the resulting bright-red solution, and the crystalline precipitate was removed by filtration, washed with ether, and dried.

β-Carbolines (Va-f, VIa,b). Gaseous ammonia was passed into a suspension of 0.01 mole of perchlorates IIIa-f or IVa,b in 50 ml of alcohol in the course of 30 min, after which the solution was refluxed for 30 min, cooled, and diluted with 250 ml of water. The resulting precipitate was removed by filtration and dried.

β-Carbolines (Vg,i). A 0.01-mole sample of perchlorate IIIg or IIIi was added to a mixture of 3.8 g (0.05 mole) of ammonium acetate and 50 ml of acetic acid, and the resulting solution was refluxed for 30 min. It was then cooled and treated with 250 ml of water, and the precipitate was removed by filtration and dried.

Hydrochlorides of Va-i. These compounds were obtained by the addition of the calculated amount of concentrated hydrochloric acid to alcohol solutions of the β-carbolines.

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SYNTHESIS AND CONFIGURATION OF DIASTEREOMERIC 2,4-, 2,5-, AND 2,6-PIPERIDINEDICARBOXYLIC ACIDS AND THEIR DIMETHYL ESTERS

L. I. Mastafanova, K. F. Turchin, M. I. Evstratova, Yu. N. Sheinker, and L. N. Yakhontov

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The reduction in an acidic medium over a platinum catalysts of 2,4-, 2,5-, and 2.6-pyridinedicarboxylic acids gave cis-2,4-, -2,5-, and -2,6-piperidinedicarboxylic acids, heating of which in an alkaline medium led to thermodynamically equilibrium mixtures of diastereomers. Individual trans-2,5-piperidinecarboxylic acid was isolated. The configurations of the 2,4-, 2,5-, and 2,6-piperidinedicarboxylic acids and their methyl esters were established by means of the PMR spectra.

Substituted 2-piperidinecarboxylic acids are of interest as medicinals (dimecolin, mepivacin, etc.) [1], but little study has been devoted to the synthesis and steroisomerism of piperidinedicarboxylic acids with a carboxy group in the 2 position of the piperidine ring. 2,3-Piperidinedicarboxylic acid was obtained at the end of the last century in the form of two diastereomers, which were assigned to the cis and trans series only on the basis of the difference in their melting points; the isomerization of the cis acid to the trans acid has been described [2, 3]. Later on, diethyl 2,3-piperidinedicarboxylate [4], 2,4-piperidinedicarboxylic acid, and its dimethyl ester [5] were synthesized; however, the configurations of the compounds were not established. Diethyl 2,5-piperidinedicarboxylate was obtained by hydrogenation of the corresponding pyridine ester, and a cis configuration was demonstrated for the isolated individual isomer.

The reduction of dipicolinic acid with platinum gives cis-2,6-piperidinedicarboxylic acid, whereas the reduction with sodium in alcohol or via an electrochemical method gave two forms of 2,6-piperidinedicarboxylic acid, the configurations of which were not estab-

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021.

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TABLE 1. Parameters of the PMR Spectra of Diastereomeric 2,4-, 2,5-, and 2,6-Piperidinedicarboxylic Acids and Their Dimethyl Esters

Compound	Chemical shifts,* ppm							SSCC,† Hz		$K_{cis/trans}$	ΔG, kcal/mole
	1-H	2-H	3-H	4-H	5-H	6-H	CH_3	$J_{2,3'}$	$J_{2,3''}$		
cis-Ia		3,67, q	1,73; 2,56	2,76 (32)	1,76; 2,20	3,05; 3,52		12,9	3,3		
trans-Ia		3,90, q	2,15; 2,37	2,86 (20,5)	2,09; 2,15	3,20; 3,35		9,2	4,2	4,20	−1,33
cis-Ib	2,10 br	3,35, q	1,56; 2,30	2,46	1,54; 1,91	2,66; 3,24	3,69s ; 3,74, s	11,7	2,9		
trans-Ib		3,75, t					3,70, s; 3,74, s	5,3	5,3	—	—
cis-IIa		3,80, q	1,90 —	2,15	2,92 (19)	3,27, q; 3,61, q		9,2	4,2		
trans-IIa		3,63, q	2,30; 1,75	2,30; 1,75	2,79 (31)	3,10, q; 3,62, q		11,5	~3	0,31	1,08
cis-IIb	2,02	3,50, q	1,85 —	2,10	2,52	2,97; 3,24	3,70, s; 3,73, s	7,6	4,0		
trans-IIb	1,97	3,32, q	1,54; 2,08	1,58; 2,15	2,45	2,75; 3,35	3,68, s; 3,73, s	10,8	3,0	—	—
cis-IIIa		3,79, q	2,31; 1,64	2,03; 1,64	2,31; 1,64	3,79, q		11,6	3,1		
trans-IIIa		4,18, t						~6	~6	3,50	−1,18
cis-IIIb	2,41 br	3,38, q	1,45; 2,05	1,45; 2,05	1,45; 2,05	3,38, q	3,74, s	11,3	2,7		
trans-IIIb		~3,75, t					3,74, s	~5,7	5,7	—	—

