Saturated Heterocycles. 176 [1]. Synthesis and Steric Structure of Quaternary Azeto[2,1-*a*]isoquinoline Stereoisomers

Gábor Bernáth*, Ferenc Fülöp and Judit Árva

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, P. O. Box 121, Hungary

Jenö Kóbor

Chemical Department, Pedagogical Training College, H-6702 Szeged, P. O. Box 396, Hungary

Pál Sohár

Spectroscopic Department, EGIS Pharmaceuticals, H-1475 Budapest, P. O. Box 100, Hungary

Received June 27, 1990

Starting from 1-substituted azeto[2,1-*a*]isoquinoline diastereomers, a number of quaternary salts were prepared. The reactions leading to the quaternary salts were stereospecific, independently of the configuration at C-1, resulting in diastereomers. The steric structures of the new compounds were proved by nmr spectroscopy.

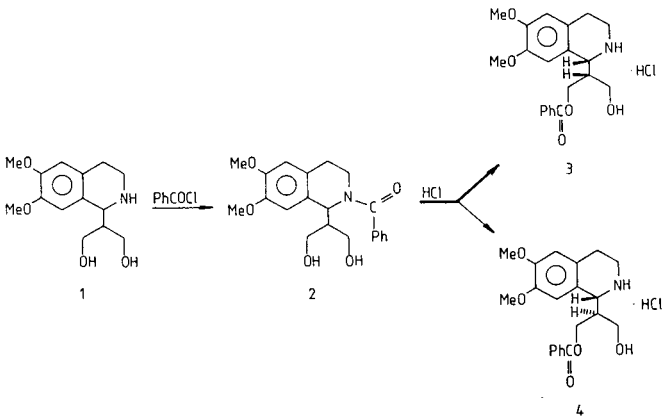
J. Heterocyclic Chem., **28**, 353 (1991).

Introduction.

Of the azeto[2,1-*a*]isoquinolines, mainly the 2-oxo derivatives are known [2-5]; their syntheses were prompted among others by pharmaceutical-chemical interest, due to the presence of the β-lactam ring. However, the products were found to be practically ineffective [2-5]. On the other hand, there are only a few publications [6-8] dealing with the synthesis and stereochemical study of stereoisomeric azetoisoquinolines; we therefore decided to carry out the synthesis and structure elucidation of such compounds and their quaternary salts.

The reactivity of the methyl group of 1-methyl-3,4-dihydroisoquinolines was earlier utilized to prepare the trifunctional aminoalcohol derivative **1** [9] by the addition of 2 moles of formaldehyde and subsequent reduction. Besides its many other valuable reactions, this versatile compound **1** is also a suitable starting material for the synthesis of azetoisoquinoline diastereomers. Benzoylation of **1** gives the *N*-acyl derivative **2** (Scheme 1). The *N*→*O* acyl migration then results in the formation of the *threo*- and *erythro*-*O*-benzoyl compounds **3** and **4** in a ratio of 3:1. Fractional crystallization can be used to separate the diastereomers in good yields [6]. The main products of the acyl migration, **3**, was earlier converted to the azeto[2,1-*a*]-isoquinolines **5** and **6** by treatment with thionyl chloride and then with alkali.

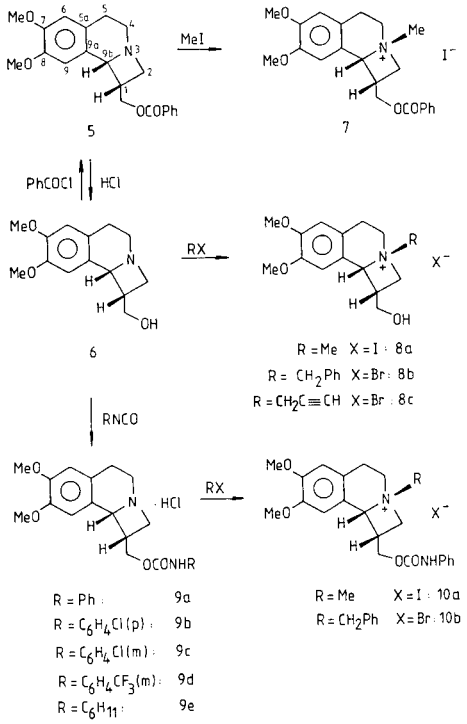
Scheme 1



Synthesis.

