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Synthesis of 3,6-Diethoxycarbonyl-3,6-epidithia-1,4-dimethyl-2,5-piperazinedione and Related Compounds. Formation of C-S Bond by the Reaction of Carbanion and Sulfur Monochloride[1]

Tohru Hino and Tadao Sato

Faculty of Pharmaceutical Sciences, Chiba University[2]

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Reaction of 3,6-diethoxycarbonyl-1,4-dimethyl-2,5-piperazinedione (**15**), prepared by heating of diethyl methylaminomalonate (**14**), with NaH in dioxane and followed treatment with S_2Cl_2 gave 3,6-epidithio- and 3,6-epitetrathio-3,6-diethoxycarbonyl-1,4-dimethyl-2,5-piperazinediones (**16b** and **16d**), which have the skeletone (**1**) observed in fungal metabolites such as sporidesmin. The reduction of **16** with $NaBH_4$ in methanol gave the dethio derivative (**15**) in good yield. The reaction of **16d** with triphenylphosphine in tetrahydrofurane gave **16c** and **16b**. The reaction of diethyl malonate derivatives (**23a**, **b**, and **c**) with NaH and S_2Cl_2 in dioxane gave the corresponding disulfides or trisulfides (**24a**, **b**, and **c**). Some reactions of proline anhydride (**5**) and sarcosine anhydride (**7**) with S_2Cl_2 or sulfur were examined.

The number of natural products containing the epidithia-2,5-piperazinedione ring **1** such as gliotoxin,[3] sporidesmin,[4] aranotin,[5] verticillin,[6] and chaetocin[7] have been isolated from the fungal metabolites. Most of these natural products have been known to exhibit strong biological activity and this unique ring system **1** is responsible for the activity since the dethio derivatives of the natural products such as sporidesmine and gliotoxin loose their activities.

The first synthesis of the ring system (**1**) has been achieved by Trown[8] in 1968, and the compound (**2**) was found to show the antiviral activity. A few related compounds were reported in patents.[9] Schmidt and his coworkers[10] later improved the method for the preparation of **2** and **3**, and further succeeded in the synthesis of **4** and the chemistry of 3,6-disubstituted 2,5-piperazinedione was discussed. Very recently Kishi and his coworkers[11] published an elegant synthesis of **1** and established the total synthesis of dehydrogliotoxin and sporidesmin A. Some other approaches to the ring system (**1**) have also been reported.[12]

1) A part of this paper was published as a communication: T. Hino and T. Sato, *Tetrahedron Letters*, **1971**, 3127.
2) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
3) M.R. Bell, J.R. Johnson, B.S. Wildi, and R.B. Woodward, *J. Am. Chem. Soc.*, **80**, 1001 (1958).
4) S. Safe and A. Taylor, *J. Chem. Soc.* (*C*), **1970**, 432; **1971**, 1189. And references cited herein.
5) R. Nagarajan, L.L. Huckstep, D.H. Lively, D.C. Delong, M.M. Marsh, and N. Neuss, *J. Am. Chem. Soc.*, **90**, 2980, 6519 (1968); *Tetrahedron Letters*, **1968**, 4467; D.B. Cosulich, N.R. Nelson, and J.H. von den Hende, *J. Am. Chem. Soc.*, **90**, 6519 (1968).
6) M. Minato, M. Matsumoto, and T. Katayama, *Chem. Commun.*, **1971**, 44; *idem*, *J. Chem. Soc., Perkin I*, **1973**, 1819.
7) D. Hauser, H.P. Weber, and H.P. Sigg, *Helv. Chim. Acta*, **53**, 1061 (1971).
8) P.W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968).
9) S.G. Svokos and R.B. Angier, *Ger. Offen.*, 2029306 [*Chem. Abstr.*, **74**, 53845*p* (1971)]; *idem*, *Ger. Offen.*, 2029305 [*Chem. Abstr.*, **74**, 100095*f* (1971)].
10) *a*) H. Poisel and U. Schmidt, *Angew. Chem. Internat. Edit.*, **10**, 130 (1971); *idem*, *Chem. Ber.*, **104**, 1714 (1971); *idem*, *b*) *Chem. Ber.*, **105**, 625 (1972); *c*) E. Ohler, H. Poisel, F. Tataruch, and U. Schmidt, *Chem. Ber.*, **105**, 3658 (1972); *idem*, **106**, 165, 396 (1973).
11) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490, 6492 (1973); Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Am. Chem. Soc.*, **95**, 6493 (1973).
12) H.C.J. Ottenheym, T.F. Spande, and B. Witkop, *J. Am. Chem. Soc.*, **95**, 1989 (1973); P.M. Pojer and I.D. Rae, *Aust. J. Chem.*, **25**, 1737 (1972); J. Yoshimura and Y. Sugiyama, *Bull. Chem. Soc.* (Japan), **45**, 1554 (1970); T. Petrzilka and C. Fehr, *Helv. Chim. Acta* **56**, 1218 (1973).

