CHEMISTRY LETTERS, pp.559-560, 1974. Published by the Chemical Society of Japan

A NEW ROUTE FOR SYNTHESIS OF 3,6-DIALKYL-1,4-DIMETHYL-3,6-EPITHIO- AND -3,6-EPIDITHIO-2,5-PIPERAZINEDIONES

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Five-steps conversion of 3,6-dialkyl-1,4-dimethyl-2,5-piperazinediones into the corresponding 3,6-epithio and -epidithio derivatives: i.e. conversion into 3,3α,6,6α-tetrabromide, substitution of 3,6-bromine atoms with methanol, reduction of 3α,6α-bromine atoms, conversion of 3,6-methoxyl groups into mercapto groups, and then oxidation, is described.

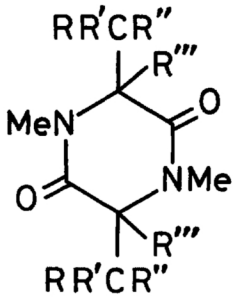
3,6-Epidithio-2,5-piperazinedione skeleton has been first synthesized through substitution of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione with NaSAc or Na_2S_4,[1] and the method was successfully applied only for 3,6-diphenyl derivative.[2] A few analogues were synthesized through the corresponding 3,6-dicarbanions obtained by treatment of appropriate 2,5-piperazinediones with bases.[3] Recently, Kishi et al. synthesized dehydroglyotoxin and sporidesmin A by alkylation of similar carbanions of 3,6-dimercapto-2,5-piperazinediones whose mercapto groups being protected as thioacetal of p-anisaldehyde.[4] In a previous paper, we found that bromination of 1,3,4,6-tetramethyl-2,5-piperazinedione gave 3,3α,6,6α-tetrabromo derivative, and substitution of the 3,6-bromine atoms with several sulfur-containing nucleophiles gave only 3,6-dimethylene derivative and sulfur, in participation with 3α,6α-bromine atoms.[5]

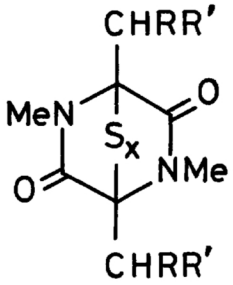
To exclude the participation, 3α,6α-bromine atoms were selectively reduced, after conversion of 3,6-bromine atoms into methoxyl groups. Substitution of the methoxyl groups with mercapto groups in the presence of $ZnCl_2$,[6] and successive treatment with H_2S and KI_3 gave the desired epithio and epidithio derivatives.

Methylation of 3,6-dialkyl-2,5-piperazinediones in DMF with NaH and CH_3I under cooling gave quantitatively cis and trans mixture of the corresponding 1,4-dimethyl derivatives (Ia-d). Bromination of I in CCl_4 with 4 equimolar amount of NBS gave the corresponding 3,3α,6,6α-tetrabromo (IIa,b) or 3,6-dibromo derivatives in good yields, depending on the chain or α-branched structure of alkyl groups, respectively. Treatment of IIa,b with excess methanol gave the corresponding 3,6-dimethoxy derivatives (IVa,b), which were quantitatively converted into debromo derivatives (Va,b) by hydrogenation with Bu_3SnH in toluene. 3,6-Dibromo derivatives could not be purified. However, it was confirmed by conversion into the corresponding dimethoxy derivative (IIIc) in the case of Ic. Treatment of the crude dibromides in $CHCl_3$ with gaseous H_2S, and successive oxidation of the product with KI_3 gave concurrently the corresponding 3,6-epithio (VIc,d) and 3,6-epidithio (VIIc,d)

Table 1.

Compound	Mp (°C)	Yield (%)
IIa	188 (dec.)	72
IIIc	113 - 115	43[a]
IIIc'[b]	193 - 194	
IVa	160	86
IVa'[b]	198 - 200	
Va	160 (sublime)	95
Va'[b]	201 - 202	
Vb	165 - 167	72[a]
VIa	63 - 65	72
VIb	76 - 78	19
VIc	146 - 147	43
VId	89 - 90	19[a]
VIIa	145 - 146	18
VIIb	110 - 111	33
VIIc	109 - 110	2.3





Ia-d: R''= R'''= H
IIa,b: R''= R'''= Br
IIIc: R''= H, R'''= OMe
IVa,b: R''= Br, R'''= OMe
Va,b: R''= H, R'''= OMe

VIa-d: x = 1
VIIa-c: x = 2

a: R = R'= H
b: R = CH_3, R'= H
c: R = R'= Me
d: R = Et, R'= Me

a) Overall yield from the corresponding compound I.
b) The prime on compound number means the corresponding isomer.

derivatives. Conversion of Va,b into VIa,b was successfully performed by the method of Schmidt et al.[6] Yield and mp of isolated compounds were summarized in Table 1, whose analytical values consisted with theoreticals.

Conversion of III or V into VI and VII seems to proceed through SN_1 mechanism, since the ratio of VI to VII was the same in the case of cis or trans isomers of III and V. The higher chemical shifts of N-CH_3 protons in VI (δ 2.70 - 2.81) than those in VII (δ 3.05) indicate that the more compressed structure of VI makes N-methyl groups closer to the shielding zone of the carbonyl group of opposite side. More detailed discussions on the problem of isomers and reaction mechanism will be made elesewhere.

References

1) P. W. Trown, Biochem. Biophys. Res. Commun., 33, 402 (1968); H. Poisel and U. Schmidt, Chem. Ber., 104, 1714 (1971).
2) S. G. Svokos and R. B. Angier, Ger. 2029305 (1971).
3) E. Ohler, H. Poisel, F. Tataruch, and U. Schmidt, Chem. Ber., 105, 635 (1972); T. Hino and T. Sato, Tetrahedron Lett., 3127 (1971).
4) Y. Kishi, T. Fukuyama, and S. Nakatsuka, J. Amer. Chem. Soc., 95, 6490, 6492, 6493 (1973).
5) J. Yoshimura, Y. Sugiyama, and H. Nakamura, Bull. Chem. Soc. Japan, 46, 2850 (1973).
6) H. Poisel and U. Schmidt, Chem. Ber., 106, 165 (1973).

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(Received March 30, 1974)