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DESULFURIZATION OF EPIDITHIO-2,5-PIPERAZINEDIONE DERIVATIVES AND THEIR OPEN CHAIN ANALOGS WITH TRIPHENYL PHOSPHINE

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Abstract—Desulfurization of epidithio-2,5-piperazinediones (**6** and **7**) by triphenylphosphine in THF gave dimeric compounds (**8** and **15**). In the presence of water or phenol the desulfurization gave 3-hydroxy (**9**) or 3-phenoxy-2,5-piperazinedione (**10**). Reaction of **6c** with triphenylphosphine in ethyl vinyl ether yielded 2,5-diazabicyclo[2.2.2]octane-3,6-dione (**11**), indicating the presence of 1,4-dipole (**B**) as an intermediate of the desulfurization. Similar cycloaddition products (**13** and **14**) were obtained by the desulfurization of **6c** in the presence of benzofuran, indole or skatole. Desulfurization of open chain disulfides (**16**, **21**, **23** and **25**) by triphenylphosphine gave reduced products (**17**, **22** and **26**) and an isoxazole (**18**), but C–C bond formation was not observed.

Desulfurization of dialkyl trisulfide by trivalent phosphorous compounds is known to give the disulfide though the S atom removed is either the central one or the terminal one depending on the structure of trisulfide and the phosphine used.[1] On the other hand, the disulfides which have been known to give monosulfides by use of triphenylphosphine were limited to acyl and vinylogous acyl disulfides. However, aminophosphine reacted with a variety of disulfides to give the corresponding monosulfides.[2] On the desulfurization of the epipolythio-2,5-piperazinediones the trisulfide (**1**) was reported to be desulfurized to the disulfide (**2**) and further to the monosulfide (**3**) by triphenylphosphine[3] and the disulfide (**4**) was known to be converted to the monosulfide (**5**) by aminophophine.[4]

In the previous papers we reported the synthesis of epipolythio-2,5-piperazinediones (**6** and **7**) and the desulfurization of **6a** to **6d** and **6c**.[5,6] In this paper we describe the desulfurization of **6** and **7**, and their open chain analogs by triphenylphosphine to give dethio derivatives, which has not previously been reported.

When a solution of **6c** in anhydrous THF was treated with one equivalent of triphenylphosphine under ice-cooling, a dimeric compound (**8**), m.p. 178–181°, was obtained in 35% yield besides triphenylphosphine sulfide, but the monosulfide (**6d**) was not isolated. The yield of **8** increased to 55% in the reaction using two equivalents of triphenylphosphine. The same compound (**8**) was obtained in 72% yield when the monosulfide (**6d**)[5] was treated with one equivalent of triphenylphosphine under a similar reaction condition. The mass spectrum of **8** showed a weak molecular ion peak at *m/e* 568 and a base peak at *m/e* 284 corresponding to M/2. The IR spectrum showed a ester CO band at 1760 cm^{-1} and an amide CO band at 1698 cm^{-1} which are similar to those of the parent 3,6 - diethoxycarbonyl - 1,4 - dimethyl - 2,5 - piperazinedione.[5] Its NMR spectrum (in $CDCl_3$) showed two overlapped triplets at 1·35 and 1·38 ppm and a broad quartet at 4·35 ppm for the ester group, and two singlets for N-Me at 3·14 and 3·18 ppm. The NMR spectrum was not consistent with either one of two possible isomeric structures (**8** and **8'**) which are both synmmetric and thus whose four N-Me groups should be equivalent. Although the compound showed a single spot on TLC in various solvent systems and the ratio of the N-Me signals did not change by recrystallizations, the compound was assumed to be an equimolar mixture of **8** and **8'**. These reactions are different from those of **2** and **4**, though the reaction may proceed via monosulfide. The C–C bond formation accompanied by desulfurization is a well known reaction as "Sulfur extrusion reaction[7]" or "Sulfur contraction reaction[8]" in which the episulfide is an intermediate. In our present reaction an episulfide is not a possible intermediate to **8**. The formation of **8** might be interpreted by the reaction of two molecules of intermediate A or B which involve the carbanion stabilized by the ethoxy-CO group (Chart 2). To prove the presence of the carbanion intermediate the reaction of **6d** with triphenylphosphine in aqueous THF was carried out. The dimeric product (**8**) was not isolated but a hydroxy derivative (**9**), m.p. 94–97°, was obtained in 66% yield. The structure of **9** was confirmed by elemental analysis and the following spectral data. IR(KBr); 3375(OH), 1745 (ester C=O), and 1690 (amide C=O) cm^{-1}. Mass *m/e* (rel. intensity); 285 (0·8, M-OH), 229 (100, M-CO_2Et) (the molecular ion peak was not observed). NMR($CDCl_3$); 1·29 (t, CH_3), 1·33 (t, CH_3), 2·96 (s, NMe), 3·03 (s, NMe), 4·23 (q, CH_2), 4·26 (q, CH_2), 4·66 (s, 5-CH), 5·05 (s, OH, exchangable with D_2O). The stereochemistry of **9** has not been established yet. The disulfide (**6c**) also gave **9** in 19% yield under the same condition. Desulfurization of **6c** with two moles of triphenylphosphine in THF containing phenol gave 3-phenoxy derivative (**10**), m.p. 130–132°, in 75% yield. The structure of **10** was confirmed by elemental analysis and spectral data (Experimental). The trans relationship of the two ethoxy CO groups in **10** was assumed by the fact that the NMR signal of the methylene group of one of them was higher than that of the corresponding methylene group of **9** which must be ascribed to the shielding effect of benzene ring of phenoxy group.