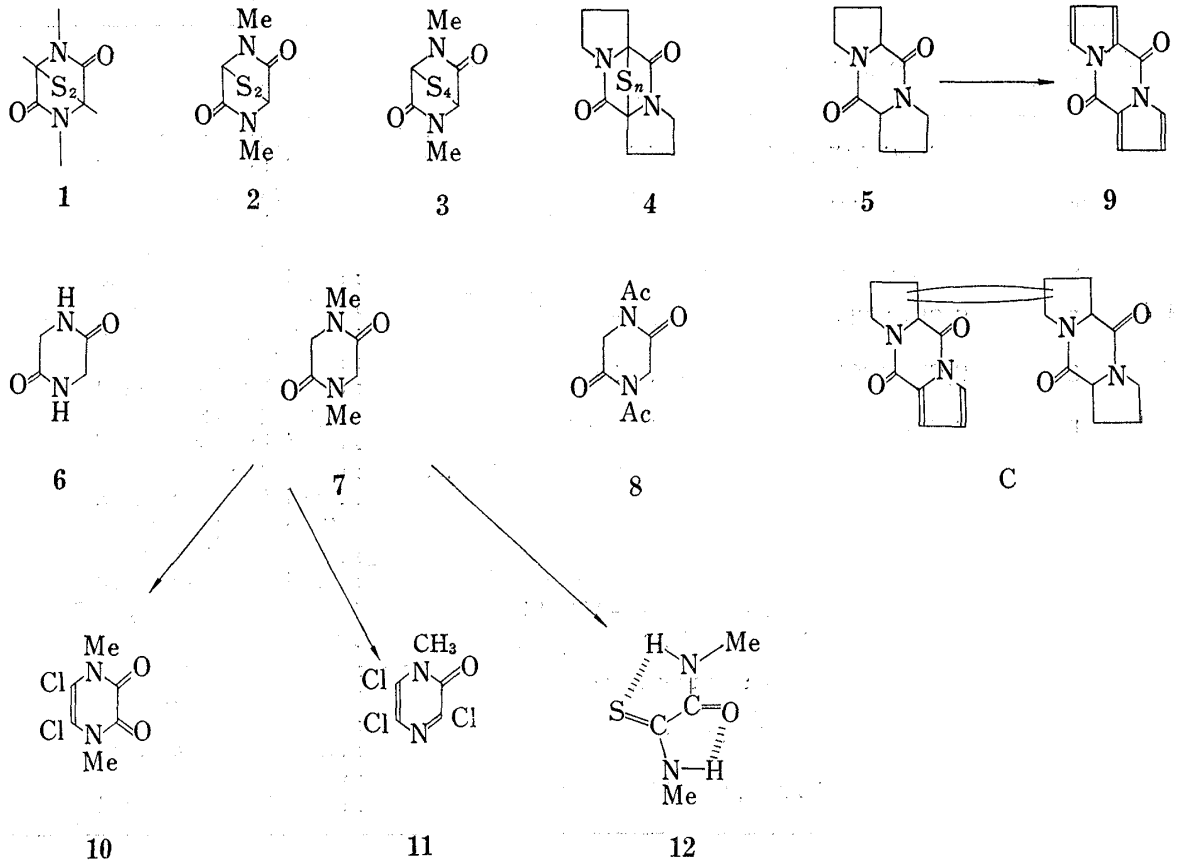


Chart 1

In this paper we describe a new approach to **1** by the reaction of a carbanion and S_2Cl_2 and the application of this method into some open chain compounds is discussed. Our first attempts to introduce the C-S bond into 2,5-piperazinediones by the reaction with S_2Cl_2 or sulfur without bases were unsuccessful. Wiles and coworkers[13] reported the reaction of the active methylene compounds with S_2Cl_2, and they obtained tristhiobis (malonamide) by refluxing of malonamide with S_2Cl_2 in dioxane. The application of some variations of this method to 2,5-piperazinediones (**5** and **7**) has not been successful (See Table I). However, the chlorinated compounds (**10** and **11**) were obtained when **7** was treated with $POCl_3$ and S_2Cl_2. The reaction of **5** with an excess of sulfur at high temperature produced a trace of dehydrogenated compound (**9**) and a dimeric product. These results indicated that the 3, and 6-positions of 2,5-piperazinediones are rather innert towards S_2Cl_2 or sulfur.

Treatment of **5** with NaH in benzene or toluene and then with S_2Cl_2 resulted in recovery of the starting material. This suggested that the hydrogens at 3- and 6-positions in the 2,5-piperazinedione (**5**) were not acidic enough to form a carbanion under these reaction conditions. More recently Schmidt's group, however, reported the formation of 3,6-dithiol derivative of **5** by treating **5** with $NaNH_2$ in liquid NH_3 and then with sulfur.

We now examined the reaction of S_2Cl_2 and the more activated 2,5-piperazinedione which has two additional ethoxycarbonyl groups at 3, and 6-positions. The compound (**13**) was reported[14] to be found in the residue of the distillation of diethyl aminomalonate. However, when diethyl aminomalonate was heated at 160—165° under nitrogen, **13** was not obtained and polymerization and decomposition products of aminomalonate were found. On the

13) P. Hope and L.A. Wiles, *J. Chem. Soc.*, **1965**, 4583; L.A. Wiles and Z.A. Ariyan, *Chem. & Ind* (London), **1962**, 2102.

14) G.W.H. Cheesemann, *J. Chem. Soc.*, **1960**, 242.

Table I. Reactions of 2,5-Piperazinediones with S_2Cl_2 or Sulfur

2,5-Piperazinedione	Reaction condition	Result
5	S_2Cl_2–CH_2Cl_2, reflux, overnight	most of the starting material was recovered
5	S_2Cl_2–pyridine, room temperature overnight	most of the starting material was recovered
5	S_2Cl_2–AcOH, reflux, 6 hr	most of the starting material was recovered
5	S_2Cl_2–$AlCl_3$–CH_2Cl_2, reflux 3 hr	most of the starting material was recovered
5	S_2Cl_2–$POCl_3$–PhH, 50—60°, 6 hr	most of the starting material was recovered
5	S_2Cl_2–$ClCH_2CH_2Cl$, AIBN, reflux 5.5 hr	most of the starting material was recovered
5	S_2Cl_2–CH_2Cl_2-*hν* (254 nm), room temperature, 5.5 hr	most of the starting material was recovered
5	S_8 (excess), 160—180°, 9 hr	**9** (trace), C (trace)
6	S_2Cl_2–dioxane, reflux, 6.5 hr	most of starting material was recovered
7	S_2Cl_2–$POCl_3$–PhH–CH_2Cl_2, 60—65°, 4 hr	**10** (19%), **11** (0.5%)
7	S_8(excess), 180—190°, 6.5 hr	**12** (trace), **7**
7	S_8-conc. NH_3, room temperature	most of starting material was recorvered
8	S_2Cl_2–dioxane, reflux, 6 hr	most of starting material was recovered
8	S_2Cl_2–Ac_2O–AcONa, 95—100°, overnight	most of starting material was recovered

