ture was handled and worked up to the point as described by the first paragraph in the procedure for **2**.

Using an *uncovered* 250-ml erlenmeyer flask, the dark red syrup in 25 ml of ethanol was treated with an equal volume of concentrated hydrochloric acid, and the resulting solution was disgested at 75–80° for 2.0–2.5 hr, during which a lightening in color could be observed. The hot solution was treated with a small amount of charcoal and filtered, and the filtrate was allowed to stand undisturbed to yield a yellow, crystalline product. A 25-ml portion of water was then added and after 1–3 hr, the product was collected and vacuum dried. The yield was 0.65 g. When recrystallized by adding small amounts of water to the compound's hot methanolic solution, the yield of pure **3** was 0.54 g, mp 104–105 and/or 110–111° (lit.[4] mp 110–111°). The melting point of the product depended upon the crystalline form. As described by Hooker, this substance has a very characteristic crystallization pattern. When obtained as reflecting, brilliant yellow platelets, the compound had mp 104–105 and 110–111°; as canary needles the melting point was 110–111°.

The Determination of the Quantity of the Furano-1,4-naphthoquinone 3 Produced in the Oxidation Reaction.—A 1.0-g sample of isolapachol was oxidized, and the mixture was handled and worked up to the point described by the first paragraph in the procedure for **2**. After being dried overnight *in vacuo*, the residue was dissolved in a minimum amount of benzene and adsorbed on a 25 × 4.5 cm column of Woelm neutral alumina (activity III). The column was eluted with benzene, whereupon good separation of **3** and **2** was obtained. (Compounds **6** and **7** are slowly converted to **2** by the adsorbent.) The yield of crude **3** (chromatographically pure, tlc) was 44.40 mg. Recrystallization from methanol–water gave 30 mg of canary yellow needles, mp 111–112°. The furano-1,2-naphthoquinone **2** was subsequently eluted with benzene–ethyl acetate–acetic acid (90:10:1) and recrystallized from ethanol–water. The yield was 0.60 g, mp 92–95°.

An Approximate Material Balance of the Oxidation Reaction Using 1 Mole of Mercurous Acetate.—Employing 1.0 g (4.12 mmoles) of isolapachol, 1.32 g (4.12 mmoles) of mercuric acetate, and a total volume of 50 ml of acetic acid, an oxidation was carried out as described in the first paragraph for the preparation of **2**. After the oxidation solution had cooled to room temperature, the mercurous acetate was collected, washed successively with acetic acid and ether, and vacuum dried. The yield was 0.98 g (92% of theory). Tlc showed that the solution contained **2**, **6**, and **7** (as one zone), and a considerable amount of isolapachol.

The deep red oxidation solution was evaporated under reduced pressure, first at the water pump, and then using a vacuum pump to remove the last traces of acetic acid. The syrupy residue was taken up in 50 ml of ether and extracted with three 15-ml portions of 1% sodium hydroxide. The combined purple, alkaline extract was filtered and acidified with concentrated hydrochloric acid. The yellow, turbid solution deposited an orange solid, which was collected after keeping the flask in the cold for 1 hr. The vacuum-dried solid (0.38 g) was chromatographically pure (tlc) and was identical with isolapachol. Recrystallized from methanol, the compound was obtained as slender, orange needles, mp 118–122° (lit.[4] mp 120°).

The ether solution, from which the isolapachol was extracted, was washed with water and dried over anhydrous sodium sulfate. Tlc of the solution indicated three components: **2**, **3** (in low concentration), and **6** and **7** (as one zone). After removal of the ether, the syrupy mixture was converted, as previously described, but using 25 ml of ethanol, 5 ml of water, and 10 drops of hydrochloric acid, to **2**. The yield was 0.36 g, mp 91–94°.

The Attempted Oxidation of Hydrolapachol with Mercuric Acetate.—An oxidation was conducted in the usual manner, employing 0.5 g (2.05 mmoles) of hydrolapachol,[17] 1.30 g (4.10 mmoles) of mercuric acetate, and 25 ml of acetic acid. Mercurous acetate did not separate from the solution either before or after the heating period, and tlc indicated hydrolapachol as the sole reaction component. The reisolated hydrolapachol, after recrystallization from methanol–water, amounted to 0.38 g, mp 88–89°, and was identified by tlc and mixture melting point.

