Tetrahedron Vol. 46, No. 19, pp. 6859-6868, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

PHENYL-SUBSTITUTED CYCLOPENTANE- AND CYCLOHEXANE-*cis*-FUSED-1,3-OXAZINES AND -1,4-OXAZEPINONES. PREPARATION AND STEREOCHEMICAL STUDY[1]

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(*Received in UK* 22 *May* 1990)

Abstract - The cycloadditions of cyclopentene and cyclohexene with benzonitrile oxide (BNO) yielded isoxazolines 1 and 2, which were reduced to 1,3-aminoalcohols 3 and 4 with LAH and cyclized to cycloalkane-*cis*-condensed 4-phenyl-1,3-oxazines 6 and 7a,b. From the aminoalcohol 5 obtained by Na/EtOH reduction of 2, the diastereomeric 4-phenyloxazine derivative 8 was obtained. 3 and 4 were transformed through carbamates to *cis*-5,6-trimethylene- and *cis*-5,6-tetramethylene-1,3-oxazin-2-ones 9 and 10, while the analogous 2-thiones 11 and 12 were prepared *via* dithiocarbamates. With phenyl isothiocyanate, 3 furnished the 2-phenylimino-1,3-oxazine 13, while 1,4-oxazepinones (14, 15) were obtained with ethyl chloroacetate and 2-chloropropionate. The structures of the new compounds, including the configurations and preferred conformations, were elucidated by means of ir, ^1H and ^{13}C-nmr investigations.

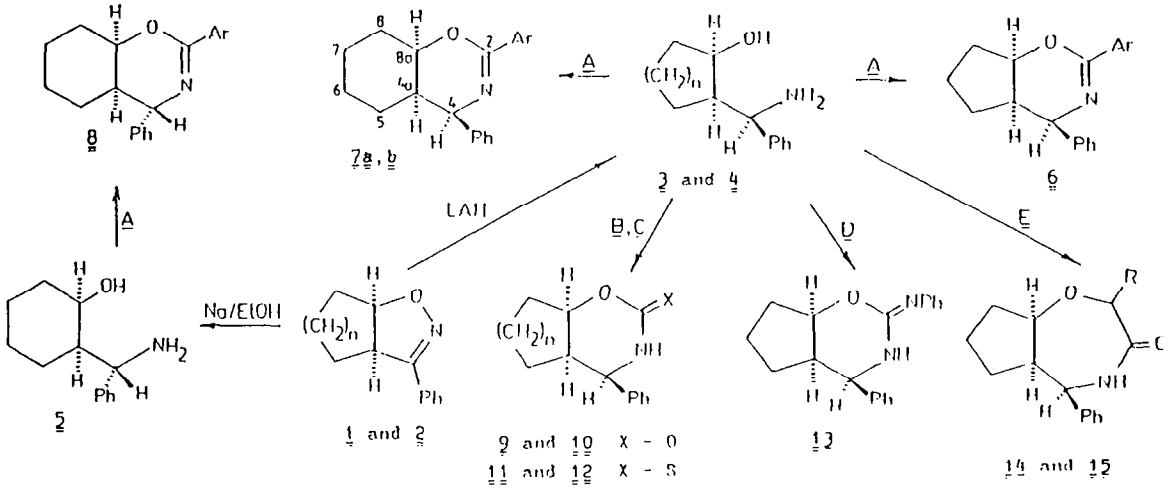
A number of cyclopentane and cyclohexane *cis*- and *trans*-fused isomeric 1,3-oxazines and related saturated 1,3-heterocycles have been prepared and comparative studies have been made of their stereochemistry.[2,3] As a continuation, further analogues were synthesized from the *N* methyl and *N* benzyl derivatives of the starting aminoalcohols.[4] By reduction of the norbornene BNO adduct, aminoalcohols were prepared, which were transformed to saturated 1,3-heterocycles.[5]

From the corresponding cyclopentene and cyclohexene adducts, aminobenzyl cyclanols have now been made by reduction. These aminoalcohols permitted the preparation of a new type of carbocycle fused saturated-1,3-heterocycles, which are phenyl-substituted at the carbon atom adjacent to the annelation. The stereochemistry of these compounds seemed to be of interest, because some related aromatic analogues, e.g. the 1-phenyl-substituted tetrahydroisoquinolines[6] and 1,3-benzothiazines,[7] were studied earlier, but similar investigations on related, fully saturated systems have not yet been reported. Further, the benzodiazepines, important minor tranquillizers, have a phenyl substituent next to the annelation in the hetero ring, and therefore our compounds might be regarded as potential pharmacons.