Ph=phenyl

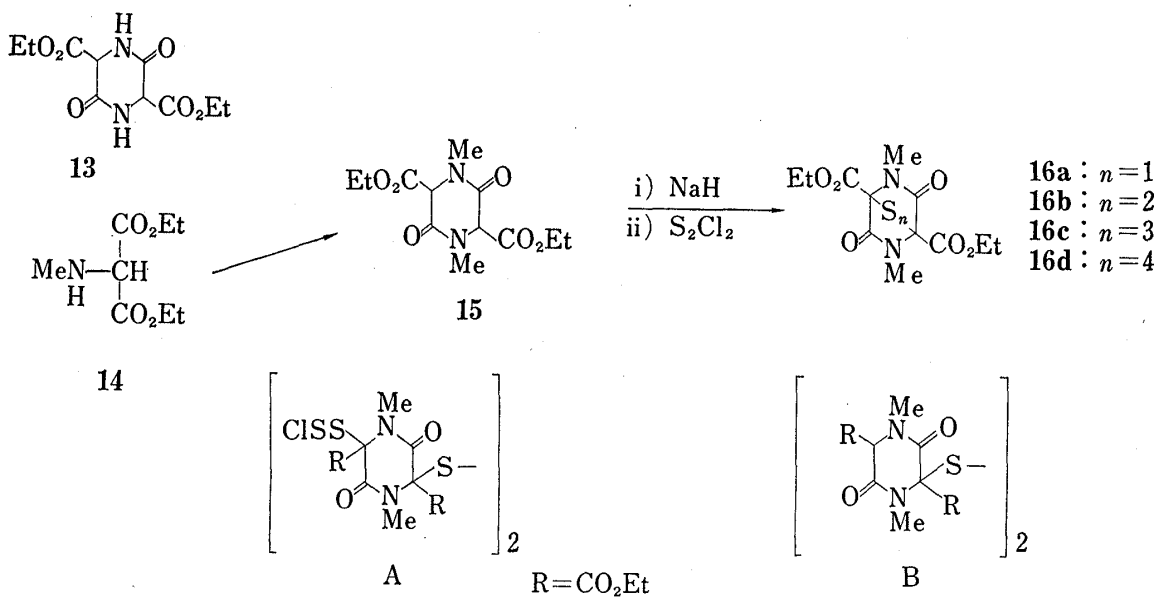


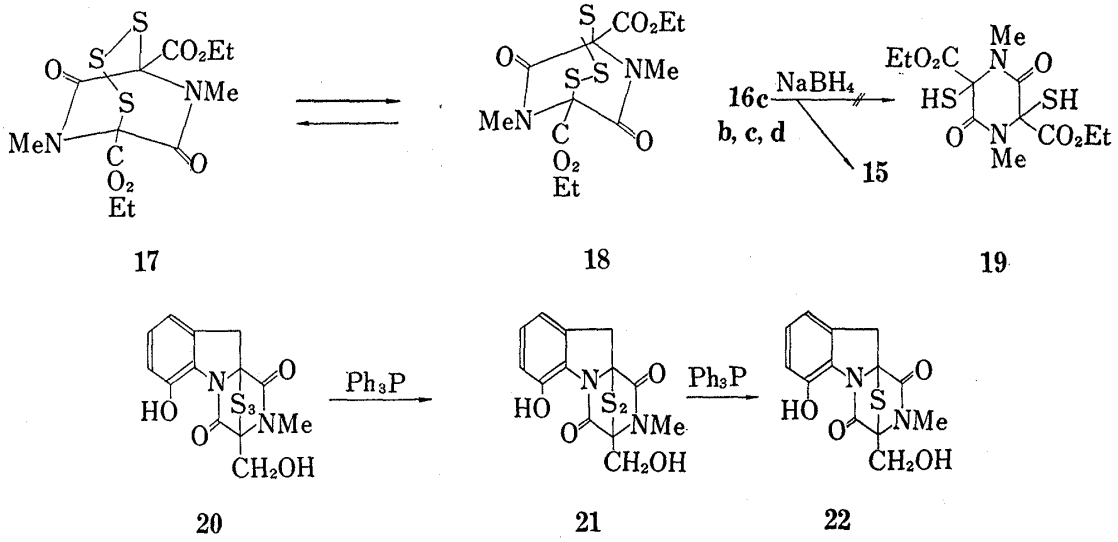
Chart 2

contrary diethyl methylaminomalonate (**14**),[15] prepared from diethyl benzylmethylaminomalonate, was cyclized to desired 3,6-diethoxycarbonyl-1,4-dimethyl-2,5-piperazinedione (**15**) in 69% yield upon heating **14** at 160—180° under nitrogen for 2 hr. Although the stereochemistry of **15** was not established yet, the spectral data and thin-layer chromatography (TLC) support that only a single isomer (*cis* or *trans*) is present.

15) E. Haadeger and H. Corrodi, *Helv. Chim. Acta*, **34**, 980 (1956).

Table II. Spectral Data of Epithiopiperazinediones

Compd No.	IR(KBr), $\nu_{C=O}$	NMR($CDCl_3$), δ NMe	NMR($CDCl_3$), δ 3,6-CH	Mass spectrum M^+ (rel. inten.)	Base peak
15	1690, 1744	3.00(s)	4.60(s)	286(56)	213(M^+–CO_2Et)
16a	1720, 1765	3.09(s)	—	316(trace)	259(M^+–MeNCO)
16b	1715, 1749	3.03(s)	—	348(8.5)	284(M^+–S_2)
16c	1695, 1756	2.97(s), 3.07(s)	—	380(2)	284(M^+–S_3)
16d	1686, 1749	3.00(s)	—	412(6)	284(M^+–S_4)



17 18 19

20 21 22

16d $\xrightarrow{Ph_3P}$ 16c + 16d Ph = phenyl

Chart 3

When **15** was treated with NaH in dioxane and then freshly distilled S_2Cl_2 was added, a mixture of sulfur containing compounds was obtained. Separation of the mixture by silica gel column and fractional recrystallizations gave the desired epidithia compound (**16b**) in 17% yield, tetra sulfide (**16d**) in 9% yield, and mono and tri sulfide (**16a** and **16c**) as minor components besides sulfur containing uncharacterized compounds. The structures of **16** were confirmed by the elemental analysis as well as the spectral data, which are listed in Table 2. The nuclear magnetic resonance (NMR) spectra of **16a—d** lacked a singlet at 4.60 ppm which corresponded to the protons at 3- and 6-positions of **15**. The trisulfide (**16c**) gave two methyl signals at 2.97 and 3.07 ppm, probably due to the slow conformational change between **17** and **18**. The two sets of triplets and quartets for ethyl ester group as well as methyl signals were observed in the deuterobenzene solution of **16c**. The similar observation was reported on sporidesmin E (a trisulfide).[16] The carbonyl stretching vibrations of the amides in **16a** and **16b** were observed in higher wave number region than that of **15**, suggesting the presence of some ring strain in **16a** and **16b**. The molecular ion peaks of **16** in mass spectra were very weak. The base peaks of **16b**, **16c**, and **16d** at *m/e* 284 may arise from the removal of sulfur bridge from the molecular ion. However, the base peak of **16a** at *m/e* 259 may arise from the loss of CH_5NCO from the molecular ion. For the further confirmation of the struc-

