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SYNTHESIS AND ISOMERIZATION OF THE 3,4,12,12a-TETRAHYDRO-2,6H- -[1,3]OXAZINO[2,3-b][1,3,4]BENZOTRIAZEPIN-7-ONE RING SYSTEM

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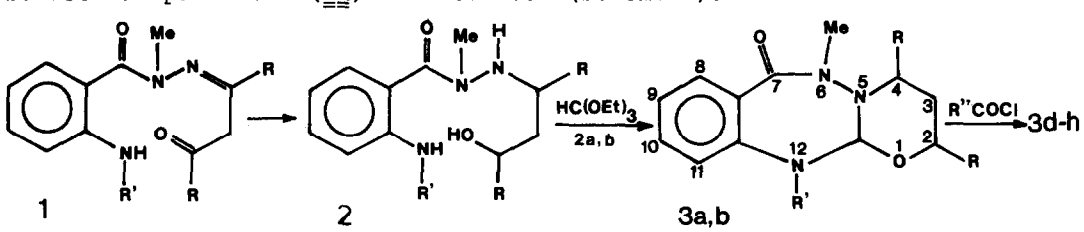
ABSTRACT – The first representative (3a) of the 3,4,12,12a-tetrahydro-2,6H- -[1,3]oxazino[2,3-b][1,3,4]benzotriazepin-7-one ring system was synthesized. Treatment of 3a with NaH evoked a cis-trans isomerization at the annelation of the hetero rings leading to the cis annelated isomer 4a. The structure and conformation of the isomers were elucidated by nmr and X-ray studies. The formation of the more crowded cis isomer may be explained by stronger conjugation due to the conformational change of the triazepinone ring. Acetylation of the isomers yielded N-acetyl derivatives with unaltered annelation while the alkylation of the trans isomer resulted in cis annelated N-alkyl products.

2-Aminobenzoic acid N-methyl-N'-(3-hydroxypropyl)-hydrazide derivatives 2a-c were prepared in the course of a study on ring-chain tautomerism[1] and reduction[2] of 1 hydrazones. In the case of 2a the diastereomers (a crystalline and an oily product) were separated. On reacting the crystalline diastereomer of 2a with triethyl orthoformate the formation of a novel tricyclic heterocycle the 2,4,6-trimethyl-3,4,12,12a-tetrahydro-2,6H-[1,3]-oxazino[2,3-b][1,3,4]- -benzotriazepin-7-one (3a) was observed (Scheme 1).

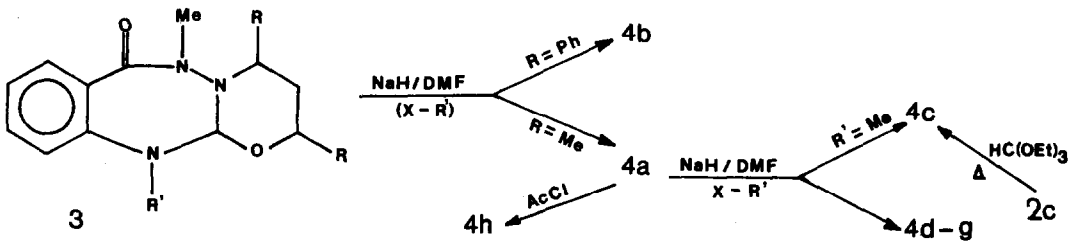


a(R: Me, R': H), b(R: Ph, R': H), c(R=R': Me), d(R: Ph, R': Ac), e(R: Me, R': CO-CH_2-Ph), f(R: Me, R': CO-CH_2-C_6H_4-pOMe), g(R: Me, R': CO-CH=CH-Ph), h(R: Me, R': Ac)

Scheme 1

The reaction of compound 2b (diastereomers not separated) with $HC(OEt)_3$ afforded a complex reaction mixture from which the stereohomogeneous 3b crystallized spontaneously. Acylation of compounds 3a,b with various acid chlorides gave the acyl derivatives 3d-h.

