PREPARATION OF CYCLOALKANO[*c*]PYRIDAZINONES AND CYCLOALKANE-CONDENSED PYRROLO[1,2-*a*]IMIDAZOLONE, -PYRIMIDINONE AND -[1,3]DIAZEPINONE STEREOISOMERS◊

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Abstract – From the 2-ethoxycarbonylmethyl-1-cycloalkanones (**1a-c**) with hydrazine, the cyclopenta- (**2a**), cyclohexa- (**2b**) and cyclohepta[*c*]pyridazinones (**2c**) were prepared. **2a-c** were transformed to the corresponding dehydro derivatives (**3a-c**) by means of a recently-developed smooth oxidation method with $CuCl_2$ in acetonitrile. Compounds (**1**) reacted with α,ω-alkylenediamines to furnish saturated cycloalkano[*b*]pyrrolo[1,2-*a*]diazinones (**4a-f**). The structures of **4a-f** were determined by ^{1}H- and ^{13}C-NMR methods, including DNOE, DEPT and 2D-HSC measurements, and for **4a** also by X-ray analysis. The rings of the 2-perhydroindolone and its homologues are *cis*-fused, while the NH group of the heterocycle containing two N atoms and the annelational hydrogen are *cis* in all compounds prepared.

In earlier experiments, we often used 2-aroyl-1-cyclohexanecarboxylic acids and the analogous norbornanecarboxylic acids for the preparation of saturated condensed-skeleton tetracyclic or pentacyclic compounds containing two heterorings and one or two cycloalkane or bicycloalkane rings at the terminal(s) and isoindolone as central structural moiety.[1-3] The aim of those investigations was the synthesis of new pharmacologically active derivatives, as some of the aromatic analogues have an anorexic effect[4] or exhibit anti-HIV-1 activity.[5] The reactions of the above saturated γ-oxocarboxylic acids with bifunctional reagents such as 1,3-amino alcohols, α,ω-diamines, *etc.* yielded isomeric compounds with different, fairly complex stereostructures.
Other cycloalkanecarboxylic esters were also used for the preparation of bicyclic lactams,[6] bicycloalkane-condensed thiophenes,[7] pyrones,[8] dibenzo[*b,f*]thiepines,[9] tricyclic pyrrolidines,[10] *etc.*

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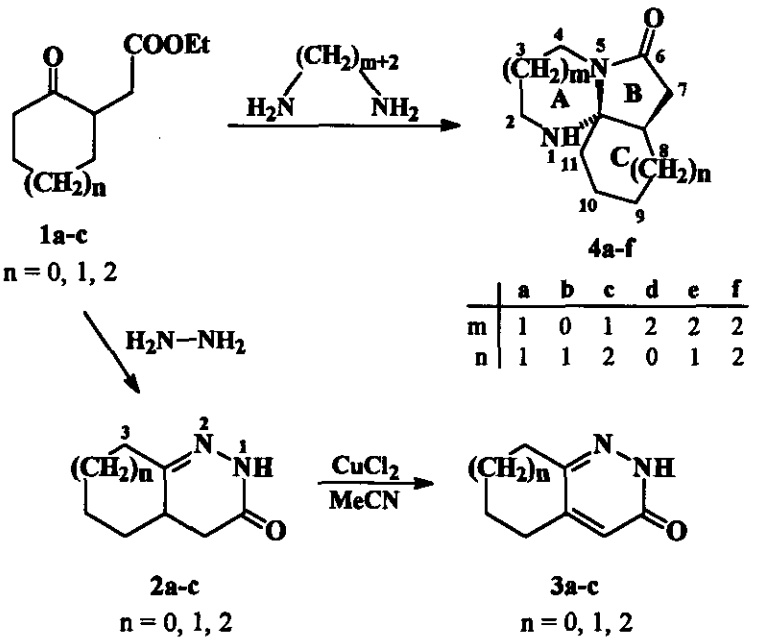
In the present paper, we extend the application of the above reactions to 2-ethoxycarbonylmethyl-cycloalkanones (**1**). While the reactions of the earlier-applied γ-oxocarboxylic acids, such as 2-aroyl-1-cyclohexanecarboxylic acid, led to isoindolones, **1** yields the pyridazinones (**2**) and saturated 2-indolone homologues of type (**4**), containing a fused saturated imidazo, pyrimido or diazepino moiety.

