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Decarboxylative C-S Bond Formation. Synthesis of 1,4-Dimethyl-3,6-epidithio-2,5-piperazinedione and Related Compounds

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Heating of dipotassium salt of 3,6-dicarboxy-1,4-dimethyl-2,5-piperazinedione (**4**) with sulfur monochloride in dioxane gave 1,4-dimethyl-3,6-epidithio-2,5-piperazinedione (**11**) in 33% yield with simultaneous decarboxylation. When the reaction mixture from **4** and S_2Cl_2 was reduced with $NaBH_4$ and ethylated with ethyl iodide, *cis* 3,6-bis(ethylthio) derivative (**17**) was obtained in 50% yield besides a trace amount of *trans* isomer (**18**) and the monoethylthio derivative (**19**). Reactions of other metal salts (**16a**, **16b**, and **16c**) with S_2Cl_2 did not improve the yield of **11**. On the other hand the reaction of **4** with ethanesulfenyl chloride in dioxane did not yield **17**, but gave **18**, **19**, and hydroxylated compounds (**20**, **21**, and **22**) in low yields. Similar results were obtained in the reaction of **4** with benzenesulfenyl chloride. The mechanism of the decarboxylative C-S bond formation was also discussed.

A previous paper[2] has described that 3,6-diethoxycarbonyl-1,4-dimethyl-2,5-piperazinedione (**1**) reacts with sulfur monochloride (S_2Cl_2) to afford 3,6-diethoxycarbonyl-1,4-dimethyl-3,6-epipolythio-2,5-piperazinediones (**2**). Introduction of various alkyl groups into the 3- and 6-positions of **1** followed by decarboxylative C-S bond formation between 3- and 6-positions might provide a new method for preparing a number of 3,6-epipolythio-2,5-piperazinediones (**3**). Along this line of research, the decarboxylative C-S bond formation was studied with 3,6-dicarboxy-1,4-dimethyl-2,5-piperazinedione (**5**) and its potassium salt (**4**).

Hydrolysis of **1** with two equivalents of potassium hydroxide in methanol smoothly gave the potassium salt (**4**) which was converted to the free acid (**5**) on acidification. The decarboxylation of **5** to 1,4-dimethyl-2,5-piperazinedione (**6**) occurred in quantitative yield by heating of **5** in dioxane at 100—105° for 40 min. Treatment of **5** with an excess of benzaldehyde at 90—100° gave the 3-(α-hydroxybenzyl)-1,4-dimethyl-2,5-piperazinedione (**7**) (15.5%) and **6** (23.5%). Although 2,5-piperazinedione (**9**) is known to react with benzaldehyde in the presence of acetic anhydride and sodium acetate to give bisbenzylidene derivative (**10**),[3] attempted reaction of **6** with benzaldehyde under the same condition failed. Therefore, the compound (**7**) can not be produced from **6** initially formed by decarboxylation of **5**, but its formation should be associated with decarboxylation step of **5**.

When a solution of the diacid (**5**) and excess S_2Cl_2 in dioxane was heated at 80—85° for 30 min, decarboxylative C-S bond formation took place and 3,6-epitetrathio-1,4-dimethyl-2,5-piperazinedione (**8**) was isolated in 20% yield from gummy reaction products. Heating of **5** with sulfur in dimethylformamide gave the decarboxylated product (**6**) as the major product (62%), only a trace of sulfur containing compounds being noticed.

Subsequently, the reaction of the potassium salt (**4**) with S_2Cl_2 was examined. Refluxing of a suspension of **4** in anhydrous dioxane with S_2Cl_2 for 1.5 hr gave the desired 3,6-epidithio-1,4-dimethyl-2,5-piperazinedione (**11**) in 33% yield together with small amounts of the tetrasulfide (**8**) and the trisulfide (**12**). When the crude reaction mixture was reduced with sodium

1) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
2) T. Hino and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **22**, 2866 (1974).
3) *a*) M. Augustin, *J. Prakt. Chem.*, **32**, 158 (1966): *cf.* M. Augustin, *Wiss. Z. Univ. Halle XV'* 66 *M,H*, **4**, 553 (1966); *b*) C. Sin, M. Masaki, and M. Ohta, *J. Org. Chem.*, **32**, 1860 (1967).

borohydride in methanol followed by oxidation with iodine according to Schmidt procedure,[4] **11** was obtained in 35% yield. Since decarboxylation of **4** was not observed in a boiling dioxane unless S_2Cl_2 was added, the disulfide (**11**) was not assumed to be formed by the reaction of carbanion (**13**) with S_2Cl_2.

