Stereochemistry of 2,6-Dipyridine Substituted N-Benzyl-4-piperidone Mono- and Dicarboxylates and of the Corresponding Reduction Products [1]

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2,6-Dipyridine Substituted N-Benzyl-4-piperidones Mono- and Dicarboxylates,
Keto-Enol Tautomerism, Configurational Isomerism, Reduction

The alkyl N-benzyl-4-piperidone-3-carboxylate (**1**) is synthesized by a Mannich procedure from pyridine aldehyde, benzylamine and the monoester of acetonedicarboxylate; the corresponding diester **2** is formed by condensation of pyridine aldehyde, benzylamine and dimethyl 3-oxoglutarate. Isomerism is observed with respect to keto-enol tautomerism and *cis* or *trans* substitution of the pyridines. The structure of the enol **1b** ($C_{24}H_{23}N_3O_3$) is determined by X-ray analysis: it crystallizes in the triclinic space group $P\bar{1}$ with $a = 9.965(2)$, $b = 10.476(2)$, $c = 10.838(2)$ Å, $\alpha = 69.48(1)$, $\beta = 81.56(1)$, $\gamma = 79.09(1)°$, $Z = 2$ and $D_x = 1.29$ g cm^{-3}. It is refined to R(unweighted) = 0.047 and R(weighted) = 0.045 using 1459 non-equivalent reflections. The structures of **1a/b** and **2a/b** were determined by ^{1}H and ^{13}C NMR data. MNDO calculations of **1a/b** are discussed. The enols **1/2b** are reduced by sodium borohydride. The configuration of the obtained alcohols is determined by NMR data.

Introduction

2,6-Disubstituted 4-piperidones are key intermediates for derivatives of the reversed esters of pethidine attracting attention as opioid analgesics [2]. The pharmacological effect of these compounds depends sensitively on the relative configuration of the substituents in the piperidine ring as well as on the conformation of the ring [3]. These results have prompted the present study of the stereochemistry of the 2,6-dipyridine substituted N-benzyl-4-piperidone-3-carboxylates and -3,5-dicarboxylates **1** and **2.** Usually dimethyl 4-piperidone-3,5-dicarboxylates **2** are synthesized by a Mannich procedure from dimethyl acetonedicarboxylates, an aldehyde and an alkylamine [3–6] and the monoester of the piperidone **1** by a condensation of the monoester of acetonedicarboxylates, aldehyde and alkylamine [7, 8], respectively. These syntheses characteristically yield a mixture of isomeres, which could be identified as keto-enol-tautomerism as well as configurational isomers at C-2/C-6, especially in the case of the 2,6-diphenyl substituted N-methyl and N-benzyl-4-piperidone-3,5-dicarboxylates [4b, 5a]. The purpose of this paper is to elucidate the stereochemistry of the 2,6-dipyridine substituted mono- and diesters of N-benzyl-4-piperidones by the means of NMR spectra and X-ray analysis as well as a discussion of the thermodynamic stability of these isomers of the monoester **1** from MNDO and FF (force field) calculations. Additionally, the structure of alcohols obtained from reduction of piperidones by sodium borohydride will be discussed.

Experimental

The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Jeol JNM 270 (270.05 MHz), JNM 400 (399.65 MHz) and a Bruker AM 360 L (360.134 MHz) spectrometers, the heteronuclear ^{13}C–^{1}H shift correlations of **1/2b** were measured using a Bruker AM 300 (300.133 MHz), the ^{13}C NMR spectra using the Jeol JNM 270 (67.80 MHz) and a Bruker AM 360 L (90.556 MHz). The IR spectra were recorded with a Beckman Acculab 10, and the melting points with a Tottoli apparatus (Büchi). The elemental analyses were carried out by Mikroanalyt. Labor I. Beetz, Kronach. The silica gel used for the separation by column chromatography was Kieselgel 60, Merck, 0.063–0.2 mm.

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Synthesis of the 2,6-di-2-pyridine substituted dimethyl N-benzyl-4-piperidone-3,5-dicarboxylate (**2**)

A solution of 5.5 g (0.05 mol) N-benzylamine in 10 ml methanol was dripped into a solution of 10.7 g (0.1 mol) freshly destilled pyridine-2-aldehyde and 8.7 g (0.05 mol) dimethyl acetonedicarboxylate in 20 ml methanol at −5 to 0 °C. The reaction mixture became brown and was allowed to stand at room temperature until **2b** crystallized. **2b** was recrystallized from methanol. Yield 18.2 g (61%) **2b,** m.p. 162 °C.

$C_{26}H_{25}N_3O_3$ *(459.5)*

Calcd	C 68.0	H 5.48	N 9.1,
Found	C 68.0	H 5.58	N 9.1.

The syntheses of the ketone isomer **2a** has already been reported by Merz and Haller [5b].

The synthesis of the 2,6-di-2-pyridine substituted methyl N-benzyl-4-piperidone-3-carboxylate (**1b**) was carried out as reported by Haller *et al.* [7, 8]. The ketone isomer **1a** was obtained along with **1b** from the first crystallisation fraction, only. It was not possible to purify the ketone because **1a** isomerized very quickly to **1b** during this procedure.