We report here the preparation of cis-condensed 1,3- and 1,4-heterocycle among them condensed phenyl-substituted 1,3-oxazines, by cyclization of the isomeric 2-(amino-phenyl)methyl-1-cyclohexanols 4 and 5.

SYNTHESIS

Isoxazolines 1 and 2, prepared from cyclopentene or cyclohexene and *in situ* BNO, were reduced in THF with LAH to the cis-1-(α-aminobenzyl)-2-cyclopentanol 3 and -2-cyclohexanol[8] 4. Reduction of the adduct 2 with Na in EtOH yields the diastereomeric aminoalcohol 5. The starting 3-5 were cyclized with imidates to 5c-phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.3.0]non-3-ene (6), 5c-phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.4.0]dec-3-ene (7a,b) and the diastereomeric 5t-phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.4.0]dec-3-ene (8) (Scheme).



n = 1: 1, 3, 9, 11; n = 2: 2, 4, 10, 12; 6 and 7a: Ar = C_6H_4Cl(p); 7b and 8: Ar = C_6H_4Cl(m); 14: R = H; 15: R = CH_3; A: HN=C(OEt)C_6H_4Cl(m or p); B: ClCOOEt/NaOMe; C: CS_2/KOH/$Pb(NO_3)_2$; D: PhNCS/MeI/KOH; E: $ClCH_2COOEt$ or $CH_3CHClCOOEt$/NaH

Scheme

With ethyl chloroformate and EtONa, the cis-5,6-trimethylene- and 5,6-tetramethylene-5-phenyl-1,3-oxazin-2-ones 9 and 10 were prepared, while the corresponding 2-thiones 11 and 12 were made with CS_2 and lead(II) nitrate. The methyl-substituted 1,3-oxazin-2-one diastereomeric pair analogous to 9 were earlier prepared from the isomeric aminoalcohols with diethyl carbonate.[8]

The base catalysed cyclization of the intermediate thiourea prepared with phenyl isothiocyanate yielded 2-phenylimino-4-phenyl-5,6-cis-trimethylene-1,3-oxazine (13) *via* the isothiuronium salt. With ethyl chloroacetate,

the 6,7-cis-trimethylene-1,4-oxazepin-3(4H)-one (14) was obtained, while the corresponding 2-methyl-1,4-oxazepin-3(4H)-one (15) was prepared with ethyl 2-chloropropionate.

STRUCTURE

The ir, ^{1}H- and ^{13}C-nmr data (Tables 1 and 2) provide convincing evidence of the structures of the new compounds.

Table 1. Characterisctic ir frequencies[a] and ^{1}H-nmr data[b] on compounds 6, 7a,b and 8-15

Compound	νC=O νC=N[d]	H-4 d(1H)[e]	H-8a m(1H)[f]	H-4a m(1H)[g]	CH_2 (5,6,7,8) m's (6/8H)[h]	ArH (m's: 5/9/10H)[i]
6	1658	4.98	4.80	~2.52	1.2 - 2.05	7.2-7.5 8.02[j]
7a	1652	4.90	4.68	2.05	0.8 - 2.2	7.2-7.4 8.05[j]
7b	1658	4.92	4.68	2.05	0.8 - 2.2	7.2-7.5 8.00[k] 8.09[l]
8	1652	4.61	4.21	<1.9[m]	1.3 - 2.05[m]	7.2-7.5 7.96[k] 8.07[l]
9	1717[n]	4.95	4.82	~2.35	1.2 - 2.0	7.2-7.4
10	1705	4.80	4.65	1.95[m]	0.7 - 1.95[m]	7.2-7.5
11	-	4.95	4.90	~2.45	1.25- 2.2	7.25-7.55
12	-	4.87	4.73	~2.0[m]	0.65- 2.0[m]	7.15-7.45
13	1666	4.92	4.73	~2.4	1.1 - 2.0	6.93[o] 7.2-7.55[m]
14	1675	5.11	4.18	1.7-2.1[m]	1.55- 2.1[m]	7.3-7.4
15	1665	5.15	4.22[p]	1.7-2.0[m]	1.55- 2.0[m]	7.3-7.4

