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A STEREOSELECTIVE DECARBOXYLATION OF 1,6-DIMETHYL-3-(3'-INDOLYL)METHYL-3-CARBOXY-2,5-PIPERAZINEDIONE

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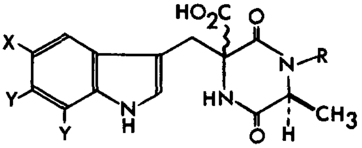
In connection with synthetic study on sporidesmins,[1] we have had a chance to synthesize the carboxylic acids (Ia) and (Ib) as synthetic intermediates. When the acids (Ia) and (Ib) were heated in dioxane, a stereoselective decarboxylation took place to afford the cis diketopiperazine (IIa) as a major product. In this communication we would like to report this reaction, which is expected to have an extensive application not only for the new synthetic method of cis diketopiperazine but also for an asymmetric synthesis of α-amino acids and the related compounds.

The procedure used for decarboxylation is as follows: after the acid (100 mg) is refluxed in dioxane (10 ml) for 60 min under a nitrogen atmosphere, the product is isolated by a silica gel column chromatography. Thus, from the trans acid (Ib),[2,3] the optically active cis diketopiperazine (IIa)[4] and the trans isomer (IIb)[5] were produced in the ratio 6:1 (>90% yield). The configuration of the new asymmetric center was deduced from the analysis of nmr spectra; namely, the methyl signal of the L-alanine moiety of the cis isomer (IIa) appears in an abnormally up-field position (0.32 ppm), while the signal of the trans isomer (IIb) appears in a normal position (1.25 ppm).[6] Starting from the cis acid (Ia),[3] the cis (IIa) and the trans diketopiperazine (IIb) were obtained in the exactly same ratio as the one obtained from the trans acid (Ib). The possibility that this reaction is thermodinamically controlled was excluded from the equilibrium experiments on IIa and IIb.[7]

To examine the generality of the stereoselective decarboxylation, the compound bearing no substituents on the indole ring was examined next. Either from the trans acid (IIIb)[3] or



(Ia) X=Cl, Y=OCH$_3$, R=CH$_3$: cis isomer

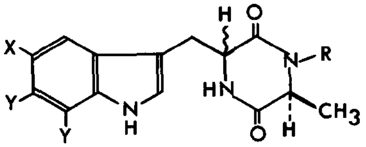
(Ib) X=Cl, Y=OCH$_3$, R=CH$_3$: trans isomer

(IIIa) X=Y=H, R=CH$_3$: cis isomer

(IIIb) X=Y=H, R=CH$_3$: trans isomer

(VIa) X=Y=R=H: cis isomer

(VIb) X=Y=R=H: trans isomer



(IIa) X=Cl, Y=OCH$_3$, R=CH$_3$: cis isomer

(IIb) X=Cl, Y=OCH$_3$, R=CH$_3$: trans isomer

(IVa) X=Y=H, R=CH$_3$: cis isomer

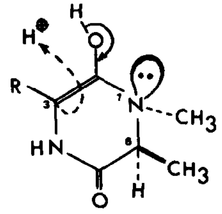
(IVb) X=Y=H, R=CH$_3$: trans isomer

(VIIa) X=Y=R=H: cis isomer

(VIIb) X=Y=R=H: trans isomer

from the cis acid (IIIa)[3], the optically active cis diketopiperazine (IVa)[8] and the trans isomer (IVb)[9] were yielded in the ratio 6:1 (>90% yield), which was exactly same as the one obtained from the acid (Ia) or (Ib). As the cis diketopiperazine (IVa) had been already synthesized from L-tryptophan and L-alanine by Witkop et al,[10] it was possible to determine the optical purity of the material synthesized by this method from a comparision of $[\alpha]_D$ values: $[\alpha]_D^{20}$ +22° (c, 0.33 in DMF) was given by Witkop et al and $[\alpha]_D^{20}$ +22.5° (c, 0.33 in DMF) was obtained from this experiment.

One of the explanations for this reaction is that the stereoselectivity could be resulted from a stereospecific protonation to the enol (V), which is produced either from the cis acids (Ia and IIIa) or from the trans acids (Ib and IIIb). Now, the stereospecific protonation could be attributed to the steric hindrance of the lone pair electrons of the N$_1$-nitrogen atom against the protonation to the enol (V) from its top side, because the methyl groups on C$_6$ and N$_1$ are supposed to occupy a quasi-equatorial conformation from a steric reason and hence the lone pair electrons of the N$_1$-nitrogen atom, which is located in the position of 1,3-relationship with the reaction center, will have a quasi-axial orientation. If this proposal is correct, a different situation is expected on decarboxylation of the compounds (VIa) and (VIb), in which the



(V)

