

Synthesis of 3,8-Dihydroxyspiro[4.4]nona-3,8-diene-2,7-dione via a Diacyloin Condensation

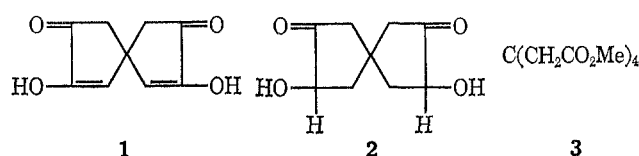
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Tetramethyl methanetetraacetate and sodium formed an intermediate dienediol that was oxidized by air or iodine to give the title compound. The intermediate in the oxidation with iodine appears to be a disemidione. A modified acyloin condensation, using sodium-liquid ammonia followed by evaporation of the ammonia and the addition of trimethylchlorosilane (TMCS), has been shown to be of particular utility in the synthesis of 2,3,7,8-tetrakis(trimethylsilyloxy)spiro[4.4]nona-2,7-diene.

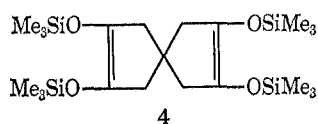
As a starting material for the synthesis of polyspiro compounds we planned to prepare the title compound **1** from the diacyloin **2**, which was to be synthesized from **3** by the acyloin reaction. Since the last review article²



on the reaction, a new procedure³ has evolved which consists of addition of trimethylchlorosilane (TMCS) as a reactant in a solvent such as xylene. The product of the reaction is the silylated enediol, which is easily solvolyzed³ to acyloin.

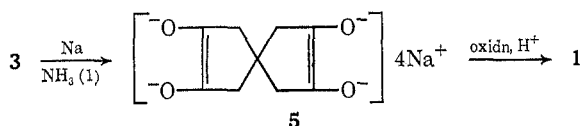
We have developed a modified procedure, which consists of a classical acyloin condensation using liquid ammonia followed by evaporation of the ammonia and the addition of TMCS. In certain instances this procedure cannot be used, but in our reaction it gives higher yield of silylated enediol than is obtained by the xylene solvent method.

When the double acyloin condensation of tetramethyl methanetetraacetate (**3**) was attempted using sodium dispersed in xylene with TMCS, nmr studies indicated a small yield of the desired product **4**. Re-

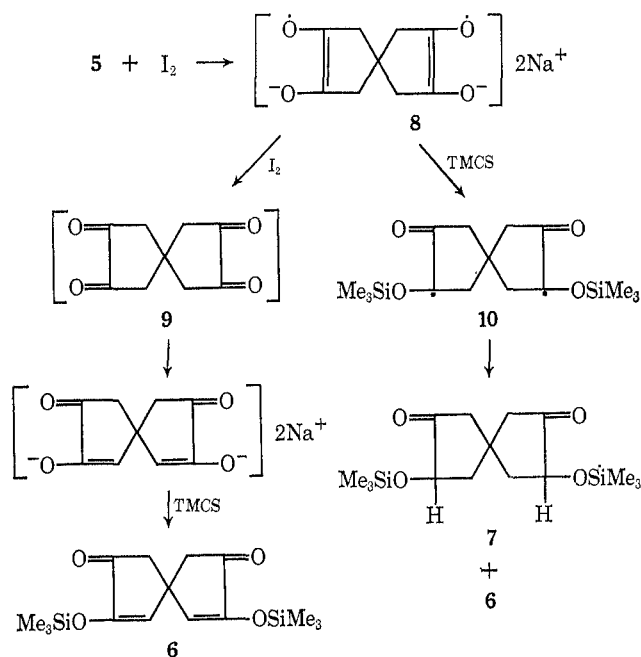


action of **3** with sodium-liquid ammonia followed by TMCS gave an 88% yield of the silylated dienediol **4**. Isolation of pure **2** from the silylated product was not possible. Compound **2** was shown by nmr studies to be formed by the methanolysis of **4**, but on removal of the methanol the diacyloin **2** polymerized.⁴

