[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of 8-Methylhydrindan-1,4-dione[1]

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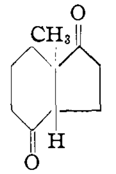
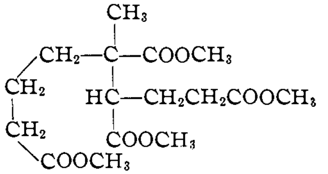
Several approaches to the synthesis of polynuclear hydroaromatic structures related to steroids have been reported,[4] utilizing intermediates either with preformed C and D rings or with functional groups prerequisite for their formation. In view of investigations currently in progress in this Laboratory[5] it seemed that 8-methylhydrindan-1,4-dione might prove to be a valuable intermediate. Two attempts to prepare this cyclic diketone have been reported.[6]

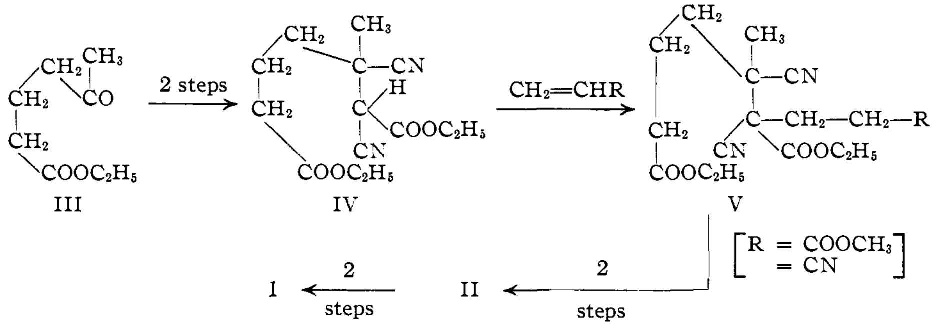


I



II

The present paper describes the preparation of 1,3,4,7-tetracarbomethoxy-4-methylheptane (II) and the formation of I from this tetraester in 43% yield by dicyclization, hydrolysis and decarboxylation. Several steps were involved in the synthesis of II.



Ethyl γ-acetobutyrate (III), prepared in 65% yield from ethyl acetoacetate by known procedures,[7] was converted into the dicyano diester (IV) by the method previously described[7b] in 79% yield for two steps. The addition of IV to both methyl acrylate and acrylonitrile was investigated. With the former, potassium ethoxide was used as the catalyst, while with the latter, the procedure of Bruson[8] for cyanoethylation was followed, using "Triton B" as the catalyst, this being the preferred method because of the excellent yield and simplicity of operation. The tricyanodiester (V, R = CN) thus obtained was hydrolyzed and decarboxylated by prolonged treatment with hot concentrated hydrochloric acid, the acidic product being isolated as a nitrogen-free yellow glass. Esterification with methanol and sulfuric acid afforded II in 61% yield based on the dicyanodiester (IV).

Of the four most likely products of the Dieckmann cyclization, *viz.*, VIa, VIb, VIc and VI; only that (VI) formed from the desired dicyclization could give rise to a neutral substance after hydrolysis and decarboxylation, the other three yielding acidic products.

The dicyclization of II was accomplished with sodium hydride and the course of the reaction was followed by means of a constant pressure eudiometer. Long and irregular induction periods were observed during preliminary runs, but later studies showed that the reaction could be initiated within thirty minutes when a small amount of methanol was added to the tetraester. Usually the crude cyclization product was directly hydrolyzed and decarboxylated by refluxing with a constant boiling mixture[9] of hydrochloric acid, acetic acid and water. The neutral diketone (I) was obtained in 43% yield together with some acidic material.

In order to determine the course of the cyclization, monocyclization of the tetraester (II) was effected by treatment with a slight excess over a one molar equivalent of sodium hydride in reflux-

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(4) (a) Rapson and Robinson, *J. Chem. Soc.*, 1285 (1935); (b) Chuang, Ma and Tien, *Ber.*, **68B**, 1946 (1935); (c) Nenitzescu and Cioranescu, *ibid.*, **75B**, 1765 (1942); (d) Bagchi and Banerjee, *J. Ind. Chem. Soc.*, **23**, 397 (1946); (e) Mukharji, *ibid.*, **24**, 91 (1947); (f) Dimroth, *Angewandte Chem.*, 215 (1947).