Reduction of **1b** *and* **2b**

A solution of 0.25 g $NaBH_4$ in 10 ml water was dripped into a solution of 1 g of the enol isomer **1b** or **2b** in 50 ml dioxane and 40 ml water. The reaction mixture was allowed to stand in a refrigerator overnight, then hydrolysed with diluted hydrochloric acid (pH = 6) and evaporated *in vacuo* to 30 ml. The resulting suspension was extracted with dichloromethane, the organic layer dried with sodium sulfate and the solvent evaporated *in vacuo.*

The epimeric alcohols **3/4** (yield 45%) obtained by reduction of **2b** were separated by column chromatography (100 g silica gel, eluent: ethyl acetate 4.0, methanol 3.0, toluene 6.0, conc. ammonia 0.1).

3: R_f = 0.8; crystallized from ethanol; m.p. 219 °C.

$C_{26}H_{27}N_3O_5$ *(461.5)*

Calcd	C 67.7	H 5.90	N 9.1,
Found	C 67.7	H 5.81	N 9.1.

IR (KBr): 3440 (OH), 1730 and 1740 cm^{-1} (C=O).

4: R_f = 0.7; crystallized from ethanol/water = 1:1; m.p. 143 °C.

Calcd	C 67.7	H 5.90	N 9.1,
Found	C 67.6	H 5.99	N 9.1.

IR (KBr): 1730 and 1745 cm^{-1}.

The isomeric alcohols **5/6** (yield 75%) obtained by reduction of **1b** were separated by column chromatography (100 g silica gel, eluent: dichloromethane 6.0, ethyl acetate 3.5, methanol 0.5, conc. ammonia 0.1).

5: R_f = 0.8; crystallized from methanol/water = 5:1; m.p. 131 °C.

$C_{24}H_{25}N_3O_3$ *(403.5)*

Calcd	C 71.4	H 6.25	N 10.4,
Found	C 71.5	H 6.33	N 10.4.

IR (KBr): 3460 (OH), 1745 cm^{-1} (C=O).

6: R_f = 0.6; crystallized from ethylacetate/petrolether = 1:1; m.p. 125 °C.

Calcd	C 71.4	H 6.25	N 10.4,
Found	C 71.5	H 6.21	N 10.5.

IR (KBr): 3500 (OH), 1705 cm^{-1} (C=O).

Crystal structure analysis

Crystals investigated in the present study are clear transparent idiomorphic crystals. A crystal measuring 0.500×0.200×0.075 mm was used for data collection on an automatic Siemens AED 2 four-circle diffractometer with graphite monochromaticed MoK_α radiation (λ = 0.71069 Å) and ω-2ϑ scan (ϑ_{max} = 30°). The intensities of 6338 reflections were recorded of which 1766 were rejected; 1459 had $I \geq 3\sigma(I)$ and were used for the subsequent refinement. The refined cell dimensions given in the program DIF 4 (Siemens-Software) using 38 reflections. Lorentz and polarization but no absorption corrections were applied. The positions of the atoms were determined by direct methods (SHELXS-86, [9]) and refined by full-matrix least-squares methods with the program SHELX-76 [10]. The atomic scattering factors for neutral atoms C, H, N, O were taken from Cromer and Mann [11]. Anisotropic refinements of the crystal structure converged at *R*(unweighted) = 0.047 and *R*(weighted) = 0.045.

Final atomic parameters are given in Table I and bond length and angles in Table II. Lists of observed and calculated structure factors have been deposited at the "Fachinformationszentrum"*.

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* List of observed and calculated structure factors to this papers can be ordered from the Fachinformationszentrum Energie, Physik, Mathematik, D-7514 Eggenstein-Leopoldshafen 2, FRG. Please quote reference no. CSD 53758, the names of the authors and the title of the paper.

