207°.

*Anal.* Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.87; H, 7.16; N, 15.82. Found: C, 59.03; H, 7.08; N, 16.03.

**Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic Acid (V).**—The freshly distilled[14] aldehyde III (50 g.) was added in very fine drops to 160 ml. of concentrated sulfuric acid, which was stirred vigorously and cooled in an ice-bath. After the addition was completed, the ice-bath was removed and the mixture was allowed to stand at room temperature for a period of five to twelve hours. The dark red solution was poured onto 300 g. of crushed ice with stirring, and the crude crystalline product was collected on a sintered glass funnel and washed with ice water. The wet product was heated on a steam-bath with 200 ml. of 5% potassium hydroxide for thirty minutes, until a clear solution was obtained. The solution was cooled, made strongly acidic with hydrochloric acid and extracted with several portions of ether. The ether solution was treated with Norit, dried over magnesium sulfate and concentrated. The residue of V, m. p. 135–135.5°, weighed 27.5 g. (69%). A sample which was recrystallized from methylcyclohexane had m. p. 133.8–134.3°. The acid rapidly decolorized aqueous potassium permanganate.

*Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66: neut. equiv., 180.1. Found: C, 66.94; H, 6.81; neut. equiv., 180.

**Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid 2,4-dinitrophenylhydrazone**, prepared from V in aqueous ethanol containing sulfuric acid[13] and recrystallized from nitromethane, had m. p. 259–261° (dec.).

*Anal.* Calcd. for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.44; N, 15.59. Found: C, 53.53; H, 4.68; N, 15.62.

**Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid amide** was prepared by heating V with thionyl chloride in benzene solution, and adding the crude acid chloride prepared in that manner to concentrated ammonium hydroxide. The amide was separated by extraction with ether and was recrystallized from methylcyclohexane as slender white needles, m. p. 126–128°.

*Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 66.96; H, 7.30; N, 7.82. Found: C, 67.01; H, 7.51; N, 8.17.

**Bicyclo[3.3.1]nonan-9-one-1-carboxylic acid (VII).**—Hydrogenation of 35 g. of V in 150 ml. of 95% ethanol in the presence of 5 g. of 10% palladium-on-Norit[15] at 30–15 p.s.i. stopped after one and one-half hours and the absorption of 150% of one molar equivalent of hydrogen. The catalyst was separated by filtration and the solvent was removed under reduced pressure. A solution of the partially crystalline residue in 70 ml. of glacial acetic acid was treated with a solution of 34 g. of potassium dichromate and 8 ml. of concentrated sulfuric acid in 150 ml. of water. The mixture was cooled during the addition to keep the temperature below 45° and allowed to stand for eighteen hours at room temperature. It was then warmed on a steam-bath for approximately thirty minutes until the temperature reached 80° and allowed to cool to room temperature. The mixture was extracted seven times with 100-ml. portions of ether, and the combined extracts were washed with a small amount of water to remove most of the chromium salts. The ether was distilled and the residue was extracted with boiling methylcyclohexane, which on cooling yielded VII as thick white needles, which on recrystallization from 100 ml. of boiling water yielded 19.0 g. (53%) of VII, m. p. 135–137°. An analytical sample recrystallized from methylcyclohexane melted at 138.6–139.4°, and apparently was isomorphous with the unsaturated acid V (m. p. 133.8–134.3°) since the mixed m. p. was 134–135.5°.

*Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.95; H, 7.68; neut. equiv., 182.1. Found: C, 65.99; H, 7.66; neut. equiv., 183.

**Bicyclo[3.3.1]nonan-9-one-1-carboxylic acid 2,4-dinitrophenylhydrazone** was prepared[13] from VII and recrystallized from nitromethane as orange needles, m. p. 260–261.5° (dec.), which appeared to be isomorphous with the 2,4-dinitrophenylhydrazone of V since the mixed m. p. was 260–261.5° (dec.).

*Anal.* Calcd. for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.00; N, 15.49. Found: C, 53.10; H, 5.49; N, 15.52.

**Bicyclo[3.3.1]nonan-9-one-1-carboxylic acid amide** was prepared by heating VII (5 g.) with 6 g. of thionyl chloride in 25 ml. of benzene for one hour on a steam-bath, and adding the crude acid chloride prepared in that manner to concentrated ammonium hydroxide. The amide (3.2 g.) was separated by extraction with ether, and was recrystallized from methylcyclohexane as slender needles, m. p. 127–128°. This amide apparently was isomorphous with the amide of the unsaturated acid V (m. p. 126–128°), for the mixed m. p. was 127–128°.