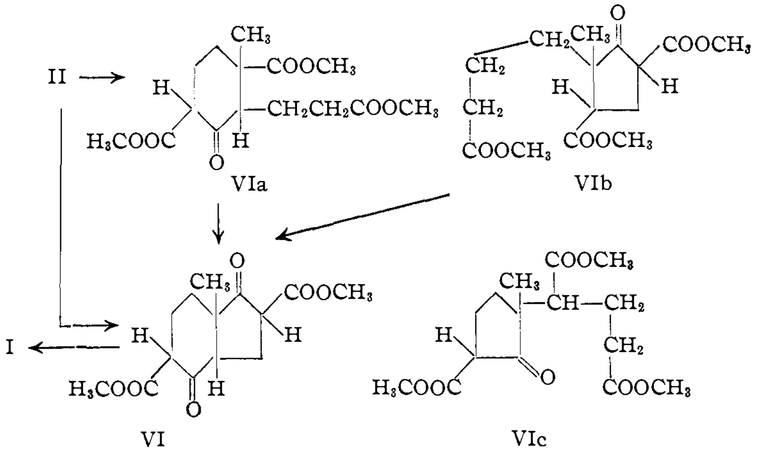
(5) Johnson, *et al.*, unpublished work.

(6) (a) Goldberg, Hunziker, Billeter and Rosenberg, *Helv. Chim. Acta*, **30**, 200 (1947); (b) Schwenk and Bloch, THIS JOURNAL, **64**, 3050 (1942).

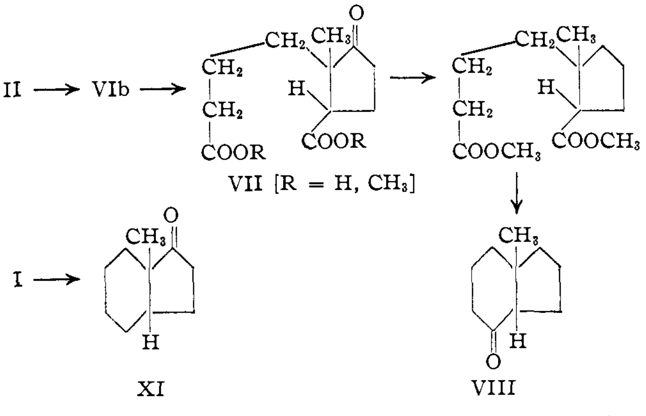
(7) (a) Wilds, private communication; (b) Banerjee, *J. Ind. Chem. Soc.*, **17**, 453 (1940); (c) Albertson, THIS JOURNAL, **70**, 669 (1948).

(8) (a) Bruson and Riener, *ibid.*, **65**, 23 (1943); (b) Bruson, "Organic Reactions," Vol. V, Chapt. 2, John Wiley and Sons, Inc., New York, N. Y., 1949.

(9) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 78 (1947).



ing benzene solution. The resulting crude product was hydrolyzed and decarboxylated to give a viscous tan oil. A part of the acidic material was esterified and characterized as a ketodimethyl ester. The remainder was reduced by a modified Wolff–Kishner method,[10] esterified and cyclized as described above. Hydrolysis and decarboxylation in the usual manner afforded a neutral ketonic material which was proved to be 8-methylhydrindanone-4 by direct comparison of the semicarbazone and the 2,4-dinitrophenylhydrazones with those of an authentic sample.[4d] Isolation of 8-methylhydrindanone-4 as the only product from the above series of reactions indicates that the five-membered ring was preferentially formed as the initial step of the dicyclization and also proves the basic ring system as well as the C-4 carbonyl group in the diketone (I).



To further demonstrate the structure of I, the diketone was reduced by the Clemmensen method, employing a refluxing mixture of hydrochloric acid, acetic acid, water and an amount of amalgamated zinc slightly in excess over that stoichiometrically required for the reduction of one carbonyl group. Selective reduction was achieved since the only product isolated was found to be *cis*-8-methylhydrindanone-1,[11] thus proving the basic hydrindane ring structure with an angular methyl adjacent to the C-1 carbonyl group and also the expected *cis* configuration of the parent diketone.