The treatment of 3a or 3b in DMF with alkylating agents in the presence of NaH gave 4a,b (Scheme 2). The elemental analysis of the products (4a and



a(R: Me, R': H), b(R: Ph, R': H), c(R=R': Me), d(R: Me, R': CH_2-CH_2-NEt_2), e(R: Me, R': CH_2-CH_2-CH_2-NMe_2), f(R: Me, R': CH_2-Ph), g(R: Me, R': CH_2-CH_2-CH_2-morpholino), h(R: Me, R': Ac)

Scheme 2

4b, resp.) was the same as that of the starting compounds (3a and 3b, resp.), showing that no alkylation occured. The ^1H nmr spectra (Table 1) of the pairs 3a - 4a and 3b - 4b were, however, characteristically different, but they proved the presence of the same functional groups both in the starting compounds and the products. During prolonged reaction time the alkylation of 3a with various alkylating agents of type X-R' afforded N-alkyl compounds (4c-g) the nmr spectra of which were analoguous with those of 4a,b. On the other hand 4c could also be obtained by ring closure of 2c with $HC(OEt)_3$. This reaction, however, took place only on heating. Thus, the formation of 4-type compounds may be thermodynamically controlled, while 3-type derivatives could be obtained by a kinetically controlled process.

In order to establish what is the difference between the two types of structures represented by 3a-b and the acyl derivatives 3d-h, on one hand, and by 4a-b and the alkyl derivatives 4c-g, on the other, X-ray study was performed on 3a. The X-ray data (Table 4) proved the assumed structure of 3a (Fig. 1). The seven-membered hetero ring, presumably due to the presence of the planar amide group, is forced into a slightly distorted boat conformation. The lowest asymmetry factor[3] of fC_2 (C12A)=6.3 10^{-2} Å indicates a pseudo two-fold axis which bisects the bond

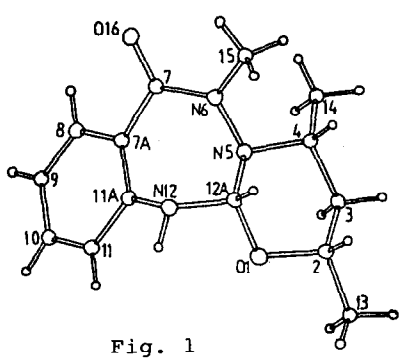
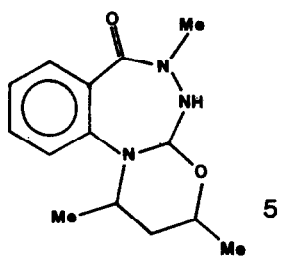


Fig. 1

C(7A)-C(7). From this it follows that the orientation of O(1) to the seven-membered ring is ambivalent, i.e. partly pseudo-axial [O(1)-C(12A)-N(12)--C(11A)=-83.3(2)°] partly equatorial [O(1)-C(12A)-N(5)-N(6)=175.1(2)°]. The oxazine ring assuming an almost perfect chair shape is bound to the seven-membered ring via a trans-junction maintained by the N(5)-C(12A) single bond [1.470(1) Å]. In this ring junction N(5) retains its pronounced pyramidality[4] of χ=0.92 rad. The methyl substituents of the oxazine ring occupy equatorial orientation. The β-axial C(15) and the α-equatorial C(14) methyl moieties make a non-bonded torsion angle of -91.5(2)° around the C(4)...N(6) axis [2.405(2) Å]. The glide plane related molecules are bound together by weak hydrogen bonds of N(12)-H(12)...O(16) of (0.5+x, 0.5-y, z-0.5)-type, N...O=3.052 Å, H...O=2.17 Å, NH...O=158.7°.

On the basis of the X-ray data on 3a the structure elucidation of 4-type compounds was effected by means of comparing the nmr spectra of the pairs 3a - 4a and their acetyl derivatives. For this reason 4h, the pair of 3h, was also synthesized from 4a (Scheme 2).

Due to the identical elemental analysis and the presence of the same functional groups in 3a and 4a the isomerization possibilities of the ring system were taken into consideration. Isomerization may proceed by ring transformation, by a change in the annelation or in the conformation of the hetero rings or in the cis/trans arrangement of the C-methyl groups via transitional opening of the oxazine ring. The latter ring opening, on the other hand, could lead to structure 5, while a ring transformation could re-



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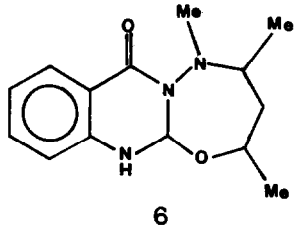

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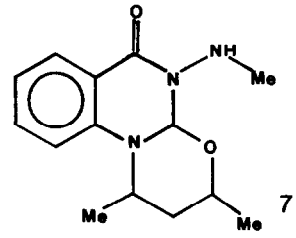

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sult in compounds 6 or 7 according to the known rearrangement of 1,3,4-benzotriazepines into quinazolines.[5]

The nmr spectra (Tables 1 and 2) of 3a, 4a and 3h, 4h afforded the following evidences for the elimination of several isomerization pathways:

1) The significant paramagnetic shift of H-9 and H-11 signals (0.35 and 0.7 ppm, resp.) in ^{1}H nmr spectra of both acetylated derivatives 3h and 4h as compared to the corresponding signals of the parent compounds proved that the acetylation occured at N-12, in consequence the structures of type 5 and 7 for 4a could be excluded.