16) R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc.*, (*C*), **1969**, 1665.

ture of **16a**, it was alternatively prepared by the reaction of **15** with SCl_2 instead of S_2Cl_2. However, the monosulfide (**16a**) was obtained only in 2.3% yield and the disulfide (**16b**) was formed in 10% yield. This indicated that the considerable amount of disproportionation of SCl_2 has occured during the reaction.

Thus the introduction of the sulfur bridge to the 2,5-piperazinedione by a single step was successful, but satisfactory yields are not obtained. In order to improve the yields of **16** the reaction of **15** with NaH and S_2Cl_2 in dimethyl formamide (DMF) or hexamethyl phosphoric triamide (HMPA) was attempted but the better result was not obtained. In order to obtain **16b** by reduction of **16c** and **16d** to the thiol (**19**) followed by oxidation, a mixture of **16b**, **16c**, and **16d** was reduced with $NaBH_4$ in methanol at room temperature. However, the expected **19** was not obtained and instead **15** was isolated as a sole product. The reduction of C-S bond with $NaBH_4$ usually does not occur readily and the presence of the ethoxycarbonyl group may be responsible for the easy reduction of C-S bond since the disulfide **2** has been known[10a] to give the corresponding dithiol with $NaBH_4$. This fact also suggests that the isolation of the trans or cis dithiol or mono thiol by the reduction of the sulfur containing 2,5-piperazinediones such as A and B which might be involved in the reaction products of **15** and S_2Cl_2, could not be possible.

Secondly the desulfurization of the tetrasulfide (**16d**) with triphenylphosphine was examined, since the trisulfide (**20**), analogs of gliotoxin was known to give dehydrogliotoxin (**21**) by the reaction with triphenylphosphine in tetrahydrofuran and the further reaction of **21** with triphenylphosphine in tetrahydrofurane proceeded slowly to give the monosulfide (**22**).[4] The tetrasulfide (**16d**) was converted to the trisulfide (**16c**, 58%) and the disulfide (**16b**, 19%) by the reaction with one mole of triphenylphosphine in tetrahydrofurane at −5—0°. On the other hand desulfurization of **16b** to the monosulfide (**16a**) under similar reaction conditions did not proceed. Further investigation of the desulfurization of **16** with triphenylphosphine will be presented later.

The reaction of the carbanion with S_2Cl_2 to form the disulfide was now extended to the open chain compounds. The reaction of diethyl acetamidomalonate (**23a**) with NaH in dioxane and followed treatment with S_2Cl_2 gave the disulfide (**24a**, $n=2$) as a main product (70%). The similar reaction of **23a** in pyridine gave the trisulfide (**24a**, $n=3$). Under similar conditions **23b** gave **24b** ($n=2$) in 80% yield and **23c** gave a mixture of **24c** ($n=2$ and 3) in about 50% yield. On the contrary to the case of the piperazinedione, the tetra sulfide was not isolated in the open chain compounds. This could be explained by the fact that the 8-membered ring containing sulfur atom such as S_8 is known to be stable. The reaction of the carbanion with S_2Cl_2 to form the disulfide was considered as a general method for the formation of the C-S bond.

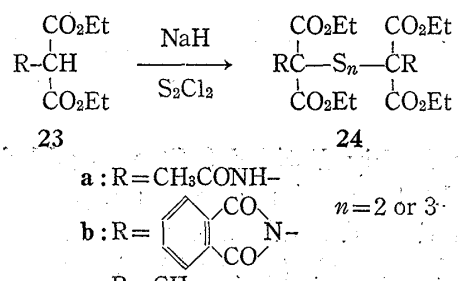


Chart 4

Experimental[17]

Reaction of Sarcosine Anhydride (7) with Sulfur——An intimate mixture of 7[18] (852 mg, 6 mmoles) and sulfur (7.7 g, 30 mmoles) was heated at 180—190° (bath temperature) for 9.5 hr under N_2. After cooling, the mixture was powdered and extracted with hot MeOH. The MeOH solution was evaporated *in vacuo* to leave a dark brown semisolid (510 mg), which was chromatographed on silica gel (50 g). Elution with

17) All melting points are measured in capillary tubes and uncorrected. The infrared (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.

18) S.M. McElvain and P.N. Laughton, *J. Am. Chem. Soc.*, 73, 448 (1951).

CH_2Cl_2 gave recovered sulfur (9 mg). Elution with CH_2Cl_2–MeOH (20%) gave pale yellow crystals (10 mg) which was further purified by silica gel column to give orange-red crystals (6 mg), mp 122—124°. IR(KBr); 3300, 3250 (NH), 1680 (C=O), 1530 cm^{-1}. NMR ($CDCl_3$) δ 2.92 (d, 3H, J=5 Hz, NMe), 3.22 (d, 3H, J=5 Hz, NMe), 8.2 (br. s, 1H, NH), 9.6 (br. s, 1H, NH). On the addition of D_2O, the two doublets changed to two singlets and two singlets at 8.2 and 9.6 disappeared. Mass Spectrum *m/e* (relative abundance): 132 (M^+, 100), 117 (M^+-Me, 10), 103(8), 91(7), 74(99), 58(32). The structure of this compound was tentatively assigned as **12**. Further elution with CH_2Cl_2–MeOH (20%) gave a pale brown semisolid (480 mg) which was found to be a mixture of **12** and **7** (main) on TLC.