RESULTS

Compounds (**1**), prepared by standard methods,[11] reacted with hydrazine to yield the cyclopentano- (**2a**), cyclohexano- (**2b**) and cycloheptano[*b*]pyridazinones (**2c**) (Scheme). On dehydrogenation, **2a-c** gave the new pyridazinones (**3a-c**). The dehydrogenation was performed with $CuCl_2$, by means of a recently-developed method[12] optimized for *cis*- and *trans*-hexahydrophthalazin-8(1*H*)-ones.



Scheme

In the present case, anhydrous $CuCl_2$ in acetonitrile proved to be the most suitable agent for dehydrogenation; after boiling for 1 h, the dehydrogenated products (**3a-c**) were obtained in good yields (87-90%). It is advantageous that no side-reactions were observed on the application of $CuCl_2$, whereas they frequently occurred in earlier methods (*e.g.* Br_2/AcOH).[13] A 2:1 molar ratio of $CuCl_2$ – **2a-c** was found to be most appropriate. As a possible mechanism, halogen substitution on the annelational carbon and subsequent spontaneous dehydrohalogenation may be postulated.[12]

In the reactions of **1** and α,ω-diaminoalkanes during refluxing in toluene with a catalytic amount of *p*-TsOH, the tricyclic lactams (**4a-f**) were formed stereoselectively in moderate yields (29-65%).

SPECTROSCOPIC INVESTIGATIONS

The ^{13}C-NMR lines and most characteristic IR frequencies of **2-4** are listed in Table 1. The ^{1}H-NMR data are mostly not characteristic, but support the structures in every case. The olefinic signal (*s*, 1H) of **3a-c** appears at 6.74 (**3a**) or 6.68 ppm (**3b,c**). For **2a-c**, the NH signal at 9.10 (**2a,b**) or 9.40 ppm (**2c**) is sharp, while in the other cases it is broadened; for **3a-c**, it is shifted significantly downfield (at 11.85, 12.70 and 12.10 ppm), and for **4a-f** it occurs at about 1.55 ppm. Two parts can be distinguished in the mostly characterless overlapping multiplets of the CH_2 and CH groups: the signals of the C–CH_2–C hydrogens appear in the interval 1.10–1.90 ppm, while the others are shifted downfield and only those in the vicinity of the nitrogen in **4a-f** are separated. For **4a-c**, the merged signals of the CH_2 group vicinal to the NH group appear at about 2.95 (**4a,c**) or 3.30 ppm (**4b**), and in the cases of **4a** and **4c** they also overlap with the signal of one of the hydrogens of the CH_2 next to the amide group. For **4a** and **4c**, the other hydrogen of the latter CH_2 group gives the separated signal at 4.00 (*qad*) and 4.12 (*ddd*) ppm, respectively. The high shift is a consequence of the anisotropic effect of the coplanar C=O group.[14a] In the spectrum of **4b**, the two corresponding multiplets are situated at 3.00 and 3.60 ppm.

Table 1. Characteristic IR frequencies (cm^{-1}, KBr) and ^{13}C-NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds **2a-c**, **3a-c** and **4a-f** in $CDCl_3$ solution at 63 MHz[a]