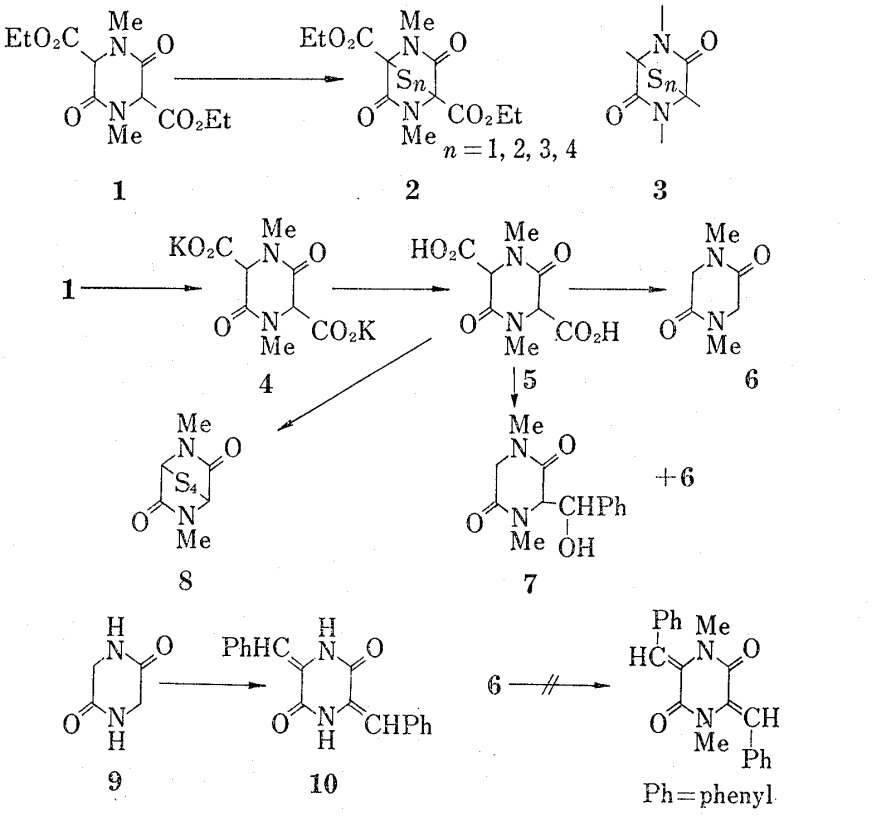

Chart 1

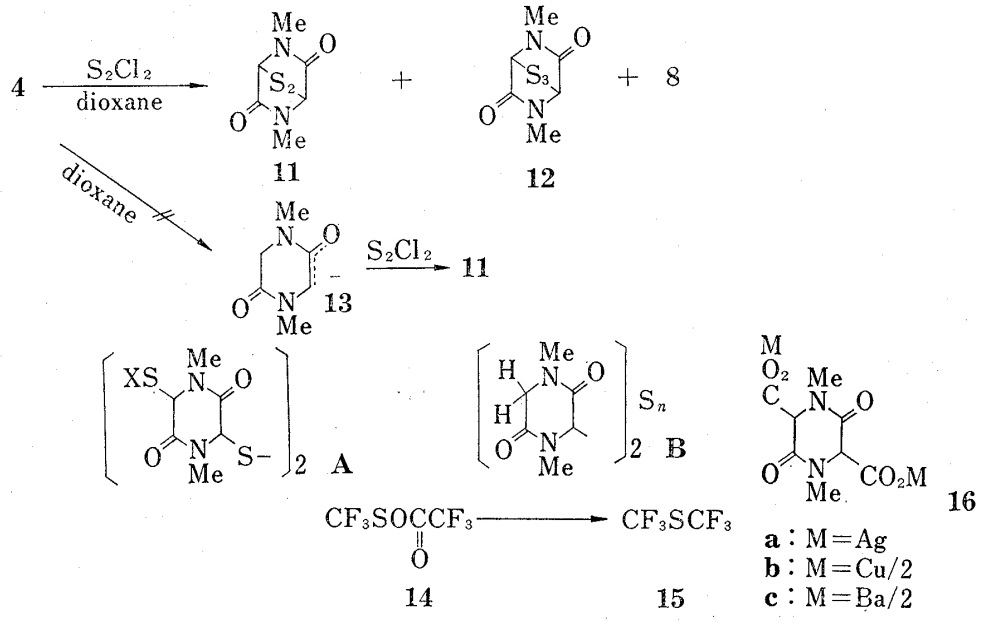

Chart 2

4) H. Poisel and U. Schmidt, *Chem. Ber.*, **104**, 1714 (1971).

Although trifluoromethanesulfenyl trifluoroacetate (**14**) was reported to convert into bis(trifluoromethyl) sulfide (**15**) by heating at 170°,[5] and the displacement of two carboxyl groups by disulfide function was described in a review by Ciustea,[6] no detailed information is available on decarboxyative C-S bond formation. Hence further examinations were carried out to improve the yield of **11**. The reaction of **4** with sulfur instead of S_2Cl_2 in a boiling dioxane did not proceed and **4** was recovered. The reaction of **4** with S_2Cl_2 in a boiling carbon tetrachloride with or without benzoyl peroxide did not proceed, however, that in a boiling chlorobenzene yielded the disulfide (**11**) and the tetrasulfide (**8**) in 10.5% and 4.7% yields, respectively, after successive treatment of the crude reaction mixture with sodium borohydride and iodine. The use of silver salt (**16a**) instead of **4** gave **11** and **8** in rather poor yields. The similar reaction of bivalent metal salts such as cuppuric (**16b**) and barium (**16c**) salts in boiling dioxane did not improve the yield of **11**.

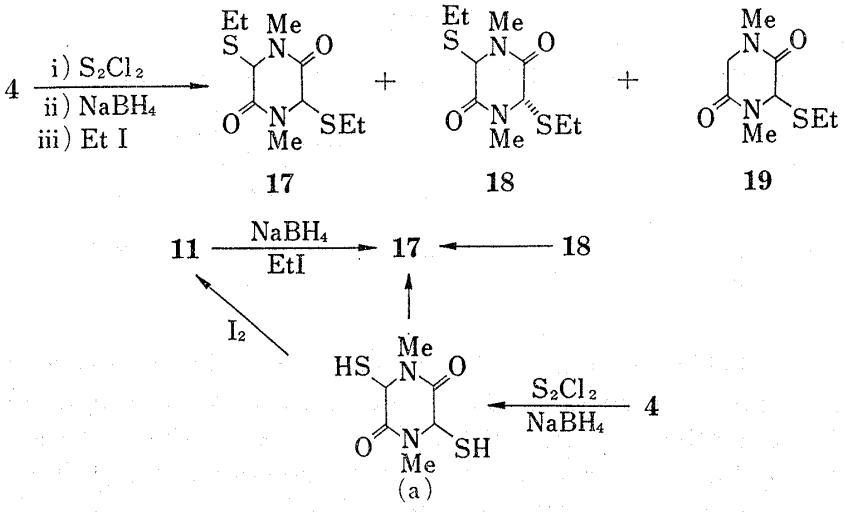

Chart 3

To find out the total amount of sulfur containing products including not only episulfides (**11**, **12**, and **8**) but the other type of sulfides such as A and B, the reaction mixture obtained by the reaction of **4** with S_2Cl_2 was treated with sodium borohydride and with ethyl iodide to give *cis* 3,6-bis(ethylthio)-1,4-dimethyl-2,5-piperazinedione (**17**), its *trans* isomer (**18**), and 3-ethylthio-1,4-dimethyl-2,5-piperazinedione (**19**) in 50%, 1%, and 23% yields respectively. This result indicates that C-S bond formation other than episulfide type did occur to some extent. The yields of **17**, **18**, and **19** were not much altered depending upon whether the reaction was carried out in N_2 or O_2 atmosphere, indicating that a free radical course is improbable, though it could not completely be ruled out.