A possible intermediate to the dimer (**8**) is zwitter ionic B which can be considered as a 1,4-dipole[9] as is shown in Chart 2. To prove the presence of B as an intermediate the desulfurization of **6c** by triphenylphosphine in the presence of dipolarophile was carried out. The most

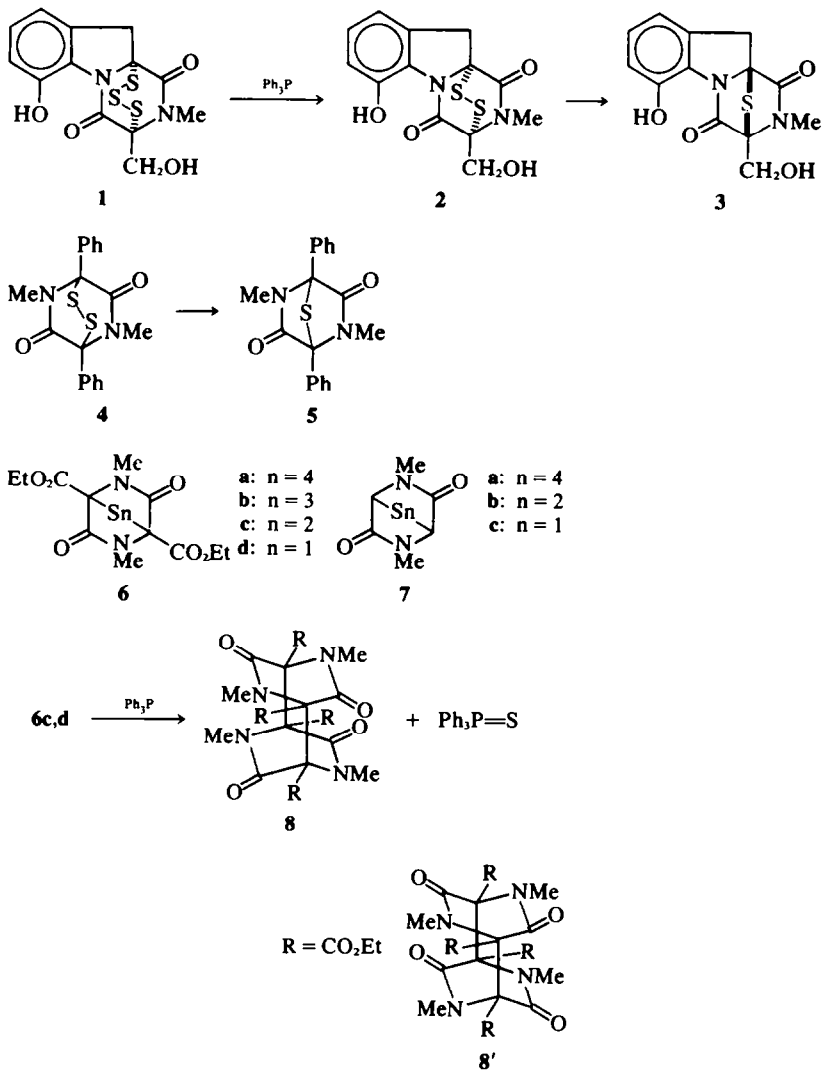


Chart 1.

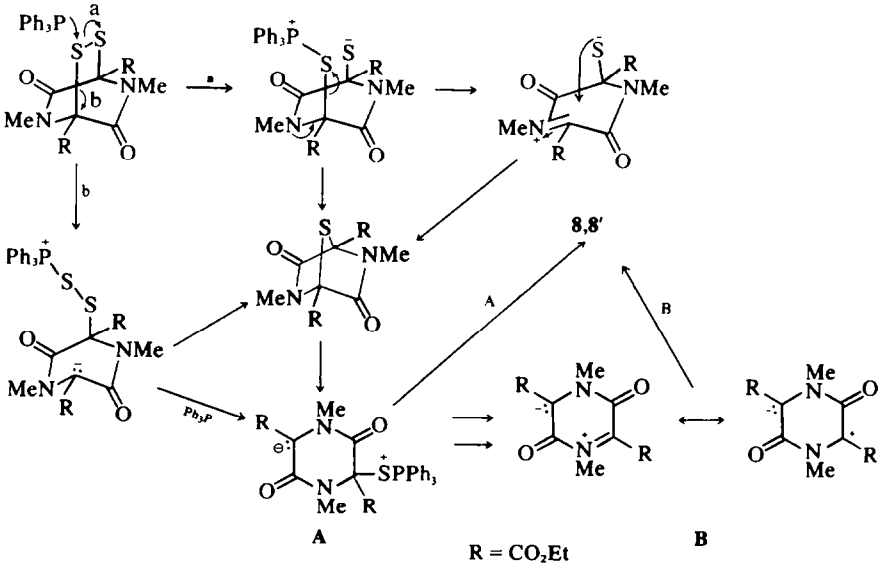


Chart 2.

