Tetrahedron Letters No. 38, pp 3393 - 3396, 1976. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF EPIDITHIAPIPERAZINEDIONES

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(Received in USA 14 June 1976; received in UK for publication 9 August 1976)

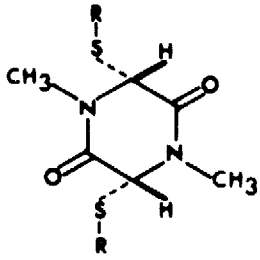
The epidithiapiperazinedione ring is the functional group common to natural products in the gliotoxin-sporidesmin class. We reported a general synthetic method to construct the epidithiapiperazinedione system[1] and demonstrated its applicability in a total synthesis of dehydrogliotoxin,[2] sporidesmin A,[3] sporidesmin B,[4] and gliotoxin.[5] This method was also applied in a total synthesis of hyalodendrin by Strunz and Kakushima.[6] In our continuing efforts toward broadening the synthetic methods of epidithiapiperazinediones, we recently observed clean cis dialkylation of 1,4-dimethyl-3,6-dimethylthio-2,5-piperazinedione.[7] In this communication, we wish to report the application of this reaction to the synthesis of symmetrically and unsymmetrically disubstituted and monosubstituted epidithiapiperazinediones.

On treatment with chloromethyl methyl ether in THF containing 2.3 molar equivalents of potassium *tert*-butoxide at 0°, 1,4-dimethyl-3,6-dimercapto-2,5-piperazinedione 1[8] was converted to 1,4-dimethyl-3,6-dimethoxymethylthio-2,5-piperazinedione 2[9] (mp 141-2°) in 90% yield. The cis configuration was tentatively assigned to 2, based on the thermodynamic stability of the corresponding dimethylthio derivative.[10] The dianion[11] generated from 2 by lithium diisopropylamide (LDA) or butyllithium (2.2-2.3 eq) in THF at -78° reacted with various alkyl halides (excess; -78°→room temperature), to afford exclusively the cis dialkylated piperazinediones 3a-d, which were successfully converted to the corresponding epidithiapiperazinediones 4a-d by boron trichloride treatment, followed by iodine oxidation.

A remarkable reactivity difference between the dicarbanion[11] of 2 and the carbanion of the monoalkylated derivative of 2 was observed. When the dicarbanion was reacted with excess alkyl halide and worked up with acetic acid at -78°, the cis monoalkylated piperazinediones 3e-f were obtained in high yield. The cis stereochemistry probably resulted from stereoselective protonation of the anion of the monoalkylated piperazinedione.[7] The monoalkylated piperazinediones 3e-f were converted to the corresponding epidithiapiperazinediones 4e-f

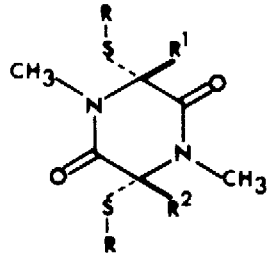
by the method established for the disubstituted compounds.

The unsymmetrically disubstituted epidithiapiperazinediones are readily available by further alkylation of the monosubstituted derivatives, that was demonstrated in synthesis of 4g. Furthermore, one pot synthesis of the unsymmetrically disubstituted epidithiapiperazinediones was realized by choosing correct order of addition of the alkylating reagents. This was demonstrated in a synthesis of hyalodendrin 4h, a metabolite of a *Hyalodendron* species.[6,12]

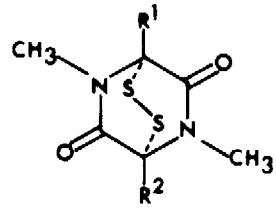


1 : R=H

2 : R=CH_2OCH_3



3a-h : R=CH_2OCH_3



4a-h

Results are summarized in the Table.[13] The present method is more convenient than the previous procedure,[1] especially for synthesis of simple epidithiapiperazinediones. Careful chromatographic separations are not required to isolate products and rather large scale preparations are possible. On the other hand, the original method is more applicable to multi-stage syntheses of natural products because of the high stability of the bridged thioacetal under both strongly acidic and basic conditions.[2-6]

The details of the new methods are illustrated by the following examples.

1,4-Dimethyl-3,6-dibenzyl-3,6-epidithia-2,5-piperazinedione 4a.