It was possible, however, to obtain **1** in 25% yield from the diacyloin condensation of **3**. This was done



by formation, from **3** and sodium-liquid ammonia, of the tetrasodium salt of the dienediol intermediate **5**, followed by air oxidation under carefully controlled conditions.⁵ A large excess of air gave a low yield of **1**, methanetetraacetic acid, and unidentified material. The oxidation of **5** was also effected by iodine⁶ to give **1** in the same yield as by the oxygen method. In order to understand the nature of this reaction, TMCS was added to trap intermediates. When **5** was treated with 2 mol of iodine followed by evaporation of ammonia and addition of TMCS, the silylated derivative of **1**, namely compound **6**, was obtained. Treatment of **5** with 1 mol of iodine gave **6** and **7**, the silylated derivative of the acyloin **2**. We believe that these results are explained in terms of the following equations.



The electron-transfer reaction of **5** and iodine formed the disemidione **8**, which should be a stable species⁷ at low temperature in solution. Reaction of **8** with iodine formed the di-1,2 diketone **9**, which as the enol form⁸ was trapped by TMCS as compound **6**. In the absence of iodine for a further electron-exchange reaction, species **8** reacted with TMCS to give the radical **10**

(1) Taken in part from the Ph.D. Thesis of F. M. F. Chen, 1969.

(2) F. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

(3) (a) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964);

(b) K. Ruhlmann, A. Seefluth, and H. Becker, *ibid.*, **100**, 3820 (1967);

(c) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968).

(4) J. C. Sheehan, R. C. O'Neill, and M. A. White [*J. Amer. Chem. Soc.*, **72**, 3376 (1950)] reported the dimerization of acyloins.

(5) M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).

(6) Use of this reagent was suggested by Larry L. Miller.

(7) Semidiones have been extensively studied by G. A. Russel, *et al.*, *J. Amer. Chem. Soc.*, **89**, 6636, 6781 (1967); **91**, 2813 (1969).

(8) Sodium methylate generated from the condensation served as base.

that underwent disproportion⁹ to give the saturated system 7 and the unsaturated compound 6. No dimer resulting from 10 was formed but a silted residue remained. The silted products 6 and 7 are solids. Compound 7 underwent methanolysis, as does compound 6.

We also attempted to prepare 1 by the hydrolysis of 4 to give 2 followed by direct oxidation of the diacyloin with cupric acetate. The reaction failed for the reason that 1 is itself oxidized by cupric acetate.

The structure of 1 was confirmed by nmr, ir, and mass spectral data and its conversion into the diquinoxaline derivative. The nmr spectrum of 1 in deuterium oxide-sodium hydroxide was of interest in that all protons exchanged in about 20 min at ambient temperature. On aqueous acidification, the exchanged material showed no proton signal in the nmr.¹⁰

The tetraester 3 was made from methanetetraacetic acid, which was prepared using a modified procedure of Ingold and Nickolls¹¹ starting from diethyl acetonedicarboxylate. Rather than following the literature procedure after the preparation of diethyl 3-dicarbethoxymethylglutaconate, the latter was treated with ethyl sodiocyanoacetate to give diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate. The glutaric ester on hydrolysis and decarboxylation gave methanetetraacetic acid.

Experimental Section¹²

Diethyl Acetonedicarboxylate.—Citric acid was converted into acetonedicarboxylic acid,¹³ which was esterified.¹⁴ The reported overall yield of the diester was 39–43%. This was raised to 58% by employing anhydrous citric acid and using a connecting 5-l. overflow flask at the stage of addition of citric acid to the cooled fuming sulfuric acid.

Diethyl 3-Chloroglutaconate.—To 101 g (0.5 mol) of diethyl acetonedicarboxylate in a 1-l., round-bottom flask was added, as rapidly as the brisk evolution of hydrogen chloride gas allowed, 105 g (0.5 mol) of phosphorus pentachloride. The mixture was stirred during addition and kept below 50° by means of an ice bath. The solution was poured into 1 kg of ice contained in a

large flask, since evolution of hydrogen chloride was vigorous. The red oil at the bottom of the flask was separated and the aqueous layer was extracted with 300 ml of chloroform. The combined oil and chloroform extract was washed with 10% potassium carbonate, followed by saturated salt solution, and then was dried using magnesium sulfate. Distillation gave 78 g (75% yield) of diethyl 3-chloroglutaconate,¹⁵ bp 90° (0.25 mm).