*Anal.* Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.74. Found: C, 66.39; H, 8.37; N, 7.32.

**1-Carbethoxybicyclo[3.3.1]nonan-9-one 2,4-dinitrophenylhydrazone** was prepared from the ester VI, which was not isolated. A 0.6-g. sample of IV in 20 ml. of 95% ethanol was hydrogenated at atmospheric pressure in the presence of 1 g. of 5% palladium on barium sulfate in a period of four hours, during which one molar equivalent of hydrogen was absorbed. The product (VI) was converted[13] to the 2,4-dinitrophenylhydrazone, which was recrystallized from 95% ethanol; m. p. 174–177°. The derivative appeared to be isomorphous with the 2,4-dinitrophenylhydrazone of IV (m. p. 174–176°), for a mixed m. p. showed no depression.

*Anal.* Calcd. for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.67; N, 14.35. Found: C, 54.91; H, 5.54; N, 14.37.

**1-Bromobicyclo[3.3.1]nonan-9-one (VIII).**—A solution of 20 g. of VII in 50 ml. of methanol was titrated to the pink phenolphthalein end-point with a solution of potassium hydroxide in methanol. A solution of 18.6 g. of silver nitrate in 20 ml. of water and 50 ml. of methanol was added dropwise with stirring, and the silver salt was collected on a filter, washed with methanol and dried at 70° and 0.5 mm. for eighteen hours. The crude silver salt weighed 38 g. (theoretical yield 31.5 g.) and contained potassium nitrate. The pure silver salt was prepared in water, with losses due to solubility, but appeared to yield no better results than did the crude salt containing potassium nitrate in the following reaction with bromine. A solution of bromine (17.5 g., dried by shaking with sulfuric acid and distilling from phosphorus pentoxide) in 100 ml. of carbon tetrachloride (dried by distillation from phosphorus pentoxide or by standing over barium oxide) was stirred in a thoroughly dried flask, and the crude silver salt (38 g.) (protected from atmospheric moisture) was added slowly. The mixture was cooled occasionally so that it remained at room temperature, and loss of carbon dioxide proceeded smoothly. The mixture was stirred and warmed at 50° for fifteen minutes, filtered to remove salts and concentrated under reduced pressure. A solution of the residue in 50 ml. of ether was shaken with sodium bisulfite solution until the color change showed that excess bromine had been removed and then was dried over magnesium sulfate. Concentration under reduced pressure yielded a crystalline residue of 17.5 g. (74%) of VIII. Treatment with Norit in petroleum ether and recrystallization from petroleum ether yielded VIII as colorless crystals, m. p. 59–60°.

*Anal.* Calcd. for $C_9H_{13}OBr$: C, 49.79; H, 6.03; Br, 36.81. Found: C, 49.38; H, 6.10; Br, 37.05.

(14) Work by Eric Graham has shown that the aldehyde III should be used immediately after distillation for the preparation of V, or the yield is decreased.

(15) "Organic Syntheses," Vol. 26, John Wiley and Sons, New York, N. Y., 1946, p. 32.

**1-Bromobicyclo[3.3.1]nonan-9-one 2,4-dinitrophenylhydrazone** was prepared[13] from VIII and recrystallized from 95% ethanol; m. p. 185–186°.

*Anal.* Calcd. for $C_{15}H_{17}N_4O_4Br$: C, 45.35; H, 4.32; N, 14.10; Br, 20.12. Found: C, 45.55; H, 4.50; N, 14.23; Br, 20.13.

**Bicyclo[3.3.1]nonane (IX).**—Amalgamated zinc was prepared by stirring 100 g. of 20–30 mesh granulated zinc with 200 ml. of 10% mercuric chloride solution for one hour and washing with water. Amalgamated zinc (15 g.), 1 g. of VIII and 20 ml. of concentrated hydrochloric acid were heated under reflux for one-half hour, during which period the product (IX) sublimed and collected in the reflux condenser as a crystalline solid. The solid (0.4 g., 70%) was purified by sublimation at atmospheric pressure and 100° and by recrystallization from methanol, and then had m. p. 145–146° and was analytically pure. An authentic sample of IX prepared from bicyclo[3.3.1]nonan-2,6-dione[4,16] by Clemmensen reduction under the conditions described above did not depress the m. p. of IX prepared from VIII. The two samples also had identical infrared spectra.

