

Molecular and crystal structures of a tricyclic γ -lactam ketone and its Mannich base

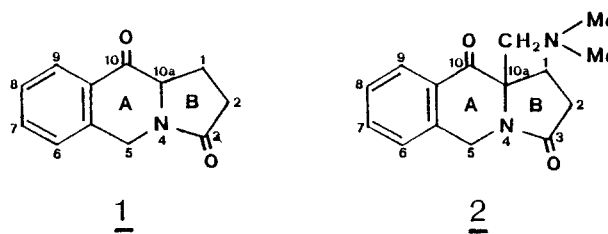
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A tricyclic γ -lactam ketone, 1,10a-Dihydropyrrolo[1,2]isoquinoline-3,10(2H,5H)-dione, and its corresponding Mannich base, 10a-(Dimethylaminomethyl)-1,10a-dihydropyrrolo[1,2b]isoquinoline-3,10(2H,5H)-dione hydrochloride, have been synthesized. The molecular and crystal structures of both compounds were studied by NMR-spectroscopy and X-ray crystallography. Unit cell parameters are: $a = 8.799(7)$, $b = 7.137(6)$, $c = 16.156(8)$ Å, $\beta = 76.28(5)^\circ$, space group $P2_1/c$ for the first compound, and $a = 15.343(9)$, $b = 7.490(6)$, $c = 13.465(8)$ Å, $\beta = 110.98(3)^\circ$, space group $P2_1/c$ for the second. The structures were refined to discrepancy factors $R = 0.068$ for 1261 and $R = 0.047$ for 2138 observed $\text{CuK}\alpha$ data, respectively. The conversion of the tricyclic γ -lactam ketone to its corresponding Mannich base does not affect the *cis* configuration between the fused tetrahydropyridine and γ -lactam rings, but does result in conformational changes in both rings.

Introduction

During the process of the synthesis of fused γ -lactam derivatives (Miquel *et al.*, 1980; Rigo and Kolocouris, 1983; Rigo *et al.*, 1984), the conversion of the tricyclic γ -lactam ketone **1** to the corresponding Mannich base **2** was accomplished. Since the formation mechanism of the Mannich base **2** presumes an enolization of the carbonyl carbon (C-10) and therefore an intermediate sp^2 hybridization of the C-10a, the question arises whether the geometry between the A and B fused rings could be modified during the reaction. Thus, in the present paper we describe X-ray crystallographic and NMR spectroscopic studies on the ketone **1** and the Mannich base **2** which were carried out to determine the



Scheme 1

cis or *trans* configuration of the A and B rings. The hydrochloride of compound **2** was studied crystallographically. Moreover, in compound **2**, the conformation of the dimethylaminomethyl group was defined.

Experimental

Melting points were determined with a Buchi apparatus and are uncorrected.

NMR spectroscopy

¹H-NMR and ¹³C-NMR spectra were obtained on a AC200 Bruker spectrometer with deuteriochloroform

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as a solvent. Chemical shifts are reported in ppm relative to internal TMS, and coupling constants (J) in Hz.

Synthesis

1,10a-Dihydropyrrolo[1,2]isoquinoline-3,10(2H,5H)-dione 1. The compound was prepared by using the Friedel-Crafts reaction on 1-benzyl-5-oxo-pyrrolidine-2-carbonylchloride according to Rigo and Kolocouris (1983). m.p. 108°C, IR (Nujol) $\nu(\text{C}=\text{O})$: 1680 cm^{-1} .

$^1\text{H-NMR}$. (CDCl_3) $\delta(\text{ppm})$ 2.36–2.65 (m, 4H, 1-H, 13-H), 4.33 (m, 1H, 2-H), 4.37(d, AB, J 17.5 Hz, 10- H_A), 5.28 (d, AB, 17.5 Hz, 10- H_B), 7.29–7.65 (m, 3H, 6-H, 7-H, 8-H), 8.09 (m, 1H, 5-H).

$^{13}\text{C-NMR}$. (CDCl_3) $\delta(\text{ppm})$ 20.455 (1-C), 29.806 (13-C), 41.337 (10-C), 61.665 (2-C), 126.44, 127.614, 127.738, 134.396, (5,6,7,8-C), 130.067, 139.620, (4,9-C), 173.850 (12-C), 194.086 (3-C).

