Tetrahedron Vol. 42, No. 18, pp. 5139 to 5148, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

STEREOCHEMICAL STUDIES, 100[1]. SATURATED HETEROCYCLES, 104[1]

SYNTHESIS, AND NMR AND X-RAY STUDY OF 1-SUBSTITUTED AZETO[2,1-a]ISOQUINOLINE DIASTEREOMERS[1]

GÁBOR BERNÁTH,[+*] JENŐ KÓBOR,[x] FERENC FÜLÖP,[+] PÁL SOHÁR[o] GYULA ARGAY[□] and ALAJOS KÁLMÁN[□]

[+]Institute of Pharmaceutical Chemistry, University Medical School, P.O. Box 121, H-6701 Szeged; [x]Chemical Department, Pedagogical Training College, H-6720 Szeged; [o]Spectroscopic Department, EGIS Pharmaceuticals, P.O. Box 100, H-1475 Budapest; [□]Central Research Institute for Chemistry, Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary

(*Received in UK* 14 *July* 1986)

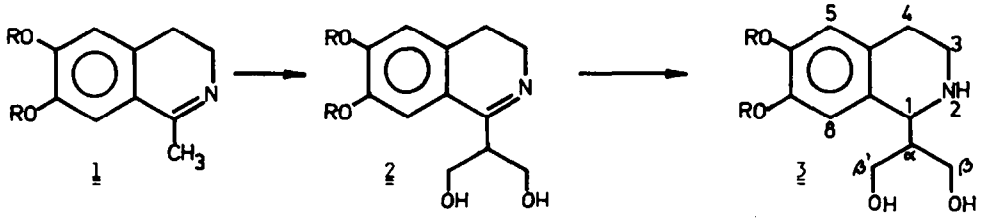
Abstract - N→O acyl migration of the N-benzoyl derivatives (4) of 1-[bis(hydroxymethyl)-methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a) gave the threo- and erythro-O-benzoyl compounds (6a, 6b), which were converted to cis- and trans-1-hydroxymethyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolines (11a, 11b). The structures of the compounds prepared were proved by X-ray diffraction and NMR spectroscopic measurements.

Introduction

The wide current interest in small heterocycles such as azetidines and their fused-ring derivatives is due not only to the chemical aspects, but also to their appreciable role as chemotherapeutic agents.[2] A number of azeto[2,1-a]isoquinolines have recently been synthesized (see, e.g.[3-5]), mostly by means of cycloaddition to the C=N bond of 3,4-dihydroisoquinoline.[6] Several such compounds have antibiotic activity characteristic of β-lactams,[7] while others exhibit analgesic[8] and anti-inflammatory[9] action. The synthesis of the title compounds seemed to be of promise, in view of the potential biological activity of the products.

Syntheses

The starting material was 1-[bis(hydroxymethyl)-methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a); a rapid and convenient synthesis of this compound was recently reported.[10] By virtue of the high reactivity[11] of the active methyl group in 1, the addition of 2 molecules of formaldehyde and subsequent reduction gave the tetrahydroisoquinolines 3 in excellent yields.



a: R = CH_3, b: R = C_2H_5

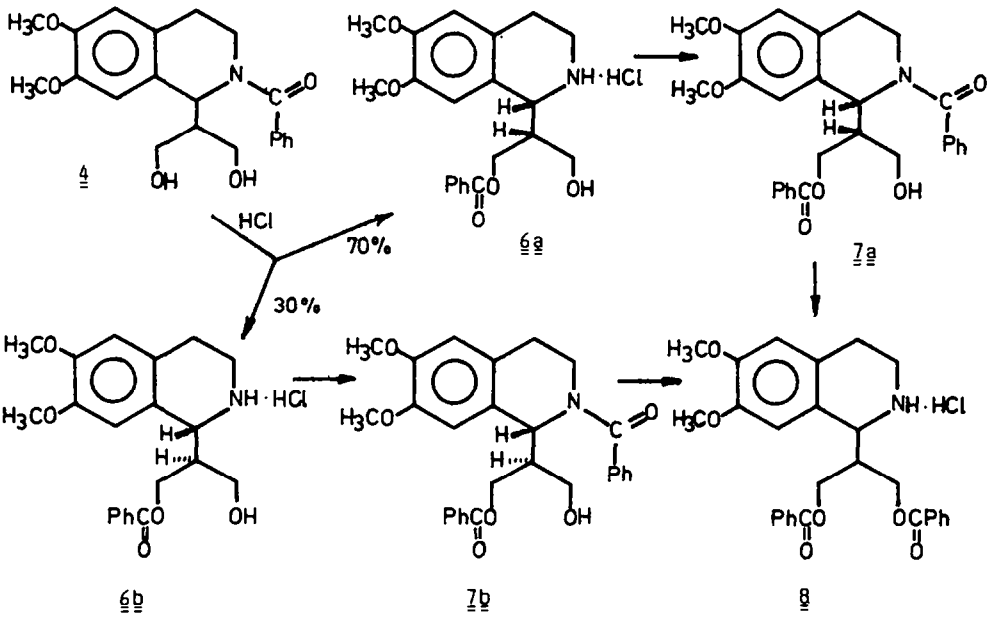
Scheme 1

The N-benzoyl derivative 4, prepared by benzoylation of 3a, was heated with hydrochloric acid to achieve N→O acyl migration, giving a mixture of the diastereomeric O-benzoyl derivatives (6a, 6b); the components were separated by frac-

tional crystallization from ethanol. The erythro-threo isomeric structures of the O-benzoyl derivatives produced by acyl migration were proved both by NMR measurements and by chemical conversions. The derivatives 6a,b were N-benzoylated to give the N,O-dibenzoyl compounds 7a,b; in both stereomers, N→O acyl migration furnished the same O,O-dibenzoyl derivative 8.

