SYNTHESIS AND REACTION OF EXOCYCLIC UNSATURATED 2,5-PIPERAZINEDIONES

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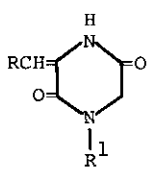
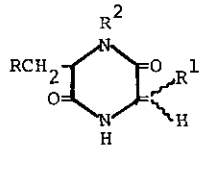
Recently, increasing interests were directed to the cyclic dipeptide antibiotics, containing alkylidene and/or alkoxy or hydroxyl group at 3 or 3,6-positions. Here, the synthesis and the reaction of the above dipeptide derivatives were investigated.

To generalize the synthesis of 3-alkylidene-2,5-piperazinedione (PDO) by the cyclization of α-(N-haloacetyl)-α-dehydroamino acids with amines, ethyl 2-(haloacetyl)amino-2-alkenoate (1) was cyclized with NH_2OH, CH_3NH_2, $C_6H_5CH_2NH_2$, or NH_2NH_2 to give the expected 1-substituted-PDO (2). As the starting materials for the optically active 3-alkyl-6-alkylidene-PDO (6 and 7), (3L)- and (3D)-alkyl-PDO (4) was prepared by the coupling of Boc-amino acids with Gly-OMe, followed by the cyclization of the dipeptide obtained. The desired (3L)- and (3D)-alkyl-(6Z)-alkylidene-PDO (7) were obtained by the condensation of individual 1,4-diacetyl-(3L)- and (3D)-PDO (5) with aldehydes, followed by the deacetylation of the 4-acetyl-(6Z)-alkylidene derivatives (6) prepared. Moreover, (3L)- or (3D)-(6Z)-6 was isomerized by the irradiation with high pressure mercury lamp to give the corresponding (E)-isomers of 6, which was subsequently worked-up similarly to give (3L)- and (3D)-(6E)-7, respectively. Very interestingly, the sign of the optical rotation and the Cotton effect was reversed not only between each pair of (L) and (D) isomers, but also that of (Z) and (E) isomers. These facts may imply the transformation of the conformations, for example, flagpole half boat and bowsprit half boat, depending upon the (Z)- or (E)-configuration at C-6.

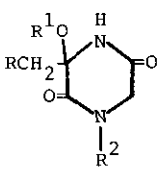
On the other hand, 2, 1-benzyl-3-(6-hydroxypropylidene)-PDO (16), and 3,6-dialkylidene-PDO were treated with NBS in alcohol to give the corresponding 3-(β-bromoalkyl)-3-alkoxy-PDO (9), 3,6-bis(β-bromoalkyl)-3,6-dialkoxy-PDO (12), and spiro derivative (17), respectively. The subsequent reduction of bromo and benzyl groups in 9 and 17 with Pd-C gave 3-alkyl-3-alkoxy-, 3-hydroxy-PDO (10) and its 3-spiro derivative (20)respectively.



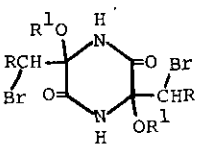
(2): R=CH_3
(16): R=$HOCH_2CH_2$



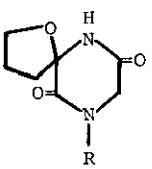
(6 and 7)



(10)



(12)



(20)