[a] In KBr, cm^{-1}. Further ir bands: νNH band: ~3225 (9), ~3235 (10, 14, 15), ~3170 (11), ~3180 (12), 3300-2500 (13); $\gamma C_{Ar}H$ (phenyl): 732-775, $\gamma C_{Ar}H$ (p- or m-disubst.): 840 (6, 7a), 800 (7b, 8), $\gamma C_{Ar}C_{Ar}$ (Ph): 700 ± 6; [b] In $CDCl_3$ solution at 250 MHz; chemical shifts in ppm, $\delta_{TMS} = 0$ ppm, coupling constants in Hz. Further signals: NH (1H, broad): 6.55 (9), 7.5 (10), 7.8 (11), 9.8 (12), 7.4[m] (13), 5.9 (14) and 5.8 (15); $COCH_2O$ (14): 4.26 s (2H), CH_3 (15): 1.38 d (J: 6.5), COCHO (15): 4.26[p] qa(1H); [c] Except for 10 and 12, where the solvent was DMSO-d_6; [d] νC=N band for 6, 7a,b, 8 and 13, νC=O band for 9, 10, 14 and 15; [e] J: 5.0 (6, 11), 4.7 ± 0.1 (7a,b, 9, 10), 2.0 (8), 5.2 (12), 4.4 (13) and 3.5 (15); [f] Triplet- or quartet-like signal with coalesced lines and half-bandwidth of 5-10 Hz; [g] Broad, half-bandwidth ca. 30 Hz; [h] One-five partially coalesced multiplets with total intensity of 6H (6, 9, 11, 13 15) or 8H (7a,b, 8, 10, 12); [i] Total intensity is 9H (6, 7a,b, 8), 5H (9-12, 14, 15) or 10H (13); [j] H-2',6'(2-aryl), d(J: 8.7); [k] H-6' 2-aryl) ~t(J: ~8); [l] H-2'(2-aryl), ~d(J: ~2); [m] Overlapped signals; [n] Split band with the second maximum at 1680; [o] H-4'(aryl), ~t(J: ~8).

The elucidation of the steric structure begins conveniently with the isomeric pairs 7b-8. These cyclohexane-condensed derivatives are con-

formatively homogeneous and a comparison of the spectral data on the isomers facilitates the structure determination.

Investigations of numerous cis-condensed 5,6-bridged 4-unsubstituted 1,3 oxazines have demonstrated[9-11] that these are conformatively homogeneous and, of the two relatively stable conformers containing the cycloalkane ring in chair form, that one is preferred in which the oxygen attached to the cyclohexane ring is axial.

Table 2. ^{13}C-nmr chemical shifts for compounds 6, 7a,b and 8-15[a]

Compd.	C-2	C-4	C-4a	CH_2(5)	CH_2(6)	CH_2(7)	CH_2(8)	C-8a	C-1[b]	C-2,6[b]	C-3,5[b]	C-4[b]
6	154.5	55.4	43.5	21.8[c]	23.2[c]	–	33.2	80.2	143.7	128.2[d,e]	128.8[d]	126.
7a	154.4	60.0	38.0	20.3[c]	25.0	20.0[c]	31.1	74.4	142.4	128.1[d]	128.7[d]	126.
7b	153.8	59.7	37.6	20.0[c]	24.7	19.8[c]	30.7	74.2	142.0	126.8	127.9	127.
8	154.6	61.3	39.8	26.9[c]	24.7[c]	20.7	30.2	69.3	144.0	127.1	128.4	127.
9	154.5	54.2	43.0	20.8[c]	22.1[c]	–	32.5	82.3	139.5	125.5	128.4	127.
10	155.2	59.3	38.8	21.1[e]	25.8	21.1[e]	31.6	76.3	141.0	129.8	128.2	128.
11	187.4	55.4	42.5	20.9[c]	22.9[c]	–	32.3	84.9	138.1	125.8	128.7	128.
12	188.3	60.3	37.6	21.8	25.4	20.9	31.1	78.5	139.5	129.7	128.0	128.
13		55.0	43.7	21.6[c]	22.9[c]	–	33.1	81.0	143.8	126.4	128.7	126.
14	175.2	57.5	51.8	22.9[c]	22.7[c]	–	33.9	86.8	143.0	129.9	128.8[d]	128.
15	174.4	56.8	50.1	21.3[c]	20.7[c]	–	33.2	86.3	141.1	126.3	128.8	127.