We have made a very thorough study of N→O acyl migration in the 1,2- and 1,3-aminoalcohols,[12-15] and in our experience, in agreement with the results of other authors,[16,17] this is usually an intramolecular process. In the acyl migration reaction 4→6, however, besides the epimers 6a,b, the hydrochloride of the bis(hydroxymethyl) derivative 3a can also be isolated, which is formed by transesterification with the participation of ethanol used as solvent, i.e. through an intermolecular process.

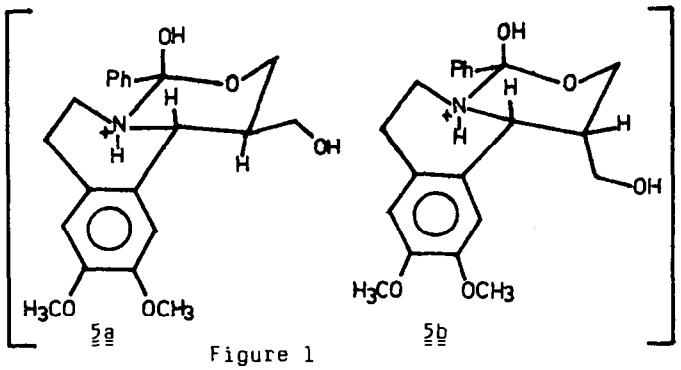
It is noteworthy that the bases can be liberated from the O-acyl hydrochlorides (6a,b, 8) under mild conditions, whereas O→N acyl migration (which occurs very readily in aminoalcohols containing an acyclic nitrogen atom) can be effected only by relatively vigorous treatment in the present case. This can be explained by the lower reactivity of the cyclic secondary nitrogen atom in 6a,b, which starts the O→N acyl migration by nucleophilic attack.



Scheme 2

Formation of the two isomers (6a,b) in a ratio of 3:1 can be accounted for by the relative stabilities of the 1,3-oxazine-type transition states occurring in the acyl migration.[14] The main component is the threo O-acyl isomer, which is formed from the thermodynamically more stable transition product 5a, containing an equatorial hydroxymethyl group; the secondary component, the erythro isomer, arises via the less favoured transition state 5b, where the hydroxymethyl group is in the axial position (Fig. 1).

The hydroxy group of isomers 6a,b can readily be exchanged for chlorine. The resulting 9a requires more vigorous, but 9b only mild alkaline treatment to undergo conversion into the corresponding 1-(benzoyloxymethyl)azetidines (12a,b). Acid hydrolysis of 9a or 9b furnishes the threo (10a) or erythro (10b) 1-(1[1]-hydroxy-



5a 5b

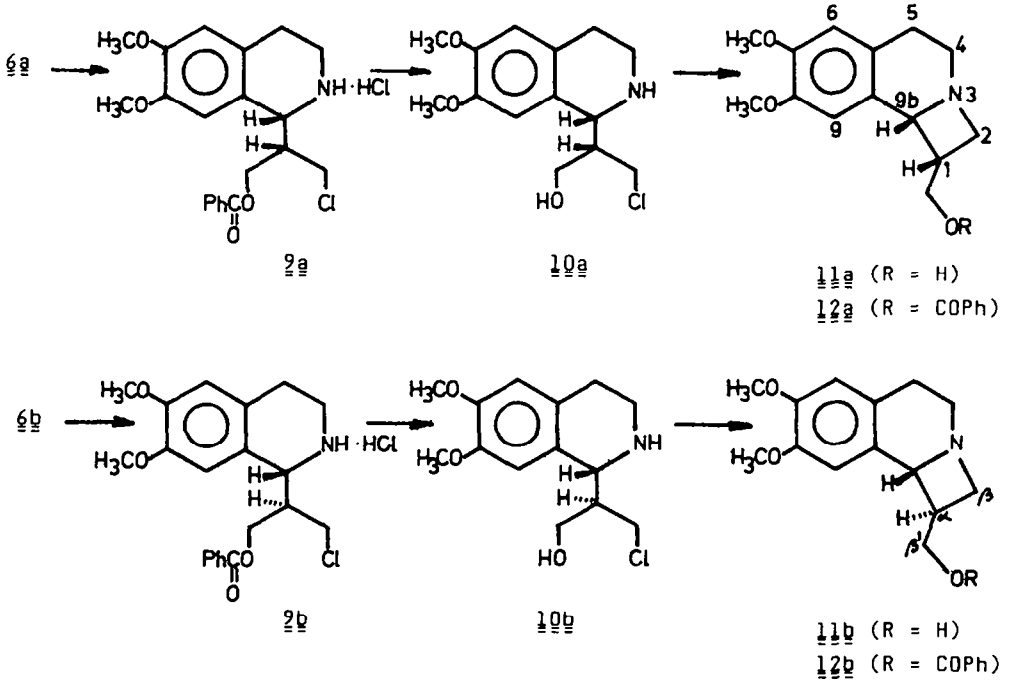
Figure 1

methyl-1[1]-chloromethyl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline hydrochloride. As is characteristic of γ-chloro-amines,[18] 10a and 10b are cyclized on mild alkaline treatment, to give cis- and trans-1-hydroxymethyl-7,8-di-methoxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolines (11a, 11b). Conversions of the hy-droxy group of the stereo-isomeric azetidines 11 lead to potential drugs with different biological actions.[19]

