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[R1 = H, R2 = Me, R3 = CO2Et] obtained by the catalytic hydrogenation of 1,2,3,8-tetrahydropyrroloindole.

When N\textsubscript{b}-methoxy carbonyl-DL-tryptophan methyl ester was dissolved in 85% H\textsubscript{3}PO\textsubscript{4} at room temperature for 3 hr followed by neutralization, a cyclic tautomer 2[R1 = H, R2 = OMe, R3 = CO2Me], mp 104.5-106.5°, was obtained in 85% yield. The same compound was obtained in 70-85% H\textsubscript{2}SO\textsubscript{4} or CF\textsubscript{3}COOH. In a similar way N\textsubscript{b}-acetyl-L-tryptophan ethyl ester N\textsubscript{a}-methyl-N\textsubscript{b}-methoxy carbonyl-DL-tryptophan methyl ester, and cyclo-L-tryptophanyl-L-proline gave the corresponding cyclic tautomers(2). Cyclic tautomers(2, R1 = H) were stable in solid states but easily reverted to the indolic form(1) in MeOH-HCl or AcOH at room temperature. N\textsubscript{a}-Acetylation of 2 increased the stability toward acid, and a cyclic tautomer of N\textsubscript{b}-methoxy carbonyl tryptamine was isolated only after the N\textsubscript{a}-acetylation.

The cyclic tautomer (2, R1 = H, R2 = OMe, R3 = CO2Me) gave the N\textsubscript{a}-methyl derivative(2, R1 = Me) on treatment with CH3I-acetone-K\textsubscript{2}CO\textsubscript{3}, and the N\textsubscript{a}-dimethylallyl derivative of the indole type(1, R1 = Me2C=CHCH\textsubscript{2}) by dimethylallyl bromide. Reactions of the cyclic tautomer (2, X = H, R1 = Ac, R2 = OMe, R3 = CO2Me) with NCS in AcOH gave the 5-chloro derivative(2, X = Cl) in 93% yield which was converted to 1(X = Cl, R1 = H) on treatment with MeOH-H\textsubscript{2}SO\textsubscript{4}. Finally nitration of the cyclic tautomer with H\textsubscript{2}SO\textsubscript{4}-HNO\textsubscript{3} at room temperature gave the 5-nitro derivative(2, X = NO\textsubscript{2}) in 79% yield at shorter reaction times and 5-nitro derivative of the indole type (1, X = NO\textsubscript{2}) at longer reaction times.