[a] In $CDCl_3$ solution, but for 10, 12 and 14 in DMSO-d_6 solution; at 20.14 (6, 7a, 11, 12 and 15) or 62.89 MHz (7b, 8-10, 13 and 14); δ_{TMS} = 0 ppm. Further signals: CH_3: 16.9 (15), OCH_2: 72.3 (14), $OCH(CH_3)$: 73.1 (15), 2-aryl group, C-1': 132.8 (6, 7a), 134.0 (7b), 134.3 (8), 148.5 (13), C-2',6': 126.7 (6), 127.0 (7a), 118.8 (13), C-2': 129.1 (7b), 129.4 (8), C-3',5' 128.2[d] (6, 7a, 13), C-3': 135.8 (7b, 8), C-4': 136.6 (6, 7a), 126.3 (7b), 126.9 (8), 121.4 (13), C-5': 130.2 (7b), 130.5 (8), C-6': 125.4 (7b, 8). [b] Phenyl group. [c,d] Assignments may also be reversed. [e] Two overlapping lines.

As the H-8a signal in the ^{1}H-nmr spectra of 7b and 8 is a 5 Hz broad quartet, with coalesced lines, it follows unequivocally that the skeletons are identical in the two cases and the conformation is "0-in" (containing axial oxygen), in accordance with our earlier findings[9-11] (Fig. 1). In the case of axial H-8a, diaxial vicinal coupling would undoubtedly occur with one of the 8-CH_2 hydrogens, which would therefore cause a higher splitting and consequent a signal width of about 30 Hz. Thus, for 7b and 8 the steric structures shown in Fig. 1 are possible, in which the C-4 configurations (i.e. the positions of the 4-phenyl group) are different.

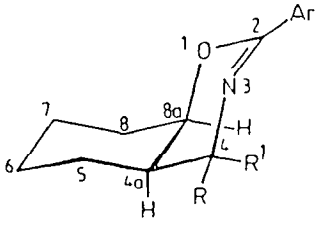
As the H(4α)-C-C-H(4a) and H(4β) C-C-H(4a) dihedral angles are ~30° and ~90°, respectively, a higher coupling constant can be expected for the β-position of the phenyl substituent according to the Karplus relation.[12] The J(H-4,H-4a) splitting measured for the oxazine prepared from the isoxazole 2 with LAH and imidate is 4.7 Hz, while that for the oxazine obtained from 2 by

Na/EtOH reduction and cyclization is 2 Hz. The 4R* (7b) and 4S* (8) structures are therefore plausible, i.e. a 4β-phenyl group in the former, and a 4α-phenyl group in the latter.

In agreement with these structures, H-8a in 8 is more shielded by 0.47 ppm, in accordance with the anisotropic effect of the 1,3-diaxial 4α-phenyl group.[13] A similar but smaller effect can be seen for the H-4a signal (δH-4a: 2.05 ppm for 7b and <1.9 ppm for 8). For 7b, the shielding effect of the phenyl ring is exerted on the hydrogens of the 6-methylene group; these signals can be found in the interval 0.8-1.2 ppm, while the chemical shift is higher than 1.3 ppm for 8 (see Table 1). The assignments were proved by measuring NOE effects (see below).

The ^{13}C-nmr data support the conclusions derived from the ^{1}H-nmr data. For 8, the upfield shift of the C-8a signal (4.9 ppm) is a result of the steric hindrance between H-8a and the phenyl group in the 1,3-diaxial position (steric compression shift[14]). However, C-5 is more shielded (by 6.9 ppm) in the spectrum of 7b, because of the strong steric hindrance between the phenyl group in the β-position and the hydrogens of the 6-methylene group (all of the other carbon shifts are identical within 2.2 ppm).

The above steric structures were unequivocally proved by DNOE measurements. For 7b, a mutual NOE effect was found between H-4 and H-8a, as evidence of their 1,3-diaxial position: saturation of one of the signals causes a significant increase in the other. The proof of the assignment of these two signals is that H-4a and H-8a give a response only on irradiation of H-4, while on saturation of the H-8a signal both the multiplets of H-4 and H-4a and the signals of the two methylene protons (about 2.2 and 1.6 ppm) become more intense. This fact is a further indication that the signal at 2.2 ppm is due to H-8eq.