Diethyl 3-Dicarbethoxymethylglutaconate.—The Michael addition reaction was carried out in a 1-l. flask containing 1.1 mol of diethyl sodiomalonate dissolved in 300 ml of ethanol. Diethyl 3-chloroglutaconate (22.5 g, 1 mol) was added dropwise with stirring at such a rate that boiling occurred. After addition, the reaction mixture was heated under reflux for 0.5 hr, cooled, and poured into 1 kg of ice. The oil that formed at the bottom of the flask was separated, and the water layer was extracted with 400 ml of ether. The combined oil and the ether extract was washed with dilute hydrochloric acid, followed by saturated salt solution, and then dried with magnesium sulfate. After removing the ether, the product was heated under reduced pressure at 70° (0.25 mm) to remove the low-boiling impurities. The undistilled residue¹⁶ (ca. 70% yield) was nearly pure diethyl 3-dicarbethoxymethylglutaconate and was used in the next step.

Diethyl 2-Carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate.—To a solution of 1 mol of ethyl sodiocyanoacetate and 300 ml of ethanol contained in a 1-l. flask was added, with stirring, 172 g (0.5 mol) of crude diethyl 3-dicarbethoxymethylglutaconate from the previous step. The reaction mixture was heated under reflux for 8 hr, cooled, and poured into 180 ml of 6 N ice-cooled hydrochloric acid. The oil that formed at the bottom of the flask was collected and the water layer was extracted with 400 ml of ether. The combined oil and ether extract was washed with 10% potassium carbonate, followed by saturated salt solution, and then dried with magnesium sulfate. Distillation under reduced pressure gave 137 g (60% yield) of diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate, bp 180° (0.5 mm).

Anal. Calcd for C₂₁H₃₁N₂O₁₀: C, 55.13; H, 6.83. Found: C, 54.70; H, 6.64.

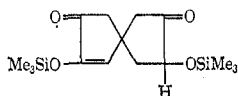
Methanetetraacetic Acid.—A solution of 116 g (0.25 mol) of diethyl 2-carbethoxy-4-cyano-3,3-dicarbethoxymethylglutarate and 230 ml of concentrated sulfuric acid was allowed to stand at room temperature for 12 hr. The mixture was diluted with twice its volume of water and heated until the vapor reached the boiling point of water. A water condenser was then attached, and the mixture was refluxed for a total reaction period of 48 hr. The mixture was cooled and filtered using a coarse, sintered-glass funnel. The product was recrystallized from water and gave 44 g (70% yield) of methanetetraacetic acid as a white solid, mp 230° (lit.¹¹ mp 226°).

Tetramethyl Methanetetraacetate (3).—To a solution of 50 g (0.2 mol) of methanetetraacetic acid and 500 ml of absolute methanol in a 1-l., three-neck flask was added slowly with stirring 90 ml of concentrated sulfuric acid. A stream of methanol generated from another flask was passed into the main reaction flask under the liquid surface, and at the same time the main reaction flask was heated. Following removal of about 2 l. of distillate, the mixture was cooled and poured into 1 l. of cold, saturated salt solution. It was extracted three times with 300-ml portions of ether. The ether extract was washed with 10% sodium bicarbonate, followed by saturated salt solution, and dried with magnesium sulfate. Distillation under reduced pressure gave 56 g (93% yield) of tetramethyl methanetetraacetate, bp 155–160° (0.25 mm) [lit.¹⁷ bp 192–195° (12 mm)].

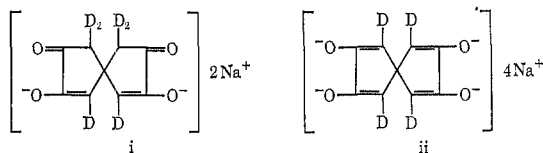
The nmr spectrum (CCl₄) shows peaks at τ 6.35 (12 H) and 7.2 (8 H).