Table I. Positional and thermal (×10^4) parameters for $C_{24}H_{23}N_3O_3$ with standard deviations. The anisotropic temperature factors have the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots + 2U_{23}klb^*c^*)]$. The standard deviations in parentheses refer to the last digit.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	0.2726(4)	0.2952(4)	0.3258(5)	354(31)	441(32)	422(37)	−113(28)	−36(28)	−91(24)
C2	0.1219(5)	0.3104(6)	0.3553(6)	334(37)	461(39)	474(44)	−126(35)	−6(33)	−72(30)
C3	0.0583(6)	0.2041(6)	0.3271(6)	411(40)	407(40)	553(49)	−145(37)	−94(36)	−85(32)
C4	0.1261(7)	0.1385(6)	0.2454(7)	618(49)	412(42)	608(52)	−116(39)	−267(41)	−113(36)
C5	0.2686(6)	0.1585(6)	0.1772(6)	475(40)	500(42)	544(49)	−164(37)	−36(36)	−103(33)
C6	0.3092(6)	0.2873(6)	0.1915(6)	385(37)	532(42)	382(45)	−138(35)	−36(33)	−48(31)
C7	0.3406(6)	0.1784(6)	0.4284(6)	539(40)	391(38)	402(44)	−107(35)	−117(34)	−8(31)
C8	0.3593(5)	0.2135(7)	0.5483(6)	286(33)	579(44)	418(46)	−152(38)	−43(31)	−51(31)
C9	0.3773(6)	0.1092(7)	0.6695(7)	495(42)	584(47)	549(52)	−206(44)	−59(38)	27(34)
C10	0.4051(6)	0.1338(8)	0.7809(7)	493(43)	880(61)	637(57)	−332(50)	−78(38)	88(40)
C11	0.4150(6)	0.2708(9)	0.7697(8)	443(42)	992(64)	646(61)	−266(55)	−42(39)	−29(43)
C12	0.3970(6)	0.3771(8)	0.6491(8)	563(46)	907(57)	601(56)	−308(50)	−70(42)	−160(42)
C13	0.3684(6)	0.3469(7)	0.5395(7)	561(44)	555(47)	539(51)	−125(39)	−68(37)	−204(36)
C14	0.4601(6)	0.3004(6)	0.1489(6)	451(52)	514(44)	373(44)	−76(36)	−23(35)	−30(36)
N15	0.5274(6)	0.2215(6)	0.0791(6)	638(44)	780(43)	652(45)	−285(37)	83(35)	−108(34)
C16	0.6629(8)	0.2335(8)	0.0392(8)	586(57)	970(65)	936(72)	−366(55)	249(49)	−85(49)
C17	0.7294(7)	0.3181(9)	0.0711(9)	541(53)	915(66)	941(72)	−72(54)	−33(49)	−243(47)
C18	0.6588(8)	0.4025(8)	0.1416(8)	552(50)	1103(69)	819(66)	−275(56)	180(47)	−264(49)
C19	0.5217(7)	0.3920(7)	0.1804(7)	636(53)	856(54)	714(59)	−420(47)	92(43)	−295(44)
C20	0.0595(6)	0.4594(6)	0.2851(6)	343(46)	466(45)	427(44)	−120(37)	26(32)	−106(31)
N21	−0.0055(5)	0.4833(5)	0.1785(6)	496(34)	531(38)	632(42)	−109(32)	−203(32)	−63(29)
C22	−0.0579(7)	0.6136(8)	0.1145(7)	596(46)	504(47)	755(58)	−15(46)	−230(42)	9(39)
C23	−0.0487(7)	0.7277(7)	0.1514(8)	556(47)	726(56)	614(59)	−135(48)	−41(42)	−62(41)
C24	0.0185(8)	0.6981(7)	0.2626(9)	952(61)	406(47)	967(68)	−341(48)	−27(53)	0(43)
C25	0.0733(7)	0.5638(7)	0.3306(7)	820(51)	551(49)	709(58)	−274(45)	−154(43)	−131(40)
O26	0.0719(5)	0.0437(4)	0.2176(5)	893(35)	618(32)	991(43)	−447(31)	−232(31)	−146(27)
C27	−0.0773(6)	0.1727(7)	0.3866(7)	429(47)	489(48)	621(56)	47(41)	−124(40)	−101(37)
O28	−0.1341(5)	0.0867(5)	0.3718(5)	697(35)	671(34)	1105(48)	−195(32)	−165(31)	−393(29)
O29	−0.1335(4)	0.2479(5)	0.4645(5)	456(29)	702(34)	785(40)	−170(30)	89(27)	−207(24)
C30	−0.2686(6)	0.2234(8)	0.5285(8)	386(43)	1016(59)	1068(70)	−259(52)	187(45)	−304(40)
H1	0.0999(29)	0.2922(30)	0.4593(30)	476(98)					
H2	0.2733(38)	0.1718(39)	0.0687(41)	1009(147)					
H3	0.3346(29)	0.0706(30)	0.2180(32)	499(99)					
H4	0.2511(30)	0.3723(31)	0.1258(32)	546(102)					
H5	0.2981(29)	0.0871(31)	0.4606(32)	542(105)					
H6	0.4413(34)	0.1404(34)	0.3861(35)	753(121)					
H7	0.0919(41)	0.0188(42)	0.1781(42)	1107(155)					
H8	0.3634(31)	0.0113(33)	0.6709(33)	639(111)					
H9	0.4438(59)	0.0511(61)	0.8641(62)	2166(272)					
H10	0.4567(66)	0.2800(66)	0.8513(68)	2412(319)					
H11	0.3915(59)	0.4809(61)	0.6358(62)	2126(264)					
H12	0.3532(33)	0.4236(34)	0.4559(35)	687(114)					
H13	0.7092(51)	0.1535(52)	−0.0143(54)	1710(222)					
H14	0.8209(45)	0.3311(45)	0.0513(47)	1350(179)					
H15	0.7270(71)	0.4677(71)	0.1584(75)	2722(344)					
H16	0.4624(36)	0.4560(35)	0.2300(38)	908(138)					
H17	−0.1012(44)	0.6386(46)	0.0250(46)	1333(179)					
H18	−0.0923(50)	0.8266(51)	0.0853(53)	1642(209)					
H19	0.0292(37)	0.7796(38)	0.2924(39)	961(139)					
H20	0.1262(37)	0.5446(38)	0.4108(39)	964(140)					
H21	−0.2694(54)	0.1206(57)	0.6005(56)	1679(216)					
H22	−0.2937(46)	0.2766(49)	0.5885(48)	1350(178)					
H23	−0.3257(41)	0.2216(42)	0.4607(45)	1104(158)					

Table II. Bond lengths (Å) and angles (°). The standard deviations in parentheses refer to the last digit.