Spectroscopic studies

The structure of 3a is unequivocally substantiated, in part by the H-1 signal, and in part by the very large chemical shift of the C-1 signal (at 168.6 ppm in the spectrum of 2a) to the range characteristic of saturated carbon atoms (58.2 ppm).

There is scarcely any difference between the spectral data of the O-benzoyl diastereomers 6a and 6b. The presence of the benzoyl group is shown by the IR ester carbonyl band (6a: 1711, 6b: 1715 cm^{-1}), and also by the proton and carbon reso-nance signals of the aromatic ring. The H-1 signal half-bandwidth is a little larger for 6a (~5 Hz) than for 6b (~3.5 Hz); it follows that the open-form rotamer containing H-1 and H-α in the antiperiplanar position has a higher population in the 6a isomer, thereby showing the threo configuration of 6a. In this configuration of the rotamer the isoquinoline skeleton and the O-benzoyl group are in the sterically favoured anti position, whereas in the erythro structure their vicinity gives rise to steric hindrance; the occurrence of the latter rotamer is therefore less probable.



Scheme 3

Table 1. ^{1}H NMR data (δ_{TMS} = 0 ppm, coupling constants in Hz) on compounds 2a, 3a, 6a,b, 11a,b and 12a,b in $CDCl_3$ at 250 MHz[28].

Compound	H-1 s/d[a](1H)	H-3 m(2H)	H-4 m(2H)	H-5 s(1H)	H-8 s(1H)	CH_3O(6,7) 2xs(2x3H)	H-α m[b](1H)	H-β m[c](2H)	H-β' m[c](2H)	OH/NH broad(2H)
2a	-	3.61	2.62	6.70	7.07	3.90 3.92	3.24	3.95-4.10[d]		~4.8
3a	4.49	~2.6[e], ~3.2[e]	~2.9	6.58 6.60		3.81 3.86	2.13	3.65-3.90[d]		4.09[f]
6a[g]	4.41	2.55-2.85[d] ~3.0[e], ~3.15[e]		6.68	6.48	3.78 3.83	~2.7[d]	4.02 4.10	4.42 4.56	~3.6
6b[g]	4.45	~2.6[e], ~3.25[e]	~2.9,	6.62	6.55	3.82 3.83	2.42	3.70[h]	4.61 4.87	~4.15
11a	4.81	2.4-3.5[d,i]		6.66	6.59	3.82 3.87		2.4-3.5[d,i]		
11b	4.52	2.3-3.5[d]		6.65	6.55	3.81 3.87	2.3-3.5[d]		~4.05	4.95[e]
12a[g]	4.93	2.42[e], 2.68[e] 2.85-3.2		6.66	6.50	3.84 3.56[d]	3.22	~3.55[d]	3.86 3.96	-
12b[g]	4.62	2.45-3.10[d]		6.68	6.48	3.87 3.64	~2.6[d]	3.31 3.55	4.73 4.80	-

[a] Broad signal, half-bandwidth ~5 Hz (3a,6), d, J(H-1,H-α): 3.5 (6b), ~7 (11a), ~3 (11b), 7.4 (12a) and 3.3 Hz (12b). [b] Multiplicity: quintet (2a), sextet (3a, 6b), broad s (12a). [c] A or B part of an ABX spin-system (dd) for 6a (β and β'), 6b (β'), 12a (β') and 12b (β and β'); J(A,B), J(A,X) and J(B,X): 11, 4.2 and 3.2 (6a, β), 11.2, 8.6 and 5.3 (6a, β'), 11.4, 7.7 and 6.6 (6b, β'), 11.5, 8.0 and 5.3 (12a, β'), 8.3, 9.0 and 4.0 (12b, β), and 10.8, 9.2 and 6.5 Hz (12b, β'), respectively. β' denotes the methylene protons vicinal to the O-benzoyl group (6a,b and 12a,b) or to the hydroxy group (11a,b). [d] Overlapping signals. [e] Intensity 1H. [f] OH: d, J(H-β,OH): 5.4 Hz, intensity: 2H, NH? [g] The aromatic part in the spectra of 6a,b, 12a,b: ArH-3',5'(td,2H) 7.36-7.47; ArH-4'(td,1H) 7.50-7.66; ArH-2',6'(dd,2H) 7.82-8.10 ppm. [h] ~s(2H); AB spin-system, near to the A_2 limiting case ($\delta A \cong \delta B$). [i] Total intensity of the overlapping multiplets: 10H.