In the present work, the reactions of **5** and **6** and some related azetidine derivatives are reported. Isocyanate addition to the hydroxy group of **6** gave the urethanes **9a-9e**

Scheme 2

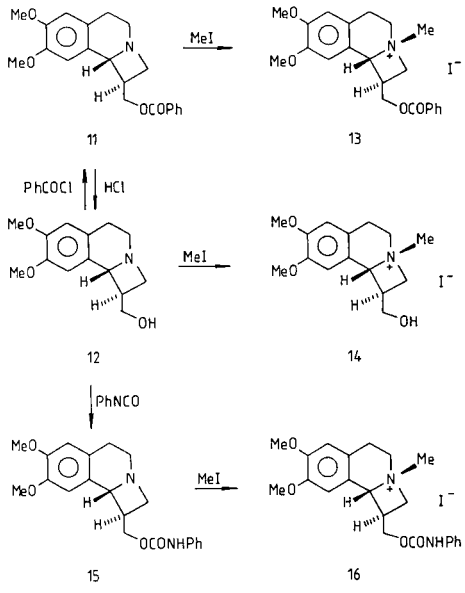


in 70-90% yields. Benzoylation of **6** in chloroform resulted in the *O*-benzoyl derivative **5**.

Treatment of **5**, **6** and **9a** with organic halides yielded the quaternary salts **7**, **8a-c** and **10a,b** (Scheme 2). Quaternization occurs extremely rapidly; with halides of high reactivity, it is virtually instantaneous.

The *trans* counterparts **11** and **12** of the *cis*-azetidines **5** and **6** can be obtained from the minor component **4** of the acyl migration on the analogy of the above descriptions [6]. Quaternary salt formation from these compounds and phenyl isocyanate addition to the hydroxy group of **12** occurred with the same reactivity as in the case of the corresponding *cis* compounds. The products of these reactions are the *trans*-azetidine derivatives **13-16** (Scheme 3).

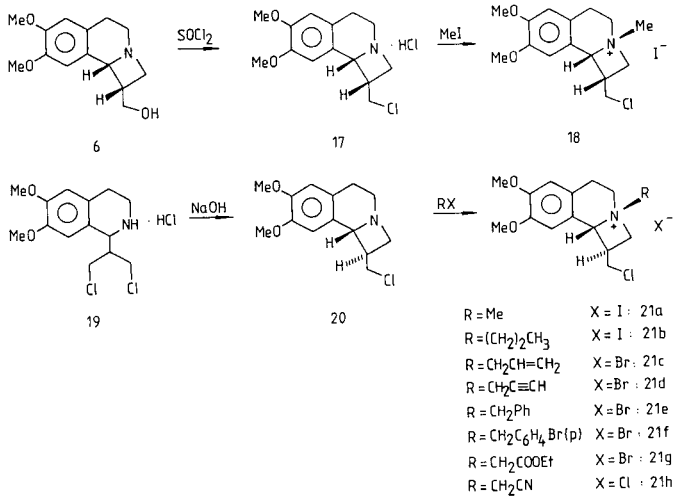
Scheme 3



The 1-(chloromethyl)azetidine isomers **17** and **20** were synthesized in different ways; the *cis* isomer **17** was prepared from **6** with thionyl chloride, by exchanging the hydroxy group for chlorine. The *trans* isomer **20** was synthesized by treatment of the aminoalcohol **1** with thionyl chloride, and the resulting dichloro compound **19** was cyclized with alkali [8]. A number of quaternary salts **21a-g** were prepared from the readily available compound **20** (Scheme 4). The reaction of the *cis* isomer **17** with methyl iodide gave the quaternary iodide **18**. No significant differences were found in the quaternization reactions of azetoisoquinolines variously substituted in position 1, nor in the case of the diastereomeric pairs.