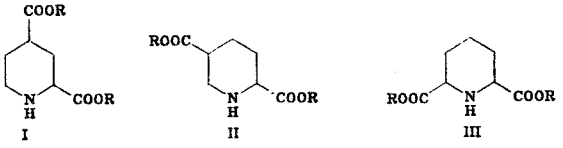
*The absence of letters denotes a multiplet, and "br" denotes a broad signal; the sum of the vicinal SSCC of a given proton (ΣJ_{vic}) is given in parentheses.

†For trans Ib, cis IIb, and trans IIIb the spectra were obtained from solutions in d_6-benzene.

lished (see [7]). The reduction of dimethyl dipicolinate gave the cis diester of the piperidine series [8]. Free 2,4- and 2,5-piperidinedicarboxylic acids have not been described.

Using an experiment to obtain the hydrochlorides of dimethyl esters of 2,4- and 2,5-piperdinedicarboxylic acids by means of reduction of the corresponding pyridine derivatives in the presence of a platinum catalyst in a methanol solution of hydrogen chloride and the hydrochloride of 2,4-pyridinedicarboxylic acid in a hydrochloric acid solution we synthesized individual isomers of free 2,4- (Ia), 2,5- (IIa), and 2,6-piperidinedicarboxylic (IIIa) acids, which, according to the spectral data (see below), were the cis isomers. The cis configuration was also retained for dimethyl 2,4- (Ib), 2,5- (IIb), and 2,6-piperidinedicarboxylate (IIIb), which were obtained by esterification of Ia-IIIa.

When Ia-IIIa were heated to 190°C in an alkaline medium, they underwent partial cis—trans isomerization. The ratios of the diastereomers in the mixtures did not change upon prolonged heating, and, consequently, corresponded to the thermodynamic equilibrium. In the case of esterification of pairs of diastereomeric acids we obtained mixtures of diastereomeric dimethyl 2,4-, 2,5-, and 2,6-piperidinedicarboxylates (Ib-IIIb). In the case of 2,5-piperidinedicarboxylic acid we were able, by crystallization, to isolate from the mixture of diastereomers individual trans isomer IIa, by esterification of which we obtained trans ester IIb.



I II III

I-IIIa R=H; b R=CH_3

From the general principles of the conformational analysis [9, p. 67] it follows that in disubstituted piperidines, depending on the configuration of the isomer, one of the two variants of the conformational equilibrium is realized:

$$\underset{\text{A}}{aa \rightleftarrows ee}; \quad \underset{\text{B}}{ae \rightleftarrows ea}.$$

For substituents of the COOR type with significant conformational energies [ΔG_{COOCH_3} = 1.1 kcal/mole, ΔG_{COOH} = 1.2 kcal/mole (9, pp. 60, 514)[one should expect a markedly pronounced preference for one of the conformers (ee) in the case of A and the absence of this preference in the case of B. In the PMR spectra this is reflected in the spin—spin coupling constants (SSCC) of the 2-H proton with the two nonequivalent protons attached to $C_{(3)}$; the expected values of these constants are

$$J_{2H,3H'} = J_{aa} - p(J_{aa} - J_{ee}); \; J_{2H,3H''} = J_{ae},$$

where p is the fraction of the conformer with an axial substituent in the 2 position;

$$J_{aa} \gg J_{ae} \approx J_{ee} \; [10].$$

In the case of an equilibrium of the A type the following relationships are valid: $p \ll 1$ and $J_{2H,3H'} \approx J_{aa}$. In the case of B the p value increases, which entails a decrease in $J_{2H,3H'}$ (the larger of the two vicinal SSCC). With allowance for these considerations the data in Table 1, which attest to a decrease in the $J_{2H,3H'}$ value in the trans-Ia,b, cis-IIa, b, and trans-IIIa,b as compared with the corresponding value for the second diastereomers, show that an equilibrium of the B type is peculiar to the compound listed above, whereas an equilibrium of the A type is peculiar to their diastereomers.* A similar dependence of the vicinal SSCC on the type of conformational equilibrium was previously observed for diastereomeric 4-hydroxypiperidine-2,6-dicarboxylic acids and their dimethyl esters [11].