10a-(Dimethylaminomethyl)-1,10a-dihydropyrrolo[1,2b]isoquinoline-3,10(2H,5H)-dione 2. A mixture of 8 g (0.04 mol) of ketone **1**, 8.11 g (0.1 mol) of dimethylamine hydrochloride, 8.9 g of paraformaldehyde, 5 drops of ethanolic hydrogen chloride solution and 90 ml of absolute ethanol was refluxed for 36 hours. Ethanol was removed *in vacuo*, water was added to the residue and the whole was extracted with benzene. The aqueous phase was then separated, made alkaline with sodium carbonate and extracted with benzene. After drying with Na_2SO_4 the benzene solution was filtered through a column of neutral aluminum oxide and was then evaporated. The remaining solid was recrystallized from ether. Yield 6 g (58%), m.p. 82–84°C, IR (Nujol) $\nu(\text{C}=\text{O})$: 1685 cm^{-1} . Hydrochloride: m.p. 188°C (dec.), recrystallized from EtOH-Et₂O. Anal. calcd. for $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_2$: C: 61.12%; H: 6.50%; Cl: 12.02%; N: 9.50% Found C: 61.05%; H: 6.57%; Cl: 11.91%; N: 9.38%

$^1\text{H-NMR}$. (CDCl_3) $\delta(\text{ppm})$ 2.28 (s, 6H, 18H, 19-H), 2.33–2.42 (m, 3H, 1-Heq, 13-H), 2.50–2.73 (m, 1H, 1-Hax), 2.63 (d, AB, J 14 Hz, 16- H_A), 2.75 (d, AB, J 14 Hz, 16- H_B), 4.50 (d, AB, J 17.7 Hz, 10- H_A), 5.28 (d, AB, J 17.7 Hz, 10- H_B), 7.30–7.64 (m, 3H, 6-H, 7-H, 8-H) 8.07 (m, 1H, 5-H).

$^{13}\text{C-NMR}$. (CDCl_3) $\delta(\text{ppm})$ 26.331 (1-C), 29.903 (13-C), 39.960 (10-C), 47.568 (18-C), 63.538 (16-C), 70.168 (2-C), 123.505, 126.240, 127.506, 134.139 (5,6,7,8-C), 129.796, 139.508(4,9-C), 174.457 (12-C), 196.915 (3-C).

X-ray crystallography

Crystals were obtained as thick needles by evaporation from acetone and from a mixture of isopropanol/

ethanol for compounds **1** and the hydrochloride of **2** respectively. A precession camera was used to determine the space group and cell parameters in both cases. The refined cell parameters were obtained by measurement of the angular parameters of 12 high angle reflections ($40^\circ < 2\theta < 60^\circ$) on a diffractometer and application of the least-squares method.

Crystals of dimensions $0.4 \times 0.5 \times 0.6$ mm and $0.5 \times 0.5 \times 0.6$ mm were chosen for data collection and determination of the cell parameters for compounds **1** and **2** respectively. Throughout the experiments a Picker Facs-1 four-circle automatic diffractometer was used. CuK_α radiation and θ - 2θ scan mode with scan speed of 1 deg/min for compound **1** and 2 deg/min for compound **2** were utilized. Three standard reflections monitored every 100 reflections showed only random variations within 6% and 5% for compounds **1** and **2**, respectively. For compound **1**, 1685 unique reflections were recorded ($3^\circ < 2\theta < 130^\circ$) of which 1261 were considered observed using $I_0 > 3\sigma(I_0)$ discrimination, whereas for compound **2**, 2448 unique reflections were recorded ($3^\circ < 2\theta < 130^\circ$) of which 2138 were considered observed using the same criterion. The intensities were corrected for Lorentz and polarization factors. No absorption corrections were performed.

The molecular structure was determined by direct methods using the SHELXS-86 program (Sheldrick, 1985) in both cases. The E-map with the best figure of merit revealed the whole structure. Subsequent least-squares refinement and difference maps revealed hydrogen atoms at C5, C6, C7, and C13 in compound **1**, and all the hydrogens except those at C5, C8, and C10 in compound **2**; the remaining hydrogen positions were calculated to fit the geometry.

The positional parameters of all the atoms, including hydrogens, were refined and anisotropic temperature factors for atoms other than hydrogen were used and allowed to vary. The isotropic temperature factors for hydrogen atoms were kept constant at $U = 0.07 \text{ \AA}^2$. The final *R* factor converged at 6.8% for compound **1**

Table 1. Crystal data.

	1	2
Space group	$P2_1/c$	$P2_1/c$
<i>a</i>	8.799(7) Å	15.343(9) Å
<i>b</i>	7.137(6) Å	7.490(6) Å
<i>c</i>	16.156(8) Å	13.465(8) Å
β	76.28(5)°	110.98(3)°
<i>V</i>	986 Å ³	1445 Å ³
<i>Z</i>	4	4

and 4.7% for compound **2** (unit weights were used). The program SHELX-76 (Sheldrick, 1976) and a Cray computer were used for all least-squares refinement calculations. Final difference electron density calculations revealed no significant residual density.

