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STEREOSPECIFIC ALKYLATION OF THE OXIDIZED DIKETOPIPERAZINE DERIVATIVE, 3,6-DIMETHOXY-1,4-DIMETHYL-2,5-PIPERAZINEDIONE

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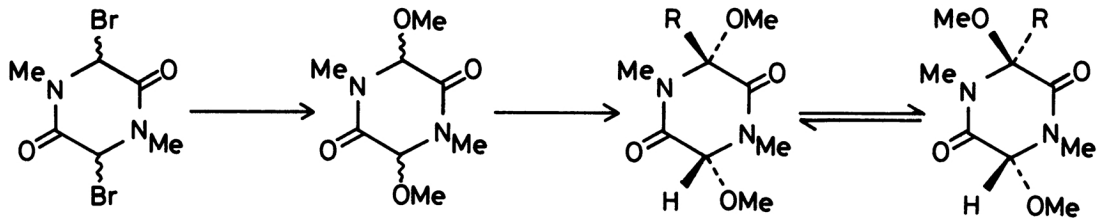
Kinetic monoalkylation of 3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione 2a via its anion gave a single stereoisomer (3) in which two methoxy groups are in the same side. Acid catalyzed equilibrium of 3 gave a mixture of 3 and its stereoisomer 4 in about 1:1 ratio. Acylation also gave a monoacylated product.

In connection with synthetic studies on natural products containing oxidized diketopiperazine, we recently reported a synthesis of neoechinulin A[1] via direct alkylation of protected diketopiperazine. Bicyclomycin[2] and fumitremorgins[3] are also included in this series; they contain hydroxy or alkoxy group(s) at 3- and/or 6-positions of the diketopiperazine. Although syntheses of oxidized diketopiperazines have been widely studied,[4] good methods applicable to the total synthesis of these natural products are scarce. Here we report a stereospecific alkylation of 2a to produce the 3-alkyl or acyl derivatives 3a-f.

Starting material 2a was obtained from the dibromide 1[5] in 85% yield by treatment with methanol in the presence of triethylamine at 0°C. Chromatography on silica gel gave 3:1 mixture of two diastereomers. The minor product 2b [mp 118-119°C; nmr 4.84 (H-3 and 6)][6] was crystallized out from the mixture by dissolving it in ether-hexane (1:1). The remaining major product 2a [oil, purity over 95% by nmr analysis; nmr 4.68 (H-3 and 6)][6] was employed for the alkylation.



1 2 3a-f 4a-f

The minor compound 2b gave an equilibrium mixture of 2a and 2b (3:1) by treatment with camphorsulfonic acid (CSA) in methanol under reflux. Stereochemistry of these compounds has not yet been clarified. Crystalline 2b was prevented from use for alkylation reaction by its low solubility in tetrahydrofuran, although it was considered to give the same anion to that from 2a.

Typical alkylation procedure was as follows. About one minute after treatment of tetrahydrofuran solution of 2a with 1.2 eq of n-BuLi at -78°C was added 1.2 eq of alkyl halide to the mixture. The solution was warmed to room temp. and the crude product was extracted as usual. Silica gel column chromatography

TABLE I

Compd.	3a	3b	3c	3d	3e	3f	4d	4f
R	CH_3	$CH_2CO_2CH_3$	$COCH_3$	COC_6H_5	$CH_2CH{=}CH_2$	$CH_2C_6H_5$	COC_6H_5	$CH_2C_6H_5$
Yield(%)	63	66	68	72	65	63	—	—
Mp(°C)	—	—	—	97-8	—	95	118-9	99-100
Pmr(H-6)[6]	4.76	4.88	4.82	4.92	4.68[9]	3.66	4.95	4.64

gave the monoalkyl derivative 3.[6] The stereoisomer was not detected on tlc plate and pmr spectra. Acylation could also be carried out in a similar manner by using acyl halide instead of alkyl halide. The yields and pmr data are listed in Table I. Stereochemistry of 3 was determined as follows. Treatment of the benzyl derivative 3f with CSA in methanol under reflux gave an equilibrium mixture of 3f and its isomer 4f[6] in a ratio of about 1:1. They were easily separated on silica gel tlc. The methine signal of the benzyl derivative 3f appeared in an abnormally high field (3.66 ppm),[7] while the corresponding signal of its isomer 4f appeared in a normal position (4.64). Only in the isomer in which the methine proton and the benzyl group in the same side, such an anisotropy effect can be expected as shown in Fig. 1.[9] This stereospecificity[8] seems to be controlled by the steric hindrance of the methoxy group at 6 position. Compounds 3a-e also gave a mixture of 3a-e and corresponding 4a-e (about 1:1 ratio), respectively, by acid treatment. Thus, the kinetic alkylation and acylation products 3a-f must have the configuration in which two methoxy groups are in the same side.

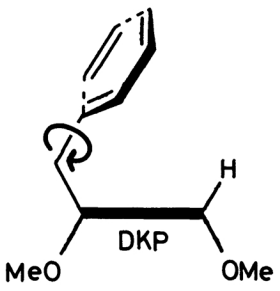


Fig. 1

Application of this stereospecific alkylation to the synthesis of natural products containing oxidized diketopiperazine is now in progress.

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