	νNH[b]	νC=O	CH_2[c]		$NHCH_2$	NCH_2[d]	CH(CO)[e]	CH[f]	C=N[g]	C=O
2a	~3215	1675	29.6	31.6	–	–	32.4	36.9	165.6	167.6
2b	3218	1674	33.3[h]	34.0[h]	–	–	32.6[h]	34.0	155.2	166.5
2c	3205	1673	30.2	32.9	–	–	35.3	35.8	160.6	168.4
3a	3400-2700	1655	30.0	30.3	–	–	123.0	150.5	154.5	162.1
3b	3300-2200	1658	28.3	28.5	–	–	126.8[i]	145.1[h,i]	146.3[h]	162.6
3c	3250-2500	1659	31.4	35.2	–	–	?[k]	?[k]	151.4	162.5
4a	3287	1657	25.5	27.8	38.8	35.3	33.9	42.0	73.0	170.6
4b	3415, 3240	1679	25.0	33.1	47.5	41.6	39.2	43.3	84.0	174.1
4c	3310	1663	30.7	32.0	38.9	35.3	36.8	46.2	78.7	170.7
4d	3320	1670	32.6	38.9	42.6	39.6	37.5	41.9	89.3	173.2
4e	3502, 3308	1664	33.2	35.4	41.2	37.7	34.1	36.8	77.7	173.0
4f	3340	1658	33.0	35.1	41.2	38.5	36.4	41.3	83.2	172.8

[a]Assignments were supported by DEPT (except for **3a-c** and **4a**) and 2D-HSC measurements for **4a-e**. Further signals: IR, νC=N: 1650 (**2a**), 1625 (**2b**), ~1600 (shoulder, **2c**), 1615 (**3a**), 1596 (**3b,c**); ^{13}C-NMR, CH_2 lines of CCH_2C-type: 23.6 (**2a**), 24.1 and 25.2 (**2b**), 25.9, 27.9 and 29.0 (**2c**), 23.8 (**3a**), 21.5 and 22.1 (**3b**), 19.5, 27.1 and 28.0 (**3c**), 20.4, 20.6 and 23.9 (**4a**), 20.1 and 21.4 (**4b**), 22.2, 25.0, 25.6 and 28.1 (**4c**), 23.1, 25.6 and 32.2 (**4d**), 20.1, 21.1, 23.0 and 28.1 (**4e**), 22.4, 23.6, 26.5, 28.3 and 30.9 (**4f**); [b]Broad band; [c]Methylene groups vicinal to annelated carbons in the alicycle; [d]Vicinal to the amide N; [e]C(sp^2)HCO for **3a-c**; [f]Quaternary C(sp^2) atom for **3a-c**; [g]NCN-type quaternary carbon for **4a-f**; [h]Interchangeable assignments; [i]Broadened lines; [k]Not precisely identified, very broad signal.

In the spectra of the analogues **4d-f**, the two pairs of hydrogens of the CH_2 in the vicinity of the two nitrogens give separate signals. For **4e**, these upfield multiplets appear overlapped with each

other at 2.66 ppm, and for **4d,f**, they occur in overlap with other CH_2 signals (2.40 and 2.70 for **4d** and 2.20-2.60 ppm for **4f**). The downfield signal of the $CONCH_2$ group exhibits a doublet at 3.95 ppm ($J \approx 13.5$ Hz), while that of the CH_2 hydrogens vicinal to the NH group is *td* at 2.95 ppm ($J \approx 15$, 3 and 3 Hz). For **4b**, the doublet doublets of the $COCH_2$ group at 2.35 ppm ($J = 15.6$ and 7.7 Hz) and 2.75 ppm ($J = 15.6$ and 12.5 Hz) are also separated.

For **4b-e**, an attempt was made to establish the configuration of the annelated carbons by DNOE measurements, but owing to signal overlaps, this was not successful. However, the data from the 2D-HSC and DNOE measurements permitted the firm assignment of the ^{1}H- and ^{13}C-NMR signals.

X-RAY DETERMINATION OF **4a**

Since the ^{1}H- and ^{13}C-NMR spectra did not provide sufficient information on the structure, for **4a** it was established by X-ray crystallography. A perspective view of the molecule (Figure) shows that in this compound the saturated 2-indolone rings are *cis*-annelated, and the NH group in the heteroring with two N atoms is *cis* to the methine hydrogen. Rings *A* and *C* are in chair forms and the lactam ring is restrained into an envelope conformation (with C7a out of the plane of the other four atoms).