3,8-Dihydroxyspiro[4.4]nona-3,8-diene-2,7-dione (1).—About 75 ml of liquid ammonia was distilled from a commercial cylinder of anhydrous ammonia through a drying tube filled with lump barium oxide into a three-neck flask equipped with mechanical stirrer and a Dry Ice-acetone cooled condenser. Sodium (1.8 g, 0.08 g-atom) cut in small pieces was added to the ammonia. After the system was flushed with helium, a solution of 3 g (0.01 mol) of 3 and 100 ml of anhydrous ether was added over a period of 2 hr. The blue color disappeared at the end of the addition. The Dry Ice was removed from the condenser, and the ammonia was evaporated using a cold-water bath. The last

(9) Had the species 8 undergone disproportionation to form 5 and 1, then compound 4 rather than 7 would have resulted. A referee suggested the following structure as a disproportionation product, but we did not observe it.



(10) This finding establishes the salt structure as i rather than ii.



Ultraviolet studies are in agreement with this conclusion in that there is only a slight bathochromic shift going from neutral to basic solution.

(11) C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, **121**, 1638 (1922).

(12) Melting points were determined with a Fisher-Johns melting point apparatus and boiling points are uncorrected. The nmr measurements were done at ambient temperature using a Varian A-60A spectrometer. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrophotometer. Mass spectra were measured with an AEI Model MS12 spectrometer. The microanalyses were done by Midwest Microlab, Inc., Indianapolis, Ind.

(13) R. Adams and H. M. Chiles, "Organic Syntheses," Coll. Vol. I, 2nd ed, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1941, p 10.

(14) Reference 13, p 237.

(15) This procedure is simpler than Ingold's method.¹¹

(16) Distillation at reduced pressure was accompanied with considerable decomposition.¹¹

(17) H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **54**, 62 (1935).

traces of ammonia were flushed out by passing helium into the system.

A. Air Oxidation Method.—Dry air was passed into the above stirred mixture for 0.5 hr at the approximate rate of 200 ml/min. Then 14 ml of 6 *N* hydrochloric acid was added and the mixture was saturated with ammonium chloride and extracted with three 50-ml portions of tetrahydrofuran (THF). The THF extract was washed with 20 ml of saturated salt solution and dried with magnesium sulfate. After removal of the THF, a yellow solid formed which was recrystallized from water to give 0.45 g (25% yield) of compound 1: mp 245° dec; nmr (D_2O) τ 3.5 (2 H) and 7.3 (4 H); ir (KBr) 1725 and 1675 cm^{-1} ; uv (95% EtOH) λ_{max} 260 $m\mu$ (ϵ 13,000) and 225 (broad shoulder) (6000); mass spectrum m/e (rel intensity, ion) 180 (65, M), 152 (40, M - CO), 137 (80, M - C_2H_5O), 69 (80), 57 (90), and 55 (base peak).

Anal. Calcd for $C_9H_9O_4$: C, 60.00; H, 4.48. Found: C, 59.98; H, 4.71.

A sample of compound 1, *o*-phenylenediamine, and 10 ml of absolute ethanol was refluxed for 5 min. The diquinoxaline derivative that formed was collected, washed with ethanol, and recrystallized from chloroform: mp 310° dec; nmr ($CDCl_3$) τ 2.1 (center of multiplet, 8 H) and 6.6 (8 H); mass spectrum m/e (rel intensity) 324 (70, M), 182 (70), 143 (60), 103 (100), and 77 (90).

B. Oxidation by Iodine.—Rather than adding air to the above mixture, a solution of 2.5 g (0.01 mol) of iodine and 100 ml of THF was added dropwise with stirring. The same work-up as in the air oxidation method was used and compound 1 was obtained in 25% yield.