Utilization of I for the synthesis of the steroid type of molecule seems to depend upon the possibility of selective reaction with one of the two carbonyl groups. It was expected that the C-1 position adjacent to the angular methyl group would be less reactive because of steric hindrance. The result of the reduction experiment (*vide supra*) supports this view. Furthermore, it was observed that the reaction of I with one molar equivalent of 2,4-dinitrophenylhydrazine yielded two isomeric monoderivatives in the proportion of 1:15. The nature of these isomers will be the subject of future investigation. It is interesting to note that the bis-derivative could not be prepared even when a large excess of the above reagent was employed, while the very sparingly soluble disemicarbazone was the only product that could be isolated when varying proportions of semicarbazide hydrochloride were used.

Acknowledgments.—Our sincerest thanks are due to Dr. William S. Johnson for his valuable advice and encouragement during the progress of this investigation. We are also indebted to Mrs. Virginia Miller and Dr. Richard Hunt for carrying out microanalyses of some of the compounds.

Experimental[12]

Ethyl γ-Acetobutyrate (III).—This compound was prepared from ethyl acetoacetate in a manner similar to that of Albertson[7c] in 65% over-all yield (based on recovered starting materials for the last two steps), the product being obtained as a colorless oil, b. p. 95–96° (7–8 mm.). Albertson reported b. p. 52–59° (1 mm.).

1,2-Dicyano-1,5-dicarbethoxy-2-methylpentane (IV).—The keto ester (III) was converted to the dicyano diester (IV) in two steps following essentially the method of Banerjee,[7b] except that the modified method of Cope[13] was employed for the condensation of ethyl cyanoacetate with ethyl γ-acetobutyrate (III).

From a mixture of 96.6 g. (0.61 mole) of ethyl γ-acetobutyrate, 70 g. (0.618 mole) of ethyl cyanoacetate, 10 g. (0.13 mole) of ammonium acetate, 30 ml. (0.5 mole) of glacial acetic acid and 150 ml. of benzene, there was obtained finally 108.3 g. (87.5% yield based on recovered starting material) of 1,5-dicarbethoxy-1-cyano-2-methylpentene-1, b. p. 144–148° (0.4 mm.), together with 19.2 g. of unchanged ketoester, b. p. 92–96° (8 mm.). Banerjee reported[7b] b. p. 155–160° (3 mm.).

The addition of hydrocyanic acid to the above unsaturated cyanoester according to the method of Hope and Sheldon[14] was carried out as previously described.[7b] The yield of 1,2-dicyano-1,5-dicarbethoxy-2-methylpentane,

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[10] Huang-Minlon, This Journal, **68**, 2487 (1946).

[11] Johnson, *ibid.*, **66**, 215 (1944).

[12] All melting points are corrected.

[13] Cope, Hofmann, Wyckoff and Hardenbergh, This Journal, **63**, 3452 (1941).

[14] Hope and Sheldon, *J. Chem. Soc.*, **121**, 2223 (1922).

b. p. 180–185° (0.7–0.9 mm.) from the above unsaturated cyanoester was 90%. Banerjee reported[7b] b. p. 192–193° (4 mm.).

1,3,4-Tricyano-3,7-dicarbethoxy-4-methylheptane (V, R = CN).—Bruson's method for cyanoethylation[8] was employed for this preparation. To an ice cold solution of 20 g. (0.07 mole) of IV, 3.8 g. (0.07 mole) of acrylonitrile, and 7 g. of dioxane was added slowly 0.5 ml. of "Triton B" (38% aqueous solution of trimethylbenzylammonium hydroxide). The solution, which became yellow immediately, was allowed to stand at 0° for one hour with occasional swirling and then at room temperature (26°) for twenty-four hours. The reaction mixture was taken up in benzene, washed thoroughly with dilute hydrochloric acid followed by water, and the solvents removed, finally *in vacuo*, leaving 23.6 g. (98.5% yield) of the crude product as a viscous tan oil. The tricyano diester (V, R = CN) was used for the next step without further purification. A small sample was evaporatively distilled in a sublimation apparatus at 160–165° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95. Found: C, 61.67; H, 6.96.