2) The C-7 carbon signal in the proton coupled ^{13}C nmr spectra of both iso-

Table 1. ^{1}H nmr data (δ_{TMS} = 0 ppm, coupling constants in Hz) of compounds **3a,b,d-h** and **4a-h** in $CDCl_3$ solution at 90[a] or 250 MHz.

Compound	CH_3(4) 2xd[b]/2x3H	CH_3(2) t[c]/1H,	CH_2(3) d[c]/1H	CH_3[d] s/3H	H-4 m/1H	H-2 m/1H	H-12a s/1H	H-11 dd/1H	H-10 dt/1H	H-9 dt/1H	H-8 dd/1H
3a	1.02[e]	1.17[e]	1.30	1.65	3.20	3.25	3.55	5.26	6.80	7.29	7.06	7.66
3b	7.5-7.7[f]		1.78	2.05	3.13	4.45	4.67	5.63	6.92	7.5-7.7[f]		7.68
3d	6.95-7.45[f]		1.70	2.07	3.04	4.48	4.86	6.77	6.95-7.45[f]			7.75
3e	0.93	≈1.15[f]	≈1.15[f]	1.62	3.07	3.25	3.75	6.35	7.00	7.1-7.5[g]		7.72
3f	0.93	≈1.15[f]	≈1.15[f]	1.62	3.10	≈3.3[h]	≈3.7[i]	6.33	7.15	≈7.5[g]		7.72
3g	1.00	≈1.2[f]	≈1.2[f]	1.65	3.14	3.32	3.85	6.30	7.20	7.2-7.6[g]		7.75
3h	0.95[e]	1.18[e]	1.15	1.65	3.16	3.27	3.76	6.37	≈7.5[f]	7.22	≈7.5[f]	7.70
4a	1.01[e]	1.21[e]	1.43	1.60	3.29	3.12	4.14	5.87	6.67	7.26	6.80	7.86
4b	7.05-7.55[f]		1.94	2.30	2.83	4.26	5.14	6.20	6.62	7.1-7.5[f]	6.68	7.90
4c	0.98[e]	1.15[e]	1.36	1.50	3.30[e]	3.02	3.52	5.64	6.89	7.37	6.92	7.74
4d	0.97[f]	1.14	1.35	1.50	3.29	3.00	3.72	5.73	7.03	7.35	6.93	7.71
4e	0.93	1.12[f]	1.0-1.65[f,k]		3.25	2.6-3.9[l]		5.68	6.95	7.32	6.88	7.68
4f	0.97	1.18	1.32	1.50	3.25	3.00	3.70	5.63	6.85-7.35[g]			7.70
4g	0.96	1.05[f]	1.0-1.65[f,k]		3.16	2.6-3.7[l]		5,55	6.90	7.25	6.85	7.62
4h	0.96	1.16	1.30	1.45	3.31	2.50	3.80	≈6.65[j]	7.37	7.45	7.56	7.82

Further signals: N(12)H, broad s(1H): ≈4.1 (**3a**), ≈4.3 (**3b**), ≈4.7 (**4a**), ≈4.8 (**4b**); N(12)Ac/Me, s(3H): 1.82 (**3h**), 1.87 (**3d**), ≈1,95[j] (**4h**), 2.92[e] (**4c**); AB-type multiplet (2xd) of methylene or olefinic hydrogens: 3.32 and 3.38 (**3e**, ^2J: 16.6 Hz), 3.23 and 3.32[h] (**3f**, ^2J: 15.6 Hz), 6,10 and 7.80[m] (**3g**, ^3J: 15.7), 4.50 and 4.60 (**4f**, ^2J: 16.3 Hz); CH_3(ethyl, **4d**): 0.96[f] t(6H, J: 7.0 Hz); OCH_3(**3f**): 3.73[i] s(3H); CH_2(ethyl, **4d**): 2.49 qa(4H), $(Me_2)NCH_2$ (**4d**): ≈2.6 m(2H), N(12)CH_2(**4d**): ≈3.5 m(2H); Overlapping signals of hydrogens in $-CH_2N(CH_n)_2$ group: 2.12 (**4e**, n=3) s(6H)+t(2H) ≈2.2 (**4g** n=2), 2xt(2+4H).