N1–C2	1.480(7)	C6–N1–C2	110.0(5)
N1–C6	1.475(9)	C7–N1–C2	111.0(4)
N1–C7	1.465(7)	C7–N1–C6	113.4(4)
C2–C3	1.516(10)	C3–C2–N1	112.8(5)
C2–C20	1.530(7)	C20–C2–N1	109.2(4)
C3–C4	1.338(10)	C20–C2–C3	113.9(5)
C3–C27	1.454(9)	C4–C3–C2	120.2(6)
C4–C5	1.517(9)	C27–C3–C2	120.9(6)
C4–O26	1.353(10)	C27–C3–C4	118.9(7)
C5–C6	1.543(10)	C5–C4–C3	125.1(7)
C6–C14	1.524(8)	O26–C4–C3	121.6(6)
C7–C8	1.514(11)	O26–C4–C5	113.3(6)
C8–C9	1.393(8)	C6–C5–C4	109.3(5)
C8–C13	1.387(11)	C5–C6–N1	112.6(4)
C9–C10	1.395(13)	C14–C6–N1	110.6(6)
C10–C11	1.418(13)	C14–C6–C5	112.9(5)
C11–C12	1.398(10)	C8–C7–N1	113.1(5)
C12–C13	1.411(12)	C9–C8–C7	120.0(6)
C14–N15	1.337(10)	C13–C8–C7	121.7(5)
C14–C19	1.389(12)	C13–C8–C9	118.2(7)
N15–C16	1.372(10)	C10–C9–C8	122.6(7)
C16–C17	1.359(15)	C11–C10–C9	118.4(6)
C17–C18	1.394(14)	C12–C11–C10	120.0(9)
C18–C19	1.383(10)	C13–C12–C11	119.5(8)
C20–N21	1.332(9)	C12–C13–C8	121.4(6)
C20–C25	1.383(12)	N15–C14–C6	116.6(7)
N21–C22	1.337(8)	C19–C14–C6	120.7(6)
C22–C23	1.409(13)	C19–C14–N15	122.7(6)
C23–C24	1.376(13)	C16–N15–C14	117.0(7)
C24–C25	1.386(9)	C17–C16–N15	122.7(8)
C27–O28	1.217(10)	C18–C17–C16	120.4(7)
C27–O29	1.344(10)	C19–C18–C17	117.0(9)
O29–C30	1.446(7)	C18–C19–C14	120.1(7)
		N21–C20–C2	117.2(6)
		C25–C20–C2	120.6(6)
		C25–C20–N21	122.2(5)
		C22–N21–C20	117.8(7)
		C23–C22–N21	124.7(7)
		C24–C23–C22	115.6(6)
		C25–C24–C23	120.7(8)
		C24–C25–C20	119.0(7)
		O28–C27–C3	125.0(7)
		O29–C27–C3	112.1(7)
		O29–C27–O28	122.8(6)
		C30–O29–C27	116.1(6)

Results and Discussion

The condensation of the monoester of acetonedicarboxylates, pyridine-2-aldehyde and N-benzylamine yields mainly the piperidone **1b,** which is characterized by the enol structure of the β-ketoester skeleton as the IR absorptions at 1655 (C=O) and 1625 cm^{-1} (C=C) indicate [7, 8]. Haller *et al.* postulated equatorial positions for the pyridine rings at C-2 and C-6 as well as for the carboxylate function at C-3 in analogy to the ketone form of the dimethyl piperidone 3,5-dicarboxylates [12]. There is no indication of the configuration at C-2 in the ^{1}H NMR spectra of **1b** because the hydrogen at C-2 does not have a coupling partner on C-3. The elucidation of the structure **1b** was achieved by the X-ray analyses, shown in the pluto plot (Fig. 2) and the stereoscopic view of the unit cell (Fig. 3). The structure is different from the one proposed by Haller *et al.* [7, 8]: The pyridine substituent at C-2 takes an axial position whereas the pyridine ring at C-6 has an equatorial position which results a *trans* substitution of the pyridine rings*. The benzyl residue at the nitrogen N-1 takes an axial position to prevent a steric compression with the aromatic substituents at C-2 and C-6. The full designation of the compound **1b** is, therefore, methyl 1-benzyl-2a,6e-di-2-pyridyl-4-piperidone-3e-carboxylate. It is remarkable, that the hydrogen at the enolic hydroxyl group shows neither an intramolecular nor an intermolecular hydrogen bond to the methoxycarbonyl function as usually expected in the enol form of β-ketoesters.

The synthesis of the piperidone **1** yields a second isomer **1a** in a smaller amount than **1b.** The IR spectrum in CCl_4 indicates a ketone (1710 cm^{-1}) and an ester carbonyl group (1735 cm^{-1}) [8]. The NMR coupling constant of $J = 5.5$ Hz between the hydrogens at C-2 and C-3 assigns an axial position of the pyridine ring at C-2. On consideration of these spectroscopic data and the ^{13}C NMR data (Table IV), discussed later, the second isomer seems to be a tautomeric form of **1b** (Fig. 1).

MNDO calculations [14] were carried out for four possible isomers of **1** (Fig. 4): two ketone forms with pyridine rings *trans* (I) as well as *cis* (II) and also two enolic forms with pyridine substituents *trans* (III) as well as *cis* (IV). The calculations reveal an energetic advantage of the enolic form III (= **1b**) over the other isomers. This corresponds to two experimental observations: first, the enol isomer **1b** is formed in great excess during the synthesis and second, it is possible to transform the ketone **1a** into the enol **1b** quantitatively by refluxing in ethanol. This suggests, that **1b** is a thermodynamically controlled product. Force-field calculations using MAXIMIN [15] ex-

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* This stereochemistry is comparable to that of the oxidation product of **1b,** the 5-oxo-4,5-dihydro-2,6-methano-2-benzazocine-6-carboxylate [13], in which the pyridine rings are also *trans* substituted.