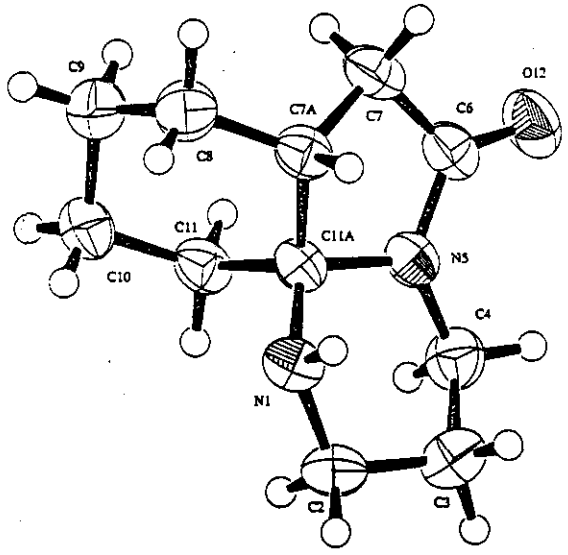


Figure. The molecular structure of **4a**, determined by X-ray crystallography

Bond lengths and angles are in the expected ranges. In ring *A*, some distorsion from ideal chair geometry is observed in the C11a–N5–C4 bond angle [119.2(2)°], due to the planarity of the amide nitrogen bond. The hydrogen atom on N1 forms a strong peak in difference Fourier calculations and it participates in a weak intermolecular hydrogen-bond with O12, thereby forming endless chains of hydrogen-bonded molecules along axis *b* of the unit cell. The position of the hydrogen atom reinforces the tetrahedral geometry around N1.

EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer equipped with an Aspect 2000 computer at 250.13 (^{1}H) and 62.89 (^{13}C) MHz, respectively, using the deuterium signal of the solvent as the

lock and TMS as internal standard. Conventional CW irradiation of ~0.15 W was used in the DR experiments. DEPT spectra[15] were run in a standard way,[16] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. For DNOE measurements,[14b,17] the standard Bruker microprogram "DNOEMULT.AU" to generate NOE was used. The 2D-HSC spectra[18] were obtained by using the standard Bruker pulse program "XHCORRD.AU".

Crystal data on **4a** ($C_{11}H_{18}N_2O$, $M_r = 194.27$). Unit cell parameters: $a = 12.047(2)$ Å, $b = 5.790(1)$ Å, $c = 15.148(4)$ Å. $Z = 4$, space group $Pna2_1$, $d_x = 1.204$ g.cm^{-3}, $\mu = 0.625$ cm^{-1}, $T = 296$ (2) K.

Data collection, analysis and refinement. A total of 1121 reflections were measured to $2\theta_{max} = 75.14°$. X-ray crystallographic data collection was carried out at room temperature on a Rigaku AFC6S diffractometer with graphite monochromated CuK_α ($\lambda = 1.5418$ Å) radiation. The intensity data were collected in an ω-2θ scan mode at an ω scan speed of 8.0°/min width an ω scan width of $1.63 + 0.30 \tan\theta$. All data were corrected for Lorentz polarization effects and for secondary extinction [coefficient = 0.0100(13)]. The intensities of three check reflections showed only statistical fluctuations. The structures were solved by using SHELXS-86,[19] while refinement was carried out with SHELXL-93.[20] Calculations and graphical display were carried out in the user environment provided by the TEXSAN package.[21] Heavy atoms and hydrogens were refined with anisotropic and isotropic thermal motion parameters, respectively. The positions of all hydrogens apart from that bonded to N1 (which was taken from difference Fourier calculations) were generated on the basis of geometric evidence. Atomic coordinates are listed in Table 2, and bond lengths and angles in Table 3.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **4a**