Reaction of 7 with $POCl_3$–S_2Cl_2——To a stirred solution of **7** (4.26 g, 30 mmoles) in benzene (60 ml) and CH_2Cl_2 (25 ml) was added $POCl_3$ (9.18 g, 60 mmoles) in benzene (20 ml) at room temperature. After stirring at room temperature for 30 min, S_2Cl_2 (16.2 g, 12 mmoles) in benzene (60 ml) was added dropwise to the mixture. The mixture was stirred at room temperature for 30 min and at 65—70° for 12 hr to give an orange mixture. The mixture was evaporated *in vacuo* to leave a dark brown viscous oil which was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with 5% NaOH, saturated NaCl solution, and dried. The residue obtained after evaporation was extracted with hot EtOH and hot CH_2Cl_2. The combined extracts were evaporated to yield a semi-solid (3.98 g) which was chromatographed on silica gel. Elution with CH_2Cl_2 gave pale purple crystals (40 mg, unknown structure), brown crystals (**11**, 50 mg), and then **10** (1.12 g, 19%), mp 163—172°, which showed a single spot on TLC. The crude **11** was further purified by silica gel column to give brown crystals (34 mg), mp 75—78°. IR(KBr) 1660, 1550, 1470, 1410, 1260, 1160 cm^{-1}. NMR($CDCl_3$); δ 3.75 (s). Mass Spectrum *m/e* (relative abundance): 214 (29, M^++2), 212(29, M^+), 186(89), 184(89, M^+−CO), 145(89), 143(89), 78(37), 76(100). The crude **10** was recrystallized from EtOH to give an analytical specimen, mp 176—178°. *Anal.* Calcd. for $C_6H_6O_2N_2Cl_2$: C, 34.43; H, 2.89; N, 13.40; Cl, 33.92. Found: C, 34.53; H, 2.94; N, 13.49; Cl, 34.37. NMR ($CDCl_3$); δ 3.57 (s, NMe). IR(KBr); 3000, 1700, 1615, 1420, 1350, 1105, 1000 cm^{-1}. Mass Spectrum *m/e* (relative abundance): 210(14, M^++2), 208(18, M^+), 182(12), 180(18, M^+−CO), 165(9, M^+−(CO+Me)), 151(25. M^+−MeNCO), 116(15), 78(34), 76(100).

Reaction of Proline Anhydride (5) with Sulfur——A mixture of **5**[19] (1.16 g, 6 mmoles), sulfur (7.7 g, 30 mmoles), and sea sand (2 g) was heated at 160—180° for 9 hr with stirring under N_2. The mixture kept at room temperature overnight was powdered and extracted with portions of hot MeOH. The MeOH solution was evaporated *in vacuo* to yield an orange brown semi-solid (580 mg), which was chromatographed on silica gel (18 g) and eluted with benzene–CH_2Cl_2. The first fraction gave sulfur (50 mg), the second fraction gave a pale yellow solid (A, 30 mg), and the third fraction gave an orange yellow viscous oil (B, 470 mg). The fraction A was recrystallized from hot benzene to give pale yellow plates, mp 200—220° (sublimed on a hot plate). IR(KBr); 3125, 1695, 1555, 1460, 1410, 1320, 1170, 780 cm^{-1}. Mass Spectrum *m/e*: 186 (M^+, 100%). Its structure was assumed to be **9** (reported mp, 268—269°[20]). The fraction B was further chromatographed on silica gel with AcOEt. The first fraction gave a pale yellow semi-solid (C, 210 mg), mp 255—266°. The second fraction gave the starting material (70 mg). Repeated recrystallizations of C from AcOEt gave fine needles, mp 270—273° (sublime). Its structure was not determined yet but the following spectral data suggested a dimeric compound such as C. *Anal.* Calcd. for $C_{20}H_{20}O_4N_4$: C, 62.93; H, 5.34; N, 14.66. Found: C, 63.15; H, 5.30; N, 14.73. IR(KBr): 3100, 2980—2880, 1735, 1700, 1695, 1655, 1470, 1420, 1367, 1335, 1275, 1165, 775, 740 cm^{-1}. UV λ_{max}^{EtOH} 255—265, 280^{sh}, 298 nm. NMR ($CDCl_3$); δ 1.5—4.4 (m, 17—18H), 6.49 (t, 1H, J=2.5 Hz), 7.10 (d—d, 1H, J=2.5 Hz and 1 Hz), 7.44 (d—d, 1H, J=2.5 and 1 Hz). Mass Spectrum *m/e* (relative abundance): 380 (4, M^+), 352 (5, M^+−CO), 310 (9), 192 (100), 164(8), 131(10).

Diethyl N-Methylaminomalonate (14)——i) Diethyl N-Methylbenzylaminomalonate: Previously reported method[15] was modified as follows: To a stirred mixture of N-benzylmethylamine (322 g, 2.66 mole), anhyd. K_2CO_3 (240 g) in anhyd.$CHCl_3$ (1 liter) was added dropwise diethyl bromomalonate[21] (425 g, 1.77 mole) during 30 min under ice cooling. The mixture was stirred at room temperature for 7 hr. Further N-methylbenzylamine (106 g) was added to the mixture, which was allowed to stand overnight. The precipitates were filtered and washed with $CHCl_3$. The combined $CHCl_3$ solution was washed with 5% HCl, H_2O, dried, and evaporated to leave a brown oil which was distilled under reduced pressure and N_2 atmosphere. Colorless liquid (307 g, 78%), bp 142—146°/2 mmHg (reported bp 160—165°/5 mmHg[15]).

ii) Debenzylation: The above malonate (307 g) in EtOH was debenzylated with 5% Pd-C(15 g) and H_2. The usual work up gave N-methylamino malonate (178 g, 85%), bp 80—84°/2 mmHg).

1,4-Dimethyl-3,6-diethoxycarbonyl-2,5-piperazinedione (15)——Diethyl N-methylaminomalonate (178 g) was heated at 180—190° (bath temperature) for 2 hr with stirring under N_2. The cooled mixture was tritulated with acetone (80 ml) and left in a refrigirator. The separated crystals (69.6 g, 65%), mp 183—189°, were collected and washed with chilled acetone. The combined filtrate was left in a refrigirator for several weeks to give further crops of crystals (4.7 g, total 74.3 g, 69%). Recrystallizations from acetone gave an analytical specimen, mp 184—187°, as colorless prisms. *Anal.* Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.34; N,

19) J. Kapfhammer and A. Mathes, *Z. Physiol. Chem.*, **223**, 43 (1934).
20) G.L. Ciamician and P. Silber, *Ber.*, **17**, 103 (1884).
21) C.S. Palmer and P.W. McWherter, *Organic Syntheses*, Coll. Vol. 1, 245 (1941).