Schmidt and his co-workers[4] have discussed the stereochemistry of 3,6-disubstituted 2,5-piperazinediones and deduced that the *cis* form having a shallow boat conformation is more stable than the *trans* form in 3,6-dimercapto, bis(methylthio)- and bis(ethylthio) derivatives. The *cis* isomer (**17**) has the same melting point as the reported *cis* isomer,[4] and its *cis* configuration was further supported by the following reactions. The *cis* isomer (**17**) was also obtained by the reduction of the disulfide (**11**) with sodium borohydride followed by ethylation with ethyl iodide, and the *trans* isomer (**18**) isomerized to **17** on treatment with base. Furthermore, the disulfide (**11**) was obtained when the *cis* dimercapto derivative (a) prepared by the reduction of **11** with sodium borohydride was oxidized with iodine.

From the above-mentioned results the direct preparation of 3,6-bis(alkylthio)-2,5-piperazinediones was now examined by using alkanesulfenyl chlorides instead of S_2Cl_2. A suspension

5) A. Haas and D.Y. Oh, *Chem. Ber.*, **102**, 77 (1969).
6) G. Ciustea, C. Demetrescu, and L. Ivan, *Revista. de Chim.* (*Bucharest*), **13**, 757 (1962) [*C.A.*, **59**, 62146 (1963)].

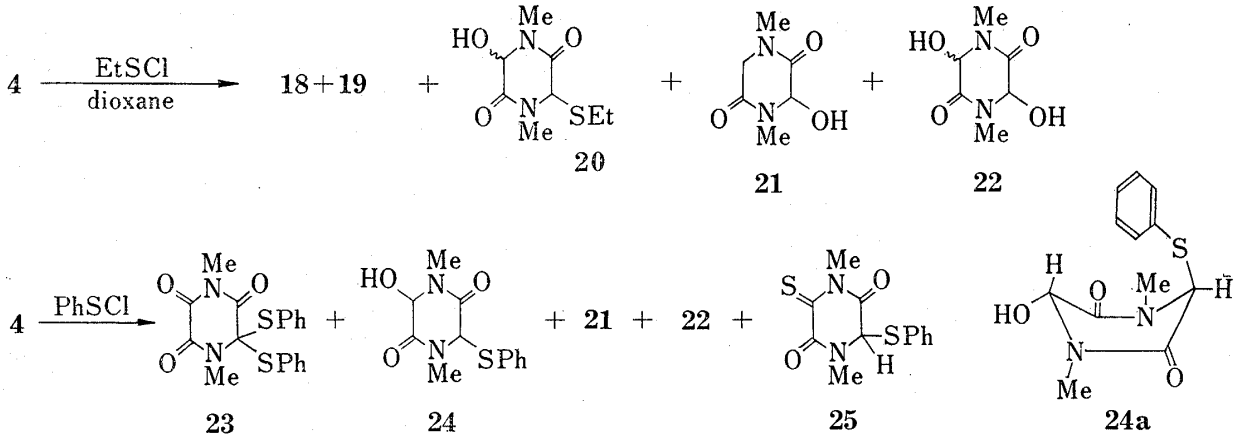

Chart 4

Table I. Reaction of 4 with Ethanesulfenyl Chloride in Dioxane

Condition	Products yield %				
	18	19	20	21	22
Under N_2 atmosphere	1.8	8.3	10.1	9.2	8.0
Under O_2 atmosphere	2.5	9.1	10.6	6.3	11.5

of **4** and ethanesulfenyl chloride in dioxane was refluxed for 1.5 hr to give a complex mixture of products. Separation by preparative TLC afforded the *trans* bis(ethylthio)derivative (**18**) and monoethylthio derivative (**19**), but not the *cis* isomer (**17**). Besides these products, there were also obtained hydroxylated compounds, 3-ethylthio-6-hydroxy-1,4-dimethyl-2,5-piperazinedione (**20**), 3-hydroxy-1,4-dimethyl-2,5-piperazinedione (**21**), and 3,6-dihydroxy-1,4-dimethyl-2,5-piperazinedione (**22**); these products had not been obtained on treatment of the reaction mixture obtained from **4** and S_2Cl_2 with sodium borohydride and ethyl iodide. The structures of **20**, **21**, and **22** were confirmed by elemental analyses and spectral data (see Experimental). Since yields of the hydroxylated compounds, **20**, **21**, and **22**, were not increased when the reaction was carried out under O_2 atmosphere (see Table I), the hydroxyl group may not originate from molecular oxygen. A possible pathway of their formation may involve the initial chlorination of the 3- and/or 6-positions with Cl_2 or an equivalent species produced by decomposition of ethanesulfenyl chloride in boiling dioxane and subsequent hydrolysis of the chlorides.

The similar reaction of **4** with benzenesulfenyl chloride gave 1,4-dimethyl-6,6-bis(phenylthio)-2,3,5-piperazinetrione (**23**, 7.8%), 3-hydroxy-1,4-dimethyl-6-phenylthio-2,5-piperazinedione (**24**, 3.4%), **21** (7%), **22** (25%), and 1,4-dimethyl-6-phenylthio-3-thioxo-2,5-piperazinedione (**25**) (trace). The structures of **23** and **24** were assigned by spectral data and elemental analyses (see Experimental). The NMR spectrum of **24** in DMSO-d_6 showed two doublets at 3.20 and 6.75 ppm. On addition of D_2O, the former became a singlet at 3.19 ppm and the latter doublet disappeared; these two doublets corresponded to CH–OH. The chemical shift of the methine proton was in higher field compared with that of the methylene protons in **6** (3.96 ppm), suggesting the conformation of **24** is a folded form (**24a**), where the hydroxy and phenylthio groups are *trans*. The NMR spectrum of **7** also suggested that **7** has a similar folded conformation. The similar observation has been reported in the case of 3-benzyl-2,5-piperazinedione.[7] The structure **25** was tentatively assigned from spectral data (see Experimental).

7) C.F. Liu and L.E. Webb, *J. Am. Chem. Soc.*, **95**, 6803 (1973).

