SYNTHESES OF 3-SPIRO- AND 3,6-BRIDGED 2,5-PIPERAZINEDIONES

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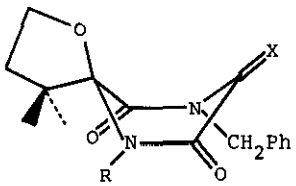
In connection with our synthetic work on 3,6-bridged cyclodipeptides, we have investigated a new cyclization of 1-benzyl-3-hydroxypropylidene (1)- and -3-hydroxypropyl-2,5-piperazinedione (PDO) (2) derivatives with NBS or with NBS in the presence of water to 3-spiro- and 3,6-bridged PDO derivatives.

Starting 1, derived from α-dehydroglutamic acid derivative in two steps, was treated with NBS to give the expected 3-spiro-PDO in ca. a 90% yield. Similarly, 4-methyl derivative of 1, prepared from 1 and MeI-NaH, was worked up to give 4-methyl-3-spiro-PDO in a good yield. It was found that the spiro compounds thus obtained were further treated with NBS in the presence of water to give the corresponding 3-spiro-piperazine-2,5-dione-6-ol (3) as diastereomers and 3-spiro-piperazine-2,5,6-trione (4) in good yields respectively.

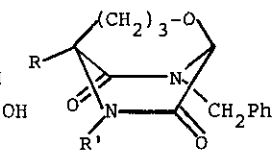
On the other hand, when 2 and its 4-methyl derivatives, respectively, were treated with NBS, the cyclization was occurred to give the desired bicyclo compounds (5) in comparatively lower yields. However, treatment of 3-t-butoxypropyl-piperazine-2,5-dione-6-ol derivatives, obtained by the reaction of 2 or its 4-methyl compound with NBS in the presence of water, with CF_3COOH gave 5 in almost quantitative yields respectively. Furthermore, similarly, 3-t-butoxypropyl-3-methoxy-1-benzyl-4-methyl-PDO, derived from 1 in four steps, was treated with NBS in the presence of water to give the corresponding piperazine-2,5,6-trione and piperazine-2,5-dione-6-ol derivatives. Subsequently, the latter was acetylated, followed by the treatment with CF_3COOH gave 3-methoxy-2,6-bridged PDO derivative (6) in a 56% yield.



R=H, X=H
R=CH_3, X=H

3: R=H, X=H, OH
R=CH_3, X=H, OH

4: R=H, X=O
R=CH_3, X=O



5: R=H, R'=H
R=H, R'=CH_3

6: R=OCH_3, R'=CH_3