Tetrahedron Letters, Vol.22, No.27, pp 2565 - 2568, 1981
Printed in Great Britain

0040-4039/81/272565-04$02.00/0


# CYCLIC TAUTOMERS OF TRYPTAMINES AND TRYPTOPHANS. V[1]. FORMATION AND REACTIONS OF CYCLIC TAUTOMERS OF CYCLO-L-TRYPTOPHANYL-L-PROLINE.

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Abstract Two stereoisomeric cyclic tautomers (5 and 6) of cyclo-L-tryptophanyl-L-proline whose stereochemistry was established by x-ray analysis, gave 5- and 6-hydroxytryptophanyl derivatives (10, 11, and 19) on the hydroxylation with lead tetraacetate in trifluoroacetic acid.

We have reported that Nb-methoxycarbonyltryptophan methyl ester (1) cyclized to its cyclic tautomers (2 and 3) in an acid such as 85% phosphoric acid and trifluoroacetic acid[2]. The brief acid treatment under lower temperature gave the cis cyclic tautomer (3a) as the major isomer which was isolated as the Na-acetyl derivative (3b), while the stable trans isomer (2a) was obtained in excellent yield on prolonged treatment with the acid[1].

In this paper we describe that two isomers (5 and 6) were also obtained by the similar cyclization of cyclo-L-tryptophanyl-L-proline (4), and the stereoisomers showed different regioselectivity on the hydroxylation reaction. Cyclo-L-tryptophanyl-L-proline (4) was reported by us[2] and Sammes group[3] to form a single cyclic isomer (5a) in excellent yield when dissolved in 85% phosphoric acid or trifluoroacetic acid at room temperature. However, the other isomer (6a), mp 165-178°(decomp)[4], was isolated in 45-50% yield when 4 was dissolved in trifluoroacetic acid at -10° for 1-2 min followed by rapid quenching with an excess of 10% sodium carbonate. The nmr spectrum of the crude mixture showed that the formation of 6a predominated over that of 5a. These data showed that 6a was the less stable isomer and kinetically controlled product, while 5a was the stable isomer. The stable isomer (5a) was reverted to 4 within 2.5 hr, whereas 5 min for the less stable isomer (6a) on addition of 5 % hydrochloric acid into the methanolic solution (followed by the UV spectrum). Acetylation of the both isomers with acetic anhydride-pyridine furnished Na-acetyl derivatives, 5b, mp 257-259°, and 6b, mp 231-236°. However, the acetylation of 6a proceeded slower than that of 5a, indicating Na-nitrogen of 6a was more hindered. 5a: UV(in EtOH) $\lambda_{max}$ ($\epsilon$);243(7600), 298(2500). NMR (in $CDCl_3$) $\delta$; 3.52(t, J=6, $C_3$-H), 5.64(d, J=7, $C_{11a}$-H). $[\alpha]_D$ = - 498°(c= 0.2, EtOH). CD($\theta$); -17300 (249 nm) and - 2100(288 nm). 6a: UV(in EtOH) $\lambda_{max}$ ($\epsilon$); 240(7500), 294(2500). NMR(in $CDCl_3$) $\delta$; 3.48 (d, J=7, $C_3$-H), 5.75(dd, J=8 and 2, $C_{11a}$-H). $[\alpha]_D$ = + 212 (c=0.2, EtOH). CD($\theta$); +13200(244 nm) and -3090(300 nm). 5b: UV(in EtOH) $\lambda_{max}$nm($\epsilon$); 244(11300), 275(1850), 283(1610). NMR(in $CDCl_3$) $\delta$; 2.66 (s, Ac), 3.53(t, $C_3$-H), 6.23(d, J=6, $C_{11a}$-H), 7.96(d, J=8, $C_{10}$-H). CD($\theta$); +60200(245.5 nm). 6b: UV(in EtOH) $\lambda_{max}$nm($\epsilon$); 245(10200), 276(1810), 284(1600). NMR(in $CDCl_3$) $\delta$; 2.56(s, Ac), 3.0-3.6(m, $C_3$-H), 6.05(d, J=6, $C_{11a}$-H), 7.87(dd, J=7 and 2, $C_{10}$-H). CD($\theta$); -82300 (236 nm).