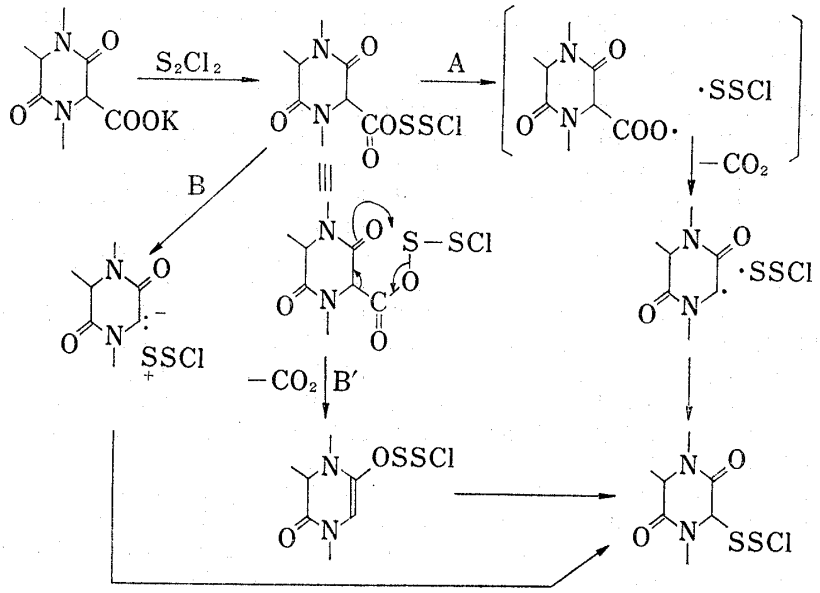

Chart 5

Thus the compound (**4**) was shown to undergo decarboxylative C-S bond formation on treatment with S_2Cl_2 or sulfenyl chlorides in a boiling dioxane. Apparently the reaction with S_2Cl_2 proceeded more readily than that with sulfenyl chlorides, and some hydroxylated compounds were also produced in the latter cases. Differences between their reactivities are not satisfactorily explained yet, but are partly due to their different stabilities in boiling dioxane. Since this decarboxylative reactions bear some resemblance to the Hunsdiecker bromination, the silver salt (**16a**) was heated with bromine in carbon tetrachloride and expected 3,6-dibromide was obtained in 76% yield. However, the reaction of potassium propionate with S_2Cl_2 in dioxane did not give diethyl disulfide, while the Hunsdiecker reaction of silver propionate is known to give ethyl bromide.[8]

The decarboxylative C-S bond formation may be explained by the initial formation of sulfenyl carboxylate, which undergoes consecutive decarboxylation and C-S bond formation either by radical cage reaction, path A, or by concerted ionic course such as path B or B′. At present there is no evidence permitting a choice among these pathes.

Experimental[9]

Dipotassium Salt (4) of 3,6-Dicarboxy-1,4-dimethyl-2,5-piperazinedione——To a stirred suspension of the diester (**1**, 5.72 g, 0.02 mole) in MeOH (50 ml) was added KOH (2.8 g, 0.05 mole) in MeOH (10 ml) and H_2O (2.8 ml) at room temperature. The mixture was stirred at room temperature for 2 hr during which period the diester dissolved and then white precipitates appeared. Further H_2O (5—10 ml) was added and stirring was continued with ice-cooling for 20 min. The precipitates were collected, washed with MeOH–H_2O (20: 1), and recrystallized once from MeOH–H_2O to yield crude **4** (5.18 g, after dry), mp 199—206° (decomp). The mother liquor gave additional **4** (960 mg, total 6.09 g, 90%) upon concentration. The crude **4** was dried over P_2O_5 *in vacuo* at 60—70° before use. IR (KBr); 1673, 1630, 1360, 1220, 1040 cm^{-1}. NMR (D_2O); δ 2.95 (s, 6H, NMe), 4.48 (s, 2H, CH).

3,6-Dicarboxy-1,4-dimethyl-2,5-piperazinedione (5)——A solution of crude **4** (prepared from **1** (5.72 g)) in H_2O (8 ml) was acidified with 10% HCl under ice-cooling. The precipitates were collected and washed with chilled water to give crude **5** (4.0 g, 87%), mp 102—104° (decomp). The crude **5** was partially decarboxylated during recrystallization from ethanol. Partial decarboxylation was also observed when **5** was dried over

8) C.V. Wilson, *Organic Reactions*, **9**, 332 (1957); D.D. Tanner, "The Chemistry of Acyl Halides," ed. by S. Patai, Interscience Publishers, 1972, Chapter 13.

9) All melting points are uncorrected. The IR spectra were taken with a Hitachi G-3 spectrophotometer, the NMR spectra were recorded on a JEOL 4H-100 spectrometer, and the mass spectra were measured with a Hitachi RMU-6 spectrometer.

P_2O_5 *in vacuo* at room temperature for a long time. IR (KBr): 3550, 3420 (broad), 2775, 2500 (broad), 1730, 1660, 1620^{sh}, 1290, 1253, 1043, 920, 730 cm^{-1}.

Decarboxylation of 5——A suspension of **5** (230 mg) in dioxane (5 ml) was heated at 100—105° (bath temperature) for 40 min. The solvent was evaporated *in vacuo* to leave colorless crystals (**6**, 142 mg, quantitative), mp 129—138°, which showed a single spot on TLC. Recrystallization from iso-Pr_2O yielded **6** (110 mg), mp 137—141°, which was identical with a standard sample (IR and TLC).