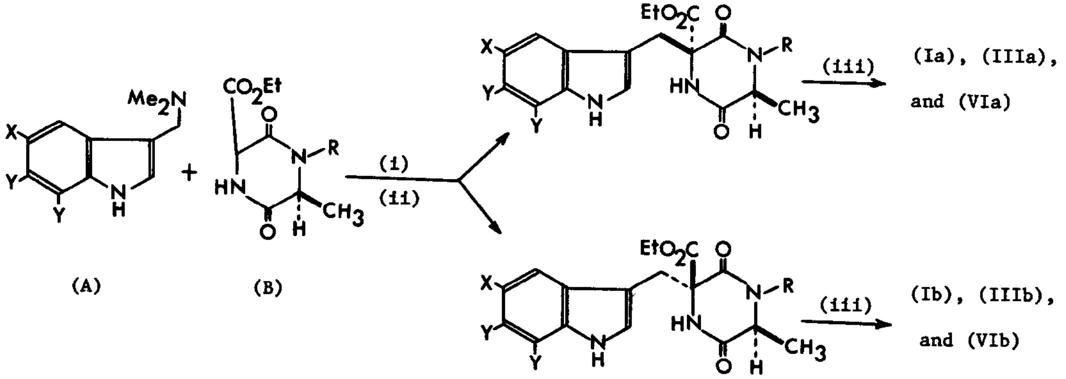
methyl group on the N_1-nitrogen is lacking. Namely, because in the enol derived from these acids the lone pair electorns of the N_1-nitrogen and the methyl group on C_6 are supposed to occupy a quasi-equatorial conformation from a steric reason and hence the proton on the N_1-nitrogen will have a quasi-axial orientation, a more space is open for the protonation to the enol from the top side of the molecule compared with the previous case. Indeed, either from the trans acid (VIb)[3] or from the cis acid (VIa)[3] the mixture of the cis (VIIa) and the trans diketopiperazine (VIIb) were produced in the ratio 3:2.[11]

The study to apply the stereoselective decarboxylation to a general synthesis of the optically active diketopiperazines and to extend it to an asymmetric synthesis of α-amino acids and the related compounds is in progress.

REFERENCES AND FOOTNOTES

1. Y. Kishi, S. Nakatsuka, and T. Goto, unpublished work.
2. Satisfactory analytical and spectroscopic data were obtained for all the new compounds.
4. mp 304-6°; $[\alpha]_D^{20}$ +43.8° (c, 0.33 in DMF); ms 365 and 367 (M^+); ν_{max}^{KBr} 1690, 1640cm^{-1}; λ_{max}^{MeOH} 226nm (ε 40,000), 283 (6,160); $\delta_{ppm}^{DMSO-d_6}$ 0.32 (3H, d, J=7), 2.67 (3H, s), 2.8-4.2 (4H), 3.78 (3H, s), 3.89 (3H, s), 7.01 (1H, d, J=2), 7.32 (1H, s), 8.2 (1H, broad)
5. mp 230-1°; ms 365 and 367 (M^+); ν_{max}^{KBr} 1685, 1638cm^{-1}; λ_{max}^{MeOH} 227nm (ε 35,100), 283 (5,580); $\delta_{ppm}^{DMSO-d_6}$ 1.25 (3H, d, J=7), 2.67 (3H, s), 2.9-4.3 (4H), 3.77 (3H, s), 3.92 (3H, s), 7.03 (1H, d, J=2), 7.38 (1H, s), 8.0 (1H, broad)

3. The acids used for decarboxylation in this study were synthesized as depicted below; (i) condensation of gramine (A) with diketopiperazine (B), synthesized from L-alanine, in the presence of powdered sodium hydroxide in toluene, (ii) chromatographic separation of cis and trans ester, and (iii) hydrolysis of the ester with 0.1N sodium hydroxide in aq.dioxane.



6. E. Houghton, and J. E. Saxton, J. Chem. Soc. (C), 1003 (1969)

7. When the compound IIa was heated in ethanol containing triethylamine at 120° for 3 days in a sealed tube, a mixture of the compounds IIa and IIb with the ratio 5:2 was produced. However, the equilibrium was still not established under this condition, because the compound IIb give a mixture of the compounds IIa and IIb with the ratio 1:1 under the same condition.

8. mp 179-180°; $[\alpha]_D^{20}$ +22.5° (c, 0.33 in DMF); ms 271 (M^+); ν_{max}^{KBr} 1680, 1635cm^{-1}; λ_{max}^{MeOH} 220nm (ε 30,200), 274 (4,850), 281 (5,080), 290 (4,370); $\delta_{max}^{DMSO-d_6}$ 0.21 (3H, d, J=7), 2.57 (3H, s)

9. mp 238-240°; ms 271 (M^+); ν_{max}^{KBr} 1680, 1635cm^{-1}; λ_{max}^{MeOH} 220nm (ε 31,200), 274 (4,990), 281 (5,270), 290 (4,500); $\delta_{ppm}^{DMSO-d_6}$ 1.20 (3H, d, J=7), 2.62 (3H, s)

10. M. Ohno, T. F. Spande, and B. Witkop, J. Am. Chem. Soc., 90, 6521 (1968) and 92, 343 (1970)

11. The ratio was estimated from the nmr spectrum of the reaction mixture.