In the conformation of the erythro isomer containing the O-benzoyl group in the anti position relative to the isoquinoline skeleton, the CH_2OH group is subjected to the anisotropic shielding effect of the aromatic ring;[20a] accordingly, the upfield shift (3.70 ppm) of the corresponding signal (H-β) in the spectrum of 6b as compared with that (4.06 ppm) for 6a affords further evidence in support of the suggested configurations.

In the compounds containing an azetidine ring (11a,b and 12a,b), the NMR data prove the configurations unambiguously. The presence of the acyl group in the benzoyl derivatives 12a,b is clearly shown by the IR carbonyl bands (12a: 1705, 12b: 1715 cm^{-1}) and by the ^{1}H and ^{13}C NMR signals of the aromatic ring.

The upfield shifts, mainly of the C-1 and C-α signals, but to a lesser extent of the C-4a and C-8a signals too, in 11a and 12a relative to those in 11b and 12b indicate a more crowded steric structure, i.e. the cis configuration of H-1 and H-α (steric compression shift[21]). A noteworthy feature is the extensive shielding of the methylene carbon in the azetidine ring adjacent to the nitrogen; this is

also a consequence of the field effect, and can be explained by the strong steric hindrance between H-α and H-4.

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) for compounds 2a, 3a, 6a,b, 11a,b and 12a,b in $CDCl_3$ solution at 20.15 MHz[a,28]

Compound[b]	C-1	C-3	C-4	C-4a	C-8a	C-5,8	C-6,7	OCH_3(6,7)	C_α	C_β	$C_{\beta'}$
2a	168.6	46.1	25.6	121.3	131.7	109.5 110.9	147.9 151.5	55.9	56.4	45.1	62.7[c]
3a	58.2	42.4	29.4	128.2[d]	128.4[d]	108.9 112.0	147.6[c]	55.9	56.1	45.6	62.3[e] 64.3[e]
6a[f]	57.6	42.4	29.4	128.1[d]	128.8[d]	109.8 112.8	147.9 148.0	56.0	56.3	44.0	62.4[e] 63.6[e]
6b[f]	56.7	42.0	29.3	128.2[d]	128.9[d]	110.1 112.7	147.9 148.1	56.0	56.3	44.2	61.7[e] 64.4[e]
11a	61.5[g]	43.4	21.9	125.9	127.2	110.6 111.6	147.3 147.4	55.45	55.53	38.5	61.5[g] 49.2[h]
11b	61.5	44.8	22.5	126.1	129.5	109.3 111.7	147.4 148.1	55.67	55.72	43.5	64.3 48.7[h]
12a[f]	61.7	43.6	21.8	125.7	127.4	110.3 111.8	147.5 147.6	55.2	55.4	35.6	63.5 48.7[h]
12b[f]	62.2	45.1	22.7	126.7	129.8	109.1 112.0	147.6 148.3	55.6	55.9	40.6	67.3 48.6[h]

[a] At 62.89 MHz for 2a and 3a. [b] Assignments were proved in all cases by DEPT measurements. [c] Two overlapping lines. [d,e] Assignment may be reversed. [f] Aromatic C-1'—C-6' lines (6a,b, 12a,b) 127.8-133.1 ppm. [g] Two overlapping lines, proved by proton-coupled spectrum. [h] Methylene ($C_{\beta'}$) carbon of the azetidine.

The proton resonance spectra also support the configurations. The H-1,H-α vicinal coupling constants for 11a and 12a are larger than 7 Hz, while for the isomers 11b and 12b they are about 3 Hz. Corresponding to the dihedral angle of 0° and in accordance with the Karplus relation[22] for four-membered cycles,[20b] $J^{cis} > J^{trans}$. Thus, the cis position of H-1 and H-α relative to the azetidine ring in 11a and 12a also follows from these data.

Definitive evidence is provided by the signals of the hydrogen of the exocyclic methylene group attached to the benzoyloxy group (in 12a an upfield shift of almost 1 ppm is observed as compared with the isomeric counterpart), and also by the H-α signal, which changes in the opposite sense (in 12b a shielding greater by about 0.6 ppm was observed). This is due to the anisotropic effect of the fused benzene ring, acting on the methylene group situated above the plane of the ring in the cis isomer 12a, and on the H-α atom in the similar position in 12b.

X-Ray analysis of 11a and 11b

X-Ray analysis of diastereomers 11a and 11b was undertaken not only to distinguish between them, i.e. to determine the relative configurations at the chiral centres, C(9b) and C(1), but also to clarify the effects of the different orientations of the 1-CH_2OH group on the conformation of the four-membered azetidine