Data on the sums of the vicinal SSCC of the secondary methylidyne proton (4-H or 5-H, respectively) are in agreement with the above-presented assignment of the 2,4- and 2,5-piperidinedicarboxylic acid isomers. As in the case of $J_{2H,3H'}$ (or $\Sigma J_{2H} = J_{2H,3H'} + J_{2H,3H''}$),

*For trans-IIIa,b the decrease in $J_{2H,3H'}$ up to the $J_{2H,3H''}$ value is possible and apparent and may be due to random coincidence of the chemical shifts of the 3-H' and 3-H" protons. However, a comparison of the $\Sigma J_{2H} = J_{2H,3H'} + J_{2H,3H''}$ values of the unambiguously determined (from the spectra) for trans-IIIa,b ($\Sigma J_{2H} \leq 12$ Hz) and their isomers cis-IIIa,b ($\Sigma J_{2H} \geq 13.8$ Hz) confirms the correctness of the proposed assignment of the isomers to conformational-equilibrium types.

the ΣJ_{4H} value decreases with an increase in p, i.e., in the case of an equilibrium of the B type. It is precisely this that is characteristic for trans-Ia and cis-IIa ($\Sigma J \sim 20$ Hz) when one compares them with the corresponding diastereomers cis-Ia and trans-IIa ($\Sigma J > 30$ Hz).

Independent evidence that cis-IIIa,b are affiliated with a conformation equilibrium of the A type is the nonequivalence of the geminal protons attached to $C_{(4)}$. In the case of an equilibrium of the B type for trans-IIIa,b the p = 0.5 value, because of the symmetry of the molecule and the geminal protons attached to $C_{(4)}$, are chemically equivalent.

The type of conformational equilibrium that is peculiar to each of the cis- and trans-Ia-IIIa is manifested in the ratios of the isomers in their equilibria. In each of the pairs of diastereomers the thermodynamically more favorable equilibrium is of the A type. Evidently, the preferability of these isomers is explained by their existence in the energically favorable chair conformation with a diequatorial orientation of the substituents (which is impossible for diastereomers trans-Ia, cis-IIa, and trans-IIIa). This explanation is confirmed by the weak dependence of the difference in the free energies of the diastereomers $[\Delta G_{COOH(n)}]$;* (n = 4, 5, 6) on the position of the second carboxy group in the piperdine ring and the closeness of the $[\Delta G_{COOH(n)}]$ values to the conformational energy of the COOH group (determined for cyclohexane derivatives (9, pp. 60, 514).

Thus it may be asserted that piperidinedicarboxylic acids I-III, which were obtained by hydrogenation of the corresponding pyridinedicarboxylic acids, are the cis isomers.

EXPERIMENTAL

The PMR spectra were recorded with XL-100A and XL-200 spectrometers (100 and 200 MHz). As the solvents and standards we used D_2O and dioxane for cis- and trans- acids Ia-IIIa and $CDCl_3$ and tetramethylsilane (TMS) for cis- and trans- esters Ib-IIIb. The ratios of the stereoisomers in the equilibrium mixtures (C_{cis}/C_{trans}) were determined as the ratios of the integral intensities of the least overlapped signals that correspond to the different diastereomers.

