HETEROCYCLES. Vol.12, No. 1, 1979

SYNTHESIS AND REACTIONS OF CYCLIC TAUTOMERS OF TRYPTAMINES AND TRYPTOPHANS. BEHAVIOUR OF INDOLES IN ACIDIC MEDIA.

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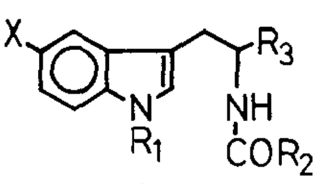
1,2,3,3a,8,8a-Hexahydropyrrolo[2,3-b]indole(2) have been considered as possible tautomers of tryptamines and tryptophans(1). These cyclic tautomers(2) would undergo the Na-alkylation and the electrophilic substitution at the 5-position instead of the 2-and 6-positions in the indolic form(1). This may provide a general method for the preparation of the 5-substituted tryptophans, provided 2 reverts to 1 with ease. However, a general direct synthesis of 2 from 1 has not been known except 2(R_1,X=H,R_2=Me,R_3=CO_2Et) obtained by the catalytic hydrogenation of 1,2,3,8-tetrahydropyrroloindole.

When N_b-methoxycarbonyl-DL-tryptophan methyl ester was dissolved in 85% H_3PO_4 at room temperature for 3 hr followed by neutralization, a cyclic tautomer 2(R_1,X=H, R_2=OMe,R_3=CO_2Me), mp 104.5-106.5°, was obtained in 85% yield. The same compound was obtained in 70-85% H_2SO_4 or CF_3COOH. In a similar way N_b-acetyl-L-tryptophan ethyl ester N_a-methyl-N_b-methoxycarbonyl-DL-tryptophan methyl ester, and cyclo-L-tryptophanyl-L-proline gave the corresponding cyclic tautomers(2). Cyclic tautomers(2, R_1,X=H) were stable in solid states but easily reverted to the indolic form(1) in MeOH-HCl or AcOH at room temperature. Na-Acetylation of 2 increased the stability toward acid, and a cyclic tautomer of N_b-methoxycarbonyltryptamine was isolated only after the N_a-acetylation.

The cyclic tautomer (2, R_1 X=H,R_2=OMe,R_3=CO_2Me) gave the N_a-methyl derivative(2, R_1=Me) on treatment with CH_3I-acetone-K_2CO_3, and the N_a-dimethylallyl derivative of the indole type(1, R_1=Me_2C=$CHCH_2$) by dimethylallyl bromide. Reactions of the cyclic tautomer (2, X=H,R_1=Ac,R_2=OMe,R_3=CO_2Me) with NCS in AcOH gave the 5-chloro derivative(2, X=Cl) in 93% yield which was converted to 1(X=Cl,R_1=H) on treatment with MeOH-H_2SO_4. Finally nitration of the cyclic tautomer with H_2SO_4-HNO_3 at room temperature gave the 5-nitro derivative(2, X=NO_2) in 79% yield at shorter reaction times and 5-nitro derivative of the indole type (1, X=NO_2) at longer reaction times.



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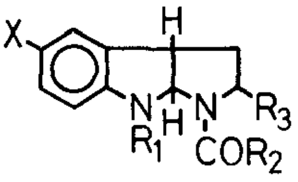

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