Decarboxylation of 5 in the Presence of Benzaldehyde——A mixture of **5** (1.15 g) and freshly distilled benzaldehyde (6 ml) was heated at 90—100° (bath temperature) for 1.5 hr under N_2. The excess benzaldehyde was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous $NaHSO_3$ solution, saturated $NaHCO_3$ solution, and saturated NaCl solution, and dried. The residue (256 mg) obtained on evaporation of the solvent was triturated with ether to give **7** (192 mg, 15.5%), mp 181—184.5°. Recrystallizations from acetone–ether gave an analytical sample, mp 180—184°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.79; H, 6.55; N, 11.17. IR (KBr) 3370, 1670, 1645 (C=O) cm^{-1}. Mass Spectrum *m/e* (relative abundance): 142 (M^+–PhCHO, 100), 113 (M^+–(PhCHO+CO), 11), 77(8), 71(14). NMR ($CDCl_3$); δ 2.77 (s, 3H, NMe), 2.83 (s, 3H, NMe), 3.17 (AB quartet, $J_{AB}=17$ Hz, $\Delta_{AB}=47$ Hz, –CO–CH_2=N), 4.15 (d, 1H, $J=3.5$ Hz, CO–CH–N), 4.46 (d, 1H, $J=7.5$ Hz, OH), 5.12 (q, 1H, $J=7.5$ Hz and 3.5 Hz, C<u>H</u>-OH), 7.30 (m, 5H, arom.H). On addition of D_2O a singlet at 4.46 disappeared and a quartet at 5.12 became a doublet. The $NaHCO_3$ washings were salted out with NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated to leave a solid (42 mg) which was identical with an authentic specimen of **6** (TLC). The $NaHSO_3$ washings were salted out with NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated to leave a solid (426 mg), which was dissolved in acetone (5 ml) and CH_2Cl_2 (5 ml) to remove insoluble materials. The residue (320 mg) obtained on evaporation of the solvents was separated by preparative TLC (silica gel/CH_2Cl_2–acetone (6: 1)) to give **6** (125 mg, total 167 mg, 23.5%). The similar reaction of **4** with an excess of benzaldehyde in boiling dioxane did not proceed and **4** was recovered in 96% yield.

Decarboxylation of 5 in the Presence of S_2Cl_2——A mixture of **5** (230 mg) and freshly purified S_2Cl_2 (1 ml) in anhydr. dioxane (5 ml) was heated at 80—85° for 30 min. The solvent was evaporated *in vacuo* to leave a residue, to which MeOH (5 ml) and $NaBH_4$ (190 mg) were added at room temperature. Insoluble white powder and gummy products were collected and the white powder (60 mg, 22%) was separated from gummy products. The white powder melted at 180—185° (decomp) and was recrystallized from AcOH to give an analytical specimen (**8**), mp 205—206° (decomp) (reported[4] mp 195—205° (decomp)). *Anal.* Calcd. for $C_6H_8O_2N_2S_4$: C, 26.85; H, 3.00; N, 10.44. Found: C, 26.97; H, 2.92; N, 10.32. IR (KBr); 2920, 1675^{sh}, 1663 (C=O), 1411, 1310, 1263, 1032, 785, 750 cm^{-1}. Mass Spectrum *m/e* (relative abundance): 268 (M^+, 1.7), 256 (6, S_8), 236 (2.4, M^+–S), 204 (3, M^+–S_2), 192 (25, S_6), 172 (31, M^+–S_3), 140 (100, M^+–S_4), 115 (8), 112 (14), 42(47). NMR (CF_3COOH); δ 3.19 (s, 6H, NMe), 5.52 (s, 2H, CH).

The Reaction of 4 with S_2Cl_2 in Various Solvents. Formation of 11——i) In Dioxane: A mixture of **4** (1.84 g, 6 mmoles) and freshly purified S_2Cl_2 (810 mg, 6 mmoles) in anhdr. dioxane (100 ml) was gently refluxed for 1.5 hr under N_2. The solvent was evaporated *in vacuo* to leave a residue, to which saturated NaCl solution (30 ml) and H_2O (25 ml) was added. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated to leave a pale brown caramel (1.29 g) which was dissolved in CH_2Cl_2 (8 ml) and left in a refrigerator. The separated crystals (**11**, 341 mg), mp 180—190° (decomp.), were collected. The mother liquor was evaporated, and the residue (590 mg) was chromatographed over silica gel (15 g). Elution with CH_2Cl_2 gave pale yellow powder (101 mg) which was found to be a mixture of **11** (main product) and other sulfides from its NMR spectrum (the ratio of intensities of 3,6-CH signal revealed that about 3/5 of the mixture was **11**). Total yield of **11** was thus assumed to be 400 mg (33%). Elution with MeOH gave a mixture (713 mg) which was not further investigated. The crude **11** was recrystallized from AcOH to give a pure sample, mp 187—189° (reported mp 185°[4]). *Anal.* Calcd. for $C_6H_8O_2N_2S_2$: C, 35.28; H, 3.95; N, 13.71. Found: C, 35.30; H, 3.88; N, 13.43. IR (KBr); 2990, 1705, 1690, 1440, 1397, 1245, 1007, 790, 670, 620 cm^{-1}. NMR (CF_3COOH) δ 3.20 (s, 6H, NMe), 5.70 (s, 2H, CH). Mass Spectrum *m/e* (rel. abundance): 204 (M^+, 34), 149 (9), 140 (100, M^+–S_2), 112 (36, M^+–S_2–CO).

When the reaction mixture was treated with $NaBH_4$ in MeOH and then with I_2 in $CHCl_3$,[4] the disulfide (**11**) was obtained in 35.5% yield.

Refluxing a suspension of **4** in dioxane in the absence of S_2Cl_2 for 1.5 hr gave unchanged **4**.

ii) In CCl_4: A mixture of **4** (918 mg) and S_2Cl_2 (405 mg) in CCl_4 (50 ml) was refluxed for 1.5 hr under N_2. Since the evolution of CO_2 was not observed, benzoyl peroxide (10 mg) was added to the mixture and the mixture was refluxed for further 1.5 hr and cooled. The precipitates (880 mg, 96%), mp 204—206°, obtained by filtration were identical with the starting material (IR).

iii) In Chlorobenzene: A mixture of **4** (612 mg) and S_2Cl_2 (270 mg) in chlorobenzene (20 ml) was stirred at room temperature for a while and then refluxed for 10 min under N_2 (purified through Fieser solution). Worked up as above crude **8** (25 mg, 4.7%), mp 182—195°, which was identical with a standard sample (IR). The mother liquor was reduced with $NaBH_4$ and followed by oxidation with I_2–KI to give **11** (43 mg, 10.5%), mp 183—195°, which was identical with a standard sample (IR and TLC).

Reaction of 4 with Sulfur——A mixture of **4** (612 mg, 2 mmoles) and sulfur (512 mg, 2 mmoles) in anhydr. dioxane (20 ml) was gently refluxed for 3 hr under N_2. The solvent was evaporated and H_2O (20 ml) was added to the residue. The insoluble solid (sulfur recovered, 496 mg, 97%) was collected and the aqueous layer was evaporated *in vacuo* to give a residue. The residue was recrystallized from MeOH to give recovered **4** (553 mg, 91%).