Ar = $C_6H_4Cl(p)$
7b: R = Ph, R^1 = H
8: R = H, R^1 = Ph

Fig. 1

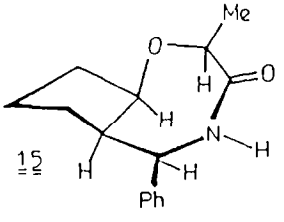


Fig. 2

Analogous DNOE measurements on the diastereomer 8 do not reveal an interaction between H-4 and H-8a. The intensity increase when the H-4 signal is saturated proves that the H-4a multiplet appears at about 1.85 ppm. Direct proof of the α-position of the phenyl group is that irradiation of the signal of H-8a causes an increase in intensity of the signal of the ortho-hydrogens.

As saturation of the H-8a signal affects both the H-4a signal and the multiple at 2.05 ppm, the assignment of the latter to H-8eq is obvious.

As a consequence of the entirely analogous spectral data (among others the H-4,H-4a coupling constant, which is decisive for the steric structure, and the similar chemical shifts of H-4,4a,6,6',8a and C-5,8a), the analogous stereostructures of 7a and 7b (and hence the 4R* configuration of C-4, i.e. the β-position of the phenyl group in 7a) are obvious. For confirmation of the assignments of the H-4,4a,8,8a signals, double resonance experiments were also made with 7a. Irradiation of the H-4 signal decreased only the number of lines in the H-4a multiplet, while saturation of the H-8a signal simplified H-4a and H-8 simultaneously.

Analogous spectral data were observed for the 2-oxo (10) and 2-thioxo (12) derivatives, as an indication of the analogous stereostructure, i.e. the 4R* configuration and the conformation in which the oxygen is attached axial to the cyclohexane ring. In this respect, the J(H-4,H-4a) coupling (4.6 and 5.2 Hz) and the H-4,6,6',8a and C-5,8a chemical shifts are decisive.

The presumed stereostructure was supported by DNOE measurements on the thione 12. Saturation of the H-4 and H-8a signals caused mutual NOE effects, proving the nearness of these two hydrogens.

The conformation relations of the cyclopentane and cyclohexane homologues of fer considerably only that in the case of β phenyl substitution the "O-out" form containing a quasi-equatorial oxygen is sterically very unfavourable owing to the strong phenyl—H-6(endo) interaction. However, if an α-phenyl substituent were assumed, the H(4)-C-C-H(4a) dihedral angle would be ≈180°, which is high improbable due to the magnitude (5 Hz) of the corresponding coupling. Further the 0.6 ppm downfield shift of the H-4a signal compared with that for 8 also contradicts the structure, with an α-phenyl substituent and "O-out" conformation, because this signal would be shifted in the opposite direction, owing to the anisotropic effect of the aromatic ring.

Hence, the 4β-phenyl-substituted "O-in" form is probable for 6. This is supported by the magnitude of the ^{3}J(H-4,H-4a) coupling and the downfield shifts of the H-4, H-8a and C-8a signals, the values of which are similar to those for 7a,b. Opposite shifts could be expected for the diastereomer analogous to 8.

Since the ^{3}J(H-4,H-4a) coupling constant and the H-4, H-8a and C-8a chemical shifts (considering the substituent effect) for the oxo 9, thioxo 11 and phenylimino 13 analogues are similar to those measured for 6, the analogous steric structure is obvious for the series 6, 9, 11 and 13.

The structures of the oxazepinones 14 and 15 pose a special problem. In these derivatives, the conformational conditions are different and the steric

position of the methyl group in 15 must also be clarified. In the spectrum of 15, the close-lying lines of the multiplet arising from the annelated CH vicinal to the oxygen ("H-8a)* are merged to a signal with a half-bandwidth of 5-10 Hz. Hence, the quasi-equatorial position of H-8a, i.e. the preferred "O-in" conformation, is also plausible in this case. In an "O-out" form, the H-8,H-8a and H-8',H-8a coupling would presumably cause a higher splitting and signal width because of the dihedral angles ~15 and ~30°.