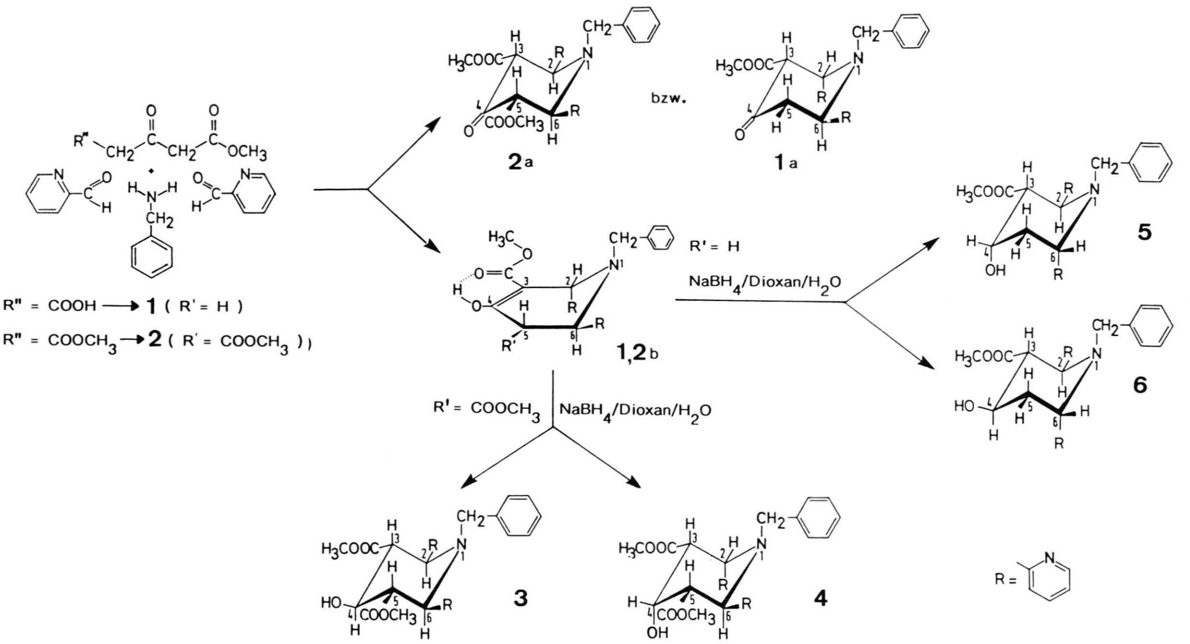


Fig. 1. Synthesis and reduction of the 2,6-dipyridine substituted N-benzyl-4-piperidone-3-carboxylates and -3,5-dicarboxylates.

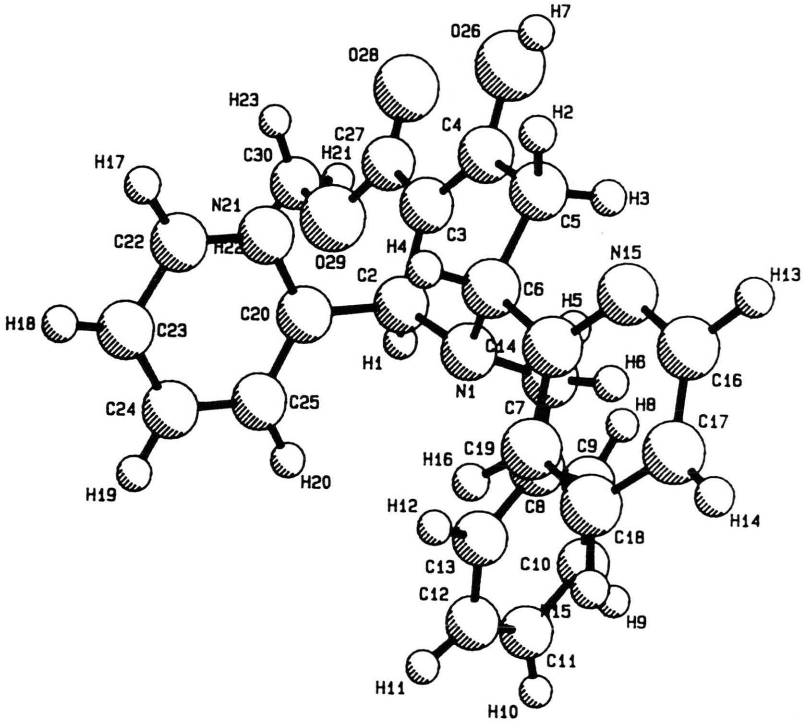


Fig. 2. Pluto plot of **1b**.

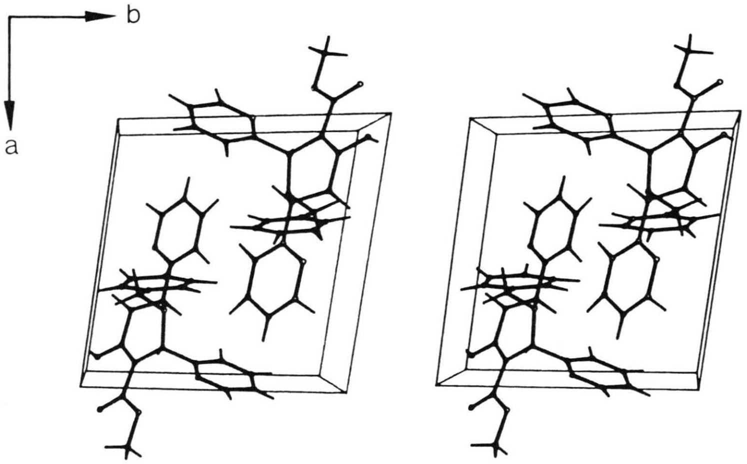


Fig. 3. Stereoscopic view of the unit cell of **1b.**

Table III. ^{1}H NMR data of the N-benzyl-4-piperidones **1, 2** and the corresponding alcohols (chemical shifts, TMS internal standard, coupling constants (Hz) in brackets).