Decarboxylation of Ag Salt (16a) of 5 in the Presence of S_2Cl_2——i) Preparation of Ag Salt (**16a**) of **5**: To a solution of **4** (612 mg) in H_2O (4 ml) was added $AgNO_3$ (748 mg) in H_2O (8 ml). The mixture was warmed on a water-bath and then cooled. The precipitates were collected and washed with chilled water and MeOH mp 137—140° (decomp). The Ag salt was dried over P_2O_5 *in vacuo* at 60° before use.

ii) Decarboxylation of **16a**: A mixture of Ag salt (666 mg, 1.5 mmoles) and S_2Cl_2 (203 mg, 1.5 mmoles) in anhydr. dioxane (15 ml) was refluxed for 1.5 hr under N_2. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2. Insoluble materials were removed and the filtrate was evaporated. The residue was recrystallized from CH_2Cl_2 to give **8** (12 mg, 3%) which was identical with a standard sample (TLC, IR). The mother liquor was evaporated and the residue was trated with $NaBH_4$ and then with I_2–$CHCl_3$. The disulfide (**11**, 44 mg, 14.5%), mp 178—195° (decomp.), was obtained from the reaction mixture.

Decarboxylation of Cu Salt (16b) of 5 in the Presence of S_2Cl_2——i) Preparation of Cu Salt (**16b**) of **5**: To a solution of **4** (918 mg) in H_2O (2 ml) was added 4 ml of $CuSO_4$ solution (prepared from $CuSO_4 \cdot 5H_2O$ (2.5 g) in H_2O (10 ml)). The mixture was warmed at 80—85° for 20 min. The pale blue precipitates were collected and washed with H_2O, and dried over P_2O_5 *in vacuo*. Yield: 769 mg (88%), mp 170—172° (decomp.).

ii) Decarboxylation of **16b**: A mixture of above Cu salt (582 mg) and S_2Cl_2 (270 mg) in dioxane (30 ml) was refluxed for 40 min under N_2. Work-up as above gave crude reaction mixture (331 mg) from which tetra-sulfide (**8**, 10 mg), mp 190—195° (decomp), was obtained after silica gel chromatography.

Decarboxylation of Ba Salt (16c) of 5 with S_2Cl_2——i) Preparation of Ba Salt of **5**: Barium hydroxide octahydrate (2.6 g) was dissolved in MeOH (50 ml) and insoluble materials were removed by filtration. The diester (**1**) (2.0 g) was added to the clear solution. The resulted pasty mixture was diluted with H_2O (15 ml) and stirred at room temperature for 2 hr. The precipitates were collected and washed with MeOH–H_2O (2: 1) and dried over P_2O_5 *in vacuo*. Yield: 2.52 g (98%), mp 210° (decomp.).

ii) Decarboxylation of **16c**: A mixture of the above Ba salt (1.09 g) and S_2Cl_2 (405 mg) in anhydr. dioxane (50 ml) was refluxed for 3 hr. Work-up as above gave a crude mixture (399 mg). Recrystallization from CH_2Cl_2 gave **8** (33 mg), mp 179—190° (decomp.), which was identical with a standard sample (IR and TLC). Silica gel chromatography of the mother lipuor gave further crop of **8** (10 mg, total 43 mg, 7.0%).

Reaction of 4 with S_2Cl_2 and followed by the Reduction and Ethylation. Formation of 1,4-Dimethyl-3,6-bis(ethylthio)-2,5-piperazinedione——i) Under N_2: A mixture of **4** (1.17 g, 3.8 mmoles) and freshly purified S_2Cl_2 (570 mg, 4.2 mmoles) in anhyd. dioxane (30 ml) was refluxed for 1 hr under N_2 (purified through Fieser solution). The solvent was evaporated *in vacuo* and the residue was dissolved in MeOH (15 ml) and CH_2Cl_2 (10 ml). $NaBH_4$ (760 mg) was added portionwise to the solution under ice-cooling. After stirring at room temperature for 1 hr, ethyl iodide (3 ml, excess) was added to the mixture and stirred overnight. The mixture was refluxed for 30 min and evaporated *in vacuo*. The residue was mixed with H_2O (15 ml) and extracted with CH_2Cl_2. The extracts were dried and evaporated to yield pale yellow semi-solid (816 mg). Recrystallization from benzene–hexane gave crude *cis* isomer (**17**, 423 mg), mp 110—138°, which showed a single spot on TLC. The mother liquor was separated by preparative TLC (silica gel/iso-Pr_2O–acetone (3: 1)). The least polar zone gave **18** (11 mg, 0.9%). The less polar zone gave **17** (70 mg). The more polar zone gave a pale yellow solid (37 mg, structure unknown). The most polar zone gave **19** (170 mg, 23%), mp 95—98°. The crude (**17** (total 493 mg, 50%) was recrystallized from benzene–hexane to give pure **17**, mp 140—142.5° (reported mp 138—140°[4]). *Anal.* Calcd. for $C_{10}H_{18}O_2N_2S_2$: C, 45.77; H, 6.91; N, 10.68; S, 24.44. Found: C, 45.99; H, 7.10; N, 10.88; S, 24.79. IR (KBr) 2970, 2930, 2875, 1670, 1485, 1445, 1405, 1303, 1253, 1020, 760 cm^{-1}. NMR ($CDCl_3$) δ 1.34 (t, 6H, $CH_2C\underline{H}_3$), 2.85 (m, 4H, $SC\underline{H}_2CH_3$), 3.08 (s, 6H, NMe), 4.61 (s, 2H, CH). Mass Spectum *m/e* (rel. abundance): 262 (M^+, 16), 202 (M^+–S=CHCH$_3$, 55), 201 (M^+–SEt, 59), 200 (M^+–EtSH, 20), 173 (M^+–SEt–CO, 41), 141 (64), 102 (100), 104 (34), 42 (56). This sample was identical with the sample obtained from **11** by reduction and ethylation (IR and mixed mp). The crude **19** was recrystallized from benzene–hexane to give an analytical sample, mp 99—100°. *Anal.* Calcd. for $C_8H_{14}O_2N_2S$; C, 47.43; H, 6.83; N, 13.59; S, 16.13. Found: C, 47.50; H, 6.98; N, 13.85; S, 15.85. IR (KBr); 2953, 2920, 2860, 1665 (CO), 1485, 1450, 1406, 1330, 1300, 1268, 1238, 1010, 750 cm^{-1}. NMR ($CDCl_3$); δ 1.32 (t, 3H, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.76 (m, 2H, $SC\underline{H}_2CH_3$), 3.02 (s, 3H, NMe), 3.06 (s, 3H, NMe), 3.98 (AB quartet, J_{AB}=17 Hz, Δ_{AB}=33 Hz, CO–CH_2–N), 4.69 (s, 1H, CO–C$\underline{H}$–S). Mass Spectrum *m/e* (rel. abundance): 142 (100, M^+–S=CHCH$_3$), 141 (65, M^+–SEt), 113 (47, M^+–SEt–CO), 44 (10), 42 (7). The crude **18** was recrystallized from acetone–iso-Pr_2O to give colorless crystals, mp 151—155°. IR (KBr) 2970, 2930, 2860, 1660 (splitted into 3 bands), 1480, 1450, 1400, 1300, 1258, 1150, 1020, 980, 765 cm^{-1}. NMR ($CDCl_3$): δ 1.27 (t, 6H, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.60 (m, 4H, $SC\underline{H}_2CH_3$), 3.10 (s, 6H, NMe), 4.82 (s, 2H, C$\underline{H}$–SEt). Mass Spectrum *m/e* (rel. abundance): 262 (M^+, trace), 202 (71. M^+–S=CHCH$_3$), 201 (100, M^+–SEt), 200 (74, M^+–EtSH), 173 (M^+–SEt–CO, 33), 141 (78), 112 (45), 104 (20), 42 (33). A solution of **18** (10 mg) in CH_2Cl_2 (0.5 ml)–MeOH (1 ml) was treated with $NaBH_4$ (5 mg), and work up as usual to give the *cis* isomer (**17**, 6 mg) which was identical with a standard sample (TLC and IR).