Results and discussion

Positional and isotropic thermal parameters of non-hydrogen atoms are listed in Tables 2(a) and 2(b), and bond lengths and angles and selected torsion angles in Tables 3(a) and 3(b) for compounds **1** and **2**, respectively.

A perspective view of molecules **1** and **2** showing the atomic numbering scheme used is given in Figs. 1(a) and 1(b).

In both compounds **1** and **2** the *cis* configuration between the A and B rings is observed. However, the angle between the best planes passing through the A and B rings is slightly different: in compound **1** this angle is 40° , whereas in compound **2** it is approximately 47.5° . Apparently, a similar situation pertains in solution as well. Thus, the downfield small NMR-shifts of the H_{ax} (1) and C(1) in the Mannich base **2** relative to the ketone **1** might be attributed to a weak deshielding which is caused by the change of the angle between the planes of the A and B rings, owing to the introduction of the bulky dimethylaminomethyl group.

Interestingly, the substitution at C(2) in **2** is accompanied by conformational differences in the A and B

Table 2(a). Fractional atom coordinates ($\times 10^4$) for non-H-atoms and equivalent isotropic temperature factors ($A^2 \times 10^4$) with esd's in parentheses of compound **1**

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U_{eq}^a
C1	2214(6)	6905(10)	3271(3)	489(45)
C2	3016(6)	7983(8)	2454(3)	381(39)
C3	4763(6)	7620(8)	2161(3)	392(40)
C4	5436(6)	7376(8)	1230(3)	349(37)
C5	7028(6)	7005(8)	939(3)	418(42)
C6	7682(7)	6811(10)	82(3)	489(45)
C7	6751(7)	7013(10)	-494(3)	487(47)
C8	5178(6)	7379(10)	-218(3)	433(43)
C9	4490(6)	7547(7)	644(3)	348(37)
C10	2755(6)	7893(10)	942(3)	438(43)
N11	2205(5)	7315(6)	1820(3)	373(32)
C12	952(6)	6215(8)	2120(3)	427(43)
C13	813(7)	5945(12)	3064(5)	548(52)
O14	93(5)	5584(6)	1701(3)	581(37)
O15	5569(5)	7602(8)	2671(3)	631(37)

$$^a U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j \text{ (Hamilton, 1959).}$$

Table 2(b). Fractional atom coordinates ($\times 10^4$) for non-H-atoms and equivalent isotropic temperature factors ($A^2 \times 10^4$) with esd's in parentheses of compound **2**

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U_{eq}^a
C1	7555(3)	7050(5)	5024(3)	411(20)
C2	7366(1)	5019(3)	4925(1)	294(16)
C3	8144(1)	4140(5)	4636(3)	343(17)
C4	8841(1)	3037(5)	5450(3)	337(17)
C5	9692(1)	2657(6)	5328(3)	475(21)
C6	10341(3)	1601(6)	6061(3)	618(26)
C7	10137(3)	869(6)	6891(3)	618(26)
C8	9297(3)	1212(5)	7020(3)	452(20)
C9	8647(1)	2338(3)	6309(1)	322(16)
C10	7749(1)	2825(5)	6473(3)	325(17)
N11	7419(1)	4541(3)	6000(1)	304(14)
C12	7325(1)	5979(5)	6574(3)	378(19)
C13	7188(3)	7623(5)	5892(3)	451(21)
O14	7357(1)	5896(3)	7497(1)	501(15)
O15	8180(1)	4420(3)	3761(1)	505(15)
C16	6391(1)	4724(5)	4072(3)	337(17)
N17	5940(1)	2989(3)	4120(1)	314(14)
C18	6399(3)	1401(5)	3862(3)	401(19)
C19	4925(1)	3030(6)	3406(3)	427(20)
CL20	5446(1)	2023(1)	6036(1)	435(4)

$$^a U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j \text{ (Hamilton, 1959).}$$

rings in the two molecules. The central 6-membered heterocycle in **1** has a half-chair conformation with N(11) situated 0.54 \AA out of the plane of the other five atoms, while the same ring in **2** has a slightly twisted boat conformation, with N(11) and C(4) lying 0.41 and 0.13 \AA from the plane of the other four ring atoms. The five-membered ring in molecule **1** is planar, whereas in **2** it adopts an envelope conformation with C(1) positioned 0.48 \AA off the plane described by the other four atoms.