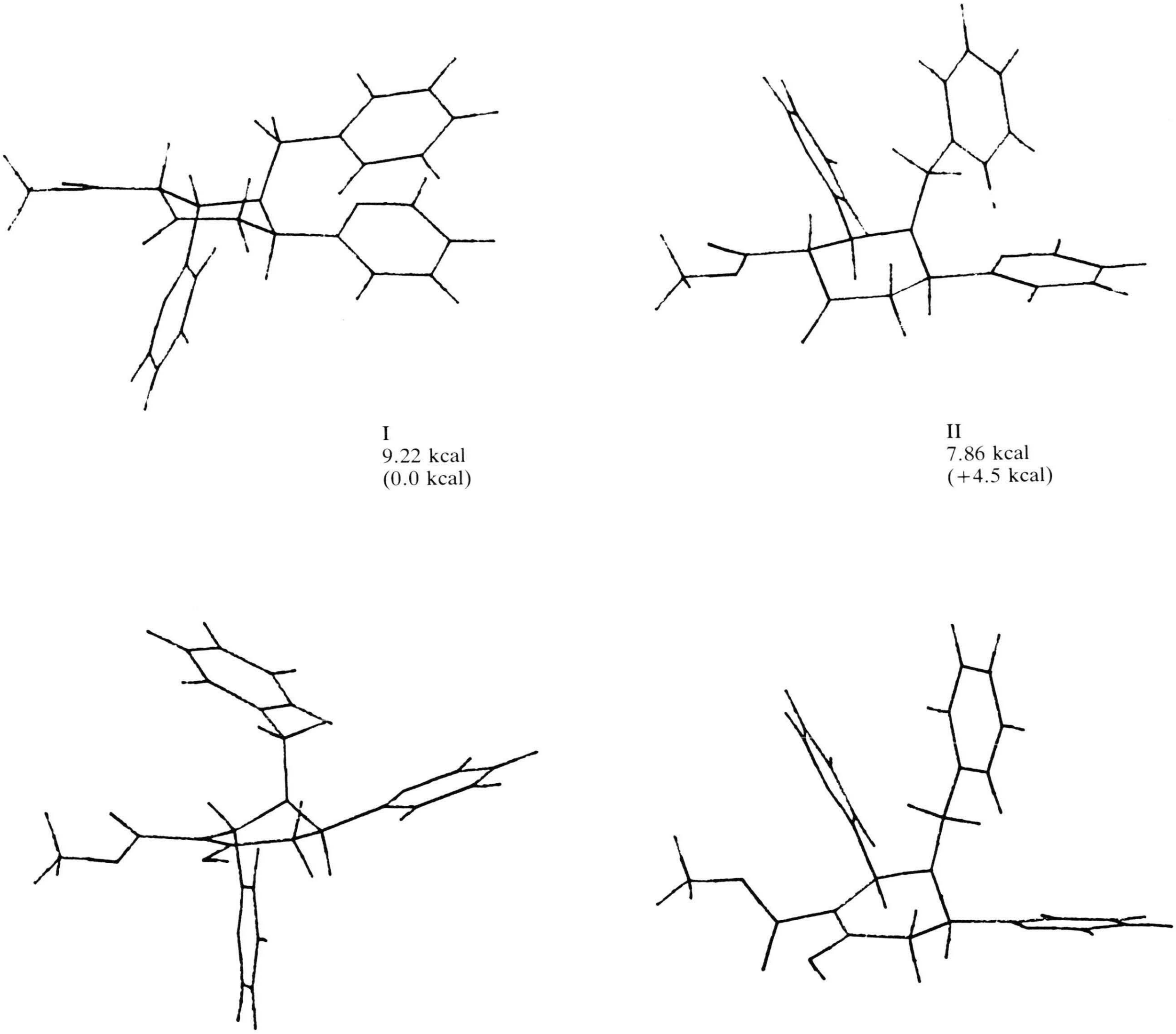
Comp.	H-2	H-3	H-4	H-5		H-6	N−CH$_3$	O−CH$_3$
1a	4.71 d(5.47)	3.83 d(5.47)		3.03 d(6.0)		4.34 t(6.0)	3.51	3.74
2a	5.10 d(10.8)	4.63 d(10.8)		4.63 d(10.8)		5.10 d(10.8)	3.71	3.66
1b	4.76 s			3.22 dd	2.78 dd	4.44 dd	3.50	3.53
2b	4.82 d(1.1)			4.30 d(9.3,1.1)		4.77 d(9.3)	3.53, 3.59 AB(10.4)	3.50, 3.74
2c	4.98 s			4.86 dd(4.0,1.0)		4.62 d(4.0)	3.53, 3.59 AB(10.4)	3.50, 3.74
3	4.20 d(10.0)	3.10 d(10.0)	4.60 t(10.0)	3.10 d(10.0)		4.20 d(10.0)	3.50	
4	4.73 d(4.00)	3.34 t(4.00)	4.85 t(broad)	3.91 dd(8.9,4.2)		4.75 d(8.9)	3.02, 3.28 AB(14.6)	3.73, 3.66
5	4.66 d(10.8)	3.57 dd	4.60 m	2.53 m(14.8,6.5,4.4)	2.26 m(14.8,2.0)	4.21 d(6.8)broad	3.17, 3.42 AB(14.1)	3.61
6*	4.63 d(5.9)	3.13 t(5.8)	4.48 m(6.5,5.5,4.4)	2.60 ddd(13.4,7.3,4.2)	2.16 ddd(13.4,6.6,4.4)	4.42 dd(7.08,4.2)	3.52, 3.12 AB(14.5)	3.69
6**	4.30 d(10.7)	3.00 t(10.7)	3.37 m(4.5,6.1, 10.7,10.7)	2.61 dm(13.0,4.5,1.5)	1.99 m(13.0,11.0,5.2,1.0)	4.00 dm(5.2)	3.60, 3.48 AB(13.7)	3.34

* In CDCl$_3$; ** in DMSO-d$_6$. The interpretation of **6** (in CDCl$_3$) is ensured by COSY90 and PSDQF-COSY90. LR-COSY's exhibits small coupling constants between H-2/pyridine, H-6/pyridine and the N−CH$_2$−C$_6$H$_5$ as well as between the hydrogens at C-2/5 and C-3/5.