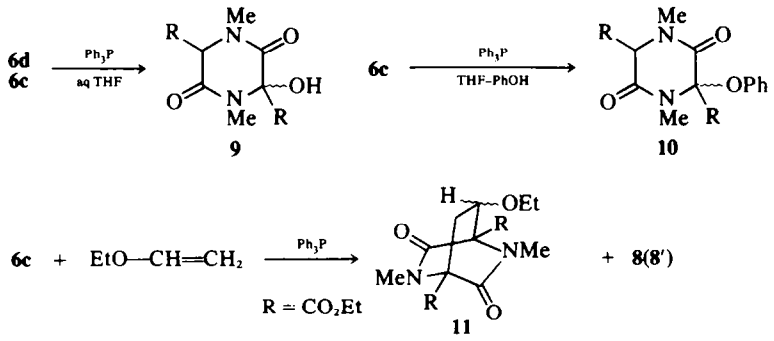
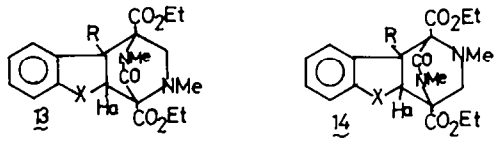


Chart 3.

popular dipolarophile such as dimethyl acetylene dicarboxylate and maleic anhydride was not adequate in this case because the intermediate carbanion(A) may react with these dipolarophile.[10] Therefore a nuclephilic olefin such as vinyl ether or enamine may be desirable, but the latter might serve as a nucleophile to displace Ph_3PS group in the intermediate A. The desulfurization of the disulfide (**6c**) with two moles of triphenylphosphine was now carried out in a excess of ethyl vinyl ether. Expected cycloaddition product (**11**), m.p. 67–69°, was obtained in 18% yield besides the dimer (**8**, 22%) and **6c** was recovered in 17% yield. The structure of **11** was confirmed by the elemental analysis and the following spectral data. Its IR spectrum showed an ester CO band at 1755 cm^{-1} and an amide CO band at 1710 cm^{-1} which is higher than that of 1,4 - dimethyl - 3,6 - diethoxycarbonyl - 2,5 - piperazinedione, indicating the presence of some ring strain in the compound. The mass spectrum showed a weak molecular ion peak at *m/e* 356 and the base peak at *m/e* 284 arrose from the retrocycloaddition reaction. Its NMR spectrum (in $CDCl_3$) showed two triplets at 1·37 and 1·39 ppm and two quartets at 4·41 and 4·42 ppm for two ethyl ester groups, two singlets at 2·90 and 3·00 ppm for two NMe groups, a triplet at 1·15 and a quartet at 3·62 ppm for ethyl ether group, two multiplets between 2·20–2·65 and 4·2–4·3 ppm for ABX pattern of CH_2–CH–O. The stereochemistry of the OEt group on the ethano bridge is uncertain, but a single isomer was obtained. Formation of **11** provide a supporting evidence for a zwitter ionic intermediate B in the desulfurization of **6c**.

Furthermore, a similar desulfurization of **6c** by triphenylphosphine were carried out in the presence of benzofuran, indole and skatole which are not known to be dienophiles in the usual Diels–Alder reaction. The desulfurization of **6c** in the presence of benzofuran (**12a**) gave two cycloaddition products (**13a** and **14a**) and the dimer as the main product. The spectral data of **13a** and **14a** are summarized in Tables 1 and 2. As the trans fusion of 6-membered ring and 5-membered ring is not likely to be formed in these cases, the ring fusion should be *cis* on both isomers. Examination of the stereomodel revealed that one of the two N-Me groups is situated above the benzene ring in one isomer (**13**) but two N-Me groups in another isomer (**14**) is not. Therefore an isomer showing a higher N-Me signal was assigned as the isomer **13**. The desulfurization of **6c** in the presence of indole (**12b**) gave two cycloaddition products (**13b** and **14b**) in good yields and the dimer was not isolated. Likewise, in the presence of skatole (**12c**) the desulfurization of **6c** yielded **13c** and **14c**. The structure of **13b,c** and **14b,c** were confirmed by spectral data (Tables 1 and 2) as well as elemental analysis. The results indicated that the cycloaddition of **6c** with indole and skatole took place with ease in preference to the coupling reaction of 1,4-dipoles, while the cycloaddition with benzofuran and vinyl ether was competitive with the dimerization. These results might suggest that the indoles attached to intermediate A to form indolenines by displacement of Ph_3PS group and the indolenine cyclized to **13** and **14**, while enol ethers reacted with intermediate **B** to form cycloaddition products.

Table 1. Spectral data of cycloaddition products



Compd No	X	R	UV λ_{max}^{EtOH} nm(ε)	IR(KBr) NH	Ester C=O	Amide C=O	M⁺	Mass Base peak
13a	O	H	273[s], 280, 287.5 (2300) (3300) (3300)	-	1752	1717, 1705	402 (5)	284
14a	O	H	273[s], 280.5, 287.5 (2400) (3300) (3400)	-	1760, 1743	1730, 1700	402 (7)	284
13b	NH	H	248, 309 (6700) (2900)	3400	1758, 1733	1715	401 (16)	284
14b	NH	H	247, 307 (6200) (2700)	3340	1753	1707, 1694	401 (16)	284
13c	NH	Me	244, 308 (7000) (2900)	3420	1750	1710	415 (15)	284
14c	NH	Me	245, 305 (6200) (2600)	3335	1758	1705, 1695	415 (10)	284

Table 2. NMR spectra of cycloaddition products (in $CDCl_3$, δ-value)

Compd No	$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	NMe	R	Ha	NH	Arom-H
13a	1.43(t)	4.52(q)	2.50(s) 3.01(s)	4.52[a](d)	5.53(d)[b]	-	6.94-7.40
14a	1.43(t)	4.50(q)	2.96(s) 2.99(s)	4.60(d)[a]	5.62(d)[b]	-	6.6-7.5
13b	1.44(t)	c	2.60(s) 3.01(s)	c	c	c	6.4-7.3
14b	1.41(t)	d	2.96(s) 2.99(s)	d	d	d	6.4-7.4
13c	1.39(t)	e	2.41(s) 3.03(s)	1.71(s)	e	e	6.4-7.6
14c	1.40(t)	4.24(q)	2.97(s) 3.08(s)	1.66(s)	4.22(br)[f]		6.4-7.7

a: On irradiation at H_a it became a singlet; b: On irradiation at R it became a singlet; c: These signals were overlapped between 4.25-4.85 ppm(7H,including one exchangable H) d: These signals were overlapped between 4.25-4.85 ppm(7H,including one exchangable H) e: These signals were overlapped between 4.20-4.58 ppm(6H). On addition of D_2O methylen protons appeared at 4.43(q) and Ha proton appeared at 4.23(s); f.On addition of D_2O H_a proton appeared at 4.22(s).