The Attempted Oxidation of 2-O-Acetylisolapachol with Mercuric Acetate.—A solution of 0.1 g (0.35 mmole) of isolapachol acetate[4] and 0.23 g (0.70 mmole) of mercuric acetate in 15 ml of acetic acid was kept at room temperature for 22 hr. Precipitation of mercurous acetate was not observed. A chromatogram, eluted in benzene, showed only isolapachol acetate. Brief warming of the solution did not cause oxidation.

(17) S. C. Hooker, *J. Am. Chem. Soc.*, **58**, 1163 (1936).

Registry No.—**1**, 4042-39-1; **2**, 13019-42-6; **3**, 13019-43-7; **6**, 13019-44-8; **7**, 13019-45-9; mercuric acetate, 1600-27-7.

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N-(2-Mercaptoethyl)alanine and Related Compounds[1]

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The synthesis of N-(2-mercaptoethyl)alanine (**3**) and related compounds was undertaken as a result of a general interest in ω-(2-mercaptoethylamino)alkanoic acids accruing from the reported radioprotective properties of N-(2-mercaptoethyl)glycine.[2] Synthesis of the glycine derivative was accomplished in two ways: one[2] involving ring opening of ethyl 1-aziridineacetate with hydrogen sulfide followed by hydrolysis, and the other[2b] by alkylation of 2-(benzylthio)ethylamine with ethyl chloroacetate followed by hydrolysis and debenzylation. A method based on the addition of 2-(tritylthio)ethylamine to acrylic compounds followed by detritylation was recently applied to the synthesis of mercaptoethylated β-alanine derivatives,[3] but is obviously not useful in the synthesis of the α isomers. The method selected for the present investigation was adapted from the previously reported[4] reduction of 2-substituted thiazolidines with sodium borohydride and proved to be advantageous in spite of a subsequently encountered functional group limitation. The route that evolved is outlined in Scheme I.

2-Methyl-2-thiazolidinecarboxylic acid (**1**), the precursor of both **3** and the corresponding carboxamides **6** (**a** and **b**), was prepared by the reported[5] condensation of pyruvic acid and 2-aminoethanethiol in good yields, but the preparation of **1** was later made more convenient by *in situ* neutralization of commercially available 2-aminoethanethiol hydrochloride with triethylamine. The product isolated after ring opening of **1** by sodium borohydride in 2-propanol under reflux and in methanol at room temperature was the water-insoluble N,N′-(dithiodiethylene)bisalanine (**2**), oxidation apparently occurring during the isolation process. The preferred preparation of **2**, however, involved reduction

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

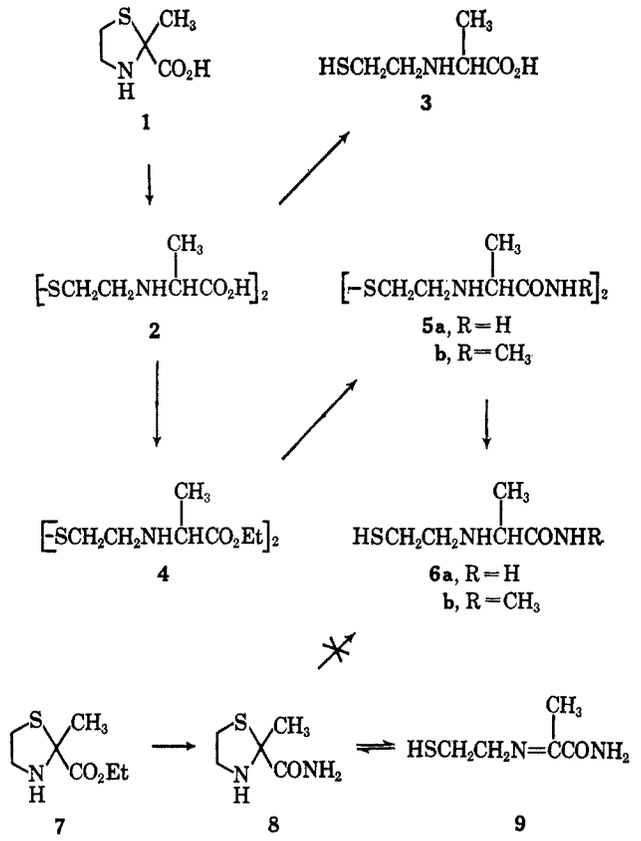
(2) (a) E. Felder, F. Bonati, and S. Bianchi, *Experientia*, **15**, 32 (1959); (b) E. Felder and S. Bianchi, German Patent 1,062,705 (1959).