	x	y	z	U(eq)*
N(1)	3331(2)	1829(4)	990(2)	43(1)
C(2)	2567(3)	2318(5)	254(3)	49(1)
C(3)	3076(3)	3880(6)	-447(3)	56(1)
C(4)	3471(3)	6108(6)	-27(3)	52(1)
N(5)	4188(2)	5554(4)	703(2)	42(1)
C(6)	5113(2)	6713(5)	939(3)	45(1)
C(7)	5545(2)	5638(6)	1779(3)	50(1)
C(7A)	4897(2)	3382(5)	1874(3)	42(1)
C(8)	4740(3)	2439(7)	2803(3)	57(1)
C(9)	3920(3)	3795(7)	3352(3)	63(1)
C(10)	2812(3)	3922(6)	2869(3)	56(1)
C(11)	2949(2)	5108(5)	1979(3)	45(1)
C(11A)	3799(2)	3901(4)	1384(3)	38(1)
O(12)	5508(2)	8362(4)	539	61(1)

*U(eq) is defined as one-third of the trace of the orthogonalized Uij tensor.

Refinement was performed on F^2, with all reflections included apart from 2 very negative ones. 971 reflections having $I > 2\sigma(I)$ were used in calculating $R1 = 0.035$ [$wR2 = 0.1379$ for all reflections, $w = 1/\sigma^2(F_o^2) + (0.0686P)^2 + 0.2978P$, where $P = (F_o^2 + 2F_c^2)/3$) G00F(all refl.) = 0.967].

Table 3. Bond lengths (Å) and angles (°) for **4a**

N(1)–C(11A)	1.454(3)	C(6)–N(5)–C(4)	126.1(3)
N(1)–C(2)	1.473(4)	C(6)–N(5)–C(11A)	113.4(2)
C(2)–C(3)	1.523(5)	C(4)–N(5)–C(11A)	119.2(2)
C(3)–C(4)	1.515(5)	O(12)–C(6)–N(5)	125.2(3)
C(4)–N(5)	1.440(4)	O(12)–C(6)–C(7)	127.2(3)
N(5)–C(6)	1.349(3)	N(5)–C(6)–C(7)	107.6(2)
N(5)–C(11A)	1.483(4)	C(6)–C(7)–C(7A)	104.8(2)
C(6)–O(12)	1.226(4)	C(8)–C(7A)–C(7)	117.2(3)
C(6)–C(7)	1.509(5)	C(8)–C(7A)–C(11A)	114.0(2)
C(7)–C(7A)	1.528(4)	C(7)–C(7A)–C(11A)	103.0(2)
C(7A)–C(8)	1.521(4)	C(9)–C(8)–C(7A)	113.8(3)
C(7A)–C(11A)	1.546(4)	C(8)–C(9)–C(10)	109.5(3)
C(8)–C(9)	1.512(5)	C(11)–C(10)–C(9)	110.6(3)
C(9)–C(10)	1.524(5)	C(10)–C(11)–C(11A)	112.8(2)
C(10)–C(11)	1.521(4)	N(1)–C(11A)–N(5)	111.7(2)
C(11)–C(11A)	1.534(4)	N(1)–C(11A)–C(11)	111.0(2)
C(11A)–N(1)–C(2)	113.2(2)	N(5)–C(11A)–C(11)	109.0(2)
N(1)–C(2)–C(3)	113.0(2)	N(1)–C(11A)–C(7A)	111.6(2)
C(4)–C(3)–C(2)	109.9(3)	N(5)–C(11A)–C(7A)	100.9(2)
N(5)–C(4)–C(3)	108.7(2)	C(11)–C(11A)–C(7A)	112.2(2)

Preparation of dihydrocyclopentano-, -cyclohexano- and -cycloheptano[*c*]pyridazinones (2a-c). General procedure

A mixture of oxo ester (**1a-c**)(1.70 g **1a**, or 1.84 g **1b** or 1.98 g **1c**, 10 mmol) with hydrazine hydrate (0.55 g, 11 mmol) in ethanol (20 mL) was refluxed for 1 h. After evaporation, the residue was crystallized. Data on compounds (**2-4**) are listed in Table 4.