It was earlier shown by nmr spectroscopy in solution and by X-ray diffraction in the solid state that C-1 of the azetidine ring is attached to C-9b *quasi-axially* in both diastereomers; hence, rings B and C are nearly perpendicular to each other [6,8]. The high rate of quaternization

Scheme 4



can be explained by the bridgehead nitrogen being a member of a strained ring.

The products of the direct and reversed quaternizations of different tetrahydroisoquinolines are mixtures of the *N*-epimers [10-16]. The stereoselectivity observed in the quaternization reactions of the analogues that have a fused azetidine ring is a consequence of the structure of this strained, four-membered hetereocycle, favouring attack from the β side (Figure 1).

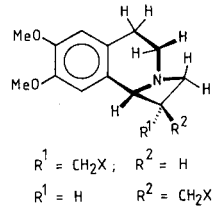


Figure 1

NMR Spectroscopy.

Of the new compounds prepared, the quaternary salts **7**, **8a**, **8b**, **10a**, **10b**, **13**, **14**, **16**, **21a** and **21e** were selected for detailed spectroscopic study. The most important spectral data proving the suggested structures are listed in Tables 1 and 2. Since *trans* annelation of the four- and six-membered hetero rings is impossible for steric reasons, the configuration at the nitrogen atom, *i.e.* the *cis* steric positions of the *N*-methyl or *N*-benzyl group and of H-9b, are certain.

Two relatively stable conformations of the six-membered hetero ring are to be considered. However, one of them, the twist-like form, with C-4 and N-3 in out-of-plane positions, is sterically unfavoured because of the close approach (~2.2 Å) of the *endo* H-2 and H-5 atoms. The possibility that the conformation may be influenced by the configuration at C-1 can be disregarded, as the C-5 chemi-

Table 1

^{1}H-NMR Chemical Shifts (δ TMS = 0 ppm) of Compounds **7, 8a,b, 10a,b, 13, 14, 16, 18** and **21a,e** in DMSO-d_6 solution at 250 MHz

Compound	OCH_3 2 x s	(7,8) (2 x 3H)	H-6 s (1H)	H-9 s (1H)	H-9 [b] d (1H) [c]	H-1 and CH_2 (2,4,5, α) m's (total intensity is 9H)	$NCH_{3/2}$ s (3H) [d]
7	3.62	3.82	6.75	6.72	6.08	~3.1, ~3.3, 4.00 [e], ~4.2, 4.25 [e], ~4.4, 4.58 [f], 4.78 [f]	3.86
8a	3.73	3.79	6.99	6.79	5.54	2.9-3.3, ~3.55, ~4.24 [g]	3.44
8b	3.74	3.78	6.97	6.91	5.87	3.0-3.2, ~3.5, ~4.21 [f], ~4.56 [f]	4.94, 5.10
10a	3.70 [h]	3.79	6.76	6.66	5.82	2.92 [i], 3.1 [i], ~3.7 [h], ~4.0, ~4.2, ~4.6 [f], ~4.7 [f]	3.71 [j]
10b	3.72 [h]	6.98 [j]		6.92	5.94	3.0-3.9, ~4.35 [f], ~4.60 [f]	5.03, 5.20
13	3.63	3.88	6.83	6.75	5.76	~3.15, ~3.35, ~4.3, 4.85, 5.0	3.71
14	3.74	3.78	7.02	6.84	5.30 [h]	~2.7, ~3.1, ~3.25, ~3.68, 4.18 [f], 4.32	3.24
16	3.67	3.78	7.02 [h]	6.82	5.40	2.9-3.4, 3.7-3.9, ~4.35, 4.35, ~4.55	3.32
18	3.74	3.79	7.01	6.83	5.56	~3.0, 3.1-3.4, ~3.65, ~3.85, ~4.27	3.34
21a	3.75	3.79	7.03	6.88	5.44	~3.1, ~3.3, ~3.85, ~4.15, ~4.35	3.32
21e	3.75	3.76	7.01	6.98	5.80	~3.15, ~3.6, 4.1-4.4, ~4.75	4.81, 5.11