9.79. Found: C, 50.49; H, 6.31; N, 10.12. IR(KBr); 1744 (C=O, ester), 1690 (C=O, amide), 1402, 1280, 1230, 1195, 1047, 1020 cm^{-1}. NMR ($CDCl_3$) δ 1.32 (t, 6H, J=7 Hz, CH_3), 3.00 (s, 6H, NMe), 4.27 (q, 4H, J=7 Hz, OCH_2), 4.60 (s, 2H, 3, 6-CH). Mass Spectrum *m/e* (relative abundance): 286 (4, M^+), 213 (14, M^+-CO_2Et), 185 (17, M^+-CO_2Et-CO), 157 (8), 141(12), 42(100).

Reaction of 2,5-Piperazinedione (15) with NaH and S_2Cl_2——Piperazinedione (**15**, 4.30 g, 15 mmoles) in freshly distilled anhyd. dioxane (150 ml) was warmed at 50—60° to make a clear solution. NaH (1.76 g (36 mmoles) of a 50% dispersion in mineral oil) was added portionwise to the stirred solution at room temperature under N_2 atmosphere. The mixture was warmed at 80—90° for 15 min to give a yellow mixture and cooled. Freshly purified S_2Cl_2 (2.44 g, 18 mmoles) in anhyd dioxane (10 ml) was added rapidly to the mixture at room temperature with stirring. The reaction mixture was stirred at room temperature for 30 min then at 50—60° for 1 hr. Evaporation of the solvent *in vacuo* left a pale brown viscous oil to which ice water (100 ml) and CH_2Cl_2 (100 ml) were added. The aqueous layer was adjusted to pH 6—7 by the addition of 10% HCl and further extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with H_2O and dried. Evaporation of the solvent gave a partially crystallized brown oil (5.70 g) which was chromatographed on silica gel (120 g). Elution with benzene gave fraction A–G (total 1.73 g). Elution with acetone gave pale brown viscous oil (2.8 g) which was found to be a mixture of sulfur containing compounds. Fractions of A—G were found to be a mixture of the sulfides (**16a—d**) from the mass spectra. Each fractions of A—G were recrystallized from iso-Pr_2O to give crude tetrasulfide (**16d**, total 550 mg, 9%), mp 162—169°, which showed practically a single spot on TLC. Further recrystallizations from benzene–hexane gave pure tetrasulfide, mp 171—172°, as colorless prisms. *Anal.* Calcd. for $C_{12}H_{16}O_6N_2S_4$: C, 34.95; H, 3.92; N, 6.80. Found: C, 35.37; H, 4.28; N, 6.73. IR(KBr) 1749(ester), 1686(amide) cm^{-1}. NMR ($CDCl_3$) δ 1.35 (t, 6H, J=7 Hz, CH_3), 2.96 (s, 6H, NMe), 4.38 (double q, 4H, J=7 Hz, OCH_2). Mass Spectrum *m/e*: (relative abundance): 412(6.1, M^+), 348(2, M^+-S_2), 339(2. M^+-CO_2Et), 284(100, $M-S_4$), 256(15, $M-S_4-CO$), 184(60).

The mother liquors from recrystallization were evaporated and rechromatographed on silica gel. Elution with iso-Pr_2O-hexane or benzene gave crude disulfide (**16b**, 880 mg, 17%), and monosulfide (28 mg). Recrystallizations of the crude disulfide (16b) from benzene–hexane yielded an analytical sample, mp 90.5—92°, as colorless crystals. *Anal.* Calcd. for $C_{12}H_{16}O_6N_2S_2$: C, 41.38; H, 4.63; N, 8.04. Found: C, 41.33; H, 4.72; N, 8.70. NMR ($CDCl_3$) δ 1.40 (t, 6H, J=7 Hz, CH_3), 3.03 (s, 6H, NMe), 4.48 (q, 4H, J=7 Hz, OCH_2). IR (KBr): 1749 (ester), 1715 (amide) cm^{-1}. Mass Spectrum *m/e* (relative abundance): 348(8.5, M^+), 284(100, M^+-S_2), 184(67), 156(22). The monosulfide (**16a**) was identical with the sample obtained below (IR). From the mother liquor of the recrystallization of **16b** the trisulfide (**16c**) was isolated (16 mg) and confirmed by comparison with the sample obtained below (IR and TLC).

The reaction of **15** with NaH in DMF, and followed treatment with S_2Cl_2 gave the disulfide (**16b**) in 16% and the tetrasulfide (**16d**) in 11%. In HMPA **15** gave **16b** in 11% and **16d** in 8%.

Reaction of 15 with SCl_2——A mixture of **15** (2.86 g, 10 mmoles) in anhyd dioxane (100 ml) was warmed at 60—70° to make a clear solution under N_2. NaH (1.1 g (22 mmoles) of a 50% dispersion in mineral oil) was washed free of mineral oil with ether, and added to the above solution. The mixture was refluxed gently for 1 hr and cooled. Freshly purified SCl_2 (1.13 g, 11 mmoles) in dioxane (3 ml) was added rapidly to the mixture. The mixture was stirred at room temperature for 20 min and at 60—65° for 1 hr, and then evaporated. The residue was mixed with ice water (100 ml) and AcOH (3 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous saturated NaCl solution, dried and evaporated. The residue (3.77 g) was chromatographed on silica gel (57 g). Elution with hexane–iso-Pr_2O (2: 1) gave **16a** (64 mg), mp 79—81°, a mixture (A, 41 mg) of **16a** and **16b**, **16b** (270 mg), mp 90—91.5°, and a mixture (B, 77 mg) of **16b** and **16d**. Elution with CH_2Cl_2–acetone (10%) gave a mixture (3.4 g) of **15** and sulfur containing compounds. The both mixture (A and B) were further separated by preparative TLC (silica gel-iso-Pr_2O–hexane (1: 3)) to yield **16a** (8 mg, total 72 mg, 2.3%), **16b** (73 mg, total 343 mg, 10%) and **16d** (4 mg). The crude **16a** was recrystallized from benzene–hexane to yield an analytical specimen, mp 80.5—81°. *Anal.* Calcd. for $C_{12}H_{16}O_6N_2S$: C, 45.57; H, 5.10; N, 8.86; S, 10.12. Found: C, 45.38; H, 5.07; N, 9.06; S, 10.03. IR (KBr); 1765 (ester), 1720 (amide) cm^{-1}. NMR ($CDCl_3$), δ 1.36 (t, 6H, J=7 Hz, CH_3), 3.09 (s, 6H, NMe), 4.39 (q, 4H, J=7 Hz, OCH_2). Mass Spectrum *m/e* (relative abundance): 216(trace, M^+), 259(100, M^+—MeNCO), 214(15, M^+—MeNCO–OEt), 187(85), 114(15).