However, the fact that C–C bond formation was not observed in the desulfurization of open chain analogs (*vide infra*) may exclude the possibility of nucleophilic substitution of intermediate A by a nucleophile.

To examine whether the above desulfurization which removed both S atoms from the epidithio compound was restricted to the epidithio - 2,5 - piperazinedione having two extra ethoxy CO groups, the desulfurization of the disulfide (**7b**) having no ethoxy CO group was carried out. When **7b** was refluxed with triphenylphosphine (1 equiv)

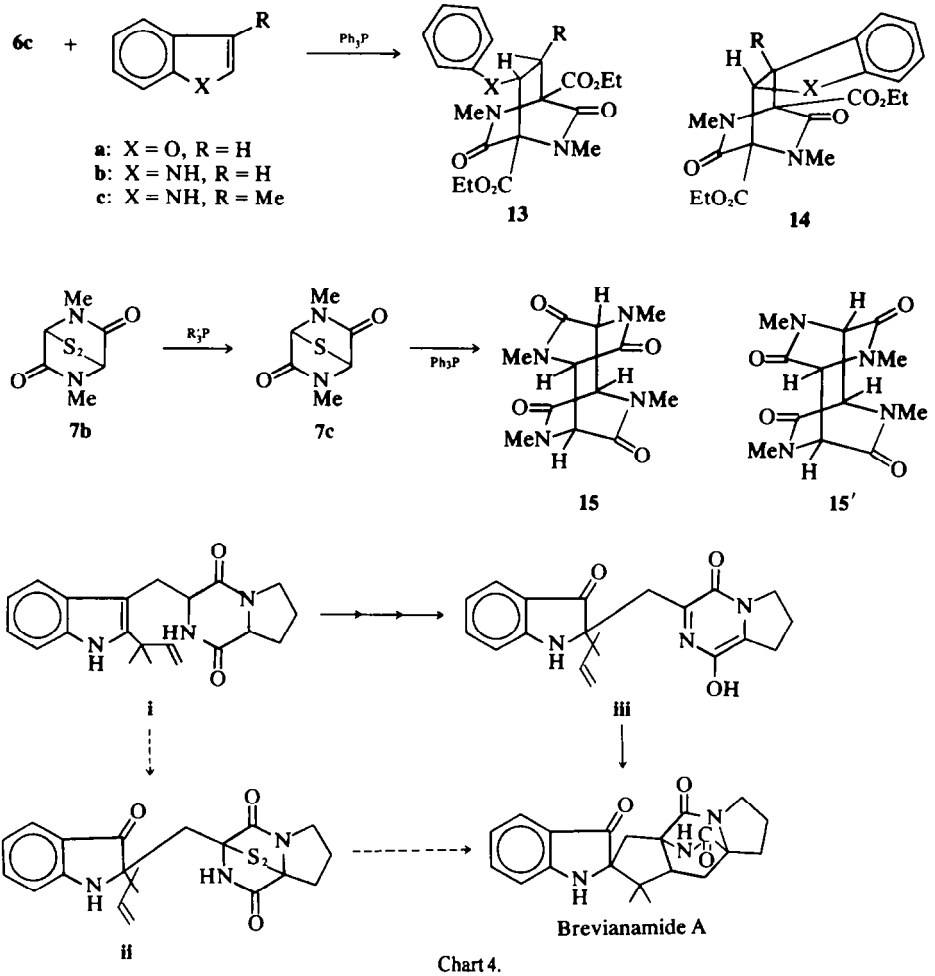


Chart 4.

in dioxane under more drastic condition than that for **6c**, the monosulfide (**7c**) was obtained in 86% yield. However the dimeric compound (**15**) was obtained in 68% yield by the reaction of **7c** with triphenylphosphine. The structure of **7c** and the dimer(**15**) were confirmed by spectral data as well as elemental analyses (Experimental). These results indicated that the formation of the dimeric compound with removal of S atom of epidithio - 2,5 - piperazinedione was not restricted to the activated 2,5-piperazinedione.

Our results suggest that the formation of 1,4-dipole by the desulfurization of epidithio - 2,5 - piperazinedione(ii) followed by a cycloaddition with the intramolecular olefin might be a possible route for the biosynthesis of brevianamide A from the general intermediate(i), for which the Diels-Adler reaction of (iii) was proposed by Sammes[11] (Chart 4).

It is now clear that the C-S bond in **6** is cleaved with triphenylphophine to leave a carbanion. The analogous reaction was examined on the open chain disulfides. The reaction of the disulfide (**16**) with two moles of triphenylphosphine in anhydrous THF proceeded slowly to give acetamidomalonate (**17**), the oxazole (**18**), the trisulfide (**19**), triphenylphosphine sulfide, and triphenylphosphine oxide, but expected dimer(**20**) was not isolated. The structures of **17**, **18**[12] and **19** were confirmed by the direct comparison with the standard samples. The formation of these compounds were interpreted as shown in Chart 5.

