HETEROCYCLES, Vol. 14, No. 11, 1980

SYNTHESIS AND STRUCTURAL ASSIGNMENT OF NATURALLY OCCURRING 3-BENZYL-6-BENZYLIDENE-2,5-PIPERAZINEDIONE

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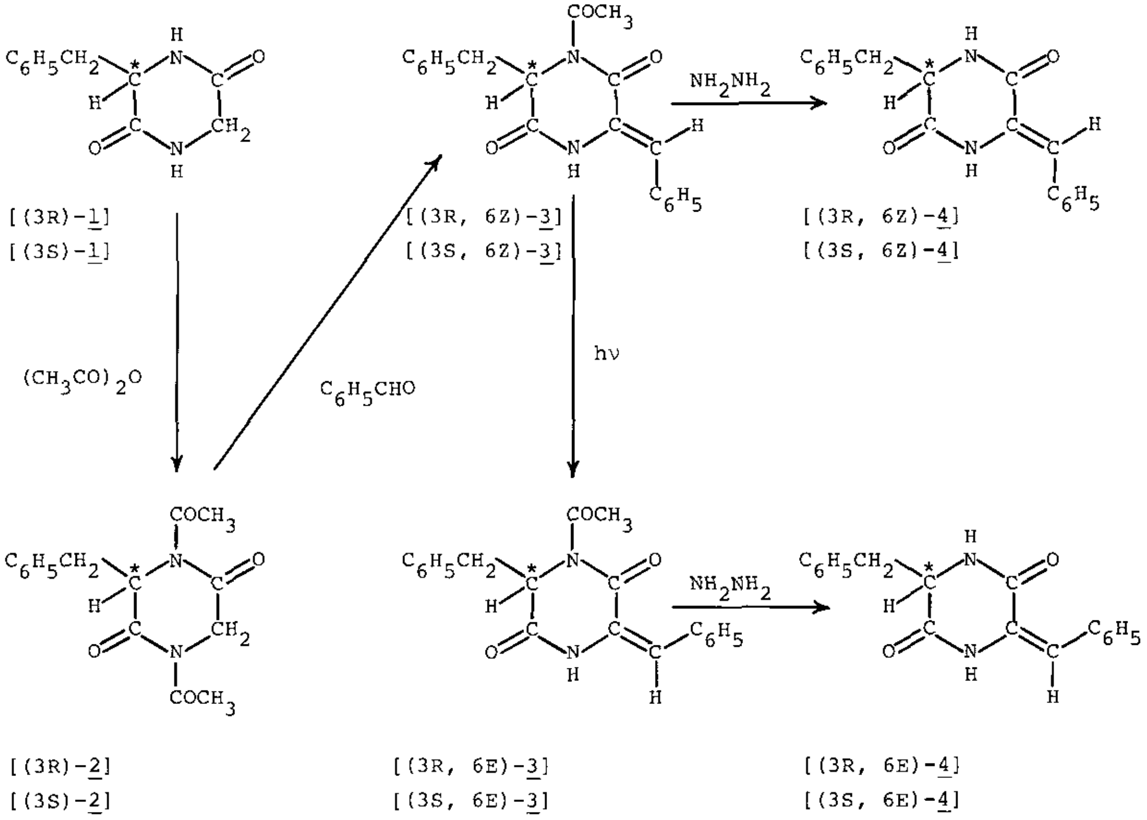
Abstract —— Four possible stereoisomers of 3-benzyl-6-benzylidene-2,5-piperazinedione were synthesized, and the configuration of the natural product isolated from Streptomyces noursei was determined to be (3R, 6Z). It was found that the sign of the optical rotations and the Cotton effect are reversed only by the difference of the (E)- or (Z)-geometry.

Although a racemic 3-benzyl-6-benzylidene-2,5-piperazinedione has been prepared by a partial reduction of 3,6-dibenzylidene-2,5-piperazinedione (2,5-piperazine= PDO),[1] the configuration of the natural product which was isolated from Streptomyces noursei by Brown *et al*.,[2,3] is not yet determined.

In this paper, the syntheses of the natural product and its three stereoisomers were successfully pursued and the structural assignments of the four products obtained were established on the basis of the spectroscopic analyses. In addition, the very interesting phenomena observed in the optical rotation and circular dichroism (CD) spectrum of each pair of geometric isomers are described. The (3R)- and (3S)-benzyl-PDO {(3R)-1; mp 254-255 °C, $[\alpha]_D^{25}$ 106.7° (c 0.2, CF_3COOH), yield 92%. (3S)-1; mp 254-255 °C, $[\alpha]_D^{25}$ -101.7° (c 0.2, CF_3COOH), yield 93%} was obtained as the starting materials by the equimolar coupling of Boc-phenylalanine (0.05 mol) with glycine methyl ester (0.05 mol) in dichloromethane (30 ml), followed by the subsequent cyclization of the dipeptide by a procedure of Nitecki et al.[4] These compounds were also obtained independently by the cyclization reaction of 2-(N-haloacetyl)phenylalanine ethyl ester with excess alcoholic ammonia[5] in a good yield. Acetylation of individual (3R)-1 and (3S)-1 with acetic anhydride by the usual way gave 1,4-diacetyl-(3R)- and (3S)-benzyl-PDO {(3R)-2; mp 101 $^{\circ}$C, $[\alpha]_D^{25}$ 79.5° (c 1.0, EtOH), yield 86%. (3S)-2, mp 100.5 $^{\circ}$C, $[\alpha]_D^{25}$ -82.5° (c 1.0, EtOH), yield 90%}, respectively. Subsequently, treatment of individual (3R)-2 and (3S)-2 (0.01 mol) with benzaldehyde (0.05 mol) in DMF (20 ml) in the presence of 5M-t-BuOK/t-BuOH (0.01 mol) at 0 $^{\circ}$C for 12 hr[6] gave the desired 4-acetyl-(3R)- and -(3S)-benzyl-(6Z)-benzylidene-PDO [(3R, 6Z)-3 and (3S, 6Z)-3] in good yields, and those geometric structure were confirmed by the NMR spectra,[7,8] as has been summarized in Table 1. The deacetylation of these isomers (0.01 mol) with hydrazine hydrate (0.02 mol) in DMF (10 ml) under cooling for 1 hr gave (3R)- and -(3S)-benzyl-(6Z)-benzylidene-PDO [(3R, 6Z)-4 and (3S, 6Z)-4] in good yields (see Table 1).