For the condensation of the dicyano diester (IV) with methyl acrylate the following method was used. To a cooled solution of 0.6 g. (0.15 atom) of potassium in 3 ml. of absolute ethanol and 50 ml. of anhydrous ether, a solution of 35.08 g. (0.13 mole) of IV in ether was slowly added. A gelatinous precipitate formed, and after standing for one-half an hour at room temperature, a solution of 12.04 g. (0.14 mole) of methyl acrylate in 25 ml. of ether was added and the mixture refluxed for two hours, giving a clear yellow solution which darkened considerably upon standing. After working up in the usual manner the thick residual oil was distilled through a heated Vigreux column, b. p. 215–227° (0.6–1.3 mm.) with decomposition, leaving considerable residue; yield 29.9 g. (65%). The structure of this product (V, R = $COOCH_3$) was confirmed by converting it to the tetraester (II).

1,3,4,7-Tetracarbomethoxy-4-methylheptane (II).—The crude tricyano diester (V, R = CN) (23 g.) was refluxed with 180 ml. of concentrated hydrochloric acid for ninety-six hours and the reaction mixture then concentrated in an evaporating dish until there was no odor of hydrochloric acid. After drying by azeotropic distillation with benzene, the sticky residue was refluxed for ninety hours on a steam-bath with a mixture of 150 ml. of methanol and 21 ml. of concentrated sulfuric acid. After working up in the usual manner, there was obtained 15 g. (61% yield based on the amount of dicyano diester (IV) used) of the tetraester (II), b. p. 160–164° (0.15 mm.), $n^{28.5}\mathrm{D}$ 1.4555.

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.53; H, 7.64.

8-Methylhydrindan-1,4-dione.—A well-stirred refluxing suspension of 9.0 g. (0.375 mole) of sodium hydride in 150 ml. of xylene, under an atmosphere of nitrogen, was brought to equilibrium with a constant pressure eudiometer. Then about one-quarter of a mixture of 27.88 g. (0.081 mole) of II, 1.5 ml. of methanol and 100 ml. of xylene was added slowly from a dropping funnel; under these conditions the reaction usually started within thirty minutes as indicated by a vigorous evolution of hydrogen. Thereafter the rate of addition was adjusted to maintain a steady evolution of hydrogen; the entire operation lasted about three hours and about 90% of the calculated quantity of hydrogen was evolved. The reaction mixture was then cooled in an ice-bath and, still under nitrogen, a solution of 40 ml. of concentrated hydrochloric acid in 100 ml. of water was added rapidly. When the evolution of hydrogen from the unreacted sodium hydride had ceased, the product was isolated by ether extraction, and the ether removed, finally by heating at 100° under reduced pressure. The residual oil, which gave a strong violet ferric chloride coloration, was refluxed for twenty hours with ten times its volume of a mixture of acetic acid, concentrated hydrochloric acid and water (in the ratio of 5:1.15:1.5 by volume).[9] The cooled homogeneous solution was saturated with ammonium sulfate and extracted repeatedly with ether. The combined ether extracts were washed successively with 5% sodium bicarbonate solution, water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After removing the ether the product was distilled through a short Vigreux column, giving 5.76 g. (43% yield for two steps) of a colorless oil, b. p. 130–132° (9 mm.), $n^{29.0}\mathrm{D}$ 1.4908.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.39; H, 8.51.

Mono-2,4-dinitrophenylhydrazones of I were formed by adding a suspension of 1.45 g. (0.0073 mole) of 2,4-dinitrophenylhydrazine in a mixture of 100 ml. of ethanol, 2 ml. of concentrated hydrochloric acid and 25 ml. of water, to a solution of 1.1676 g. (0.0070 mole) of I in 25 ml. of 95% ethanol; yield 2.084 g. of an orange powder, m. p. 192–199°. An additional 0.344 g. of material was obtained by diluting the mother liquor with water. Fractional crystallization of the crude material from ethanol gave two isomers. The first, less soluble isomer, formed bright yellow-orange needles, m. p. 208.2–209.2° (previous softening). The second isomer consisted of darker orange needles, m. p. 188.7–190.3° (previous softening), and on admixture with the first isomer a depression in melting point was observed. Based on recrystallized materials, the approximate ratio of formation of the two isomers was 1:15, the higher melting isomer being predominant.