[a] In case of **4e,g**; [b] Split by 5.8-6.3 Hz; In case of **3b,d** and **4b** m of the phenyl rings in Pos. 2,4 overlapping with the H-9,10 (**3b**), H-9,10,11 (**3d**) and H-10 (**4b**) signals, intensity: 12H (**3b**), 13H (**3d**) and 11H (**4b**); [c] Split by ca. 12 Hz. Multiplicities are given by first approximation considering only the ^2J and ^3J(axial-axial) couplings. All other splittings are <5 Hz for d and <1 Hz (long range couplings) for t; [d] N-methyl group in Pos. 6; [e] Assignments were proved by DNOE experiments, in case of **4a** also by double resonance measurements; [f,h,i] Overlaping signals; [g] Overlapping signals of H-9,10 (in case of **4f** H-9,10,11) and the multiplets of the aromatic ring hydrogens in the substituent R, total intensity is 7H (**3e,g**), 6H (**3f**) and 8H (**4f**); [j] Broadened signal due to hindered rotation of the N(12)Ac group; [k] Overlapping signals of CH_3(3), CH_2(2) and C-CH_2-C(R) groups (total intensity: 7H); [l] Coalesced with the N(12)CH_2 (**4e**), m(2H) and in case of **4g** also with the OCH_2 t(4H) signal; [m] =CHPh hydrogen.

mers 3a and 4a appeared as a quintet due to equal interactions ^3J(C-7,H-8) and ^3J(Me-6,C-7) indicating the CO-N-Me arrangement. Thus the transformed cyclic structures 6 and 7 could be eliminated.

3) The ^{1}H nmr spectra of 3a and 4a showed a quartet of 1H-intensity split by ca. 12.5 Hz originating from one of the 3-methylene hydrogens. The quartet multiplicity of the signal indicated three interactions of similar value, consequently the two vicinal interactions of H-3 must be diaxial and approximately of the same magnitude (ca. 12.5 Hz) as the geminal H-3ax,H-3eq coupling. Namely, a diequatorial or equatorial-axial vicinal coupling would give significantly smaller value (< 8 Hz).[6] The two couplings of diaxial character evidenced the assignment of this signal to H-3ax atom and confirmed the diaxial position of H-2 and H-4 and hereby the equatorial arrangement of the

Table 2. ^{13}C nmr chemical shifts (δ_{TMS} = 0 ppm) of compounds **3a,h** and **4a,c,d,h** in $CDCl_3$ or DMSO-d_6 solution[a] at 20 MHz.[b]

Compound	C-2 C-4	C-3 C-12a	C-7a C-11a	C-9 C-11	C-8 C-10	NCH_3(6) C=O(7)	CH_3 (2,4)	CH_3(Ac) C=O(Ac)
3a	70.2	41.6	131.3	122.4[c]	129.5	28.6	21.0	-
	51.7	97.1	143.8	122.7[c]	132.2	173.1	22.1	-
3h	70.7	40.0	134.9	128.6[d]	128.6[d]	26.9	19.6[c]	23.5[c]
	50.9	91.8	136.0	127.7	130.9	171.0[e]	20.6[c]	171.0[e]
4a	64.5	42.1	118.0	116.9[c]	131.9	41.1	18.7	-
	49.5	91.1	145.1	117.4[c]	132.8	169.8	21.3	-
4c	65.9	42.4	126.9	120.8	131.8	40.7	20.5	36.5[g]
	51.8	97.0	148.4	118.6	134.2	171.3	22.2	-
4d	64.1	41.3	127.3	120.1	130.6	39.2	19.1	11.8[i]
	50.2	95.6	145.6	118.9	132.0	170.4	20.6	-
4h	65.9	40.2	132.0	128.4	129.4	38.3	19.2[c]	22.6[c]
	50.4	92.6	138.2	127.8	131.8	170.6[f]	20.7[c]	169.2[f]

[a] Solvent: $CDCl_3$ (**3h, 4h,d**) or DMSO-d_6 (**3a, 4a,c**); [b] Assignmemts were proved by DEPT (**3a, 4a,c**) and proton-coupled measurements (**4a,c,d**). The proton-coupled ^{13}C nmr spectra of **4a,c** were measured at 63 MHz. Multiplicities and $J(C,H)$ coupling constants (in Hz) stated in proton-coupled spectra of **4a, 4c** and **4d** C-2,4, ddm, $^1J \approx 140$, $^3J \approx 4$; C-3, ~t, $^1J \approx 128$; C-12a, d, dqi, dqa, $^1J \approx 180$, $^3J \approx 3$; C-11a, t, m, m, $^3J \approx 8$; C-8,9,10,11, dd, ddd or ddt, ^1J=157-163, ^2J=2-3, ^3J=7-9; C-7a, dd or t, $^3J \approx 6.5$, C=O(7), qi, $^3J \approx 2$; CH_3(2,4), qad: $^1J \approx 126$, $^3J \approx 4$; NCH_3(6), qa, ^1J:139; [c,f] Reversed assignments may also be possible; [d,e] Overlapping lines; [g] NCH_3(12); [h] Further signals of **4d**: CH_2(Et): 47.2, tm, N(12)CH_2: 46.4, tt, Et_2NCH_2: 50.7 tqi (Assignments are proved by the given multiplicities observed in the proton-coupled spectra); [i] CH_3(Et).