(3) F. I. Carroll, H. M. Dickson, and M. E. Wall, *J. Org. Chem.*, **30**, 33 (1965).

(4) E. L. Eliel, E. W. Della, and M. M. Rogić, *ibid.*, **27**, 4712 (1962).

(5) E. Biekert, J. Sonnenbichler, and D. Hoffmann, *Chem. Ber.*, **95**, 1466 (1962).

SCHEME I



of **1** in aqueous solution (rather than in alcoholic suspension) followed by *in situ* air oxidation at pH 6. Conversion of **2** to **3** was accomplished by low-pressure catalytic hydrogenolysis.[6]

An approach based on the reductive ring opening of 2-methyl-2-thiazolidinecarboxamide (**8**) was considered first in a proposed synthesis of 2-(2-mercaptoethylamino)propionamide (**6a**). A tedious isolation of 2-aminoethanethiol, which is condensed with ethyl pyruvate in the reported[5] preparation of the intermediate ethyl 2-methyl-2-thiazolidinecarboxylate (**7**), was again avoided, as in the modified preparation of **1**, by the use of the aminothiol hydrochloride and 1 molar equiv of a base—this time sodium acetate. Ammonolysis of **7** in methanol at 85° afforded **8** in near quantitative yield. An aqueous solution of **8** gave a positive nitroprusside test for thiol suggesting an equilibrium with the Schiff base **9**, which is in accord with previous observations of thiazolidine equilibria.[7] The conversion of **8** to 2,2′-[dithiobis(ethylenimino)]bispropionamide (**5a**) was attempted by borohydride reduction in water in the same manner as that of **1**, but only unchanged **8** (48%) was isolated. Repetition of the reduction in the presence of acetic acid (1 molar equiv) and an increased amount of borohydride (2 molar equiv) gave a similar result (29% recovery of **8**). The use of 3 molar equiv of borohydride in 2-propanol at 65° for 1 hr resulted in a 40% recovery of **8**, but, when such a solution was refluxed for 5 hr, several products were formed as indicated by thin layer chromatography.

(6) For related examples of catalytic hydrogenolysis of disulfides, see T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **28**, 1305, 1436 (1963); T. P. Johnston and C. R. Stringfellow, Jr., *J. Med. Chem.*, **9**, 921 (1966).

(7) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936); G. Hesse and G. Ludwig, *Ann. Chem.*, **632**, 158 (1960); T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **27**, 2452 (1962).

The attempted conversion of **8** to **6a** having failed, an alternative approach was sought in which amide formation could be effected after ring opening. Esterification of **2** in refluxing ethanolic hydrogen chloride solution afforded diethyl N,N′-(dithiodiethylene)bisalaninate (**4**), which was freed from its dihydrochloride with ethanolic ammonia. Ammonolysis of **4** in methanol at 90° produced the bispropionamide **5a**. Repeated attempts to reduce **5a** catalytically (30% Pd–C, H_2 at 50 psi) in water and isolate the product as a hydrochloride gave gummy, hygroscopic solids, which could not be purified. Hydrogenolysis in ethanol instead of water proved advantageous, but not until the starting disulfide was scrupulously purified by repeated crystallizations could pure, crystalline (but hygroscopic) 2-(2-mercaptoethylamino)propionamide (**6a**) hydrochloride be isolated.

The procedure for the preparation of **6a** could not be generalized for the preparation of N-substituted congeners by replacing ammonia with primary and secondary amines. Reactions of **4** with several amines (methyl, ethyl, dimethyl, cyclohexyl, and benzyl) were attempted under varied conditions; but, of these, only methylamine gave the desired result: 2,2′-[dithiobis(ethylenimino)]bis(N-methylpropionamide) (**5b**) was obtained as a viscous oil, and 2-(2-mercaptoethylamino)-N-methylpropionamide (**6b**) hydrochloride was isolated as a pale yellow glass—both analytically pure. Forcing conditions of prolonged reaction times and higher temperatures resulted in complex reaction mixtures, as did attempted boron trifluoride catalyzed[8] and thermally promoted[9] exchange reactions of **5a** with aniline.