The attempted preparation of the bis-2,4-dinitrophenylhydrazone of the diketone (I) using an excess of the reagent yielded only the monoderivatives.

Anal. Calcd. for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24. Found: (a) 208° isomer: C, 55.71; H, 4.97; (b) 189° isomer: C, 55.79; H, 5.25.

Disemicarbazone of I, prepared in the usual manner with excess semicarbazide hydrochloride, pyridine and methanol, was recrystallized from a large volume of methanol, m. p. 246.5–246.8° (dec.), introduced in the bath at 221°.

Anal. Calcd. for $C_{12}H_{20}N_6O_2$: C, 51.41; H, 7.19. Found: C, 51.44; H, 7.44.

Methyl γ-(1-Methyl-2-keto-5-carbomethoxycyclopentyl)-butyrate (VII, R = CH_3).—To a stirred refluxing solution of 20 g. (0.058 mole) of the tetraester (II) in 200 ml. of benzene, previously dried by azeotropic distillation and under a nitrogen atmosphere, was added 0.5 ml. of methanol and then a small portion of a slurry of 2 g. (0.083 mole) of sodium hydride in benzene. The reaction started within fifteen minutes and thereafter the sodium hydride slurry was added in small amounts sufficient to maintain a vigorous evolution of hydrogen as indicated by a constant pressure eudiometer, the reaction being complete after two and one-half hours. The reaction mixture was worked up in the usual manner and the crude product, obtained as a brown oil which gave a violet ferric chloride test, was hydrolyzed and decarboxylated by refluxing for twenty hours with 150 ml. of 18% sulfuric acid. After working up in the usual manner and drying by azeotropic distillation with benzene, finally at 100° under reduced pressure, 12.3 g. (93% yield for two steps) of crude keto diacid (VII, R = H) was obtained as a viscous tan oil.

Semicarbazone of VII (R = H), prepared in the usual manner from semicarbazide hydrochloride and a saturated solution of sodium acetate, was obtained after three recrystallizations from dilute methanol as small rhombic crystals, m. p. 239.5–240° (dec.) with slight previous softening, introduced into the bath at 233°.

Anal. Calcd. for $C_{12}H_{19}N_3O_5$: C, 50.52; H, 6.71. Found: C, 50.48; H, 6.54.

Eight grams of the above crude keto diacid (VII, R = H) was esterified by refluxing with a mixture of 100 ml. of methanol and 10 ml. of concentrated sulfuric acid for ninety-six hours. The esterified product was worked up in the usual manner and distilled through a short Vigreux column, giving 8.2 g. of a thick colorless oil, b. p. 130–140° (0.1 mm.). Refractionation through a spinning band column[15] gave a total of 6.9 g. of a colorless viscous

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[15] We are indebted to Mr. W. Fahlberg and the Department of Chemical Engineering, University of Wisconsin, for this fractionation.

oil, of which 5.7 g. was composed of cuts with $n^{27}\text{D}$ 1.4656, b. p. 148–150° (1.1–1.3 mm.), and $d^{22.5}$ 1.119.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87; $M_{\text{R}}\text{D}$, 63.35. Found: C, 61.03; H, 7.99; $M_{\text{R}}\text{D}$, 63.61.

Semicarbazone of VII (R = CH_3), prepared from semicarbazide hydrochloride, pyridine and methanol, was recrystallized from aqueous methanol, giving colorless blades, 179.6–180.8° with previous softening.

Anal. Calcd. for $C_{14}H_{23}N_3O_5$: C, 53.66; H, 7.40. Found: C, 53.65; H, 7.75.

8-Methylhydrindanone-4.—The keto diacid (VII, R = H) described above was reduced according to the Huang-Minlon modification[10] of the Wolff–Kishner method following essentially the procedure described in "Organic Reactions," Vol. IV, p. 391.