Dimethyl cis-2,4-Piperidinedicarboyxlate (cis-Ib). This compound was obtained by the method in [5].

cis-2,4-Piperidinedicarboxylic Acid (cis-Ia). An 8-g (38 mmoles) sample of cis-2,4-piperidinedicarboxylic acid hydrochloride [5]† was dissolved in 16 ml of water, a 20% solution of sodium hydroxide was added until the mixture had pH 3, and the mixture was cooled to 5°C and maintained at this temperature for 6 h. The resulting precipitate was removed by filtration, washed twice with 2-ml portions of cooled (to 10°C) water, and dried to give 4.2 g of product. From the evaporated to one third of the initial volume of the filtrate we additionally isolated 1.45 g of Ia for an overall yield of 5.65 g (85%) of colorless crystals with mp 300°C (dec.). The product was only slightly soluble in water and insoluble in ordinary organic solvents. Found: C 48.6; H 6.6; N 7.9%. $C_7H_{11}NO_4$. Calculated: C 48.6; H 6.4; N 8.1%.

cis-2,5-Piperidinedicarboxylic Acid (cis-IIa). A suspension of 19 g (114 mmoles) of 2,5-pyridinedicarboxylic acid [12] in 700 ml of 13% HCl was hydrogenated in the presence of 0.5 g of Adams' platinum catalyst at room temperature and an excess pressure of 30 cm (water column), after which the catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 60 ml of water, the aqueous mixture was treated with 20% NaOH until it had pH 2.85, after which it was worked up as indicated above to give 13.12 g (69%) of colorless crystals with mp 293°C (dec.). The product was only slightly soluble in water (1.40) and insoluble in ordinary organic solvents. Found: C 48.2; H 6.5; N 7.9%. $C_7H_{11}NO_4$. Calculated: C 48.6; H 6.4; N 8.1%.

Dimethyl cis-2,5-Piperidinedicarboxylate (cis-IIb). A mixture of 5 g (28.8 mmoles) of acid II, 50 ml of methanol, and 18 ml of concentrated H_2SO_4 was refluxed for 4 h, after which it was cooled and poured over ice. The aqueous mixture was made alkaline with 50% K_2CO_3 and extracted with $CHCl_3$. The extract was dried with K_2CO_3 and evaporated, and the residue was distilled in vacuo to give 4.5 g (80%) of a product with bp 120-122°C (4 mm) and n_D^{20} 1.4658.

*The ΔG_{COOH} values were calculated from the formula $\Delta G_{COOH(n)} = RI \ln (C_{cis}/C_{trans})$ kcal/mole, where R = 2 cal/mole^{-1}·deg^{-1} and T = 190°C = 463°K.

†In [5], mp 224-226°C was erroneously presented for this compound instead of mp 252-255°C.

The product was quite soluble in ordinary organic solvents but only slightly soluble in water. IR spectrum: 3350 (NH) and 1730 cm^{-1} ($COOCH_3$). Found: C 53.6; H 7.5; N 7.4%. $C_9H_{15}NO_4$. Calculated: C 53.7; H 7.5; N 7.0%.

cis-2,6-Piperidinedicarboxylic Acid (cis-IIIa) and Its Dimethyl Ester (cis-IIIb). These compounds were synthesized by the methods described in [7, 8].

trans-2,5-Piperidinedicarboxylic Acid (trans-IIa). A solution of 2 g (11.5 mmoles) of cis-dicarboxylic acid IIa and 1.11 g (27.6 mmoles) of NaOH in 20 ml of H_2O was heated in a bomb at 200°C for 15 h, after which it was cooled, and the bomb was opened. The reaction mixture was evaporated to dryness, and the water residues were removed by distillation with benzene. The residue was dissolved in 6 ml of water, and the aqueous solution was acidified to pH 2.92 with 1 N HCl and evaporated until crystallization had started. The mixture was then allowed to stand at room temperature for 20 h. The resulting precipitate was removed by filtration, washed twice with 1-ml portions of water, and dried to give 1 g (70%) of colorless crystals with mp 294°C (dec.). The product was soluble in water but insoluble in ordinary organic solvents. The pH of a 2.5% aqueous solution at 22°C was 2.92. Found C 48.4; H 6.4; N 8.0%. $C_7H_{11}NO_4$. Calculated: C 48.6; H 6.4; N 8.1%.

Dimethyl trans-2,5-Piperidinedicarboxylate (trans-IIb). This compound, with bp 153-155°C, was obtained in 75% yield by a method similar to that used to prepare cis-IIb. The product was soluble in ordinary organic solvents but only slightly soluble in water. IR spectrum: 3350 (NH) and 1725 cm^{-1} ($COOCH_3$). Found: C 53.6; H 7.6; N 7.3%. $C_9H_{15}NO_4$. Calculated: C 53.7; H 7.5; N 7.0%.

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