Further signals: ArH-2,6, d/m (2H): 7.85 ± 0.1 (**7, 8b, 10b** [j], **21e**), 7.45 ± 0.05 (**10a, 10b** [k], **16**), 7.98 (**13**); ArH-3,5, t/m (2H) : 7.42 ± 0.03 (**7, 13, 21e** [h]), 7.55 (**8b** [h], **10b** [h,j]), 7.26 ± 0.04 (**10a, 10b** [k], **16**); ArH-4, t/m (1H): 7.55 ± 0.02 (**7, 8b** [h], **10b** [h,j], **13**), 7.00 ± 0.03 (**10a, 10b** [k], **16** [h]), 7.45 [h] (**21e**); OH, t (1H): 4.58 (**8a**), 4.68 (**8b**), 5.30 [h], (**14**); NH, s (1H): 9.65 (**10b**), 9.76 (**16**). [a] Solvent was deuteriochloroform for compounds **7, 10a** and **13**. [b] Characteristic ir-frequencies: ν OH: 3350 (**8a, 14**), ~3280 (**8b**), ν NH: ~3237 (**10a**), 3300-2750 (**10b**), ~3235 (**16**), ν C=O: 1713 (**7**), 1726 (**10a**), 1735 (**10b, 16**), 1720 (**13**). [c] Split by 9.2 (**7, 18**), 9.5 (**8a,b, 10a**), 8.5 (**10b, 13**), 6.3 (**14**) and 8.2 Hz (**16, 21a,e**). [d] NCH_2 for **8b, 10b** and **21e**, 2 x d (2 x 1H), split by 12.6 (**8b, 10b**) and 12.9 Hz (**21e**). [e] dd (1H). [f] ~t (1H). [g] ~d (2H). [h] Overlapping signals. [i] ~d (1H). [j] Benzyl group. [k] *N*-Phenyl group.

Table 2

^{13} C-NMR Chemical Shifts (δ TMS = 0 ppm) of Compounds **7, 8a,b, 10a,b, 13, 14, 16, 18** and **21a,e**, in DMSO-d_6 Solution [a] at 20 or 63 MHz [b]

Compound	C-1	C-2	C-4	C-5	C-5a	C-6,9		C-7,8		C-9a	C-9b	CH_2 (α)	OCH_3 (7,8)		NCH_3 [c]
7	32.5	60.8 [e]	55.6 [f]	24.3	127.9 [g]	109.3	111.1	148.3	149.0	123.1	73.2	60.9 [e]	55.7 [f, h]		53.8
8a [d]	35.7	63.6	56.4	25.3	125.9	112.0	113.5	149.5	150.2	121.5	74.3	50.0	57.6	57.7	54.4
8b [d]	36.1	67.7	53.7	25.3	126.6	112.4	113.5	149.6	150.5	121.7	72.9	61.0	57.5	57.6	59.9
10a	32.7	61.5 [e]	56.0	24.6	123.3 [e]	109.7	111.2	148.6	149.2	123.0 [e]	73.3	60.6 [e]	55.7	56.5	53.9
10b [b]	33.9	67.7	53.9	25.3	126.8	112.3	113.5	149.8	150.7	120.9	72.7	63.1	57.3	57.5	59.5
13 [d]	38.7	66.1 [e]	58.1	25.5	127.1	111.4	114.0	149.8	150.9	124.6	75.3	64.5 [e]	57.4	57.6	54.0
14 [d]	41.4	64.3	57.9	25.4	126.7	111.4	114.0	149.9	150.7	125.1	74.4	60.7	57.6 [h]		53.0
16	39.0	65.1 [e]	58.1	25.4	126.8	111.2	113.9	149.9	150.9	124.5	75.1	64.7 [e]	57.4	57.6	53.7
18	36.5	63.4	56.4	25.4	126.3	112.5	113.7	149.7	150.8	120.3	74.5	44.0	57.5	57.6	54.7
21a	41.2	65.6	58.2	25.4	127.0	111.8	113.9	149.8	150.9	124.1	75.6	46.1	57.6	57.7	53.6
21e [d]	42.0	67.1	63.2	25.4	127.7	112.3	114.0	149.7	151.1	124.3	74.9	46.1	57.7	57.8	55.1