The two types of N—C bonds about each N(11) atom in compounds **1** and **2** (e.g., two with distances of approximately 1.45 \AA and one of approximately 1.35 \AA) are typical for N-substituted five-membered lactams (Emge et al., 1990), reflecting the two resonance forms of the C(12)(sp^2)—N(11)(sp^2) bond as described by Birnbaum (1970).

The conformation of the dimethylaminomethyl group in compound **2** is described by the torsion angles C(1)—C(2)—C(16)—N(17) and C(2)—C(16)—N(17)—C(19) of -159.1° and 168.1° , respectively, which indicate that this group adopts an extended conformation.

The packing in both crystal structures is determined by Van der Waals interactions between the molecules. For compound **2**, N—H \cdots Cl hydrogen bonds (N—Cl = 3.028 \AA) contribute to the stabilization of

Table 3(a). Bond lengths (Å), bond angles (°) and selected dihedral angles (°) of compound 1: Estimated standard deviations are given in parentheses

C1–C2 = 1.546(7)	O15–C3–C4 = 122.0(4)
C1–C13 = 1.516(8)	C5–C4–C3 = 119.5(4)
C2–C3 = 1.520(6)	C9–C4–C3 = 120.8(4)
C2–N11 = 1.460(6)	C9–C4–C5 = 119.7(4)
C3–C4 = 1.488(6)	C6–C5–C4 = 120.5(5)
C3–O15 = 1.210(5)	C7–C6–C5 = 119.6(5)
C4–C5 = 1.394(6)	C8–C7–C6 = 120.6(5)
C4–C9 = 1.407(6)	C9–C8–C7 = 120.7(5)
C5–C6 = 1.374(7)	C8–C9–C4 = 118.8(4)
C6–C7 = 1.389(8)	C10–C9–C4 = 121.0(4)
C7–C8 = 1.374(7)	C10–C9–C8 = 120.2(4)
C8–C9 = 1.386(7)	N11–C10–C9 = 110.1(4)
C9–C10 = 1.508(6)	C10–N11–C2 = 119.4(4)
C10–N11 = 1.447(6)	C12–N11–C2 = 115.5(4)
N11–C12 = 1.347(6)	C12–N11–C10 = 125.1(4)
C12–C13 = 1.511(8)	C13–C12–N11 = 107.6(4)
C12–O14 = 1.215(6)	O14–C12–N11 = 125.4(5)
	O14–C12–C13 = 127.1(5)
C13–C1–C2 = 105.5(4)	C12–C13–C1 = 106.8(4)
C3–C2–C1 = 113.9(4)	C1–C2–C3–C4 = 138.5(6)
N11–C2–C1 = 103.7(4)	C9–C10–N11–C12 = –130.8(6)
N11–C2–C3 = 110.5(4)	C10–N11–C12–O14 = –1.4(9)
C4–C3–C2 = 117.9(4)	C10–N11–C12–C13 = 179.3(5)
O15–C3–C2 = 120.1(4)	C2–N11–C12–O14 = 177.0(7)

Table 3(b). Bond lengths (Å), bond angles (°) and selected dihedral angles (°) of compound 2: Estimated standard deviations are given in parentheses

C1–C2 = 1.545(5)	O15–C3–C4 = 122.7(3)
C1–C13 = 1.529(5)	C5–C4–C3 = 118.9(3)
C2–C3 = 1.528(4)	C9–C4–C3 = 120.8(3)
C2–N11 = 1.466(4)	C9–C4–C5 = 120.2(3)
C2–C16 = 1.542(4)	C6–C5–C4 = 120.0(4)
C3–C4 = 1.478(4)	C7–C6–C5 = 119.6(4)
C3–O15 = 1.220(4)	C8–C7–C6 = 121.3(4)
C4–C5 = 1.403(4)	C9–C8–C7 = 119.7(4)
C4–C9 = 1.395(4)	C8–C9–C4 = 119.1(3)
C5–C6 = 1.374(5)	C10–C9–C4 = 120.2(3)
C6–C7 = 1.379(6)	C10–C9–C8 = 120.7(3)
C7–C8 = 1.385(5)	N11–C10–C9 = 110.2(3)
C8–C9 = 1.390(5)	C10–N11–C2 = 122.7(3)
C9–C10 = 1.515(4)	C12–N11–C2 = 112.8(3)
C10–N11 = 1.443(4)	C12–N11–C10 = 123.1(3)
N11–C12 = 1.363(4)	C13–C12–N11 = 108.8(3)
C12–C13 = 1.505(5)	O14–C12–N11 = 124.0(3)
C12–O14 = 1.228(4)	O14–C12–C13 = 127.2(3)
C16–N17 = 1.482(4)	C12–C13–C1 = 103.1(3)
N17–C18 = 1.486(4)	N17–C16–C2 = 116.0(3)
N17–C19 = 1.510(4)	C18–N17–C16 = 115.2(3)
	C19–N17–C16 = 110.2(3)
C13–C1–C2 = 103.6(3)	C19–N17–C18 = 109.6(3)
C3–C2–C1 = 107.9(3)	
N11–C2–C1 = 102.2(3)	C1–C2–C3–C4 = 109.3(6)
N11–C2–C3 = 111.9(3)	C9–C10–N11–C12 = –118.2(6)
C16–C2–C1 = 107.9(3)	C10–N11–C12–O14 = –12.7(7)
C16–C2–C3 = 112.9(3)	C10–N11–C12–C13 = 166.8(6)
C16–C2–N11 = 113.2(3)	C2–N11–C12–O14 = –179.2(7)
C4–C3–C2 = 118.4(3)	C1–C2–C16–N17 = –159.1(8)
O15–C3–C2 = 118.8(3)	C2–C16–N17–C19 = 168.1(8)