ii) Under O_2: A mixture of **4** (1.224 g) and S_2Cl_2 (595 mg) in anhyd. dioxane (30 ml) was refluxed for 1.5 hr under O_2 bubbling. The solvent was evaporated *in vacuo* and the residue was treated as above i) to give crude **17** (666 mg, 66%), **18** (9 mg, 0.8%), and **19** (94 mg, 11.5%).

Reaction of 4 with Ethanesulfenyl Chloride——i) Under N_2: To a suspension of **4** (2.10 g, 6.6 mmoles) in anhyd. dioxane (35 ml) was added freshly prepared EtSCl (1.27 g, 1.32 mmoles) under N_2 (purified through Fieser solution). The mixture was stirred at room temperature for a while, then refluxed for 1.5 hr. The solvent was evaporated and the residue was treated with H_2O (20 ml), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a pale brown caramel (770 mg). Recrystallization from MeOH–acetone gave **22** (25 mg), mp 196—203°. The residue (740 mg) from the mother liquor was separated with preparative TLC silica gel/benzene–acetone (7: 2)). The highest zone gave **18** (32 mg, 1.8%), mp 166—169°, which was identical with the sample obtained above (IR). The second zone gave **19** (110 mg, 8.3%), mp 92—96°, which was identical with the sample obtained above (TLC and IR). The third zone gave **20** (146 mg, 10.1%), mp 115—118°. Recrystallizations from acetone–ether gave pure **20**, mp 117.5—118.5°. *Anal.* Calcd. for $C_8H_{14}O_3N_2S$; C, 44.02; H, 6.47; N, 12.74; S, 14.69. Found: C, 44.18; H, 6.53; N, 12.68; S, 14.83. IR (KBr), 3190 (OH), 1695 (C=O), 1660 (C=O) cm^{-1}. NMR ($CDCl_3$); δ 1.32 (t, 3H, $CH_2C\underline{H}_3$) 2.81 (m, 2H, $SC\underline{H}_2CH_3$), 3.08 (s, NMe), 3.10 (s, 3H, NMe), 4.74 (s, 1H, CH), 5.29 (AB quartet, 2H, $J_{AB}=7$ Hz, $\Delta_{AB}=34$ Hz, $C\underline{H}$–O$\underline{H}$). On addition of D_2O the AB quartet at 5.29 became a singlet. Mass Spectrum *m/e* (rel. abundance): 158 (M^+–S=CHCH$_3$, 37), 129 (M^+–SEt–CO, 37), 101 (44), 60 (34), 42 (100). The fourth zone gave a semi-solid (128 mg) which gave **22** (14 mg) on recrystallization from MeOH.

The aqueous solution and washings were evaporated *in vacuo*, and the residue (1.65 g) was extracted with MeOH. The MeOH solution on evaporation gave a semi-solid (590 mg) which was chromatographed over silica gel (15 g). Elution with CH_2Cl_2–MeOH (3%) gave **21** (97 mg, 9.2%), mp 138—142°. Recrystallization from EtOH–ether gave an analytical sample, mp 142—143°, as colorless crystals. *Anal.* Calcd. for $C_6H_{10}O_3N_2$; C, 45.56; H, 6.37; N, 17.71. Found: C, 45.46; H, 6.35; N, 17.61. IR (KBr); 3160 (OH). 1667 (C=O) cm^{-1}. NMR (DMSO-d_6); δ 2.85 (s, 3H, NMe), 2.87 (s, 3H, NMe), 3.96 (AB quartet, $J_{AB}=17.5$ Hz, $\Delta_{AB}=32$ Hz, CO–CH_2–N), 4.88 (d, 1H, $J=7.5$ Hz, $C\underline{H}$–OH), 6.94 (d, 1H, $J=7.5$ Hz, CH–O$\underline{H}$). On addition of D_2O, the doublet at 4.88 became a singlet and the doublet at 6.94 disappeared. Mass Spectrum *m/e* (rel. abundance): 158 (M^+, 23), 14 (M^+–OH, 5), 130 (M^+–CO, 17), 113 (M^+–CO–OH, 19), 101 (M^+–MeNCO, 56), 73 (42), 60 (50), 44 (100). Elution with CH_2Cl_2–MeOH (5%) gave **22** (53 mg, total 92 mg, 8%). Recrystallizations from MeOH gave an analytical specimen, mp 215—217° (decomp.). *Anal.* Calcd. for $C_6H_{10}O_4N_2$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.41; H, 5.82; N, 16.09. IR (KBr); 3190 (OH), 1670 (C=O) cm^{-1}. NMR (DMSO-d_6); δ 2.85 (s, 6H, NMe), 4.94 (d, 2H, $J=7.5$ Hz, $C\underline{H}$–OH), 6.89 (d, 2H, $J=7.5$ Hz, CH–O$\underline{H}$). On addition of D_2O the doublet at 4.94 became a singlet and the doublet at 6.89 disappeared. Mass Spectrum *m/e* (rel. abundance); 174 (M^+, 3), 157 (M^+–OH, 2), 117 (M^+–MeNCO, 6), 60 (100), 58 (20).