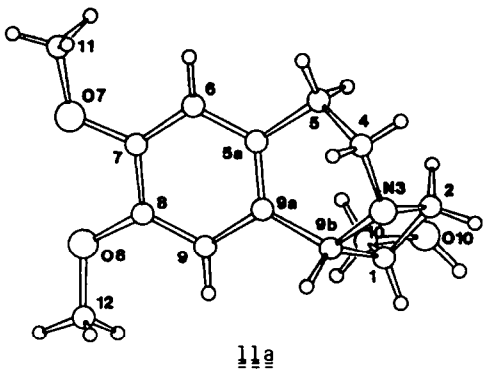
ring, fused to the isoquinoline heterocycle by the common nitrogen atom [N(3)] and the adjacent carbon atom [C(9b)]. A perspective view of the molecules **11a** and **11b** (Figure 2), computed from the final fractional atomic coordinates given with their e.s.d.'s in Table 3,[23] reveals a *cis* relative configuration in **11a** and a *trans* configuration in **11b** (the torsional angles of H(1) and H(9b) about the C(1)-C(9b) bond are -10.5 and 92.6°, respectively). As shown by the exocyclic torsional angles [**11a**/**11b**: C(10)-C(1)-C(2)-N(3): 133.7(3)/-99.3(3)°; C(10)-C(1)-C(9b)-N(3): -130.9(3)/100.4(3)°], the 1-CH_2OH group is *pseudo*-*equatorially* oriented to the azetidine ring in **11a**, whereas it is *pseudo*-*axial* in **11b**. This is accompanied by a somewhat larger puckering of the four-membered ring in **11b** [the mean torsional angle being 16.2(2)°] than in **11a** [11.2(2)°], which, through the *cis* B/C ring junction compels the distorted $^5H_4(^5S_4)$ half-chair shape of ring B (**11a**) to change towards an E_4-envelope conformation (**11b**). The puckering[24] parameters of the B rings are as follows:

ring B	**11a**	**11b**
Q(Å)	0.458(3)	0.403(3)
θ(°)	61.3(4)	54.9(4)
φ(°)	82.6(4)	71.4(4)

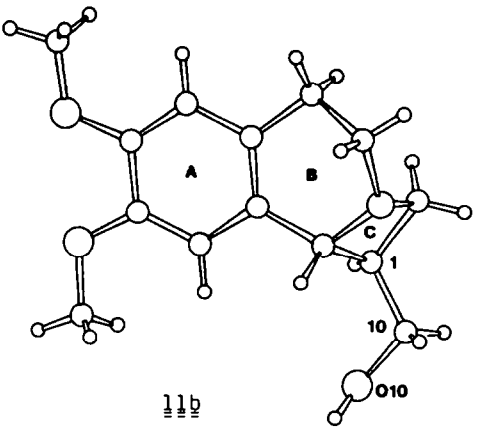
Table 3. Fractional coordinates for non-hydrogen atoms, with their e.s.d.'s in parentheses, in **11a** and **11b**[28]

	11a			**11b**		
Atom	x/a	y/b	z/c	x/a	y/b	z/c
O(7)	-0.0142(1)	-0.1350(2)	-0.2158(2)	0.9420(1)	0.3775(2)	0.2878(2)
O(8)	0.0930(1)	-0.0422(2)	-0.3637(2)	0.8804(1)	0.5443(2)	0.0591(2)
O(10)	0.3798(1)	0.3402(2)	0.2033(2)	0.5707(1)	0.6585(2)	0.0378(2)
N(3)	0.4257(1)	-0.0784(2)	0.2465(2)	0.6281(1)	0.5322(2)	0.5204(2)
C(1)	0.4167(1)	0.1146(2)	0.1512(2)	0.6044(1)	0.4836(2)	0.2643(3)
C(2)	0.4384(2)	0.0579(3)	0.3076(3)	0.5870(1)	0.4078(3)	0.4298(3)
C(4)	0.3642(2)	-0.1682(3)	0.2992(3)	0.6733(1)	0.4867(3)	0.6629(3)
C(5)	0.2597(2)	-0.1214(3)	0.2626(3)	0.7305(1)	0.3690(3)	0.6208(3)
C(5a)	0.2169(1)	-0.0974(2)	0.0959(2)	0.7691(1)	0.4218(2)	0.4722(2)
C(6)	0.1190(1)	-0.1260(2)	0.0206(3)	0.8390(1)	0.3750(2)	0.4540(2)
C(7)	0.0797(1)	-0.1068(2)	-0.1317(3)	0.8745(1)	0.4172(2)	0.3170(3)
C(8)	0.1388(1)	-0.0565(2)	-0.2127(2)	0.8408(1)	0.5102(2)	0.1911(2)
C(9)	0.2352(1)	-0.0295(2)	-0.1393(2)	0.7728(1)	0.5580(2)	0.2096(2)
C(9a)	0.2753(1)	-0.0501(2)	0.0157(2)	0.7366(1)	0.5150(2)	0.3503(2)
C(9b)	0.3833(1)	-0.0252(2)	0.0908(2)	0.6625(1)	0.5742(2)	0.3641(2)
C(10)	0.3467(2)	0.2283(2)	0.1104(3)	0.5480(1)	0.5872(3)	0.1854(3)
C(11)	-0.0716(2)	-0.2066(3)	-0.1454(3)	0.9783(1)	0.2818(4)	0.4082(4)
C(12)	0.1525(2)	-0.0146(3)	-0.4545(3)	0.8508(1)	0.6429(3)	-0.0681(3)

Within experimental error (3σ criterion), the corresponding bond lengths and angles agree well showing the excellent internal consistency of the two structure determinations. There is only one angle [C(10)-C(1)-C(9b)] which differs significantly. The larger angle [120.0(3)°] in **11a** *vs.* 114.3(3)° in **11b** can be attributed to the unfavourable promixity of the protons of C(10) and C(9a) [the C(10)-C(1)-C(9b)-C(9a) angle of -11.5(3)° indicates almost eclipsed C(10) and C(9a) atoms], which opens the angle accordingly.



