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SYNTHESIS OF 3,6-DIETHOXYCARBONYL-3,6-EPIPOLYTHIA-2,5-PIPERAZINEDIONE DERIVATIVES

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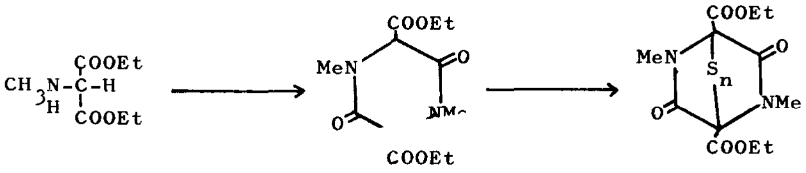
Epidithiapiperazinedione, a skeleton common to gliotoxin[1], sporidesmine[2], aranotine[3], chaetocin[4], and verticillin A[5], is a unique ring system occuring in natural products. The first synthesis of this new ring system was achieved by Trown in 1968[6]. Poisel and Schmidt[7] recently reported an improved method of the synthesis. We now describe a different approach to the synthesis of the ring system.

When diethyl N-methylaminomalonate (I)[8] was heated at 160-170° under a stream of nitrogen without solvent for 4 hr, 3,6-diethoxycarbonyl-1,4-dimethyl-2,5-piperazinedione (II), m.p. 184-187°, was obtained in 56% yield. Although two diastereomers are possible for II, a single isomer was obtained by this reaction. Heating of diethyl aminomalonate under a similar condition, however, did not give 3,6-diethoxycarbonyl-2,5-piperazinedione.

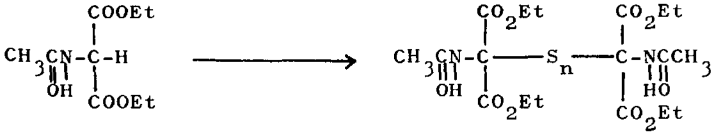
A mixture of II and NaH (2.2 equivalents) in dioxane was heated at 80-90° for 20 min, and freshly purified S_2Cl_2 (1.1 equivalents) was added to the reaction mixture at room temperature, which was then heated at 50-60° for 1 hr under a stream of nitrogen. Chromatographic separation of the crude products on silicic acid gave the disulfide (IIIc) in 17% yield and the tetrasulfide (IIIa) in 9% yield, and the starting material (II) was recovered in 17% yield. Small amounts of the trisulfide (IIIb) and the monosulfide(IIId) were also isolated. The disulfide (IIIc, 9.5% yield) and the monosulfide (IIId, 3.3% yield) were obtained besides the recovered II (13%) when the

Table

Compound	m.p.	ν_{max}^{KBr} cm^{-1}(C=O)	nmr(CDCl$_3$) NMe (ppm)	Mass M$^+$(%)	Mass base peak
II	184-187°	1690,1744	3.00	286(56)	213
IIIa	170.5-171.5°	1686,1749	2.96	412(6.1)	284
IIIb	101.5-103°	1695,1756	2.92,3.07	380(2)	284
IIIc	90.5-92°	1715,1749	3.03	348(8.5)	284
IIId	80.5-81°	1720,1765	3.09	316(trace)	259



I II III a: n=4
b: n=3
c: n=2
d: n=1



IV V a: n=2
b: n=3

reaction was carried out with SCl_2 instead of S_2Cl_2. The characteristic spectral data of II and III are shown in the Table.

The reaction of the tetrasulfide (IIIa) with triphenylphosphine (1 equivalent) in anhydrous tetrahydrofuran at -5 to 0° afforded the trisulfide (IIIb) and the disulfide (IIIc) in 58% and 19% yields respectively. The disulfide (IIIc), however, did not give the monosulfide (IIId) on the treatment with triphenylphosphine in tetrahydrofuran.

The reaction of S_2Cl_2 with a carbanion has been extended to an open chain compound to form the corresponding polysulfides. Thus, diethyl acetamidomalonate (IV) gave disulfide (Va), m.p. 105-108°, and trisulfide (Vb), m.p. 126-128°, on the treatment with NaH and S_2Cl_2 in dioxane.

Investigations of the reaction of III and V with triphenylphosphine and related compounds are now in progress.

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