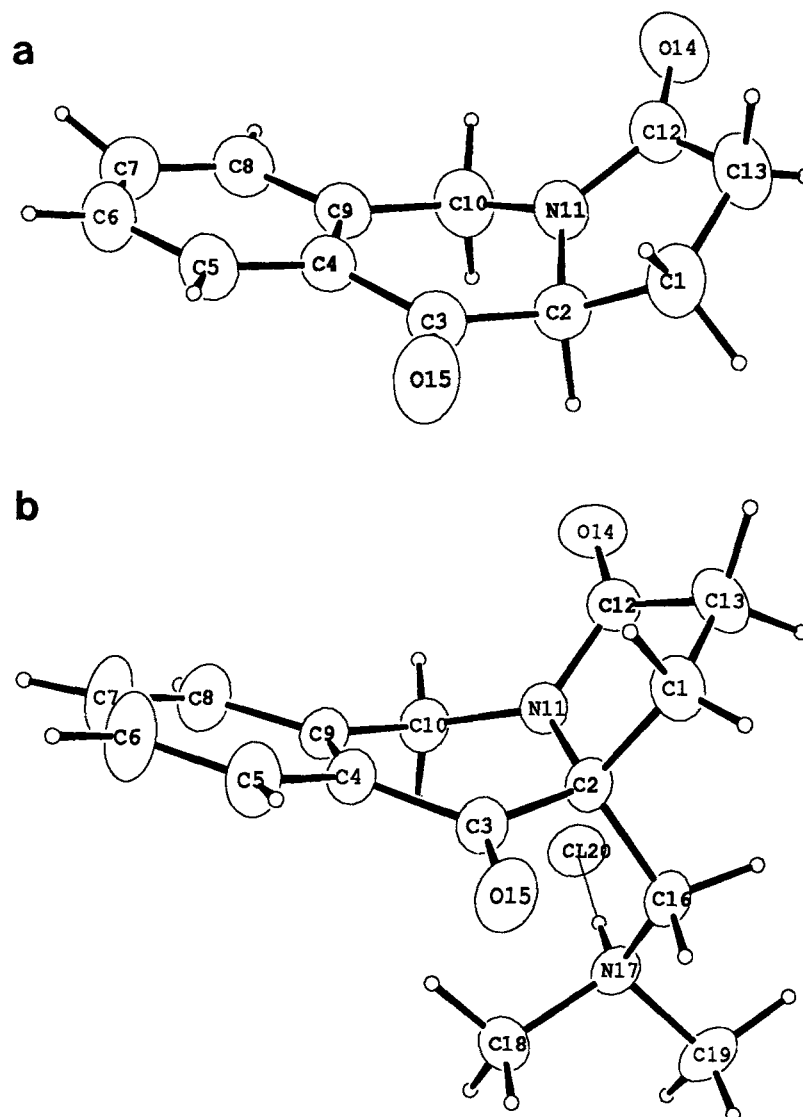


Fig. 1. Perspective view of compound 1(a) and compound 2(b) showing the atomic numbering scheme.

the structure. It is noteworthy that in both crystal structures all the polar atoms (and some carbon atoms) lie in sheets, separated by thicker sheets of only hydrophobic parts of molecules. Packing diagrams of both structures have been deposited as supplementary data.

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 Structure factor data, tables of anisotropic thermal parameters and hydrogen atom positions, and figures illustrating the crystal packing arrangements have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 67118 (19 pages).