Experimental Section[10]

2-Methyl-2-thiazolidinecarboxylic Acid (1).—A solution consisting of 2-aminoethanethiol hydrochloride (19.5 g, 0.171 mole), freshly distilled pyruvic acid (19.9 g, 0.171 mole), xylene (205 ml), chloroform (137 ml), glacial acetic acid (51.4 ml), and triethylamine (17.3 g, 0.171 mole) was heated under reflux for 3 hr. A portion of the solvent (105 ml) was removed by distillation and the remaining solution was refrigerated overnight. The deposited solid was collected, washed with benzene, and recrystallized from 4:1 ethanol–water (600 ml) to give **1** as white needles, which were dried *in vacuo* at 60° over P_2O_5: yield 15.3 g (61%); mp 225° dec (lit.[5] mp 179° dec); infrared absorption (KBr) at 3300–1800 (NH_2^+), 1610 (s, broad, NH_2^+, CO_2^-), 1350 cm^{-1} (s, CO_2^-).

Anal. Calcd for $C_5H_9NO_2S$: C, 40.79; H, 6.16; N, 9.52. Found: C, 41.03; H, 6.25; N, 9.45.

N,N′-(Dithiodiethylene)bisalanine (2).—Sodium borohydride (1.54 g, 40.7 mmoles) was added slowly (50 min) to a stirred solution of **1** (3.00 g, 20.4 mmoles) in water (30 ml) at 0°. The resulting solution was stirred for 45 min cold, adjusted at room temperature to pH 6 with 6 *N* HCl, and filtered. The collected precipitate was washed with two 5-ml portions of water and the washings were added to the filtrate. The filtrate, exposed to air, was stirred at room temperature for 1 week, during which period successive crops of crystalline **2** were collected, washed with water, and dried *in vacuo* over P_2O_5: total yield 1.65 g (55%); melting point of each crop in the range 260–277° dec. The analytical sample, mp 274–277° dec, was obtained by recrystallization from water: infrared absorption (KBr) at 3220–1850 (NH_2^+), 1615 (s, NH_2^+), and 1585 (s) and 1350 cm^{-1} (s) (CO_2^-).

Anal. Calcd for $C_{10}H_{20}N_2O_4S_2$: C, 40.53; H, 6.80; N, 9.45. Found: C, 40.45; H, 6.89; N, 9.33.

(8) F. J. Sowa and J. A. Nieuwland, *J. Am. Chem. Soc.*, **59**, 1202 (1937).

(9) J. H. MacGregor and F. Ward, *J. Soc. Chem. Ind. Japan*, **66**, 344 (1947).

(10) Melting points for which a range is recorded were determined with a Mel-Temp apparatus; those for which no range is recorded, with a Kofler Heizbank. Infrared spectra were determined with a Perkin-Elmer spectrophotometer (Model 521 or 221-G).

N-(2-Mercaptoethyl)alanine (3).—A partial solution of **2** (1.00 g, 3.37 mmoles) in water (70 ml) was shaken with hydrogen at 50 psi and 30% palladium on charcoal (0.50 g) in a Parr apparatus for a total of 48 hr, more catalyst (0.50 g) being added after the first 24 hr. The catalyst was removed by filtration through a Celite pad under nitrogen and rinsed with water (50 ml). The dark filtrate and washings were combined and evaporated to dryness *in vacuo* and the residue was extracted with methanol (100 ml) at 40°. The extract was treated with charcoal and filtered under nitrogen; the filtrate was evaporated to dryness *in vacuo* leaving **2** as a white solid, which was dried *in vacuo* over P_2O_5: yield 680 mg (68%); mp 212°; infrared absorption (KBr) at 3190–1820 (NH_2^+), 1620 (s, NH_2^+), and 1560 cm^{-1} (s, CO_2^-).

Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.24; H, 7.43; N, 9.39; SH, 22.17. Found: C, 40.00; H, 7.39; N, 9.20; SH, 22.0.