As the NH group might serve as a proton source in the above example, the reaction of the disulfides (**21** and **23**) which do not have active hydrogen, was carried out under the same condition. The reaction of **21** with triphenylphosphine (2 moles) in a boiling THF gave phthalimidomalonate (**22**) in 55% yield, but the C-C bond formation was not observed. The almost same result was obtained with tris(dimethylamino)phosphine. The desulfurization of **23** by tris(dimethylamino)phosphine (2 moles) in a boiling THF for 4 hr did not proceed and the starting material was recovered. Attempted formation of N-N bond by the reaction of the disulfide (**25**) with triphenylphosphine or aminophosphine was failed and phthalimide (**26**) was isolated as a sole product. In these

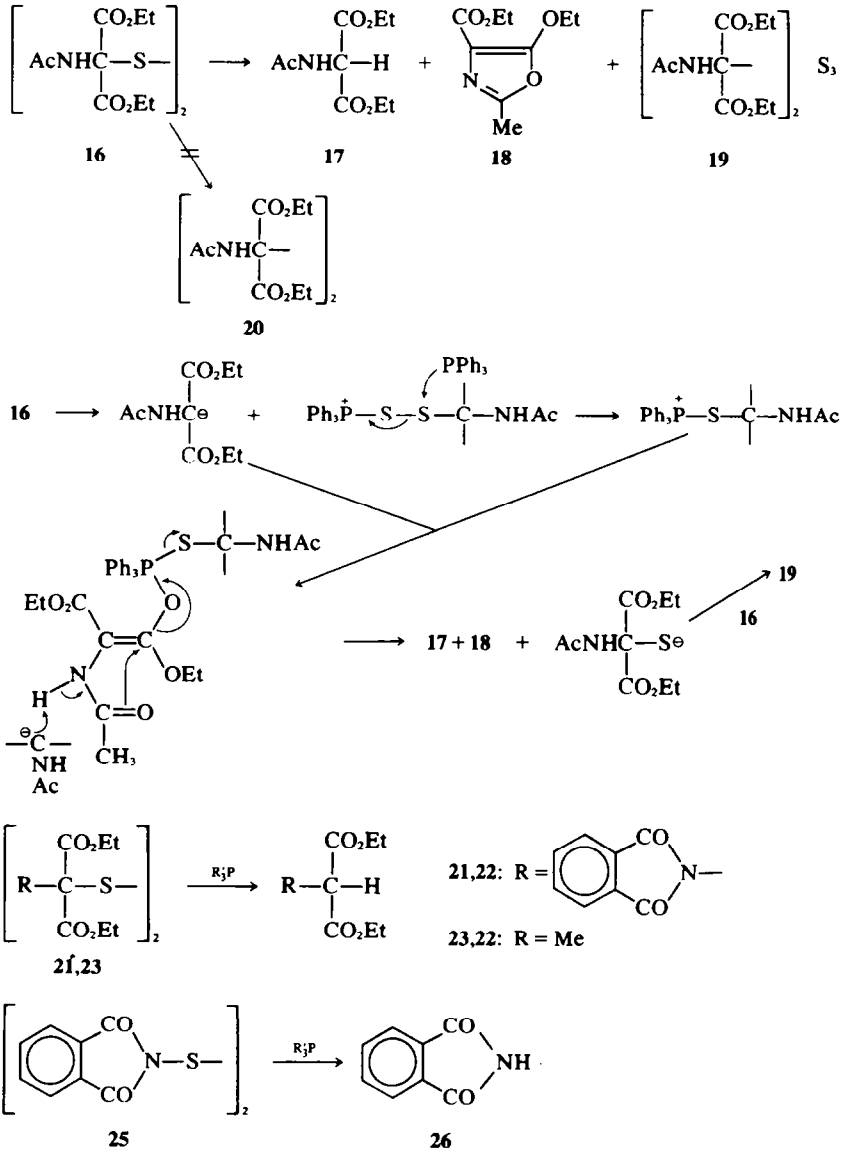


Chart 5.

open chain disulfides the desulfurization did occur in some extent, but the reduction preferentially took place in place of the C–C bond formation. The reason for this is not clear, but it may be seriously considered that an unfavourable intermolecular condensation between the sterically hindered reaction centers must be involved for the formation of the dimeric products.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were taken with a Hitachi EPI-G-3 spectrophotometer, NMR spectra were recorded on a Jeol JNM-MH-100. Mass spectra were determined with a Hitachi RMU-6E, and UV spectra were measured with a Hitachi 323 model. Elution chromatography was run on Mallinckrodt's silicic acid (100 mesh). TLC was run on silica gel GF_{254} (E. Merck).

1,2,5,6 - *Tetraethoxycarbonyl* - 3,8,10,12 - *tetramethyl* - 3,8,10,12 - *tetraazatricyclo*[4.2.2.2^{2,5}]*dodecane* - 4,7,9,11 - *tetraone* (**8**)

(i) *Desulfurization of* **6c**. To a cold stirred soln of **6c** (116 mg, 0·33 mmol) in anhyd THF (15 ml) was added Ph_3P (88 mg, 0·3 mmol) in anhyd THF (5 ml) under N_2 maintaining the temp. at 0–5°. The mixture was stirred at room temp. for 50 min and the solvent was evaporated. The residue was chromatographed over silica gel (5g). Elution with benzene-hexane (1:2) gave Ph_3P=S (80 mg, 81%), m.p. 162–163°, and recovered **6c** (58 mg, 50%). Elution with CH_2Cl_2-acetone (4:1) gave **8**, m.p. 174–176, (18 mg, 35% based on consumed **6c**) which was identical with a sample obtained below. Further elution with the same solvent gave **8** contaminated with Ph_3P=O (26 mg). The similar reaction of **6c** (348 mg) using 2 mole of Ph_3P (528 mg) gave Ph_3P=S (390 mg, 83%), **6c** (23%), **8** (120 mg, 55% based on consumed **6c**), m.p. 179–181, and a mixture of **8** and Ph_3P=O (50 mg).