2,4-C-methyl groups both in 3a and 4a. This explanation was also proved by double resonance measurements on 4a: on saturation of H-2, H-3eq and H-4 signals, respectively, the H-3ax quartet was simplified in all cases into a triplet split by ca. 12 Hz.

To clear stereostructures DNOE measurements[7,8a] were performed on 3a and 4a. The irradiation of H-12a signal of 3a caused a significant increase in the intensity of H-2 and H-4 multiplets,[9] since these protons are in 1,3-diaxial position to H-12a according to the X-ray measurement. On the contrary, in the analogous experiment the H-2 and H-4 signals of 4a did not change intensity revealing that these hydrogens must be in trans position to the saturated H-12a atoms. Accordingly, this change in the configuration of C-12a could be supposed as being the difference between 3a and 4a.

Studies on molecular models indicate that for a trans arrangement of H-12a and H-2,4, the annelation of the condensed hetero rings must be different: 4a must be the cis annelated isomer of 3a. The cis annelation of the hetero rings has to result in conformational change of the seven-membered ring compared to that of 3a. In the stable conformation of the cis annelated 2,4,6-trimethyl-3,4,12,12a-tetrahydro-2,6H-[1,3]oxazino[2,3-b][1,3,4]benzo-

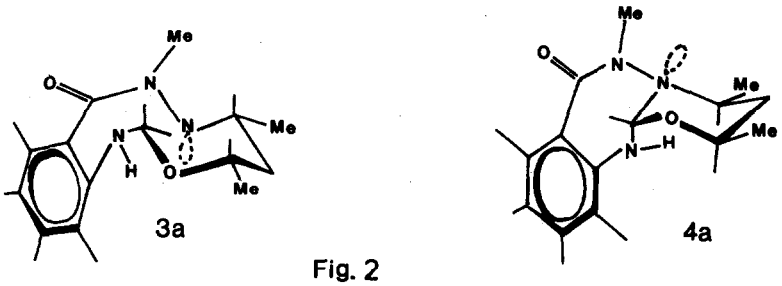

Fig. 2

triazepin-7-one (4a) the triazepinone ring is in a sofa-like conformation, where C-12a stands out from the plane of the other six atoms (Fig. 2[10]). The oxazine ring is in a chair conformation, O-1 takes the quasi-equatorial, C-4 takes quasi-axial position relative to the triazepinone ring. This conformation of 4a is confirmed by further comparison of the spectral data of 3a and 4a as well as of their acetyl derivatives 3h and 4h:

1) In 3a the carbonyl group and the benzene ring are not coplanar (cf. Fig.2) in contrast to 4a, where the lower νC=O frequency is the consequence of a stronger conjugation[11] between the carbonyl group and the aromatic ring due to their coplanar arrangement in the preferred conformation.

2) The difference in conjugation between 3a and 4a is further evidenced by the fact, that the calculated and measured carbon chemical shifts are in good agreement for 4a, whereas a significant mean deviation of 6.7 ppm was stated for 3a. The theoretical chemical shifts calculated on the basis of the substituent constants[8b] (deduced from spectra of monosubstituted benzene derivatives in which strong conjugation is realized in consequence of the coplanarity) are in agreement with the measured ones in the case of coplanar structures only.

3) The increased conjugation in the cis isomer is also demonstrated by the bathochromic shift of the uv absorption maximum of 4a and by the downfield shift of the H-8 and H-9 signals in the ^{1}H nmr spectrum of the acetylated cis isomer 4h.

4) In case of 4a the signal of H-8, being adjacent to the coplanar carbonyl group, is shifted dcwnfield as a result of the carbonyl anisotropy.[8c]

5) The H-12a atom is more shielded (by ca. 0.6 ppm) in the trans isomer 3a because of its axial position relative to the oxazine ring. (Axial protons of cyclohexanes and hetero analogues are more shielded than their equatorial counterparts.[8d])

6) The anisotropic effect of the lone electron pair[8e] of N-12 causes strong deshielding of H-2 (0.6 ppm) in the cis annelated isomer 4a.