**Reaction of VIII with Sodium in Liquid Ammonia and with Sodamide.**—Small pieces of sodium totaling 1.1 g. were added to a solution of 4.4 g. of VIII in 50 ml. of liquid ammonia. The blue color of the solution disappeared rapidly and, after the addition was completed, 2.6 g. of ammonium chloride was added and the ammonia was allowed to evaporate. The solid residue was extracted with acetone, which was then distilled under reduced pressure. The white crystalline residue (possibly X), 2.1 g. (68%) had m. p. 105–107° and was recrystallized from methylcyclohexane as glistening plates, m. p. 107–107.5°.

*Anal.* Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.86; N, 9.14. Found: C, 70.44; H, 9.96; N, 9.08.

(16) We are indebted to Edward C. Hermann for the tetramethyl-bicyclo[3.3.1]nonan-2,6-dione-1,3,5,7-tetracarboxylate used in the preparation of this compound.

Properties observed for the compound which are in accord with its formulation as an amide include its failure to form a hydrochloride or benzoyl derivative, failure to react with semicarbazide and 2,4-dinitrophenylhydrazine, and reaction with boiling sodium hydroxide forming ammonia. The same product was obtained by addition of 1 g. of VIII to the sodamide prepared from 0.25 g. of sodium and a catalytic amount of iron oxide in 50 ml. of liquid ammonia. After thirty minutes, 1 g. of ammonium chloride was added and the product (0.5 g.) was isolated by the procedure described above.

## Summary

Bicyclo[3.3.1]non-3-en-9-one-1-carboxylic acid (V) has been prepared by the Michael addition of α-carbethoxycyclohexanone to acrolein at −70°, followed by cyclization of the resulting aldehyde III by treatment with concentrated sulfuric acid and saponification of the ester IV. Both the acid V and the corresponding saturated acid VII resist decarboxylation by heating. Bicyclo-[3.3.1]nonan-9-one-1-carboxylic acid (VII) was decarboxylated by reaction of the silver salt with bromine. The carbon skeleton of the resulting bromoketone VIII has been established by reduction to the known solid hydrocarbon, bicyclo-[3.3.1]nonane (IX). Although the halogen in VIII is located at a bridgehead, the compound formed silver bromide on treatment with alcoholic silver nitrate, and reacted with sodium or sodamide in liquid ammonia to give an amide (possibly X).

CAMBRIDGE, MASS. RECEIVED MARCH 29, 1950

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

# The Synthesis of 3,5-Di-*s*-butyl-1-cyclopentenealdehyde[1]

BY EVANS B. REID AND JOHN F. YOST[2,3]

For several years work in these laboratories has been directed toward the synthesis of the plant hormones, auxins a and b,[4] and an important intermediate in our projected synthesis is 3,5-di-*s*-butyl-1-cyclopentenealdehyde. Earlier attempts to approach this compound by alkylation of the cyclopentene ring were without success.[1] Our attention then turned to the exploration of methods of synthesizing the appropriately substituted 1,2-cyclohexanediol, which should yield the desired 1-cyclopentenealdehyde through ring splitting and cyclodehydration. While engaged in this work, the last steps of our projected method were utilized by English and Barber[5] in their novel synthesis of 3,5-di-*n*-propyl-1-cyclopentenealdehyde. These authors employed a Claisen rearrangement, followed by reduction to prepare 3,5-di-*n*-propylpyrocatechol, which was then further reduced to the corresponding cyclohexanediol. On cleavage of the diol with lead tetraacetate, their cyclopentenealdehyde formed spontaneously.

Our approach to the synthesis of the 3,5-di-*s*-butyl analog was, of necessity, a direct one, and involved nuclear alkylation of phenol in the 2- and 4-positions. *s*-Butyl alcohol and anhydrous hydrogen fluoride were used since earlier work had indicated that under such conditions,[6] (1) oxygen alkylation does not occur, (2) isomerizations (excluding partial racemization[7,8] within the alkyl group are absent, and (3) no meta substitution is induced. Further, from the vast amount of experimentation on alkylation

(1) This is the second paper describing synthetic work related to the auxin field. For the first, see Reid and Yost, THIS JOURNAL, **72**, 1807 (1950).

(2) From the doctoral dissertation of John F. Yost, The Johns Hopkins University.

(3) Standard Oil Company of Indiana Fellow, 1949–1950.

(4) Kögl, Erxleben, Michaelis and Visser, *Z. physiol. Chem.*, **235**, 181 (1935), and earlier papers.

(5) English and Barber, THIS JOURNAL, **71**, 3310 (1949).

(6) Calcott, Tinker and Weinmayr, *ibid.*, **61**, 1010 (1939).

(7) Price and Lund, *ibid.*, **62**, 3105 (1940).

(8) Burwell and Archer, *ibid.*, **64**, 1032 (1942).