DNOE experiments involving saturating the NCH signal (H-4, 5.15 ppm) proved that H-4 and the two hydrogens vicinal to the oxygen ("H-8a" and the CHMe atom) are near to each other. Hence, the endo position of the methyl group (the S* configuration of the O-CMe-C=O carbon) could be concluded. The unequivocal H-4 assignment also follows from the DNOE spectrum, in which intensity enhancements of the NH and phenyl proton signals were found. The preferred conformation is probable, in which the cyclopentane ring is in an envelope form (with C-4a in the out-of-plane position) and the seven-membered ring assumes the sterically favourable conformation, in which the C and N atoms of the amide group are above, while C-8a is below the plane of the remaining three carbons and the oxygen (Fig. 2).

Since the nmr parameters are essentially the same for 14, the steric structure is analogous to that of the methyl derivative 15, and the phenyl group is also in the β-position here. However, the conclusions relating to the flexible cyclopentane-condensed oxazepinones can not be regarded as unequivocal as those concerning the stereostructures of the cyclohexane-condensed oxazines.

EXPERIMENTAL

Ir spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer.

The nmr spectra were recorded in $CDCl_3$ or DMSO-d_6 solution in 5 or 10 mm tubes at room temperature, on Bruker WM-250 (^1H, ^{13}C) or WP-80-SY (^{13}C) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 (^1H) and 62.89 or 20.14 MHz (^{13}C), with the deuterium signal of the solvent as the lock and

* For easy comparison of the analogous nmr data, the numbering of the cyclohexane-condensed oxazines is used for the cyclopentane homologues and oxazepinones; in the former the 7-CH_2 group is missing, while in the latter the (O)CH_2 and (O)$CHCH_3$ groups are not numbered.

TMS as internal standard. The most important measuring parameters were as follows: sweep width 5 and 15 or 5 kHz, pulse width 1 and 5 or 3.5 μs (~20° and ~30° flip angle), acquisition time 1.64 and 1.02 or 1.64 s, number of scans 16 or 32 (^{1}H) and 0.5-3 K (^{13}C), computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening: 0.7 and 1.0 or 2.0 Hz) was applied.

DNOE experiments were performed with the Bruker microprogram 12.5 in the Aspect 2000 Pulse Programmer. Gated decoupling to generate NOE was used with a delay time of 30 s and a decoupling power of 40 mW: number of scans 32; relaxation delay 0.1 s; dummy scans 2.

3-*p*-Chlorophenyl-5*c*-phenyl-2-oxa-4-aza-1*r*,6*c*-bicyclo[4.3.0]non-3-ene (6), and 4-*p*-chlorophenyl- (7a) and 3-*p*-chlorophenyl-5*c*-phenyl- (7b) and 5*t*-phenyl-2-oxa-4-aza-1*r*,6*c*-bicyclo[4.4.0]dec-3-ene (8)

A mixture of aminoalcohol 3, 4 or 5 (1.80 g, 1.95 g or 1.95 g; 0.01 mol), 3- or 4-chlorobenzimidate (1.6 g; 0.01 mol), EtOH saturated with HCl (1 drop) and EtOH (30 ml) was refluxed (1 h). After evaporation, the residue was crystallized from EtOH. Data on the compounds 6, 7a,b and 8 obtained are listed in Table 3.

Table 3. Physical and analytical data of compounds 6-15

Compd.	M.p. °C	Yield %	Mol. formula	Mol. weight	Analysis Calcd. %			Found %		
					C	H	N	C	H	N
6	87-89	67	$C_{19}H_{18}NClO$	311.81	73.19	5.82	4.49	72.98	5.96	4.54
7a	138-140	65	$C_{20}H_{20}NClO$	325.84	73.72	6.19	4.30	73.93	5.98	4.19
7b	97-99	57	$C_{20}H_{20}NClO$	325.84	73.72	6.19	4.30	73.76	6.03	4.25
8	123-125	63	$C_{20}H_{20}NClO$	325.84	73.72	6.19	4.30	73.65	6.10	4.41
9	197-200	58	$C_{13}H_{15}NO_2$	217.27	71.87	6.96	6.45	71.98	6.86	6.35
10	240-243	54	$C_{14}H_{17}NO_2$	231.30	72.70	7.41	6.06	72.53	7.22	5.98
11	185-187	52	$C_{13}H_{15}NOS$	233.33	66.92	6.48	6.00	66.73	6.26	5.86
12	274-275	52	$C_{14}H_{17}NOS$	247.36	67.98	6.92	5.66	67.78	7.01	5.94
13	119-121	49	$C_{19}H_{20}N_2O$	292.38	78.05	6.90	9.58	77.96	6.78	9.70
14	185-187	50	$C_{14}H_{17}NO_2$	231.30	72.70	7.41	6.06	72.61	7.60	5.96
15	140-142	53	$C_{15}H_{19}NO_2$	245.32	73.44	7.81	5.71	73.33	7.79	5.48