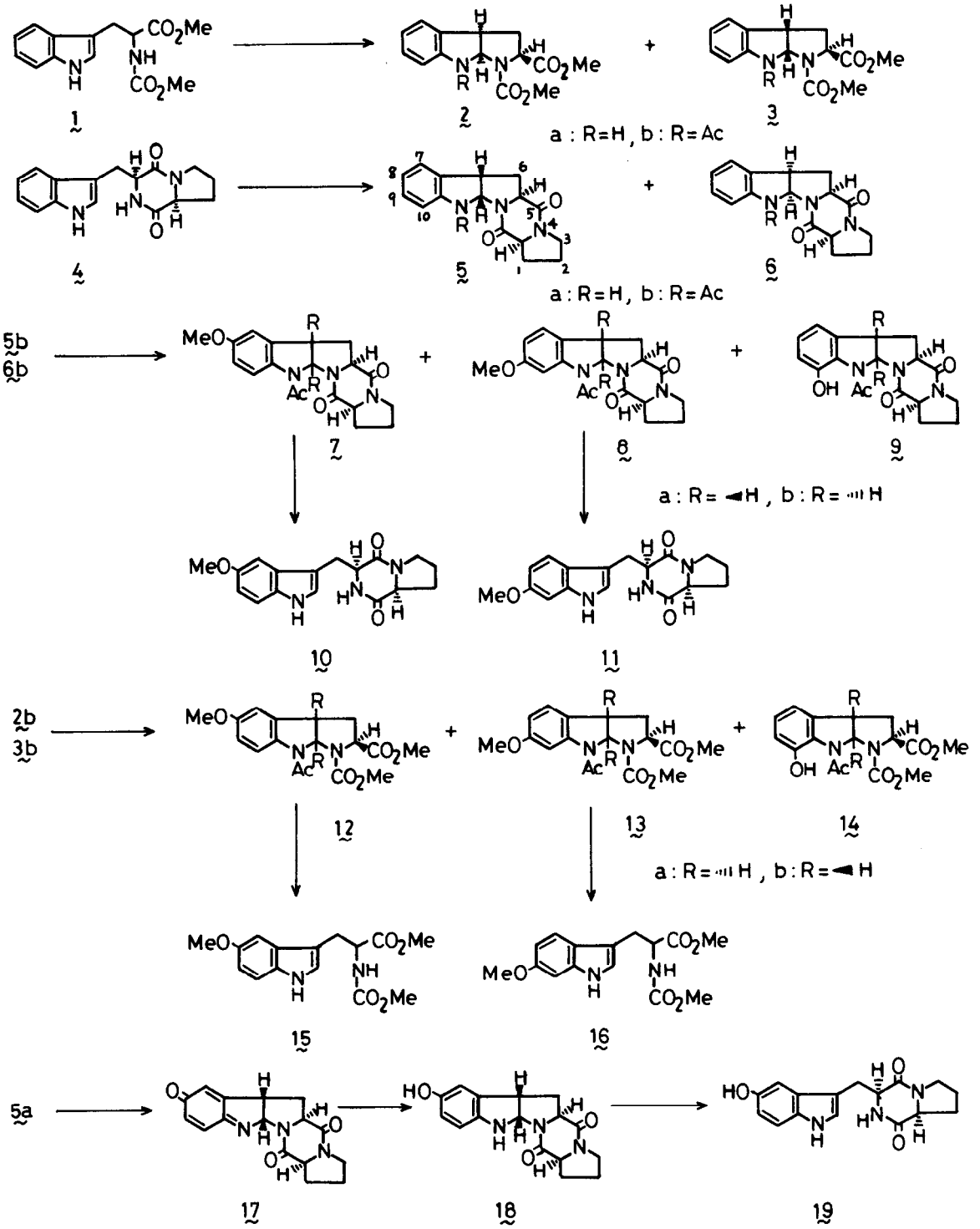
A detailed comparison of these spectral data, especially CD spectra, with those of tryptophan derivatives( 2 and 3)[1] suggested that the stable isomer (5) of the diketopiperazine series has a cis relationship between the carbonyl group at 5-position and 6a-H, in contrast to a trans relationship found in tryptophan series. In order to confirm this point, the x-ray analysis of 5b was carried out and was shown to have the cis relationship in good accordance with the CD spectra. A single crystal of 5b belonged to the orthorhombic space group, $P2_12_12_1$ with a = 9.4311 (10), b = 26.6613 (22), c = 6.4040 (3). There are 4 molecules per unit cell, corresponding to a calculated crystal density of 1.34g/ $cm^3$. The structure was solved by the MULTAN 74 and refined by block-diagonal-matrix least squares method to an R factor of 0.092.[7] The results are displayed in Fig. 1.