ii) Under O_2: To a suspension of **4** (2.1 g, 6.6 mmoles) in anhyd. dioxane (35 ml) was added freshly prepared EtSCl (1.27 g, 13.2 mmoles) under dry O_2. The mixture was stirred at room temperature for a while and refluxed for 1.5 hr. Work-up as above i) gave the following compounds. **18**: Yield 43 mg, 2.5%. **19**; yield 124 mg, 9.1%; **20**: yield 158 mg, 10.6%; **21**: yield 65 mg, 6.3%; **22**: yield 132 mg, 11.5%. Sarcosine anhydride; yield 52 mg, 6.3%. Unknown compound: 22 mg.

Reaction of 4 with Benzenesulfenyl Chloride——To a suspension of **4** (2.1 g, 6.6 mmoles) in anhydr. dioxane (35 ml) was added freshly prepared PhSCl (4.5 g, contaminated with diphenyl disulfide) under N_2 (purified through Fieser solution). The mixture was stirred at room temperature for a while and then refluxed for 1.5 hr. The solvent was evaporated and the residue was treated with H_2O (30 ml), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a pale yellow semi-solid (4.03 g). The residue was triturated with CH_2Cl_2 (5 ml) to give fine crystals (**22**, 215 mg), mp 140—155°. Recrystallization from MeOH gave **22**, mp 213—216° (decomp.), which was identical with the sample obtained above (IR and mixed mp). The mother liquor was chromatographed on silica gel (25 g). Elution with benzene gave diphenyl disulfide (2.21 g). Elution with CH_2Cl_2–MeOH (10%) gave pale yellow caramel (618 mg) and **22** (32 mg). The caramel was separated by preparative TLC (silica gel/CH_2Cl_2). The least polar zone gave **23** (191 mg, 7.8%). Recrystallization from benzene–hexane gave pure **23**, mp 119—121°. *Anal.* Calcd. for $C_{18}H_{16}O_3N_2S_2$: C, 58.02; H, 4.33; N, 7.52; S, 17.20. Found: C, 58.12; H, 4.32; N, 7.34; S, 17.13. IR (KBr); 3060, 1750, 1695, 759 cm^{-1}. NMR ($CDCl_3$); δ 2.85 (s, 3H, NMe), 3.61 (s, 3H, NMe), 7.38 (s, 10H, arom. H). Mass Spectrum *m/e* (rel. abundance): 263 (M^+-SPh, 100), 235 (M^+–SPh–CO, 8), 223 (12), 210 (9), 167 (9), 155 (36), 150 (42), 141 (25), 109 (42). The second polar zone gave pale brown caramel (126 mg) which was recrystallized from MeOH–ether to give colorless crystals (22 mg), mp 132—138°. The structure was tentatively assigned as **25** from the spectral data. IR (KBr); 3050, 1690, 750 cm^{-1}. Mass Spectrum *m/e* (rel. abundance): 280 (M^+, 10), 171 (M^+–SPh, 100), 143 (M^+—SPh–CO, 43), 109 (PhS^+, 10) 74 (45), 42 (55). The more polar zone gave colorless semi-solid (111 mg) which was recrystallized from benzene to give **24** (52 mg, 2.9%). Further recrystallization from acetone gave an analytical sample, mp 202—204°. *Anal.* Calcd. for $C_{12}H_{14}O_3N_2S$: C, 54.13; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.13; H, 5.13; N, 10.45; S, 12.14. IR (KBr); 3140 (OH), 1673 (CO), 1655^{sh}, 1630. 759 cm^{-1}. NMR (DMSO-d_6); 2.85 (s, 3H, NMe), 3.03 (3H, s, NMe), 3.20 (d, 1H, a lower signal was overlapped with DMSO signal, $C\underline{H}$–OH), 5.44 (s, 1H, $C\underline{H}$–S), 6.75 (d, 1H, CH–O$\underline{H}$), 7.37 (m, 5H, arom. H). On addition of D_2O the doublet at 6.75 disappeared and the

doublet at 3.20 became a singlet at 3.19. Mass Spectrum *m/e* (rel. abundance): 266 (M^+, 1.6), 157 (M^+–SPh, 100), 129 (M^+–SPh–CO, 29), 109 (PhS^+, 14), 101 (33), 60 (22), 42 (75). The aqueous solution and washings were evaporated *in vacuo* and the residue (1.86 g) was extracted with MeOH (50 ml). The MeOH solution on evaporation gave a colorless semi-solid (280 mg), which was chromatographed over silica gel (7 g). Elution with CH_2Cl_2–MeOH (3%) gave **21** (72 mg, 6.9%). Second elution with the same solvent gave **22** (45 mg, total yield 290 mg, 25%).

Hunsdiecker Reaction of Ag Salt (16a) of 5——To a stirred suspension of **16a** (2.22 g, 5 mmoles) in CCl_4 (40 ml) was added Br_2 (1.70 g, 10 mmoles) in CCl_4 (10 ml) at room temperature. The mixture was refluxed for 2.5 hr and evaporated. The residue was extracted with benzene. The benzene solution was evaporated *in vacuo* and the residue (1.40 g) was recrystallized from benzene to give crude 3,6-dibromide (1.16 g, 76%), mp 126—135°. Recrystallization from benzene gave pure sample mp 141—144° (sealed tube) (reported mp 139—143°[10]). IR ($CHCl_3$); 1710 cm^{-1} (reported value,[10] 1709 cm^{-1}). NMR ($CDCl_3$); δ 3.08 (s, 6H, NMe), 5.98 (s, 2H, C<u>H</u>–Br).

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