3,8-Bis(trimethylsilyloxy)spiro[4.4]nona-3,8-diene-2,7-dione (6).—Procedure B above was completed to the point of adding 2.5 g (0.01 mol) of iodine in THF, and then 10 ml of trimethylchlorosilane (TMCS) was added immediately. The mixture was stirred for 10 min and filtered, and, after removal of the THF from the filtrate, a solid resulted. It was recrystallized from carbon tetrachloride and gave 0.3 g (25% yield) of compound 6: mp 100°; nmr (CCl_4) τ 3.67 (2 H), 7.42 (4 H), and 9.74 (18 H); ir (Nujol) 1715 and 1610 cm^{-1} ; mass spectrum m/e (rel intensity) 324 (2, M), 300 (10), 281 (6), 75 (25), and 73 (base peak).¹⁸

Anal. Calcd for $C_{15}H_{24}O_4Si_2$: C, 55.54; H, 7.46. Found: C, 55.75; H, 7.44.

Compound 6 was converted into 1 by heating a methanol solution of it for 1 hr under a nitrogen atmosphere. After removal of methanol, 1 formed in 95% yield.

3,8-Bis(trimethylsilyloxy)spiro[4.4]nona-2,7-dione (7).—The iodine oxidation procedure (B) was completed to the point of adding 1.2 g (0.005 mol) of iodine in 50 ml of THF, and then 5 ml (0.05 mol) of TMCS was added immediately. The mixture

was filtered, and following removal of the THF a solid remained. A sample dissolved in carbon tetrachloride was shown by nmr analysis to contain 6 and 7, and, on treatment with methanol at reflux for 2 hr, the silyl moieties of both were lost. Recrystallization of the solid from dry Skellysolve B gave 7 in 10% yield: mp 143°; nmr ($CDCl_3$) τ 6.0 (2 H), 7.7 (4 H), 8.5 (4 H), and 9.84 (18 H); ir (Nujol) 1730 cm^{-1} ; mass spectrum m/e (rel intensity) 328 (2, M), 313 (25), 183 (3), 129 (70), 101 (40), 75 (40), and 73 (base peak).

Anal. Calcd for $C_{15}H_{28}O_4Si_2$: C, 54.86; H, 8.15. Found: C, 54.79; H, 8.42.

2,3,7,8-Tetrakis(trimethylsilyloxy)spiro[4.4]nona-2,7-diene (4).—The procedure described for the preparation of 1 was carried to the point of removing the last traces of ammonia with helium. A solution of 16 ml of TMCS and 100 ml of dry ether was added slowly to the ice-cooled reaction flask and the mixture was stirred for 0.5 hr and filtered. Distillation of the filtrate gave 4.2 g (90% yield) of 4: bp 126° (0.25 mm); nmr (CCl_4) τ 7.8 (8 H) and 9.8 (36 H); ir (liquid film) 1750, 1700, and 1650 cm^{-1} ,¹⁹ mass spectrum m/e (rel intensity) 472 (1, M), 467 (8), 385 (15), 356 (15), 255 (30), 147 (15), 75 (15), and 73 (base peak).

Anal. Calcd for $C_{21}H_{44}O_4Si_4$: C, 53.33; H, 9.38. Found: C, 53.33; H, 9.19.

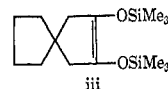
Compound 4 was also obtained in a mixture from the acyloin condensation using sodium, TMCS, and xylene heated under reflux. The mixture was separated on a silica gel column using benzene-Skellysolve B to give 4 in 20% yield.

3,8-Dihydroxyspiro[4.4]nona-2,7-dione (2).—A solution of 3 g of 4 and 25 ml of absolute methanol was refluxed under nitrogen for 2 hr. The solution was concentrated to about 6 ml by means of a rotary evaporator. The nmr spectrum of the solution showed chemical shifts typical of an acyloin. Complete removal of the methanol on a rotary evaporator gave a solid polymer that was insoluble in acetone.

Registry No.—1, 23936-85-8; 4, 23936-87-0; 6, 23936-88-1; 7, 23936-89-2; diethyl 2-carbomethoxy-4-cyano-3,3-dicarbomethoxymethylglutarate, 23936-86-9.

Acknowledgment.—We are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society (Grant 3270-A1) for financial support.

(19) These unusual absorption bands have been observed in the model compound iii.



(18) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead [*J. Org. Chem.*, **34**, 2324 (1969)] reported the mass spectra of trimethylsilyl enol ethers.