From a mixture of 3.5 g. (0.015 mole) of the crude keto diacid, 2.6 ml. of 85% hydrazine hydrate, 4.0 g. of potassium hydroxide and 30 ml. of triethylene glycol, there was obtained 3 g. of an oil which, after azeotropic drying with benzene, was esterified with diazomethane, giving 2.3 g. of material, b. p. 120–125° (0.6 mm.), which did not form a semicarbazone.

The above reduced diester (2.26 g.) was cyclized in the usual manner by refluxing with a mixture of 0.5 g. of sodium hydride, five drops of methanol and 80 ml. of benzene for five hours under a nitrogen atmosphere. The product, which was worked up as described before and gave a positive ferric chloride test, was refluxed for twelve hours with 50 ml. of 20% sulfuric acid. The neutral product, isolated in the usual way, was distilled through a short Vigreux column, giving 0.7 g. of a colorless oil (VIII), b. p. 92–94° (9 mm.). Bagchi and Banerjee[4d] reported the boiling point as 92–94° (8 mm.), and an authentic sample prepared according to their method boiled at 96–96.5° (10 mm.).

Semicarbazone of VIII, prepared in the usual manner, was obtained after four recrystallizations as clumps of thick blades, m. p. 188–188.5° (dec.) with softening from 187.2°, introduced into bath at 170°. Admixture with the semicarbazone (m. p. 188–188.5° (dec.) with softening from 187.5°) prepared from an authentic sample of VIII gave no depression in melting point.

2,4-Dinitrophenylhydrazone of VIII was prepared directly from the above semicarbazone (once recrystallized from methanol) as previously described,[16] except that concentrated hydrochloric acid was used as the catalyst. Fractional crystallization from methanol yielded two isomers. The first, less soluble isomer, formed yellow felted needles, m. p. 168.5–169.5° (micro hot stage), while the second isomer consisted of thick orange blades, m. p. 138.3–139.3° (micro hot stage), and on admixture melted at 123–128° (micro hot stage).

The same mixture of isomers was obtained from an authentic sample of VIII, the first isomer as yellow felted needles, m. p. 168–169° (micro hot stage), and the second as thick orange blades, m. p. 138–139° (micro hot stage). Admixture of each isomer with the corresponding one described above gave no depression in melting point.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: (a) 168° isomer: C, 57.66; H, 5.96; (b) 138° isomer: C, 57.82; H, 6.01.

Clemmensen Reduction of the Diketone (I).—A mixture of 1.0 g. (0.006 mole) of the diketone (I), 6 ml. of glacial acetic acid, 4 ml. of water, 2 ml. of concentrated hydrochloric acid and amalgamated zinc prepared from 1.2 g. (0.018 mole) of zinc was refluxed gently for forty hours, additional 2-ml. portions of concentrated hydrochloric acid being added after sixteen, twenty-two, and twenty-eight hours. The cooled reaction mixture was neutralized with sodium bicarbonate and steam distilled after addition of 0.1 ml. of acetic acid, the product being isolated as the semicarbazone, thereby obtaining 160 mg. (13% yield) of material which melted at 216–218° (dec.) after one recrystallization. Three recrystallizations from methanol gave small blades, m. p. 223.5–224° (dec.), introduced into the bath at 215°. Admixture with an authentic sample of the semicarbazone of *cis*-8-methylhydrindanone-1 (m. p. 224.5–225.5°)[11,17] gave no depression in melting point.

2,4-Dinitrophenylhydrazone of IX, prepared from the above semicarbazone, was obtained as orange needles, m. p. 139–140° with previous softening (micro hot state). Admixture with an authentic sample,[11,17] m. p. 139.5–140° (micro hot stage), gave no depression in melting point.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 58.14; H, 5.75.

Summary

8-Methylhydrindan-1,4-dione has been synthesized by the dicyclization of 1,3,4,7-tetracarbomethoxy-4-methylheptane. Monocyclization of the above tetraester has also been carried out and it has been shown that a cyclopentanone ring is formed at the initial stage of the dicyclization. The structure of the diketone has been proved by its reduction to *cis*-8-methylhydrindanone-1 and also by conversion of the monocyclization product into 8-methylhydrindanone-4.

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[16] Gutsche and Johnson, THIS JOURNAL, 68, 2245 (1946).

[17] Sample supplied by Dr. Johnson.