11a



11b

Figure 2. A perspective view of the molecular structures of 11a and 11b with atomic numbering. The bare numbers are for carbon atoms unless indicated otherwise. The hydrogen atoms are shown but not labelled. For structure 11b, only the rings and the differently oriented CH_2-OH moiety are numbered.

In each structure the hydroxy group forms an intermolecular hydrogen-bond with the acceptor N(3), which has pronounced pyramidality.

			D.....A	H.....A	DH.....A
11a	O(10)-H(10)...N(3)	$(1-x,\frac{1}{2}+y,\frac{1}{2}-z)$	2.826(2) Å	1.893(2) Å	176.0(2)°
11b	O(10)-H(10)...N(3)	$(x,\frac{3}{2}-y,\frac{1}{2}+z)$	2.850(2) Å	1.838(2) Å	164.2(2)°

EXPERIMENTAL

IR spectra were run in KBr discs on a Specord-75 (JENA) grating spectrometer (12a,b) or on a Bruker IFS-113v FT spectrometer (all other compounds) equipped with an Aspect 2000 computer.

The NMR spectra were recorded in 5 or 10 mm tubes at room temperature on a Bruker WM-250 FT (^{1}H spectra and, for 2a and 3a, ^{13}C spectra) or a WP-80 SY FT spectrometer (^{13}C spectra for 6a,b, 11a,b and 12a,b), controlled by an Aspect 2000 computer, at 250.13 MHz (^{1}H) and 62.89 or 20.14 MHz (^{13}C) in $CDCl_3$ solution, using the deuterium signal of the solvent as the lock and TMS as internal reference. The most important measuring parameters for the ^{1}H and ^{13}C NMR spectra were as follows: sweep width: 5 and 16 or 5 kHz, pulse width: 1 (^{1}H) and 7 or 3.5 (^{13}C) μs (ca. 20° and 30° flip angle), acquisition time 1.64 and 1.05 or 1.64 s, number of scans: 16 and 1-8 K, computer memory: 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (LB 0.7 and 1.0 Hz) and complete proton noise decoupling (ca. 1.5 or 3 W) for ^{13}C measurements were applied.

Benzoylation of isoquinolines 3a, 6a and 6a (Method A)

The isoquinoline derivative 3a, 6a or 6b (0.02 mol) was acylated with benzoyl chloride (0.11 mol) in the presence of sodium hydroxide (0.15 mol for 3a, and 0.25 mol for 6a,b) by the Schotten-Baumann method. After drying and concentration of the benzene extract, trituration of the residue with ether gave 7a and 7b, respectively, as crystalline compounds.

N → O acyl migration in N-benzoyl derivative 4 (Method B)

Compound 4 (7.45 g; 0.02 mol) was suspended in ethanol (50 ml), and ethanol containing 20% dry hydrogen chloride (10 ml) was added. Refluxing of the mixture for about 15 min gave a clear solution, which was refluxed for 1 h and then allowed to stand at room temperature. The product (6a) which deposited was filtered off and

washed with ethanol. The mother liquor was concentrated to 15 ml and stored at room temperature overnight. The precipitated product 6b was collected by filtration. After evaporation of the mother liquor and recrystallization of the residue from a mixture of ethanol and ether, compound 3a.HCl, formed by intermolecular transesterification was isolated, m.p. 212-214 °C.

OH → Cl exchange in 6a and 6b (Method C)

The hydrochloride 6a or 6b (4.08 g; 0.01 mol) was mixed with thionyl chloride (5 ml) during cooling in an ice-bath. The reaction mixture was left to stand for 4 h at room temperature with occasional shaking. It was then concentrated under reduced pressure, and the evaporation was repeated several times with the addition of benzene. Trituration of the residue with acetone gave crystalline 9a and 9b, respectively.

Table 4. Analytical data on isoquinolines 4 and 6-11[a,b]

Compound	M.p., °C Solvent	M.p. of HCl salt[a], °C	Method	Yield %	Formula M.w.	Calcd./Found % C	H	N
4	163-164 methanol	-	A	95	$C_{21}H_{25}NO_5$ 371.42	67.90 67.78	6.78 6.91	3.77 3.93
6a	103-104 ether	215-216	B	64	$C_{21}H_{26}ClNO_5$ 407.89	61.83 61.78	6.43 6.55	3.43 3.60
6b	102-103 ether	182-184	B	22	$C_{21}H_{26}ClNO_5$ 407.89	61.83 61.22	6.43 6.74	3.43 3.63
7a	136-137 benzene	-	A	90	$C_{28}H_{29}NO_6$ 475.52	70.72 70.90	6.15 6.25	2.95 2.98
7b	142-143 benzene	-	A	89	$C_{28}H_{29}NO_6$ 475.52	70.72 70.90	6.15 6.33	2.95 3.02
8		172-174	B	96[c] 92[d]	$C_{28}H_{30}ClNO_6$ 511.99	65.68 65.43	5.91 6.14	2.74 2.63
9a	118-120 ether	198-199	C	97	$C_{21}H_{25}Cl_2NO_4$ 426.33	59.16 59.34	5.91 6.18	3.29 3.44
9b	e	135-137	C	89	$C_{21}H_{25}Cl_2NO_4$ 426.33	59.16 59.29	5.91 5.99	3.29 3.49
10a	-	216-217	D	96	$C_{14}H_{21}Cl_2NO_3$ 322.23	52.18 52.68	6.57 6.56	4.35 4.48
10b	-	205-206	D	85	$C_{14}H_{21}Cl_2NO_3$ 322.23	52.18 52.68	6.57 6.64	4.35 4.23
11a	140-142 benzene	216-218	E	93	$C_{14}H_{20}ClNO_3$ 285.77	58.84 58.59	7.05 7.27	4.90 4.67
11b	123 ether	174	E	86	$C_{14}H_{20}ClNO_4$ 285.77	58.84 58.39	7.05 6.78	4.90 4.72
12a	78-81 ether	172-174	E	86	$C_{21}H_{24}ClNO_4$ 389.87	64.69 64.45	6.20 6.41	3.59 3.65
12b	96-98 ether	179-181	E	91	$C_{21}H_{24}ClNO_4$ 389.87	64.69 64.50	6.20 6.62	3.59 3.47