To a cooled (-78°) solution of 1.00 g of 2 in 70 ml of THF was added dropwise a THF solution of LDA (2.3 eq in 5.0 ml) with stirring. After 5 min, benzyl bromide (4.05 ml; 10 eq) was added to it at -78°. After the solution had been kept at -78° for 1 hr, the cooling bath was removed. The solution was allowed to warm to room temperature and then poured into sat. NaCl solution. Extraction with CH_2Cl_2 (X5), drying over Na_2SO_4 and evaporation gave a residue, which was filtered through a short silica gel column. Crystallization of the residue from ether afforded 1.34 g (83% yield; mp 106-7°) of 3a.

TABLE

	2 → alkyl halide		3		4	
		yield	mp	yield	mp
a : $R^1=R^2=CH_2C_6H_5$	$C_6H_5CH_2Br$	83%	106-7°	77%	152-3°
b : $R^1=R^2=CH_3$	CH_3I	50%	92-3°	83%	143-5°
c : $R^1=R^2=CH_2CH_3$	CH_3CH_2I	31%	95-6°	75%	113-4°
d : $R^1=R^2=CH_2CO_2Et$	EtO_2CCH_2Br	65%	85-6°	51%	179-80°
e : $R^1=CH_2C_6H_5$, $R^2=H$	1. $C_6H_5CH_2Br$ 2. (AcOH)	67%	86-7°	85%	175-6°
f : $R^1=CH_3$, $R^2=H$	1. CH_3I 2. (AcOH)	95%	78-9°	89%	127-8°
g : $R^1=CH_3$, $R^2=CH_2C_6H_5$	1. CH_3I 2. $C_6H_5CH_2Br$	75%[14]	117-8°	73%	129-30°
h : $R^1=CH_2C_6H_5$, $R^2=CH_2OH$	1. $C_6H_5CH_2Br$ 2. CH_3OCH_2Br	57%[15]	oil	28%[16]	101-2°

To a cooled (0°) solution of 3a (300 mg) in 30 ml of CH_2Cl_2 was added 1.5 ml of boron trichloride with stirring. After 5 min at 0°, the solution was evaporated to dryness under reduced pressure at room temperature. The residue was taken up in 30 ml of 10% (V/V) CH_3OH-CH_2Cl_2, to which iodine (160 mg) was added at room temperature. After 5 min, the solution was poured into sat. $NaHCO_3$ solution containing 1 ml of sat. $Na_2S_2O_3$ solution. Extraction with CH_2Cl_2 (X5), drying over Na_2SO_4 and evaporation gave a residue, which was filtered through a short silica gel column. Crystallization of the residue from ether afforded 188 mg (77% yield; mp 152-3°) of 4a.

1,3,4-Trimethyl-3,6-epidithia-2,5-piperazinedione 4f.

To a cooled (-78°) THF solution of 2 (200 mg/14 ml) was added dropwise a THF solution of LDA (2.3 eq in 1.0 ml) with stirring. After 5min, 0.6 ml (10 eq) of methyl iodide was added and the solution was kept at -78° for 2 hr. Acetic acid (0.1 ml) was added to it at -78° and the product 3f (200 mg; 95% yield; mp 78-9°) was isolated by the procedure described under 3a.

Conversion of 3f into 4f was carried out by the same procedure as used for 4a; yield=89%, mp=127-8°.

1,4-Dimethyl-3-benzyl-6-hydroxymethyl-3,6-epidithia-2,5-piperazinedione 4h.

To a cooled (-78°) THF solution of 2 (100 mg/7 ml) was added dropwise a THF solution of LDA (2.3 eq/0.5 ml) with stirring. After 5 min, 0.20 ml (5 eq) of benzyl bromide was added to it at -78°. After 20 min at -78°, 0.11 ml (4 eq) of

bromomethyl methyl ether was added. The solution was stirred at -78° for another 10 min and worked up by the procedure described under 3a, to afford 84 mg (57% yield; oil) of 3h after preparative silica gel tlc.

Conversion of 3h into 4h was effected by 1. BCl_3 in CH_2Cl_2, 2. I_2 in CH_2Cl_2 and 3. BCl_3 in CH_2Cl_2 (repeating the first step) under the same conditions described under 4a. The product (12 mg out of 58 mg of 3h; 28% yield[17]; mp 101-2°) was identical with natural hyalodendrin[17] by comparison of spectroscopic (nmr, ir, ms, uv) and tlc data.

Acknowledgment. Financial support from National Institutes of Health, Harvard University, and Hoffmann-La Roche Company is gratefully acknowledged.

References and Footnotes

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11. Formation of the dicarbanion at -78° was confirmed by quenching with AcOD.
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14. Result of two step procedure.
15. Result of one pot procedure.
16. Improvements in the second step are being studied.
17. We are indebted to Dr. G. M. Strunz for a sample of natural hyalodendrin.