On the other hand, photoisomerization of (6Z)-isomers into the corresponding (E)-isomers was performed, according to the method of Blake and Sammes.[9] Irradiation of the (3R, 6Z)-3 or (3S, 6Z)-3 (each 0.01 mol) in EtOH (10 ml) with 500 W high pressure mercury lamp under nitrogen gas at room temperature for 5 hr gave the corresponding (3R, 6E)-3 and (3S, 6E)-3 in *ca*. 50% yields, respectively. Subsequent treatment of the these (E)-isomers of 3 (0.01 mol) with hydrazine hydrate gave the corresponding deacetylated products [(3R, 6E)-4 and (3S, 6E)-4] in *ca*. 90% yields, respectively (see Table 1).

From the comparison of the physical properties of naturally occurring 3-benzyl-6-benzylidene-PDO { mp 288.5-290.0 °C, $[\alpha]_D^{25}$ -520° (c 0.028, CH_3COOH), IR: 3189, 1661, 1626 cm^{-1}, UV: 296 (log ε=4.10)}[2] with those of four isomers of 4 indicated that (3R, 6Z)-4 (IR: 3190, 1680, 1665, 1627 cm^{-1}) was identical with the natural product.

Table 1. Yields, physical constants, and spectral data of 3 and 4

Compound No.	Yield (%)	Mp °C	NMR, δ in $CDCl_3$ (CF_3COOH)			$[\alpha]_D^{25}$	UV, nm (log ε) in 95% EtOH
			NH a)	Olefinic proton a)	3-Proton (J_{Hz})		
(3R, 6Z)-3	92	syrup	8.55	6.77	5.39t (4.9)	-483° b)	
(3R, 6E)-3	50	syrup	10.19	6.21	5.33t (4.9)	+259° b)	
(3S, 6Z)-3	89	syrup	8.29	6.76	5.31t (4.9)	+558° b)	
(3S, 6E)-3	51	syrup	10.25	6.21	5.31t (4.9)	-239° b)	
(3R, 6Z)-4	78	273.5-274.5	(8.96 8.48	6.97	4.80m)	-550° c)	295 (4.10)
(3R, 6E)-4	75	260.0-261.5	(9.68 8.30	6.54	4.80m)	+360° c)	302 (4.06)
(3S, 6Z)-4	73	271.5-272.5	(9.00 8.44	6.97	4.82m)	+440° c)	294 (4.02)
(3S, 6E)-4	76	259.0-260.5	(9.60	6.54	4.80m)	-320° c)	305 (4.08)
Natural product		288.5-290.0				-520° (c 0.028, CH_3COOH)	296 (4.10)

a) Singlet. b) Recorded in EtOH (c 1.2). c) Recorded in CH_3COOH (c 0.023).

Moreover, the very interesting phenomena were observed in the specific rotation (Table 1) and the CD spectrum (Fig. 1). The sign of the optical rotation and the Cotton effect was reversed not only between each pair of (R) and (S) isomers, but also that of (Z) and (E) isomers. These facts may imply the transformation of conformations,[10] for example, falgpole boat and bowsprit boat, depending on the (Z) or (E)-configuration at C-6. Further work including the proof of the above deduction is now in progress.

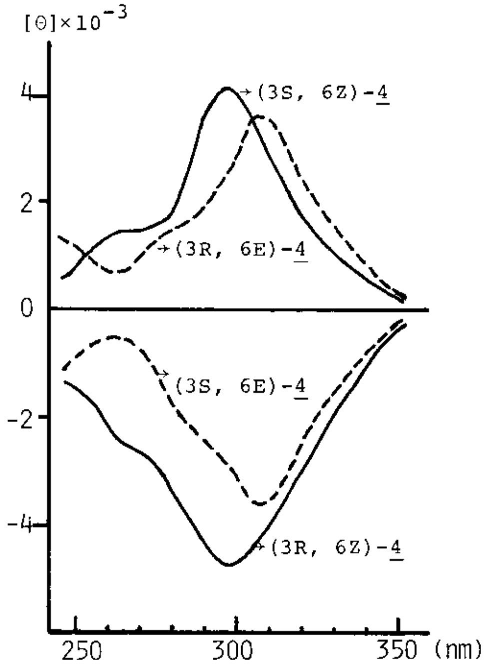


Fig. 1. The CD spectra of 4 in CH_3OH.

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Received, 5th July, 1980