Diethyl N,N'-(Dithiodiethylene)bisalaninate (4).—Ethanol (100 ml) was saturated with hydrogen chloride at room temperature and added to a suspension of **2** (10.0 g, 33.7 mmoles) in ethanol (100 ml). The solid rapidly disssolved, and the solution was heated under reflux for 2 hr. Benzene (40 ml) was added to the solution, which was slowly distilled until 130 ml of distillate was collected. The remaining solution was evaporated to dryness *in vacuo* at 60° leaving a viscous syrup, which was triturated thoroughly in ethanol (10 ml) saturated at 0° with ammonia. The white suspension was diluted with ether (200 ml) and filtered from ammonium chloride, which was washed with ether (two 30-ml portions). The filtrate and washings were combined and evaporated to dryness at 60° *in vacuo* (0.1 mm), and the residue was re-extracted with ether (100 ml). The filtered ether solution was evaporated to dryness at 60° (0.1 mm) and the residue was kept at this temperature and pressure for several hours leaving **4** as a colorless, clear oil: yield 5.18 g (44%); $n^{25}D$ 1.4942; infrared absorption (film) at 3320 (w, NH), 2975 (m), 2930, 2905, and 2840 (CH), 1730 (s, C=O), and 1175 cm^{-1} (ms, COC).

Anal. Calcd for $C_{14}H_{28}N_2O_4S_2$: C, 47.70; H, 7.97; N, 7.95; S, 18.19. Found: C, 47.84; H, 7.97; N, 7.87; S, 18.2.

2,2'-[Dithiobis(ethylenimino)]bispropionamide (5a).—A solution of **4** (3.78 g, 10.7 mmoles) in methanol (80 ml) was saturated with ammonia at 0° and heated in a stainless steel pressure vessel (glass liner) at 90° overnight. The resultant solution was evaporated to dryness *in vacuo* and the residue was dissolved in hot ethanol (15 ml), treated with charcoal, and filtered. Refrigeration of the filtrate produced **5a** as white crystals, which were washed with cold ethanol (10 ml) and dried *in vacuo* over P_2O_5: yield 2.51 g (80%); mp 125–127°; infrared absorption (KBr) at 3265 (s, sharp, NH), 3300 and 3125 (NH_2), 2977, 2910, and 2830 (CH), 1690 (s, amide I), and 1660 cm^{-1} (s, amide II).

Anal. Calcd for $C_{10}H_{22}N_4O_2S_2$: C, 40.79; H, 7.53; N, 19.03; S, 21.78. Found: C, 41.05; H, 7.56; N, 18.83; S, 21.9.

2,2'-[Dithiobis(ethylenimino)]bis(N-methylpropionamide) (5b).—A solution of **4** (7.05 g, 20.0 mmoles) and methylamine (53.0 g, 1.73 moles) in methanol (90 ml) was heated in a stainless steel pressure vessel (glass liner) at 90° for 16 hr. The reaction mixture was evaporated on a rotary evaporator to an oil, which was dissolved in ethyl acetate (20 ml), charcoaled, and filtered. Evaporation of the filtrate at 60° (0.2 mm) left **5b** as a viscous oil: yield 6.38 g (99%); $n^{27.4}D$ 1.5380; infrared absorption (film) at 3300 (m, broad, NH), 2960, 2920, and 2830 (CH), 1650 (s, amide I), and 1530 cm^{-1} (m, amide II).

Anal. Calcd for $C_{12}H_{26}N_4O_2S_2$: C, 44.69; H, 8.13; N, 17.37; S, 19.89. Found: C, 44.79; H, 8.12; N, 17.35; S, 19.8.

2-(2-Mercaptoethylamino)propionamide (6a) Hydrochloride.—A sample of **5a** (3.00 g, 10.2 mmoles), which had been recrystallized three times from ethanol, was suspended in ethanol (100 ml) and hydrogenated in a Parr apparatus at 50 psi in the presence of 30% palladium on charcoal (0.50 g). After 16 hr, additional catalyst (0.50 g) was added, and the hydrogenation was continued for 24 hr. The resulting mixture was filtered under N_2, and the filtrate was evaporated at 35° on a rotary evaporator to about 15 ml. Addition of 6.35 *N* hydrogen chloride in ethanol (3.47 ml, 22.0 mmoles) and ether (100 ml) caused the separation of an oil, which crystallized when the mixture was cooled. The **6a** hydrochloride was collected under N_2 and dried *in vacuo* over P_2O_5: yield 2.97 g (79%); mp 121–123°; infrared absorption (KBr) at 3500–2200 (NH_2^+), 1680 (s, amide I), and 1610 cm^{-1} (w, amide II).

Anal. Calcd for $C_5H_{12}N_2OS\cdot HCl$: C, 32.51; H, 7.09; N, 15.17; S, 17.36; SH, 17.90. Found: C, 32.74; H, 6.94; N, 14.92; S, 17.51; SH, 17.5.