Further signals: Aromatic carbons, C-1: 128.5 (**7**) [g], 130.5 (**8b, 10b** [i], **21e**), 131.1 (**13**), 137.7 (**10a**), 140.5 (**10b** [j], **16**); C-2,6; 127.9 (**7**) [g], 134.0 ± 0.2 (**8b, 10b** [i], **21e**), 118.6 (**10a**), 120.2 (**10b** [j], **16**), 131.0 (**13**); C-3,5: 128.9 (**7**), 128.5 (**10a**), 130.6 ± 0.1 (**8b, 10b** [h], **13, 16, 21e**); C-4: 132.8 (**7**), 131.9 ± 0.1 (**8b, 10b** [i], **21e**), 118.1 (**10a**), 124.3 (**10b** [j], **16**), 135.3 (**13**);C=O: 164.9 (**7**), 152.4 (**10a**), 154.4 (**10b**), 167.3 (**13**), 155.0 (**16**). [a] Solvent was deuteriochloroform for **7** and **10a**. [b] Measuring frequency was 20.14 MHz for **8a,b, 10b, 14** and **18** and 62.89 MHz for **7, 10a, 13, 16** and **21a,e**, respectively. [c] NCH_2 for **8b** and **10b**. [d] Assignments were proved by DEPT measurements. [e,f,g] Assignments may also be interchanged. [h] Two lines. [i] *N*-Benzyl group. [j] *N*-Phenyl group.

cal shifts are similar for all compounds. Such an H-2, H-5 interaction would give rise to a significant steric compression shift (see below) in the C-2,5 signals. In the homogeneous conformation, therefore, the six-membered hetero ring is nearly in the boat form, and the slightly distorted azetidine ring is attached to the *isoclinal* C-1 and *quasi-equatorial* C-2 atoms.

The C-1, C-9b relative configuration (*i.e.* the *cis* or *trans* position of the corresponding hydrogen atoms) can be established from the magnitude of the vicinal proton-proton coupling constant ^{3}J(H-1,H-9b). The relation $^3J_{vic}(cis)$ $^3J_{vic}(trans)$ follows from the Karplus relation [17], which is of general validity for three- and four-membered cyclic compounds [18,19]. For the analogous bases of the quaternary compounds discussed in this paper, ^{3}J(*cis*) is 7.5-8.0 Hz, whereas ^{3}J(*trans*) is 2.8-3.5 Hz, and this permits a very simple and unequivocal determination of the configuration [8].

The corresponding coupling constants in the spectra of the quaternary salts are in the range 6.3-9.5 Hz (*cf.* Table 1). If the configurations which follow from the synthetic pathways are assumed, the coupling constant intervals characteristic of the *cis* and *trans* isomers are only slightly separated; the two ranges for the compounds investigated are 8.9-9.6 and 6.3-8.5. However, if the data on the *cis-trans* pairs of isomers **7-13, 8a-14, 10a-16** and **18-21a** are compared, it can be seen that the relation ^{3}J(*cis*) > ^{3}J(*trans*) holds true without exception and the difference is