7) The C-2, C-4, C-12a and the 2,4-methyl carbon lines are shifted upfield

or the more crowded cis annelated isomer 4a, due to the well known steric ompression shift[12] causing increased shielding on the hindered carbon atoms. 8) For similar reasons the strong steric hindrance between Me-6 and H-4 in a results in the upfield shift of the N-methyl carbon signals (by ∿12 ppm). 9) The proposed conformation of the cis isomer 4a is strikingly confirmed y the differences observed in the spectra of the acetylated derivatives 3h nd 4h. Whereas the chemical shift for H-4 of the acetylated trans isomer 3h oes not vary and for H-2 the change is little (0.2 ppm) compared to 3a, in he case of the acetylated cis isomer (4h) upfield shifts of 0.62 and 0.35 pm, respectively, were measured. The N-acetyl group is namely close to H-2 nd H-4 atoms in the cis isomer 4h and its anisotropy[8c] reveals in an in-reased shielding of these near hydrogens.
0) The hindered rotation of the acetyl group in the more crowded cis isomer h is manifested in the broadening of H-12a and the acetyl methyl proton sig-als as well. Due to steric hindrance the rotamers containing the amide car-onyl perpendicular to the benzene ring are favoured. In these rotamers the nisotropic effect of the amide carbonyl[8c] causes stronger shielding of H-11 n both acetylated isomers (by 0.5-0.6 ppm) than expected.

The spectral data showed that at room temperature the trans products 3 ere formed during ring closure. Under basic conditions these trans com-ounds underwent an isomerization which might proceed via an anionic inter-ediate (formed from 3 by deprotonation at C-12a) yielding structures 4 with is annelated ring system. The possibility of a stronger conjugation in the is compounds 4 might be the driving force of the isomerization.

EXPERIMENTAL

All melting points are uncorrected. Uv spectra were taken on a Varian Cary 118 spec-rometer. Ir spectra were measured in KBr discs using a Bruker IFS 115v vacuum optic FT-pectrometer equipped with an Aspect 2000 computer. The nmr spectra were recorded in $CDCl_3$ r DMSO-d_6 solution in 5 or 10 mm tubes at RT, on Bruker WM-250 and WP-80-SY FT-spectrome-ers controlled by Aspect 2000 computer at 250.13 (^1H) and 62.89 or 20.14 MHz (^{13}C) with the leuterium signal of the solvent as the lock and TMS as internal standard. The ^1H nmr spectra f 4e,g were measured at 90 MHz on a Varian EM-390 spectrometer. Lorentzian exponential mul-iplication for signal-to-noise enhancement was applied. Line broadening: 0.7 (^1H) and 1.0 lz (^{13}C). Measuring parameters: sweep width 5 and 15 or 5 kHz, pulse width 1 and 7.5 or 3.5 μs (∿20° and ∿30° flip angle), acquisition time 1.64 and 0.5 or 1.64 s, number of scans 16 and 1-4 K, computer memory 16 K. For ^{13}C spectra complete proton noise decoupling (∿3.0 r 1.5 W) was used (except for proton coupled spectra). DEPT[13] spectra were run in a stan-lard way,[14] using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased up and down, respectively. Gated decoupling to generate NOE was used with a selective preirradiation time f 3-5 s and a decoupling power (CW mode) of ca. 30-40 mW.