2-(2-Mercaptoethylamino)-N-methylpropionamide (6b) Hydrochloride.—A solution of **5b** (3.20 g, 9.92 mmoles) in ethanol (100 ml) was hydrogenated at 50 psi in the presence of 30% palladium on charcoal (0.50 g) in a Parr apparatus for a total of about 40 hr, additional catalyst (0.50 g) being added after about 16 hr. The resulting mixture was filtered under N_2, and the filtrate was evaporated at 35° on a rotary evaporator to about 15 ml. Addition of 9.50 *N* hydrogen chloride in ethanol (2.30 ml, 21.8 mmoles) and ether (100 ml) caused the separation of an oil. The supernatant ether layer was removed by decantation, and the oily product was dried *in vacuo* over P_2O_5 to give pure **6b** as a resinous solid: yield 3.55 g (90%); melting point indefinite; infrared absorption (KBr) at 3150–2250 (NH_2^+), 1675 (s, amide I), and 1565 cm^{-1} (m, amide II).

Anal. Calcd for $C_6H_{14}N_2OS\cdot HCl$: C, 36.26; H, 7.61; N, 14.10; S, 16.14; SH, 16.64. Found: C, 36.07; H, 7.46; N, 13.90; S, 16.07; SH, 16.53.

Ethyl 2-Methyl-2-thiazolidinecarboxylate (7).—A mixture of 2-aminoethanethiol hydrochloride[11] (17.8 g, 0.157 mole), xylene (187 ml), chloroform (125 ml), acetic acid (39 ml), ethyl pyruvate (18.2 g, 0.157 mole), and sodium acetate (12.9 g, 0.157 mole) was refluxed under N_2 for 3 hr. A portion of the solvent (50 ml) was removed by distillation at atmospheric pressure; the remainder was removed *in vacuo* (water aspirator) at 100° (oil bath). The residue was stirred with benzene (100 ml) and the filtered solution was evaporated *in vacuo* (rotary evaporator). The residual oil was fractionated *in vacuo* by means of a short Vigreux column. The desired ester distilled at 56° (0.4 mm) [lit.[5] bp 87° (0.4 mm)]: yield 22.2 g (81%); infrared absorption (film) at 3310 (w, sharp, NH), 2980 (m), 2935, and 2880 (CH), 1730 (s, C=O), and 1175 cm^{-1} (s, COC).

Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48; N, 7.99. Found: C, 48.11; H, 7.60; N, 7.86.

2-Methyl-2-thiazolidinecarboxamide (8).—A solution of **7** (5.00 g, 28.5 mmoles) in methanol (30 ml) was saturated with ammonia at 0°, heated in a stainless steel pressure vessel (glass liner) at 85° for 21 hr, and evaporated to dryness *in vacuo*. Crystallization of the residual crude **8** from 1:2 methanol–benzene (24 ml) gave white crystals, which were dried *in vacuo* over P_2O_5: yield 2.95 g (71%); mp 143°; infrared absorption (KBr) at 3500–3010 (NH, NH_2, with sharp bands at 3430, 3305, and 3180), 2990, 2975, 2940, and 2875 (CH), 1670 (s, amide I), and 1570 cm^{-1} (wm, amide II).

Anal. Calcd for $C_5H_{10}N_2OS$: C, 41.07; H, 6.89; N, 19.16. Found: C, 41.19; H, 6.94; N, 18.92.

Registry No.—**1**, 13084-13-4; **2**, 13084-14-5; **3**, 13084-15-6; **4**, 13084-16-7; **5a**, 13084-17-8; **5b**, 13084-18-9; **6a** hydrochloride, 13084-19-0; **6b** hydrochloride, 13084-20-3; **7**, 13084-21-4; **8**, 13084-22-5.

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(11) Evans Chemetics, Inc., New York, N. Y.

Ring Contraction in the Clemmensen Reduction of a Cyclic β-Triketone

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Relative to our work in nmr studies of conformational isomerization in six-membered rings containing *gem*-dimethyl groups,[1,2] we have attempted to synthe-

(1) R. W. Murray, P. R. Story, and M. L. Kaplan, *J. Am. Chem. Soc.*, **88**, 526 (1966).

(2) R. W. Murray and M. L. Kaplan, *Tetrahedron*, **23**, 1575 (1967).