Reduction of Episulfide (16) with $NaBH_4$——To a stirred solution of a mixture (830 mg) of **16b** and **16d** in MeOH (20 ml) was added $NaBH_4$ (170 mg) at room temperature. The mixture was stirred at room temperature for 30 min and evaporated *in vacuo*. Ice-water (20 ml) and 5% HCl (3 ml) were added to the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, saturated NaCl solution, and dried. Pale yellow crystals (660 mg), mp 150—180°, obtained on evaporation of the solvent was chromatographed on silica gel (6 g). Elution with benzene gave sulfur (100 mg) and **15** (520 mg, 90%). The crude **15** was recrystallized from acetone to give **15**, mp 183— 187°, which was identical with an authentic sample (NMR and IR).

Desulfurization of the Tetrasulfide (16d) with Ph_3P——To a stirred solution of **16d** (206 mg, 0.5 mmoles) in anhyd tetrahydrofuran (THF) (15 ml) was added Ph_3P (131 mg, 0.5 mmole) in anhyd THF (5 ml) at −5—0° under N_2 atmosphere. The reaction mixture was stirred at −5—0° for 40 min and evaporated *in vacuo* to leave a pale yellow semi-solid (337 mg) which was chromatographed on silica gel (30 g). The first elution

with benzene gave $Ph_3P=S$ (140 mg), mp 161—163°. The second elution with benzene gave a mixture (102 mg) of tri- and disulfide whose ratio was found to be 22: 5 from the intensities of N-methyl signals in the NMR spectrum of the mixture. The third elution with benzene gave a similar mixture (10 mg, ratio of **16b**: **16c** was 11: 7). The fourth elution with benzene gave a mixture (30 mg) of **16d**, **16c**, and **16b** (ratio 3: 1: 1). The final elution with benzene gave the recovered tetrasulfide (20 mg). Calculated yield of the trisulfide was 94 mg (58% based on consumed **16d**). The disulfide was 30 mg (19%), and the recovered tetrasulfide was 30 mg (7%). The second fraction was recrystallized from benzene–hexane to give pure trisulfie (**16c**), mp 101.5—103°, as colorless prisms. *Anal.* Calcd. for $C_{12}H_{16}O_6N_2S_3$: C, 37.88; H, 4.21; N, 7.36. Found: C, 37.88; H, 4.23; N, 7.30. NMR ($CDCl_3$) δ 1.37 (t, 6H, $J=7$ Hz, CH_3), 2.92 and 3.07 (s, total 6H, NMe), 4.39 (q, 4H, $J=7$ Hz, OCH_2). IR (KBr); 1756 (ester), 1695 (amide) cm^{-1}. Mass Spectrum *m/e* (relative abundance); 380(5,M^+), 284(100, M^+-S_3), 256(10, M^+-S_3-CO), 184(82), 156(24).

Reaction of Diethyl Acetamidomalonate with S_2Cl_2——To a stirred solution of diethylacetamidomalonate (6.52 g, 30 mmoles) in anhyd. dioxane (120 ml) was added NaH (2.16 g (45 mmoles) of a 50% dispersion in mineral oil) at room temperature under N_2 atmosphere. The resulted pasty mixture was diluted with anhyd dioxane (50 ml) and warmed at 70—80° for 30 min. Then S_2Cl_2 (4.05 g, 33 mmoles) was added to the stirred mixture at room temperature. The whole mixture was stirred at 35—40° for 1.5 hr then overnight at room temperature. The solvent was evaporated *in vacuo* to leave a residue, to which H_2O was added and adjusted to pH *ca.* 7 by the addition of 10% HCl. The mixture was extracted with CH_2Cl_2, and the extracts were washed with saturated NaCl solution and dried. The solvent was evaporated to leave a pale yellow viscous oil (9.60 g), which was chromatographed on silica gel (96 g). First elution with benzene–acetone (30: 1) gave a mixture (1.44 g) of mineral oil and sulfur. The second elution with the same solvent gave a pale yellow semi-solid (620 mg) which showed four spots on TLC. The third elution with the same solvent gave the disulfide (**24a**, $n=2$) (5.33 g, 70%), mp 102—107°, as colorless crystals which showed a single spot on TLC. Recrystallizations from iso-PrOH–iso-Pr_2O (2: 5) gave an analytical specimen, mp 105—108°, as colorless minute pillars. *Anal.* Calcd. for $C_{18}H_{28}O_{10}N_2S_2$: C, 43.54; H, 5.68; N, 5.64; S, 12.91. Found: C, 43.83; H, 5.65; N, 5.84; S, 12.99. IR(KBr); 3370, 3260 (NH), 1740 (ester), 1676 (amide), 1275, 1213, 1020 cm^{-1}. NMR ($CDCl_3$) δ 1.29 (t, 12H, $J=7$ Hz, CH_3), 2.15 (s, 6H, NMe), 4.28 (q, 8H, $J=7$ Hz, OCH_2), 6.69 (br. s, 2H, NH). Mass Spectrum *m/e* (relative abundance): 496(1, M^+), 248(1, $M^+/2$), 217(32), 174(42), 74(20), 64(17), 43(100).