Dehydrogenation of 2a-c to 3a-c

A mixture of the cycloalkane-condensed dihydropyridazinone (**2a-c**) (5 mmol) and anhydrous $CuCl_2$ (1.34 g, 10 mmol) was refluxed in abs. acetonitrile (20 mL) for 1 h. The crystals that separated out on cooling were filtered off by suction and recrystallized.

Preparation of 1,2,3,4,6,7-hexahydrocyclohexa[*b*]pyrrolo[1,2-*a*]pyrimidin-6-one (4a), 2,3,5,6-tetrahydrocyclohexa[*b*]pyrrolo[1,2-*a*]imidazol-5-one (4b), 1,2,3,4,6,7-hexahydrocyclohepta[*b*]pyrrolo[1,2-*a*]pyrimidin-6-one (4c), 5*H*-1,2,3,4,7,8-hexahydrocyclopenta[*b*]pyrrolo[1,2-*a*][1,3]diazepin-7-one (4d), 5*H*-1,2,3,4,7,8-hexahydrocyclohexa[*b*]pyrrolo[1,2-*a*][1,3]diazepin-7-one (4e) and 5*H*-1,2,3,4,6,7-hexahydrocyclohepta[*b*]pyrrolo[1,2-*a*][1,3]diazepin-7-one (4f)

A mixture of the oxo ester (1a-c) (1.70 g **1a**, or 1.84 g **1b** or 1.98 g **1c**) and α,ω-diamine (0.9 g ethylenediamine, or 1.10 g 1,3-diaminopropane, or 1.32 g 1,4-diaminobutane, 10 mmol) in dry toluene (40 mL) was refluxed with a catalytic amount of *p*-TsOH (0.05 g) for 3-4 h, a Dean-Stark water separator being applied. After evaporation, the residue was transferred to a silica gel column (Acros, 0.0355-0.07 mm) and eluted with EtOAc. After evaporation of the solvent, the residue was crystallized.

Table 4. Physical and analytical data on compounds (**2-4**)

	mp °C	Yield %	Formula	Analysis Found %			Calcd %		
				C	H	N	C	H	N
2a	144-146[a]	62.3	$C_7H_{10}N_2O$	60.98	7.31	20.40	60.85	7.29	20.27
2b	111-113[b]	71.7	$C_8H_{12}N_2O$	63.00	7.97	18.43	63.13	7.94	18.40
2c	111-113[c]	76.0	$C_9H_{14}N_2O$	65.11	8.51	16.66	65.03	8.49	16.85
3a	225-227[b]	86.7	$C_7H_8N_2O$	61.90	6.14	20.71	61.75	5.92	20.57
3b	194-196[b]	86.6	$C_8H_{10}N_2O$	63.76	6.91	18.80	63.98	6.71	18.65
3c	203-205[b]	90.2	$C_9H_{12}N_2O$	65.58	7.51	17.12	65.83	7.36	17.06
4a	114-116[d]	79.9	$C_{11}H_{18}N_2O$	68.11	9.41	14.32	68.00	9.34	14.42
4b	68-70[c]	52.5	$C_{10}H_{16}N_2O$	66.48	9.01	15.73	66.63	8.95	15.54
4c	97-99[a]	28.8	$C_{12}H_{20}N_2O$	69.25	9.78	13.57	69.19	9.67	13.45
4d	67-69[a]	41.2	$C_{11}H_{18}N_2O$	68.19	9.21	14.30	68.00	9.34	14.42
4e	123-124[e]	64.9	$C_{12}H_{20}N_2O$	69.30	9.45	13.54	69.19	9.67	13.45
4f	135-137[a]	31.5	$C_{13}H_{22}N_2O$	70.10	10.14	12.58	70.23	9.97	12.60

Crystallization solvent: [a]EtOAc; [b]EtOH; [c]Benzene;

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