Table IV. ^{13}C NMR data of the N-benzyl-4-piperidones **1, 2** and the corresponding alcohols (the interpretation is ensured by 135dept and 90dept spectra).

Comp.	C-2	C-3	C-4	C-5	C-6	N−CH$_2$	O−CH$_3$	C=O
1a	62.6	58.7	202.3	43.7	62.1	52.9	52.2	169.7
2a	68.8	56.3	201.9	56.3	68.8	48.3	52.1	168.9
1b	60.2	96.6	172.4	27.4	56.2	50.9	51.3	171.7
2b	60.5	98.3	172.3	44.7	59.6	52.5	51.6	171.1
2c	63.4/62.5*	95.5	171.4	45.2	62.5/63.4	52.4		171.7
4	61.7/58.9*	48.5/47.9*	66.7	47.9/48.5*	58.9/61.7*	52.4	51.9/51.4	173.0/172.8
5$^+$	57.1/56.1*	48.7	65.8	29.2	56.1/57.1*	52.0	51.5	173.2
5^{++}	57.0/59.3*	46.2	64.9	29.2	59.3/57.0*	50.8	50.7	172.4
6$^+$	61.6/59.0*	49.4	66.4	35.1	59.0/61.6	52.6	51.7	173.8
6^{++}	62.7/59.2	50.3	67.6	30.1	59.2/62.7	51.1	50.9	174.6

* Both values are interchangeable; $^+$ in CDCl$_3$; $^{++}$ in DMSO-d$_6$. The interpretation of the spectra of **1b** and **2b** is ensured by heteronuclear CH-shift-correlations.



I
9.22 kcal
(0.0 kcal)

II
7.86 kcal
(+4.5 kcal)

III
−.19 kcal
(+3.0 kcal)

IV
6.73 kcal
(+7.0 kcal)

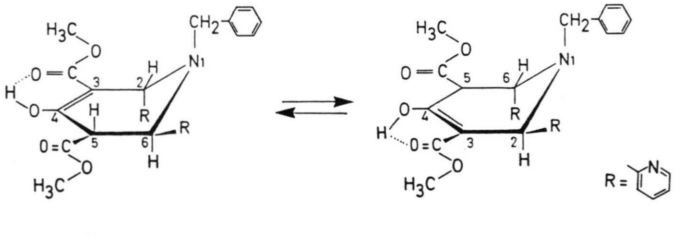
Fig. 4. Results of the MNDO calculations of 4 possible isomers of **1**; the energy values of the FF calculations in parentheses.

press the energetically small difference between the ketone isomers I and II as well as between the tautomeric isomers I and III. From the theoretical point of view all three isomers I–III should be observed in solution, but the ketone form II with diequatorial pyridine rings at C-2 and C-6 should possess the smallest probability for existence. This is nicely supported by the fact that so far only II has not been observed. As expected the MNDO calculations of **1b** (III, Fig. 4) do not show an intramolecular hydrogen bond between the hydroxyl group of the enol and the ester function as found in the X-ray analysis. This is due to the core–core repulsion term of MNDO. A version with modified core–core repulsion term, the MNDO/H program [16], is suitable to correctly calculate H-bonded systems.

The condensation of dimethyl acetonedicarboxylate, benzyl- or methylamine and various aldehydes yields mainly two isomers, explained until now as the keto-enol-tautomerism [5, 6]. In the case of 2,6-dipyridine substituted N-benzyl-4-piperidones the ketone isomer **2a,** obtained by synthesis without any solvent and recrystallization from xylene/ligroin in an excess [5b], is characterized by IR absorptions at 1745 and 1700 cm^{-1} and a half set of signals in the ^1H and ^{13}C NMR spectra (see Table III and IV). These results indicate symmetrical positions of the substituents: the coupling constant of 10.8 Hz in the ^1H NMR spectrum between the hydrogens at C-2/3 and C-5/6 assigns a equatorial position for both pyridine rings and the methoxycarbonyl functions. The ^{13}C NMR data (Table IV) of ketones **1a** and **2a** are quite different, which indicates a different stereochemistry of these ketones.