[a] All HCl salts were recrystallized from ethanol-ether. [b] Analyses are given for HCl salts. The bases, obtained from the hydrochlorides with Na_2CO_3, also gave satisfactory microanalyses. [c] From 7a. [d] From 7b. [e] When the free base was formed from 9b.HCl, it underwent conversion to the corresponding azetidine 12b.

Hydrolysis of benzyloxy derivatives 9a and 9b (Method D)

Compound 9a or 9b (4.26 g; 0.01 mol) was refluxed in a mixture of 15% aqueous hydrochloric acid (30 ml) and ethanol (20 ml) for 6 h. Water (100 ml) was added and the reaction mixture was concentrated to 50 ml, whereupon benzoic acid sublimed in needles. Product 10a or 10b crystallized from the residue when this was left to stand at room temperature.

Conversion of 9a and 10 into azeto[2,1-a]isoquinolines (11 and 12) (Method E)

Compound 9a or the hydrochloride of 10a or 10b (3.2 g; 0.01 mol) was refluxed in methanol (50 ml) containing sodium hydroxide (0.4 g; 0.01 mol) for 3 h. After evaporation to dryness, the residue was dissolved in boiling ethanol (100 ml) and the solution was filtered. When the filtrate was left to stand for a few hours, the hydrochloride of 11a,b or 12a,b separated out.

X-Ray crystal structure determination of 11a

Crystal data: $C_{11}H_{13}NO_3$, M_r = 249.31, monoclinic, a = 14.480(1), b = 10.090(1), c = 9.387(1) Å, β = 108.53(1)°, U = 1300.4(4) Å^3, D = 1.273 g.cm^{-3}, Z = 4, F(000) = 536, space group $P2_1/c$, μ = 6.9 cm^{-1} for Cu-K$_\alpha$ radiation (λ = 1.54184 Å).

Intensities of 2440 unique reflections were collected on an Enraf-Nonius CAD-4 diffractometer in the range $1.5 < \theta < 75.0$ by an ω-2θ scan, using graphite monochromated Cu-K$_\alpha$ radiation. Cell constants were determined by least squares refinement of 25 reflections. Three standard reflections were monitored in every hour and showed no significant decrease during the exposure. After data reduction, 2080 reflections with $I > 3.0\sigma(I)$ were taken as observed. The phase problems were solved by direct methods using the MULTAN 82 program.[25] In the course of the isotropic least squares refinement of the positional parameters of non-hydrogen atoms, an empirical absorption correction was calculated with the DIFABS[26] program. The minimum and maximum corrections were 0.8142 and 1.2975. The fractional coordinates of H atoms bound to carbon atoms were generated from assumed geometries, while that of the OH group was located in a difference Fourier map. The hydrogen positions were only included with a mean isotropic temperature factor (fixed as the B_{eq} of the adjacent atom +1 Å^2) in the structure factor calculation. Final R = 0.053, R_w = 0.062, R_{tot} = 0.062, S = 5.46, $w = [\sigma^2(F_o) + 0.25(pF_o)^2]^{-1}$, where p = 0.01. The highest peak in the final difference Fourier map was 0.39 e.Å^{-3}. Scattering factors were taken from standard tables.[27] All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP system of Enraf-Nonius with local modifications.

Crystal structure determination of 11b

Crystal data: $C_{11}H_{13}NO_3$, M_r = 249.31, monoclinic, a = 19.142(1), b = 8.482(1), c = 8.029(1) Å, β = 92.70(1)°, U = 1302.2(4) Å^3, D_c = 1.272 g.cm^{-3}, Z = 4, F(000) = 536, space group $P2_1/c$, μ = 6.9 cm^{-1} for Cu-K$_\alpha$ radiation.

Data collection, structure determination and refinement were basically similar to those for 11a. Of 2572 unique reflections, 2461 were taken as observed with $I > 3.0\sigma(I)$. MULTAN 82, minimum and maximum absorption corrections: 0.0278, 1.4967. H positions were only included with a mean isotropic temperature factor in the SF calculations. Full matrix refinement, $\Sigma w(\Delta F)$ minimized for 163 parameters. Final R = 0.054, R_w = 0.056, R_{tot} = 0.056, S = 13.48, $w = [1 + [(F_o - 5)/43]^2]^{-1}$. The highest peak in the final difference Fourier map was 0.28 e.Å^{-3}.