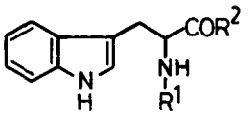
The hydroxylation of the stable isomer, 5b, with lead tetraacetate in trifluoroacetic acid at 2° followed by methylation gave the 8-methoxy derivative (7a, 36%), mp 168.5-170°, the 9-methoxy derivative (8a, 26%), mp 281-283°, and the 10-hydroxy derivative (9a, 14%), mp 296-301°. On the other hand, the similar hydroxylation of the trans isomer, 6b, gave 7b(25%), mp 264-266°(decomp), 8b(34%), mp 262-265° (decomp), and 9b(4%), mp 253-256°(decomp). Positions of the substituent were determined by the coupling pattern of the aromatic proton at 10-position in their nmr spectra which was shifted to down field by the Na-acetyl group. These methoxy derivatives were easily converted to the corresponding indoles (10 and 11) on treatment with 10% sulfuric acid in methanol. These reactions provide the first practical method for the introduction of the hydroxy group to the benzene moiety of tryptophan containing diketopiperazines. We have reported that the hydroxylation of 2b with lead tetraacetate in trifluoroacetic acid gave 13a(42%), 12a(17%), and 14a(4%).[5] In order to compare the reactivity of 2 and 3 as well as 5 and 6, the less stable isomer (3b) was treated with lead tetraacetate in a similar manner to give 12b(30%), mp 202-204°, 13b(25%), mp 200-201°, and 14b(5%). These results showed that the trans isomer prefer the hydroxylation at the 6-position and the cis isomer at the 5-position in both tryptophan and diketopiperazine series, although the mechanism of the hydroxylation is not clear.

The oxidation of the stable isomer (5a) with lead tetraacetate (2 equiv.) in trifluoroacetic acid followed by the reduction with zinc[6] gave the 5-hydroxy derivative (19, 73%), mp 226-233°, selectively as in the case of the tryptophan series (2a), providing a general method for the introduction of the hydroxy group at the 5-position of tryptophan derivatives.

The nmr spectra of the tryptophan containing dipeptides (20) in trifluoroacetic acid have been examined and 20a and 20b were found to form the corresponding cyclic tautomers. However, 20c and 20d did not form the cyclic tautomers. It is interesting to note that an epimer of the diketopiperazine (21), the trans diketopiperazine, did not cyclize in trifluoroacetic acid, suggesting the stereochemical factor for the cyclization was important and subtle.

Acknowledgement. Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research No 411102 and 577878) is gratefully acknowledged.





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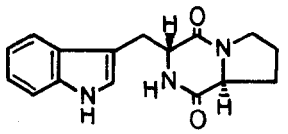
a : $R^1 = COOC_7H_7$ , $R^2 = NH\text{-}CH(CH_3)CO_2Me$

b : $R^1 = COOC_7H_7$ , $R^2 = NH\text{-}CH(CO_2Me)\text{-}CH_2$-(3-indolyl)

c : $R^1 = CO\text{-}CH(CH_3)\text{-}NHCOOC_7H_7$ , $R^2 = OMe$

d : $R^1 = CO\text{-}CH(CH_2CO_2Me)\text{-}NHCOOC_7H_7$ , $R^2 = OMe$



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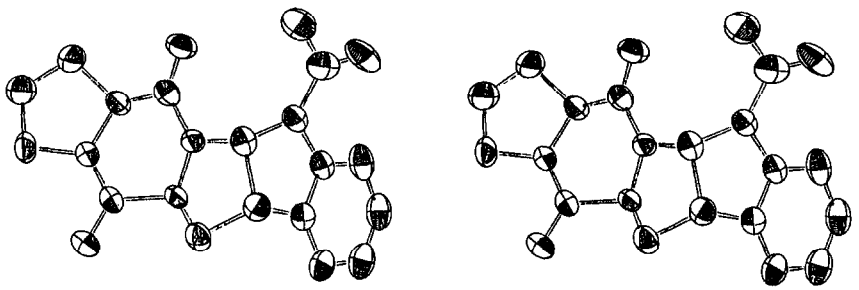

Fig. 1. Stereodiagram of 5b

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(Received in Japan 7 March 1981)