Table 3

Analytical Data on Azetoisoquinolines Prepared

No.	Mp (°C) Solvent	Yield (%)	Formula MW	Analysis Calcd/Found (%) C	H	N
7	105-110 [b]		$C_{22}H_{26}INO_4$	53.34	5.29	2.83
	EtOH-ether	[a]	495.35	53.20	5.41	2.67
8a	202-206		$C_{15}H_{22}INO_3$	46.04	5.67	3.58
	EtOH-ether	[a]	391.25	46.20	5.80	3.59
8b	192-195		$C_{21}H_{26}BrNO_3$	60.00	6.23	3.33
	EtOH-ether	[a]	420.35	59.75	6.40	3.20
8c	188-190		$C_{17}H_{20}BrNO_3$	55.75	5.50	3.82
	EtOH-ether	[a]	366.26	55.81	5.73	3.85
9a [c]	215-218	77	$C_{21}H_{25}ClN_2O_4$	62.29	6.22	6.92
	EtOH-ether		404.88	62.13	6.44	7.08
9b [c]	212-213	83	$C_{21}H_{24}Cl_2N_2O_4$	57.28	5.49	6.59
	EtOH-ether		440.33	57.28	5.67	6.58
9c [c]	163-165	80	$C_{21}H_{24}Cl_2N_2O_4$	57.28	5.49	6.59
	EtOH-ether		440.33	57.02	5.77	6.34
9d [c]	207-209	89	$C_{22}H_{24}F_3ClN_2O_4$	55.76	5.10	6.12
	EtOH-ether		441.46	55.61	5.32	6.26
9e [c]	195-197		$C_{21}H_{30}ClN_2O_4$	61.38	7.36	7.06
	EtOH-ether	[a]	410.93	61.53	7.60	7.14
10a	120-126 [b]		$C_{22}H_{27}IN_2O_4$	51.77	5.33	5.49
	EtOH-ether	[a]	510.37	51.70	5.34	5.49
10b	196-198		$C_{28}H_{31}BrN_2O_4$	62.22	5.78	5.37
	EtOH-ether	[a]	540.47	62.32	5.90	5.42
13	170-173		$C_{22}H_{26}INO_4$	53.34	5.29	2.83
	EtOH-ether	[a]	495.35	53.27	5.41	2.77
14	192-193		$C_{15}H_{22}INO_3$	46.04	5.67	3.58
	EtOH-ether	[a]	391.25	46.10	5.82	3.60
15 [c]	214-217	71	$C_{21}H_{25}ClN_2O_4$	62.29	6.22	6.92
	EtOH-ether		404.88	62.20	6.32	7.07
16	163-165		$C_{22}H_{27}IN_2O_4$	51.77	5.33	5.49
	EtOH-ether	[a]	510.37	51.65	5.42	5.33
18	189-190		$C_{15}H_{21}ClNO_2$	43.97	5.17	3.42
	EtOH-ether	[a]	409.70	44.04	5.30	3.51
21a	209-210		$C_{15}H_{21}ClINO_2$	43.97	5.17	3.42
	EtOH-ether	[a]	409.70	43.80	5.28	3.18
21b	129-134	84	$C_{18}H_{26}INO_2$	47.96	6.05	2.96
	EtOH-ether	[a]	450.77	47.93	6.05	2.96
21c	178-184		$C_{17}H_{21}BrClNO_2$	52.80	5.47	3.62
	EtOH-ether	[a]	386.72	52.76	5.71	3.40
21d	200-204		$C_{17}H_{19}BrClNO_2$	53.07	4.97	3.64
	EtOH-ether	[a]	384.70	52.90	5.07	3.66
21e	185-187		$C_{21}H_{24}BrClNO_2$	57.61	5.52	3.19
	EtOH-ether	[a]	437.78	57.39	5.36	3.40
21f	195-197		$C_{21}H_{24}Br_2ClNO_2$	48.71	4.67	2.71
	EtOH-ether	[a]	517.68	48.68	4.67	3.01
21g	137-139		$C_{18}H_{25}BrClNO_4$	49.72	5.80	3.22
	EtOH-ether	[a]	434.75	50.01	6.00	3.38

[a] Yield nearly quantitative. [b] With decomposition. [c] Hydrochloride salt.

significant (0.8, 3.2, 1.3 and 1.0 Hz, respectively). On the basis of these data, the *cis* configuration of compound **8b**, which has no counterpart, can be taken for granted; however, the *cis* or *trans* structure of **10b** and **21e** cannot be proved satisfactorily.