Reaction of Diethyl Acetamidomalonate with S_2Cl_2 in Pyridine——To a suspension of NaH (960 mg (20 mmoles) of a 50% dispersion in mineral oil) in anhyd pyridine (20 ml) was added **23a** (2.17 g, 10 mmoles) in pyridine under cooling. After stirring at room temperature for a while freshly purified S_2Cl_2 (2.72 g, 20 mmoles) was added under ice cooling. The mixture was stirred at room temperature for 20 min and poured onto crashed ice (50 g) and neutralized with 10% HCl (pH *ca.* 7), and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 10% HCl, saturated NaCl solution, dried, and evaporated. The residue (1.84 g, pale orange viscous oil) was chromatographed on silica gel (30 g). Elution with benzene–acetone (10%) gave sulfur (260 mg) and a mixture (790 mg) of sulfides. The mixture was recrystallized from iso-Pr_2O-acetone gave pure trisulfide (**24a**, $n=3$), mp 126—128°, as colorless needles. *Anal.* Calcd. for $C_{18}H_{28}O_{10}N_2S_3$: C, 40.8; H, 5.35; N, 5.30; S, 18.2. Found: C, 41.10; H, 5.35; N, 5.37; S, 17.72. IR(KBr): 3230 (NH), 1745 (ester), 1663 (amide), 1280, 1020 cm^{-1}. NMR ($CDCl_3$): δ 1.28 (t, 12H, $J=7.5$ Hz, CH_3), 2.18 (s, 6H, CH_3CO), 4.30 (q, 8H, $J=7{,}5$ Hz, OCH_2), 7.38 (br. s, 2H, NH). Mass Spectrum *m/e* (relative abundance): 528 (0.8, M^+), 483 (1), 413(1), 351(2), 313(10), 217(29), 174(45), 134(7), 99(12), 74(14), 64(14), 43(100). The presence of the disulfide (**24a**, $n=2$) was recognized on TLC but could not be isolated in pure state.

Reaction of Diethyl Phthalimidomalonate with S_2Cl_2——To a stirred solution of diethyl phthalimidomalonate (**23b**) (6.10 g, 20 mmoles) in anhyd dioxane (140 ml) was added portionwise NaH (1.01 g (21 mmoles) of a 50% dispersion in mineral oil) at room temperature. The mixture was warmed at 50—60° for 30 min. Freshly purified S_2Cl_2 (1.42 g, 10.5 mmoles) in dioxane (15 ml) was added to the mixture at room temperature during 5 min. The whole mixture was stirred at room temperature for 1 hr and evaporated *in vacuo* to leave a residue. The residue was mixed with ice water (100 ml) and AcOH (1 ml) and extracted with CH_2Cl_2. The extracts were washed with saturated NaCl solution and dried. The residue (6.49 g), on evaporation of the solvent, was recrystallized from $(C_2H_5)_2O$–hexane to give fine prisms (5.33 g), mp 162—164°. From the mother liquor further crop of the disulfide (92 mg, total 5.42 g, 80%) was obtained. Recrystallizations from acetone–iso-Pr_2O gave **24b** ($n=2$), mp 159—161°, as colorless prisms. *Anal.* Calcd. for $C_{30}H_{28}O_{12}N_2S_2$: C, 53.57; H, 4.19; N, 4.16. Found: C, 53.70; H, 4.28; N, 4.08. IR(KBr); 1795, 1765, 1750 (C=O), 1250, 1200, 1140, 720, 710, 705 cm^{-1}. NMR ($CDCl_3$) δ 1.15 (t, 12H, $J=7$ Hz, CH_3), 4.15 (q, 8H, $J=7$ Hz, OCH_2), 7.77 (m, 8H, arom H).

Reaction of Diethyl Methylmalonate (23c) with S_2Cl_2——NaH (5.4 g (0.105 mole) of a 50% dispersion in mineral oil) was washed with toluene and was added to a solution of **23c** (17.4 g, 0.1 mole) in anhyd dioxane (250 ml). The mixture was heated at 80—90° for 30 min and refluxed for 10 min and cooled. Freshly purified S_2Cl_2 (8.5 g, 0.064 mole) in dioxane (20 ml) was added rapidly to the mixture under cooling. The mixture was stirred at room temperature for 1.5 hr and evaporated *in vacuo*. Ice water (150 ml) and AcOH (3 ml) were added to the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated. The residue (17.8 g) was chromatographed on silica gel (270 g). Elution with hexane–CH_2Cl_2 (5: 1—5: 3) gave **23c** (330 mg), a pale yellow oil (A, 11.7 g), and a structure unknown mixture

(3.0 g). The fraction A was found to be a mixture of the disulfide (**24c**, $n=2$) and the trisulfide (**24c**, $n=3$) (the ratio was about 5:1 from the NMR and mass spectra). Recrystallization of A from benzene–hexane gave pure trisulfide (**24c**, $n=3$), mp 53—55°. *Anal.* Calcd. for $C_{16}H_{26}O_8S_3$: C, 43.42; H, 5.92; S, 21.74. Found: C, 43.37; H, 5.87; S, 20.31. IR(KBr); 1740^{sh}, 1725, 1270, 1235, 1110, 1020 cm^{-1}. NMR ($CDCl_3$) δ 1.28 (t, 12H, $J=7.5$ Hz, CH_3), 1.80 (s, 6H, CH_3), 4.27 (q, 8H, $J=7.5$ Hz, OCH_2). Mass spectrum *m/e* (relative abundance): 444(20, $M^+ + 2$), 442(100, M^+), 410(11, M−S), 370(22), 197(28), 174(52), 145(15), 133(30), 127(52), 119(32), 59(55).

The disulfide (**24c**, $n=2$) could not be purified by recrystallization. A pure sample of the disulfide was obtained as follows. To a stirred solution of a portion of the above fraction A (853 mg) in THF (40 ml) was added Ph_3P (1.15 g) in THF (10 ml) at room temperature during 10 min. The mixture was refluxed for 4.5 hr and left overnight at room temperature. The solvent was evaporated *in vacuo* to leave a residue (2.0 g) which was chromatographed over silica gel (30 g). Elution with benzene–hexane (2:1) gave Ph_3P (687 mg). Elution with benzene–hexane (1:1) gave $Ph_3P=S$(215 mg). The second elution with the same solvent gave **24c** ($n=2$) (690 mg), which was free from the trisulfide from the NMR spectra. NMR ($CDCl_3$); δ 1.25 (t, 12H, CH_3), 1.70 (s, 6H, CH_3), 4.20 (q, 8H, OCH_2).

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