5c-Phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.3.0]nonan-3(4H)-one (9) and 5c-phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.4.0]decan-3(4H)-one (10)

Ethyl chloroformate (1.1 g; 0.01 mol) was added dropwise to a mixture of aminoalcohol (3: 1.90 g or 4: 2.05 g; 0.01 mol), water (5 ml) and $NaHCO_3$ (0.8 g; 0.01 mol). The mixture was stirred and refluxed for 10 minutes, then evaporated. The residue was extracted with ether (3x10 ml), and the extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was heated with NaOEt (50 mg) in an oil bath (120 °C, 5 min), then extracted with ethyl acetate (3x15 ml), the extracts were combined and the solvent was evaporated. The residue was transferred onto a silica gel column (Kieselgel 60; 0.063-0.2 mm) and eluted with ethyl acetate. After evaporation of the solvent, the residue was crystallized from EtOH. Data on compounds 9 and 10 are listed in Table 3.

5c-Phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.3.0]nonane-3(4H)-thione (11) and 5c-phenyl-2-oxa-4-aza-1r,6c-bicyclo[4.4.0]decane-3(4H)-thione (12)

The aminoalcohol (3: 3.16 g or 4: 3.29 g; 0.0165 mol) in an aqueous solution (10 ml) of KOH (1.1 g) was cooled to 0 °C, was stirred with CS_2 (1.3 g) in dioxane (8 ml) for 5 min. KOH (0.55 g) in water (10 ml), and then an aqueous solution (30 ml) of lead(II) nitrate (5.5 g), were added, followed by stirring at 60 °C 10 min. The PbS was filtered off, washed with hot water and extracted with hot EtOH. The aqueous filtrate and the ethanolic extracts were combined and evaporated to dryness. The residue gave colourless crystals from EtOH. Data on compounds 11 and 12 are listed in Table 3.

5c-Phenyl-3-phenylimino-2-oxa-4-aza-1r,6c-bicyclo[4.3.0]nonane (13)

A mixture of aminoalcohol 3 (1.90 g; 0.01 mol), ether (30 ml) and phenyl isothiocyanate (1.35g; 0.01 mol) was left to stand at room temperature for 1 h. The solid that separated out was filtered off and stirred with methyl iodide (7.1 g; 0.05 mol) for 1 h. The mixture was evaporated below 30 °C and the residue was stirred with MeOH (40 ml) containing 3 N KOH for 4 h. After evaporation and addition of ice-water (10 ml), the product was extracted with $CHCl_3$ (3x20 ml). The extract was washed with water and dried (Na_2SO_4). Data on the compound (13) obtained after evaporation and recrystallization are listed in Table 3.

6c-Phenyl-2-oxa-5-aza-1r,7c-bicyclo[5.3.0]decan-4(5H)-one (14) and 3c-methyl-6c-phenyl-2-oxa-5-aza-1r,7c-bicyclo[5.3.0]decan-4(5H)-one (15)

To a solution of aminoalcohol 3 (1.90 g; 0.01 mol) in benzene (20 ml),

ethyl chloroacetate (1.26 g) or ethyl 2-chloropropionate (1.37 g; 0.01 mol) and then an 80% oily suspension of NaH in benzene (5 ml) were added dropwise under stirring. After 10 min., the mixture was refluxed (1 h) and cooled, benzene (50 ml) was added, and the mixture was then washed with cold 5% HCl (30 ml) and water (30 ml). The benzene solution was dried (Na_2SO_4) and evaporated to dryness, and the residue was transferred onto an Al_2O_3 column (Alumin acid, Woelm) and eluted with ethyl acetate. The residue of the eluate was crystallized from EtOH. Data on the colourless compounds 14 and 15 are listed in Table 3.

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