The ^{13}C-nmr spectra of the bases showed that the isomers can also be distinguished by means of the field effect. This is revealed by the upfield shift of the lines of carbon atoms carrying sterically hindered substituents 20; in the case of the bases, it was observed mainly for the C-1 and, to a smaller extent, the C-4,5 lines of the *cis* isomers. Systematic differences were also found in other carbon shifts of the isomeric base pairs, which apply, in part, in the quaternary series, too; however, the assignments of these signals are not certain, and hence these data could not be used as evidence in the determination of the configuration.

The measured field effects on the C-1 line for the four isomeric pairs are 6.2, 5.7, 6.3 and 4.7 ppm, respectively (Table 2). Thus, the configuration can be established with certainty from these data. There are only small differences in δ C-1 for the pairs **8a,b**, **10a,b** and **21a,e** ($\Delta\delta$ is 0.4, 1.2 and 0.8 ppm), which have identical configuration and differ only in the *N*-substituent (*N*-benzyl instead of *N*-methyl); this fact proves the suggested configurations of **8b** (*cis*), **10b** (*cis*) and **21e** (*trans*), even without a knowledge of the spectroscopic data on the isomeric pairs.

EXPERIMENTAL

The mp's were determined on a Boetius micro melting point apparatus and are uncorrected. The physical and analytical data on the prepared compounds are listed in Table 3. Compounds **1-6**, **11**, **12**, **17**, **19** and **20** were prepared as described earlier [6-9]. The ir spectra were determined in potassium bromide discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer. The ^{1}H- and ^{13}C-nmr spectra were recorded at room temperature in deuteriochloroform and/or DMSO-d_6 solution in 5 or 10 mm tubes, on Bruker WM-250 (^{1}H, ^{13}C) and WP-80-SY (^{13}C) FT-spectrometers controlled by an Aspect 2000 computer, at 250 (^{1}H) and 63 or 20 (^{13}C) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as the internal standard. The most important measurement parameters were as follows: sweep width 5 and 15 kHz; pulse width 1 (^{1}H) and 7 or 3.5 (^{13}C) μs (*ca.* 20° and *ca.* 30° flip angle); acquisition time 1.64 and 1.02 or 1.64 s; number of scans 16 or 32 (^{1}H) and 0.5-33 K (^{13}C); computer memory, 16 K. Complete proton noise decoupling was used (*ca.* 3 or *ca.* 1.5 W) for ^{13}C spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement with line width 0.7 (^{1}H) and 1.0 or 2.0 Hz (^{13}C).

DEPT [21] spectra were run in a standard way [22], using only the θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K; relaxation delay for protons 3 s, 90° pulse widths 10.8 and 11.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

Isocyanate Addition to 1-Hydroxymethylazetidines **6** and **12**.

Compound **6** or **12** (5 mmoles, 1.25 g) was dissolved in benzene (30 ml), and phenyl isocyanate (5.5 mmoles) was added. After re-

fluxing for 1-5 hours the solvent was evaporated off and the residue transformed to the hydrochloride with ethanolic hydrogen chloride. In toluene, the addition was complete after refluxing for 0.5-2 hours; the yields were practically the same.

Benzoylation of 1-Hydroxymethylazetidines **6** and **12**.

Compound **6** or **12** (5 mmoles, 1.25 g) was dissolved in chloroform (30 ml), and benzoyl chloride (5.5 mmoles, 0.64 ml) was added. The mixture was allowed to stand overnight at room temperature; it was then washed several times with aqueous sodium hydrogencarbonate solution. After drying (sodium sulfate) the chloroform was evaporated off and the residue was recrystalized from ether.

Compound **5** had mp 77-80°, yield 56% (lit [6] mp 78-81°).

Compound **11** had mp 96-98°, yield 51% (lit [6] mp 96-98°).

Quaternization of Azetoisoquinolines.