REFERENCES AND NOTES

1. Part 99/103: A. Kálmán, Gy. Argay, P. Sohár, J. Szabó, L. Fodor, G. Bernáth, J. Mol. Struct., submitted for publication. Part of this work was presented in a lecture by G. Bernáth, F. Fülöp, J. Kóbor, J. Lázár, G. Motika, P. Sohár, Gy. Argay, A. Kálmán at "The Third International Kyoto Conference on New Aspects of Organic Chemistry", November 18-22, 1985, Kyoto, Japan. See: Abstract p. 208.
2. A. Kleman, J. Engel, "Pharmazeutishce Wirkstoffe", 2. Aufl. Georg Thieme Verlag, Stuttgart, 1982.
3. E. Schaumann, U. Wride, G. Adiwidjaja, Chem. Ber., 117, 2205 (1984).
4. D. R. Shridhar, B. Ram, V. L. Narayana, A. K. Awasthi, G. J. Reddy, Synthesis, 1984, 846.
5. M. Miyake, N. Tokutake, M. Kirisawa, Synth. Comm., 14, 353 (1984).
6. A. K. Bose, J. C. Kapur, S. D. Sharma, M. S. Manhas, Tetrahedron Letters, 1978, 2319.

7. J. Finkelstein, K. G. Holden, C. D. Perchonock, Tetrahedron Letters, 1978, 1629.
8. Bristol Myers Co. Fr. Pat., 1,580,899; Chem. Abstr., 73, 14718 (1970).
9. A. J. Bose, U.S. Pat., 3,546,211; Chem. Abstr., 74, 125468 (1971).
10. J. Kóbor, F. Fülöp, G. Bernáth, Heterocycles, accepted for publication; G. Bernáth, J. Kóbor, F. Fülöp, E. Ezer, Gy. Hajós, É. Pálosi, L. Dénes, L. Szporny, Eur. Pat., EP 143,333; Chem. Abstr., 103, 215202 (1985).
11. L. Grethe, Isoquinolines, Part 1. In series of the Chemistry of Heterocyclic Compounds, Vol. 38 (Eds. A. Weissberger, E. C. Taylor), John Wiley, New York, 1981. p. 120.
12. G. Bernáth, K. Kovács, K. L. Láng, Tetrahedron Letters, 1968, 2713.
13. G. Bernáth, K. L. Láng, Gy. Göndös, P. Márai, K. Kovács, Tetrahedron Letters, 1968, 4441.
14. G. Bernáth, K. Kovács, K. L. Láng, Acta Chim. Acad. Sci. Hung., 65, 347 (1970) and references cited therein.
15. L. V. Pavlova, F. Yu. Rachinskii, Usp. Khim., 37, 1369 (1968).
16. M. D. Rozwadowska, Przegrupowiani a zwiazane z migracyj grupy acylowey. Universitet im Adama Miczkiewicza w Poznanin. Seria Chemia NR 24, Poznan, 1977.
17. G. Bernáth, K. L. Láng, Gy. Göndös, P. Márai, K. Kovács, Acta Chim. (Budapest), 74, 479 (1972).
18. J. Kóbor, Szegedi Tanárképző Főisk. Tud. Közl., 1973, 119; Chem. Abstr., 103, 47808 (1974).
19. G. Bernáth, J. Kóbor, F. Fülöp, A. Kálmán, P. Sohár, E. Ezer, Gy. Hajós, L. Dénes, L. Szporny, É. Pálosi, Ger. Pat., DE 3,439,157; Chem. Abstr., 103, 160404 (1985).
20. P. Sohár, Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida, 1983-84. a) Vol. 1, pp. 35-38, b) Vol. 2, pp. 19, 20.
21. D. M. Grant, B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
22. M. Karplus, J. Chem. Phys., 30, 11 (1959).
23. H atom coordinates, together with the anisotropic vibrational parameters for both structures, have been deposited at the Cambridge Crystallographic Data Centre.
24. D. Cremer, J. A. Pople, J. Am. Chem. Soc., 97, 1354 (1975).
25. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, M. M. Woolfson, MULTAN 82. A System of Computer Programs for the Automatic Solution of Crystal Structure from X-ray Diffraction Data. Univs of York, England and Louvain, Belgium (Adapted for use on the PDP-11/34 minicomputer).
26. N. Walker, D. Stuart, Acta Cryst., A39, 158 (1983).
27. International Tables for X-ray Crystallography, Vol. III. Birmingham: Kynoch Press (1962) (Present distributor: D. Reidel, Dordrecht).
28. In Tables 1 and 2 the isoquinoline numbering (see: 3 in Scheme 1) is used for the azeto/2,1-a/isoquinoline derivatives 11a,b and 12a,b in order to allow easier comparison of the corresponding ^{1}H and ^{13}C lines in the two series, i.e. H-9b, H-4, H-5, H-6 and H-9 in the azeto/2,1-a/isoquinolines 11-12 correspond to the H-1, H-3, H-4, H-5 and H-8 signals of the isoquinolines 2a, 3a, 6a and 6b. As concerns the X-ray investigations, the IUPAC numbering of azeto/2,1-a/-isoquinolines (Fig. 2) is applied for 11a and 11b.