(ii) *Desulfurization of* **6d**. To a soln of **6d** (105 mg, 0·33 mmole) in anhy THF (5 ml) was added Ph_3P (88 mg, 0·33 mmol) under N_2 with ice-cooling. The resulting blue mixture was stirred for 30 min with ice-cooling and for 50 min at room temp. The solvent was evaporated and the residue was subjected to silica gel chromatography. Elution with benzene-hexane (2:1) gave Ph_3P=S (80 mg, 82%). Elution with benzene-CH_2Cl_2 (2:1) gave **6d** (16 mg, 15%) and crude **8** (68 mg, 72%), m.p. 169–178°, which showed a single spot on TLC. Recrystallizations from benzene-hexane gave an analytical specimen, m.p. 179–181° (hot plate). (Found: C, 50·18; H, 5·70; N, 9·74. $C_{24}H_{32}N_4O_{12}$ requires: C, 50·70; H, 5·67; N, 9 9·68%). Mass *m/e* (rel. intens); 568 (M^+, 4), 523 (M^+-OEt, 2), 284 (M^+/2, 100), 256 (M/2-CO, 7), 239(5), 184(22), 156(10), 142(6), 42(43); IR and NMR data: see text.

1,4 - *Dimethyl* - 3,6 - *diethoxycarbonyl* - 3 - *hydroxy* - 2,5 - *piperazinedione* (**9**)

To a stirred soln of **6c** (371 mg, 1·07 mmol) in THF (20 ml) and H_2O (2 ml) was added Ph_3P (560 mg, 2·14 mmol) under N_2 with ice-cooling. The mixture was stirred at 0–5° for 1·5 hr and evaporated. The residue was chromatographed over silica gel (16 g). Elution with benzene gave Ph_3P=S (194 mg) and **6c** (250 mg, 67%). Elution with pet. ether-acetone (4:1) gave Ph_3P=O (426 mg). Further elution with the same solvent gave crude **9** (55 mg, 52% based on consumed **6c**) as colorless caramel which was recrystallized from benzene-hexane to give colorless plates (43 mg), Recrystallization from i-Pr_2O gave an analytical specimen, m.p. 94–97°. (Found: C, 47·58; H, 5·95; N, 9·18. $C_{12}H_{18}O_7N_2$ requires; C, 47·68; H, 6·00; N, 9·27%).

Similarly, desulfurization of **6d** (32 mg) with Ph_3P (29 mg) in aqueous THF gave **9** (20 mg, 69%), m.p. 91–95°.

1,4 - *Dimethyl* - 3,6 - *diethoxycarbonyl* - 3 - *phenoxy* - 2,5 - *piperazindione* (**10**)

Desulfurization of **6c** *with* Ph_3P *in the presence of phenol.* To a mixture of **6c** (128 mg, 0·37 mmol) and phenol (47 mg, 0·5 mmol) in anhyd ether (10 ml) was added Ph_3P (193 mg, 0·74 mmol) in anhyd ether (5 ml) at room temp. After stirring overnight at room temp. the mixture was refluxed for 2 hr. The solvent was evaporated and the residue was subjected to preparative layers chromatography (silica gel/Et_2O-hexane (2:1)). The least polar zone gave a mixture of Ph_3P=S and phenol (173 mg). The second zone gave crude **10** (97 mg, 75%) which was recrystallized from acetone-Et_2O and then from benzene-hexane to give an analytical specimen, m.p. 130–132°. (Found: C, 57·38; H, 5·97; N, 7·27. $C_{18}H_{22}N_2O_7$ requires; C, 57·14; H, 5·86; N, 7·40%). IR(KBr) 1775 (ester C=O), 1765 (ester C=O), 1693 (amide C=O), 760 (phenyl) cm^{-1}. Mass *m/e* (rel. intens.) 378 (M^+ 0·5), 305 (M-CO_2Et, 13), 285 (M–OPh, 100), 257(M–PhO–CO, 10), 184(12), 156(6), 112(6), 77(10). NMR($CDCl_3$) δ 1·33(3H, t, CH_3), 1·38(3H, t, CH_3), 2·95 (3H, s, NMe), 2·96(3H, s, NMe), 4·16 (2H, q, CH_2), 4·35 (2H, q, CH_2), 4·96 (1H, s, methine), 7·12 (5H, m, arom. H).

1,4 - *Diethoxycarbonyl* - 2,5 - *dimethyl* - 7 - *ethoxy* - 2,5 - *diazabicyclo*[2.2.2]*octane* - 3,6 - *dione* (**11**)

To a stirred soln of **6c** (348 mg, 1 mmol) in ethyl vinyl ether (20 ml) was added dropwise Ph_3P (550 mg, 2·1 mmol) in ethyl vinyl ether at room temp. under N_2. The mixture was stirred at room temp. for 5·5 hr and evaporated to leave a residue. Chromatography over silica gel (15 g) and elution with benzene-hexane gave Ph_3P=S (524 mg, 85%). Elution with CH_2Cl_2 gave **6c** (60 mg) and a colorless caramel (293 mg) which was further separated by preparative layers (silica gel/CH_2Cl_2–Et_2O (5:1)). The least polar zone gave the dimer (**8**) (63 mg,22%), m.p. 178–180·5°. The second zone gave crude **11** (64 mg, 18%). The most polar zone gave an unknown substances (69 mg). Recrystallization of crude **11** from Et_2O-hexane gave an analytical specimen, m.p. 67–69° (hot plate). (Found: C, 53·97; H, 6·75; N, 7·62. $C_{16}H_{24}O_7N_2$ requires: C, 53·92; H, 6·79; N, 7·86%) Mass *m/e* (rel. intens.); 356(M^+, 19), 311(M–OEt, 4), 284(M–EtOCH–CH_2, 100), 256(M–EtOCH=CH_2–CO, 14), 237(16), 184(59), 156(14), 103(50), 81(58), 73(56), 72(12).