Table 3. Physical data for compounds **3a,b,d-h** and **4a-h**

Compound	M.p. °C	General formula	Mol. weight	Yield %	Elemental analysis, % Found/Calculated C	H	N
3a	260-262[a]	$C_{14}H_{19}N_3O_2$	261.32	80.9	64.17/64.34	7.36/7.33	15.99/16.08
3b	236-238[a]	$C_{24}H_{23}N_3O_2$	385.47	10.8	74.81/74.78	5.97/6.01	10.96/10.90
3d	184-186[b]	$C_{28}H_{25}N_3O_3$	427.50	66.3	72.96/73.05	5.88/5.89	9.81/ 9.83
3e	230-232[a]	$C_{22}H_{25}N_3O_3$	379.46	74.2	69.67/69.63	6.60/6.64	11.10/11.07
3f	194-196[c]	$C_{23}H_{27}N_3O_4$	409.52	86.4	67.39/67.46	6.61/6.64	10.21/10.26
3g	211-213[d]	$C_{23}H_{25}N_3O_3$	391.47	66.0	70.49/70.57	6.47/6.44	10.69/10.73
3h	182-184[e]	$C_{16}H_{21}N_3O_3$	303.38	90.7	63.41/63.34	6.99/6.97	13.91/13.85
4a	160-161[f]	$C_{14}H_{19}N_3O_2$	261.32	91.5	64.41/64.34	7.30/7.33	16.11/16.08
4b	80-81[d,g]	$C_{24}H_{23}N_3O_2$	385.47	27.3	74.57/74.78	5.97/6.01	10.79/10.90
4c	114-115[d]	$C_{15}H_{21}N_3O_2$	275.35	41.0	65.48/65.43	7.65/7.68	15.20/15.25
4d	oil	$C_{20}H_{32}N_4O_2$	360.50	94.9	66.57/66.63	8.89/8.94	15.50/15.54
4e	99-101[d]	$C_{19}H_{30}N_4O_2$	346.47	93.0	65.91/65.86	8.71/8.72	16.11/16.17
4f	185-186[e]	$C_{21}H_{25}N_3O_2$	351.45	72.6	71.70/71.76	7.19/7.17	11.91/11.95
4g	108-110[d]	$C_{21}H_{32}N_4O_3$	388.51	77.2	64.87/64.92	8.30/8.30	14.37/14.42
4h	158-159[b]	$C_{16}H_{21}N_3O_3$	303.38	77.3	63.30/63.34	7.00/6.97	13.90/13.85

[a] ethanol; [b] benzene; [c] methanol; [d] chromatographed over silica; [e] ether; [f] petroleum-ether; [g] decomposed on storage.

Trans-2,4-disubstituted 6-methyl-3,4,12,12a-tetrahydro-2,6H-[1,3]oxazino [2,3-b] [1,3,4]benzotriazepin-7-ones (**3a,b**) – General procedure: To a solution of the appropriate hydrazide **2** (0.02 mol) in EtOH (100 mL) $HC(OEt)_3$ (0.09 mol) was added. The mixture was allowed to react at RT for 48 h. The precipitate was filtered off, washed with EtOH (3x8 mL) and dried. The products can be recrystallised from EtOH. Uv λ_{max}(EtOH) **3a**: 217, 239, 303 nm. Ir (cm^{-1}) **3a,b** 3300, 3300, (νNH), 1632, 1637 (amide-I), 766 and 750, 756 and 700 (γArH).

Acylation of the 2,4-disubstituted 6-methyl-3,4,12,12a-tetrahydro-2,6H[1,3]oxazino[2,3-b]-[1,3,4]benzotriazepin-7-one isomers, preparation of **3d-h** and **4h** – General procedure: To a solution of the appropriate isomer (4 mmol of **3a,b** or **4a**) in dry benzene (40 mL) and pyridine (4 mL) the solution of the acid chloride (4 mmol) in dry benzene (8 mL) was added dropwise while the reaction temperature was kept at ca. 25° C. The mixture was allowed to react overnight. The precipitate was filtered off and the solution was poured into water (200 mL). The product was extracted with benzene (2x40 mL), the combined organic layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent the residue was crystallized by trituration with ether or hexane. Ir (cm^{-1}) **3d-h**, **4h**: 1682 and 1659, 1678 and 1651, 1676 and 1657, 1678 and 1622, 1670 and 1653, 1678 and 1655 (amide-I), 752 and 710, 758 and 709, 799 and 770, 775 and 702, 777, 752 and 710 (γArH).

Cis-2,4-disubstituted 6-methyl-3,4,12,12a-tetrahydro-2,6H-[1,3]oxazino[2,3-b] [1,3,4]benzotriazepin-7-ones (**4a,b**) – General procedure: To a stirred suspension of NaH (4.4 mmol) in dry DMF (10 mL) the appropriate trans isomer (4 mmol) was added and the reaction mixture was heated at 50° C for 3 h. After cooling the excess of NaH was decomposed with a small amount of water and the solution was poured into water (400 mL). The product was extracted with $CHCl_3$ (3x30 mL), the organic extract was washed with water and dried over $MgSO_4$. After evaporation of the solvent the residue was crystallized by trituration with petroleum-ether or

hromatographed over silica. Uvλ_{max} (EtOH) 4a: 224, 251, 331 nm. Ir (cm^{-1}) 4a,b: 3302, 3356)NH), 1610, 1620 (amide-I), 762, 754 and 700 (γArH).