The azetoisoquinoline (3 mmoles) was dissolved in acetonitrile (20 ml) and the corresponding halide was added: 2-3 equivalents for the volatile halides, and 1 equivalent for the less volatile halides. After standing for 1-10 hours at room temperature, the solvent and the excess of halide were evaporated and the product was recrystallized. In many cases the crystalline product separated out from the acetonitrile solution.

Acknowledgement.

The authors' thanks are due to the Chemical Works of Gedeon Richter Ltd., Budapest, for financial support of this research. We are indebted to Miss M. Halász, Mrs. J. Csákvári, Mr. A. Fürjes and Mr. Gy. Tolnai for skilled technical assistance.

REFERENCES AND NOTES

[1] Part **175**: P. Sohár, G. Stájer, G. Bernáth, *Org. Magn. Res.*, accepted for publication.

[2] A. K. Bose, J. C. Kapur, S. D. Sharma and M. S. Manhas, *Tetrahedron Letters*, 2319 (1987).

[3] M. Miyake, N. Tokutake and M. Kirisawa, *Synth. Commun.*, **14**, 353 (1984).

[4] D. R. Schridhar, B. Ram, V. L. Narayana, A. K. Awasthi and G. J. Reddy, *Synthesis*, 846 (1984).

[5] E. Schaumann, U. Wride and G. Adiwidjaja, *Chem. Ber.*, **117**, 2205 (1984).

[6] G. Bernáth, J. Kóbor, F. Fülöp, P. Sohár, Gy. Argay and A. Kálmán, *Tetrahedron*, **42**, 5139 (1986).

[7] F. Fülöp, J. Kóbor, G. Bernáth and P. Sohár, Bio-organic Heterocycles 1986 - Synthesis, Mechanism and Bioactivity, Elsevier Science Publishers, Amsterdam, 1986, p 155.

[8] J. Kóbor, F. Fülöp, G. Bernáth and P. Sohár, *Tetrahedron*, **43**, 1887 (1987).

[9] J. Kóbor, F. Fülöp and G. Bernáth, *Heterocycles*, **24**, 2227 (1986).

[10] A. T. Bottini, Stereoselectivity in Quaternisations of Tertiary Amines in Selective Organic Transformations, Vol 1, B. S. Thyagarajan ed, Wiley-Interscience, New York, 1970.

[11] G. Bernáth, *Nature*, **189**, 304 (1961).

[12] B. Ribár, D. Lazar, A. Kálmán, J. Kóbor and G. Bernáth, *J. Chem. Soc., Perkin Trans. 2*, 1141 (1977).

[13] Gy. Argay, A. Kálmán, B. Ribár, D. Lazar, J. Kóbor and G. Bernáth, Cryst. Struct. Commun., **8**, 917 (1979).

[14] N. A. El-Sayad, R. A. Swaringen, D. A. Yeowell, R. C. Crouch, S. Hurlbert, R. W. Miller and A. T. McPhail, *J. Chem. Soc., Perkin Trans. 1*, 2067 (1982).

[15] J. B. Stenlake, W. D. Williams, N. C. Dhar and I. G. Marschall, *Eur. J. Med. Chem. Chim. Ther.*, **9**, 233 (1974).

[16] R. Smith, V. Elango and M. Shamma, *J. Org. Chem.*, **49**, 581 (1984).

[17] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *ibid.*, **33**, 1842 (1960).

[18] P. Sohár, Nuclear Magnetic Resonance Spectroscopy, Vol **2**, CRC, Press, Boca Raton, Florida, 1984, p 19.

[19] A. R. Katritzky and C. W. Rees, Comprehensive Heterocyclic Chemistry, Vol **7**, Pergamon Press, Oxford, 1984, p 237.

[20] D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).

[21] D. T. Pegg, D. M. Doddrell and M. R. Bendall, *J. Chem. Phys.*, **77**, 2745 (1982).

[22] M. R. Bendall, D. M. Doddrell, D. T. Pegg and W. E. Hull, High Resolution Multipulse NMR Spectrum Editing and DEPT, Bruker, Karlsruhe, 1982.