Desulfurization of **6c** *with* Ph_3P *in the presence of benzofuran*

Formation of **13a** *and* **14a**. To a stirred soln of **6c** (348 mg 1 mmol) and benzofuran (1·0 g, 8·5 mmol) in anhyd ether (10 ml) under N_2 was added Ph_3P (790 mg, 3 mmol) in anhyd ether (5 ml) at room temp. The mixture was refluxed for 4 hr, and evaporated. The residue (2·19 g) was chromatographed over silica gel (22 g). Elution with hexane-benzene (5:1) gave recovered benzofuran (510 mg), Ph_3P (115 mg), and Ph_3P=S (645 mg, 73%). Elution with CH_2Cl_2-acetone (5%) gave a mixture (204 mg) and Ph_3P=O (104 mg). The mixture was separated by preparative layers (silica gel, developed 4 times with hexane-Et_2O (5:3)). The least polar zone gave the dimer (**8**, 90 mg, 32%), the second zone gave crude **13a** (51 mg, 13%), and the most polar zone gave crude **14a** (43 mg, 11%). The crude **8** was recrystallized from benzene-hexane to give colorless crystals which were identical with a standard sample(IR). The crude **13a** was recrystallized from Et_2O-hexane to give an analytical specimen, m.p. 144–145°. (Found: C, 59·91; H, 5·55; N, 7·00. $C_{20}H_{22}N_2O_7$ requires: C, 59·69; H, 5·51; N, 6·96%). The crude **14a** was recrystallized from benzene-hexane to give an analytical specimen, m.p. 134–136°. (Found: C, 59·76; H, 5·51; N, 7·04. $C_{20}H_{22}N_2O_7$ requires: C, 59·69; H, 5·51; N, 6·96%).

Desulfurization of **6c** *with* Ph_3P *in the presence of indole*

Formation of **13b** *and* **14b**. To a stirred soln of **6c** (192 mg, 0·55 mmol) and indole (1·17 g, 10 mmol) in anhyd ether (20 ml) was added Ph_3P (314 mg, 1·2 mmol) in anhyd ether at room temp. The mixture was refluxed for 3 hr and evaporated to leave a residue. Chromatography over silica gel (17 g) and elution with hexane-benzene (3:1) gave recovered indole (1·0 g). Elution with benzene-hexane (2:1) gave a mixture of indole and Ph_3P=S (290 mg) and Ph_3P=S (230 mg). Elution with benzene-AcOEt (15%) gave a mixture of **13b** and **14b** (200 mg, 92%), ratio of which was determined as 3:1 from the intensities of NMe signals (NMR). The mixture was separated by preparative layers (silica gel, developed 6 times with hexane-AcOEt (4:1)). The upper band gave **13b** (130 mg, 51%), m.p. 147–160°. The lower band gave **14b** (35 mg, 15%). The crude **13b** was recrystallized from MeOH–Et_2O to give an analytical specimen, m.p. 158–160°. (Found: C, 60·01; H, 5·78; N, 10·47. $C_{20}H_{23}N_3O_6$ requires: C, 59·84; H, 5·78; N, 10·47%).

The crude **14b** was recrystallized from MeOH to give an

analytical specimen, m.p. 190–195°. (Found: C, 59·76; H, 5·86; N, 10·37. $C_{20}H_{23}N_3O_6$ requires: C, 59·84; H, 5·78; N, 10·47%).

Desulfurization of **6c** *with* Ph_3P *in the presence of skatole*

Formation of **13c** *and* **14c**. A soln of **6c** (348 mg, 1 mmol) and skatole (1·31 g, 10 mmol) in ether was treated with Ph_3P (790 mg, 3 mmol) as described above in the case of indole. Separation of mixture as above gave a mixture of Ph_3P, skatole, and Ph_3P=S (2·36 g), Ph_3P=S (158 mg), **13c** (136 mg, 33%), m.p. 167–175° and **14c** (27 mg, 6·5%), m.p. 223–230°. Recrystallization of **13c** from benzene-hexane gave an analytical specimen, m.p. 173–174·5°. (Found: C, 60·58; H, 6·07; N, 10·06. $C_{21}H_{25}N_3O_6$ requires: C, 60·71; H, 6·07; N, 10·12%). Recrystallization of **14c** from MeOH–Et_2O gave an analytical specimen, m.p. 229·5–230°. (Found: C, 60·71; H, 6·08; N, 10·14. $C_{21}H_{25}N_3O_6$ requires: C, 60·71; H, 6·07; N, 10·12%).

Desulfurization of **7b** *with* Ph_3P

A mixture of **7b** (102 mg, 0·5 mmol) and Ph_3P (194 mg, 0·73 mmol) in anhyd dioxane (10 ml) was refluxed for 80 min under N_2. The solvent was evaporated and the residue was chromatographed over silica gel. Elution with benzene gave Ph_3P=S (183 mg, 85%). Elution with CH_2Cl_2 gave **7c** (62 mg, 86%) which was recrystallized from benzene-hexane to give an analytical specimen, m.p. 126–128°. (Found: C, 41·65; H, 4·52; N, 16·04. $C_6H_8N_2O_2S$ requires: C, 41·85; H, 4·68; N, 12·63%). IR(KBr) 3040, 1730, 1712, 1443, 1386, 1210, 980, 675 cm^{-1}. Mass *m/e* (rel. intens.) 172 (M^+, trace), 115 (M–MeNCO, 100). NMR ($CDCl_3$) δ 2·97 (s, 6H, NMe), 4·72 (s, 2H, CH).