The enol **2b,** the main isomer, obtained by synthesis in ethanol, shows the typical absorption of a conjugated C=O group in the IR spectrum at 1656 and 1620 cm^{-1}. The ^1H NMR spectrum of **2b** indicates a *trans*-coupling constant of 9.3 Hz for the hydrogens at C-5 and C-6 which assigns an equatorial position of the pyridine ring at C-6 and an equatorial position of the ester function of C-5. Nothing can be said about the configuration at C-2 from the ^1H NMR spectrum, because of the isolated position of H-2. However the comparison of the ^{13}C NMR data (Table IV) of the enol of the monoester **1b,** whose stereochemistry is well known from the X-ray analysis, and of the enol of the diester **2b** shows nearly the same chemical shifts of the carbon atoms of C-2/3 and C-4. This is clear evidence for the same stereochemistry of both enol forms **1b** and **2b,** characterized by an axial position of the pyridine ring in the allylic position. The ^1H NMR data are comparable to the data for the 2,6-di-*p*-chlorophenyl substituted dimethyl N-methyl-4-piperidone-3,5-dicarboxylate, reported by Caujolle *et al.* [4b], who assumed the same stereochemistry. The ^1H NMR spectrum of the first crystalline fraction from the synthesis in xylene/ligroin shows, that it contains mainly the ketone isomer **2a** with a small amount of **2b.** In addition, there is a complete set of the signals corresponding to a isomer in which the enol is formed on the other side of the molecule (Fig. 5). This isomer **2c** is characterized in the ^1H NMR spectrum by a gauche coupling constant of 4.0 Hz for the hydrogens at C-5 and C-6*, which indicates an axial position of the pyridine ring and an equatorial one for the ester function. An additional configurational change at C-2 is unlikely, because the chemical shift of H-2 is nearly the same as in **2b** (Caujolle *et al.* [4b] measured an upfield shift of 0.3 ppm for an exchange of a phenyl ring from the equatorial to the axial position at the same carbon atom instead of a downfield shift of 0.16 ppm, observed here).

The enol isomers of the N-benzyl-4-piperidones **1/2b** were reduced by sodium borohydride in dioxane/water as solvent. The isomers, so obtained, differ in their configuration of the reduced centre C-4 as well as in the configuration of C-2 in the case of the reduction of **2b** (Fig. 1). In the case of the reduction of the diester **2b** two isomers **3** and **4** were isolated. The hydroxyl group in the alcohol **4** takes an axial position as shown by the typical axial-equatorial coupling constants of 4.0 Hz between the hydrogens at C-3/4 and C-4/5 whereas the pyridine rings are still in the same positions as in the enol **2b.** The coupling constant of 4.0 Hz between the protons at C-2/3 and of 8.9 Hz between the protons at C-5/6 indicate an axial pyridine ring at C-2 and an equatorial position of the



2b **2c**

Fig. 5. The two enolic isomers of the dimethyl N-benzyl-4-piperidone-3,5-dicarboxylates.

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* The numbering of the carbon atoms in the piperidone changes in comparison to **2b** (see Fig. 5).

pyridine ring at C-6. The ^{1}H NMR spectrum of the second isomer **3** is characterized by an axial–axial coupling constant of 10.0 Hz between all neighbouring hydrogens and by equal chemical shifts of the hydrogens at C-2/6 and C-3/5, respectively (see Table III). This indicates a symmetrical structure which is distinguished by equatorial positions of all substituents. The structure of **3** implies a configurational change of the pyridine ring at C-2 (from the axial to the equatorial position) during the reaction leading to the same isomer isolated by Haller [17] from the reduction of the ketone **2a.** The configurational change described above can be explained as resulting from the reversal of the Michael addition in the β-aminoketones to ring opening which might be favoured by the benzylic residue at the nitrogen. Closure of the ring could produce a different or the same isomer (compare to [18]).

The reduction of the enol of the monoester **1b** leads to two isomeric alcohols **5** and **6.** The coupling constants in the ^{1}H NMR spectra (measured in DMSO-d_6, Table III) of both isomers exhibit an axial position of the pyridine ring at C-6 and an equatorial position of the aromatic heterocyclus at C-2 which implies a double configurational change at C-2/C-6 during the reduction. The reduction product **5** is characterized by an axial hydroxyl function at C-4 which is proved by the small coupling constant of the proton at C-4. The alcohol **6** has an equatorial hydroxyl group at C-4 which is indicated by the large coupling constants of the hydrogens at C-4 ($J_{4,3} = J_{4,5a} = 10.5$ Hz).

The change of the solvent from DMSO-d_6 to $CDCl_3$ is accompanied by a change in the conformation in the case of **6** as the great difference of the chemical shifts and the coupling constants in both solvents exhibits. The coupling constants of the ^{1}H NMR spectrum in DMSO-d_6 are typical for the chair conformation whereas the conformation in $CDCl_3$ seems to be a skewed boat as shown by the following hints: first, the equatorial and axial protons at C-5 shows nearly the same coupling pattern (Table III) and second, in NOE difference spectra both hydrogens at C-5 show a positive NOE to the hydrogen at C-4 as well as to the proton at C-6. This is possible only in a boat conformation, which is characterized by a similar torsion angle between the hydrogens at C-5 and the protons at C-6 and C-4. This conformation might be stabilized by an intramolecular hydrogen bond from the hydrogen of the OH proton to the nitrogen N-1. Similar behaviour was observed in the ^{1}H NMR spectrum at α-promedol (1,2a,5e-trimethyl-4e-phenylpiperidin-4a-ol, measured in $CDCl_3$) by Casy *et al.* [19], who also assigned the alcohol to a skewed boat conformation in solution. The crystal structure of α-promedol [20] shows a chair conformation with the above mentioned configurations.

The ^{13}C NMR spectra of **5** and **6** (measured in DMSO-d_6) show the typical γ-gauche effect between the OH at C-4 and C-2/6: the value of C-2/6 in **5** are upfield shifted (Table IV). The ^{13}C NMR spectra of **6** measured in $CDCl_3$ and DMSO-d_6 show different chemical shifts, especially in the case of C-5 ($\Delta\delta$ = 6 ppm) which is an additional indication for the different conformation in both solvents.

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