lkylation of 3a, preparation of 4d-g – General procedure: To a stirred suspension of NaH 4.1 mmol) in dry DMF (15 mL) 3a (4 mmol) was added. After 10 minutes the solution of the ppropriate alkylating agent (4.1 mmol) in DMF (3 mL) was added dropwise into the reaction ixture and the mixture was allowed to react for 48 h at RT. The excess of NaH was decompoed by addition of a small amount of water and the solution was poured into water (200 mL). he product was extracted with $CHCl_3$ (3x30 mL), the organic extract was washed with water nd dried over $MgSO_4$. After evaporation of the solvent the product was crystallized by triiration with ether, or petroleum-ether, or purified by column chromatography. Ir (cm^{-1}) d-g: 1645, 1637, 1634, 1643 (amide-I), 752, 756, 754 and 735, 754 (γArH).

is-2,4,6,12-tetramethyl-3,4,12,12a-tetrahydro-2,6H-[1,3]oxazino[2,3-b][1,3,4]benzotriazein-7-one (4c): A mixture of 2c (0.01 mol) and excess of triethyl orthoformate (10 mL) was eated at 130° C while the formed EtOH was continuously distilled off. After 8 h the excess f triethyl orthoformate was removed under reduced pressure and the residue was chromatographed over silica, eluent benzene/ethyl acetate. Ir (cm^{-1}) 1634 (amide-I), 756 (γArH).

rystal structure and crystal data of 3a: Monoclinic, space group $P2_1/c$ with a = 9.503(1), = 12.881(2), c = 11.146(1) Å, β = 101.74(2)°, U = 1335.8(2) $Å^3$, Z = 4, D_c = 1.30 $g.cm^{-3}$, (000) = 560, μ = 0.68 mm^{-1} for CuK_α radiation (λ = 1.5418 Å). The intensities of 2653 nique reflections were collected from a crystal of 0.25x0.30x0.30 mm^3 dimensions on a CAD-4 iffractometer in the range $1.5 < \theta < 75.0°$ by an ω-2θ scan using graphite monocromated CuK_α adiation. Cell constants were determined by least-squares refinement of the angular positis of 25 reflections. Three standard reflections were monitored every hour and showed no significant decrease during the exposure. After data reduction 2512 reflections with $I > 3\sigma(I)$ were taken as observed. The phase problems were solved by direct methods using the MULTAN 82 program.[15] In the course of the isotropic least-squares refinement of the positional parameters of non-H atoms an empirical absorption correction was calculated with the DIFABS program.[16] The minimum and the maximum relative transmission coefficients ranged from 0.851 to 1.388 with an average value of 1.001. The fractional coordinates of non-H atoms bound to carbons were generated from assumed geometries, while H(N) was located in a difference Fourier map. They altogether were only included in the structure factor cal-

able 4. Final fractional coordinates for non-hydrogen atoms of 3a.[a]

tom	x/a	y/b	z/c
(1)	0.7005(1)	0.03465(7)	0.47563(7)
(16)	0.9579(1)	0.20943(9)	0.91911(8)
(5)	0.8445(1)	0.03875(7)	0.67307(9)
(6)	0.8588(1)	0.08096(9)	0.79257(9)
(12)	0.7000(1)	0.18135(8)	0.5960(1)
(2)	0.7023(1)	-0.0773(1)	0.4692(1)
(3)	0.8450(1)	-0.1131(1)	0.5442(1)
(4)	0.8700(1)	-0.0746(1)	0.6755(1)
(7)	0.9232(1)	0.1752(1)	0.8148(1)
(7a)	0.9381(1)	0.23636(9)	0.7041(1)
(8)	1.0556(1)	0.3027(1)	0.7121(1)
(9)	1.0686(1)	0.3664(1)	0.6153(1)
(10)	0.9613(1)	0.3665(1)	0.5103(1)
(11)	0.8413(1)	0.3043(1)	0.5035(1)
(11a)	0.8281(1)	0.23784(9)	0.5994(1)
(12a)	0.7066(1)	0.0701(1)	0.5957(1)
(13)	0.6770(2)	-0.1071(1)	0.3362(1)
(14)	1.0211(2)	-0.0991(1)	0.7430(1)
(15)	0.7970(1)	0.0299(1)	0.8861(1)

E.s.d's are in parentheses.

culations with isotropic temperature factors ($B_{iH} = B_{iX} + 2$, where X = C or N). Final R = = 0.049, wR = 0.049, S = 0.72: the highest peak in the final difference Fourier map 0.31(4) e.Å^{-3} (Δ/σ = 0.35). Scattering factors were taken from standard tables.[17] All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP system of Enraf-Nonius with local modifications.

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9. Due to partial isomerization 3a → 4a during the procedure we controlled our results measuring the DNOE spectra on 3h, too.

10. The compounds are racemates, one of the enantiomers is represented in Fig. 2.

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