Desulfurization of **7c** *with* Ph_3P

Formation of **15**. A soln of **7c** (258 mg, 1·5 mmol) and Ph_3P (445 mg, 1·7 mmol) in dioxane (20 ml) was refluxed for 1 hr. The solvent was evaporated and the residue was washed with warm benzene to give crude **15** (142 mg, 68%). Recrystallizations from CF_3COOH–MeOH gave an analytical specimen as colorless powder, m.p. 300°. (Found C, 51·17; H, 5·78; N, 20·25. $C_{12}H_{16}N_4O_4$ requires: C, 51·42; H, 5·75; N, 19·99%). IR(KBr) 1710, 1695, 1673 cm^{-1}. Mass *m/e* (rel. intens.) 280(M^-, 20), 140(M/2, 100), 112(M/2–CO, 20). NMR(CF_3COOH) δ 3·20(s, 12 H, NMe), 5·18(s, 4H, CH). The NMR spectrum (CF_3COOH) of the crude dimer showed two singlet at 5·10 and 5·18 in a ratio of 1:3, indicating two stereoisomers (**15** and **15'**) were obtained by the reaction but one isomer was purified in this case.

Desulfurization of **16** *with* Ph_3P

A mixture of **16** (992 mg, 2 mmol) and Ph_3P (1·04 g, 4 mmol) in anhyd THF (30 ml) was stirred at 50–60° for 5 hr under N_2. The solvent was evaporated and the residue (2·2 g) was chromatographed over silica gel (44 g). Elution with hexane-Et_2O (4:1) gave Ph_3P=S (735 mg, 46%). Elution with hexane-Et_2O (1:1) gave **18** (225 mg, 28%) which was identical with a standard sample obtained below (IR and TLC). Elution with the same solvent gave **17** (275 mg, 32%), m.p. 96–97°, which was identical with a standard sample (mmp). Further elution with the same solvent gave Ph_3P=O (351 mg). Elution with hexane-Et_2O gave crude **19** (118 mg) and a mixture of **16** and **19** (73 mg). Further separation gave **19** (total 128 mg, 12%) and **16** (42 mg, 4·5%). Both samples were identical with the standard samples (IR and m.m.p.). The similar result was obtained by the desulfurization of **6c** in benzene.

Hydrolysis of **18**

A mixture of **18** (160 mg) in 15% KOH (1 ml) was refluxed for 15 min. Usual work-up gave 4 - ethoxy - 2 - methyloxazole - 5 - carboxylic acid (52 mg, 38%), m.p. 141–142°. Recrystallization from EtOH gave pure sample, m.p. 147–148°, which was identical with the sample obtained below (IR and m.m.p.).

Alternative synthesis of **18**

A mixture of diethyl acetamidomalonate (5·0 g) and P_2O_5(20 g) in $CHCl_3$ (50 ml) was refluxed for 6 hr. The mixture was carefully basified with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried and evaporated to give an oil (4·01 g) which was distilled under reduced pressure to give **18** (3·21 g, 69%), b.p. 121·5–122°/5 mm Hg.[12] The ester was hydrolysed with 15% KOH to give the carboxylic acid.

Desulfurization of **21**

To a stirred soln of **21** (1·01 g, 1·5 mmol) in anhyd THF (25 ml) under N_2 was added Ph_3P (787 mg, 3 mmol) in THF (5 ml) at room temperature. The mixture was stirred at 50–60° for 1·5 hr and then refluxed for 4 hr. The solvent was evaporated and the residue (2·0 g) was chromatographed over silica gel (30 g). Elution with benzene gave Ph_3P=S (440 mg, 50%). Elution with hexane-Et_2O (2:5) and acetone - i - Pr_2O - hexane (1:3:2) gave **22** (502 mg, 55%) which was identical with a standard diethyl phthalimidomalonate (m.m.p.). Further elution gave Ph_3P=O (414 mg, 49%) and recovered **21** (271 mg, 27%). The desulfurization of **21** with tris(diethylamino)phosphine in anhyd THF gave **22**(54%) and recovered **21**(22%). Desulfurization of **23** with tris-diethylamino)phosphine in THF did not proceed practically, and recovered **23** in 86% yield after refluxing for 4 hr.

Desulfurization of **25** *with* Ph_3P

To a stirred soln of **25**(712 mg) in anhyd THF (40 ml) under N_2 was added Ph_3P (1·05 g, 4 mmol) in THF (10 ml) at room temp. The mixture was stirred at room temp. for 1·5 hr and evaporated to leave a residue (1·9 g) which was triturated with benzene-hexane (2:1) to separate phthalimide (210 mg). The mother liquor was evaporated to give a residue (1·69 g) which was chromatographed over silica gel (25 g). Elution with benzene gave Ph_3P=S (781 mg, 67%). Elution with CH_2Cl_2 gave the starting material (223 mg) and phthalimide (163 mg, total 373 mg, 63%). Further elution with CH_2Cl_2 gave Ph_3P=O (361 mg, 32%). The similar desulfurization of **25** with tris(diethylamin)phosphine in dioxane gave phthalimide (40%) and the phosphine sulfide (65%).

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