

Ibolya Prauda and József Reiter\*

Egis Pharmaceuticals Ltd., P. O. Box 100, 1475 Budapest, Hungary

Received April 24, 2000

New type pyrazol-3-yl-isoquinolinium hydrochloride (**8a**) and tetrazol-5-yl-isoquinolinium (**8b**) zwitterions were synthesised. Their structures were proved by ir, pmr, cmr, ms spectra as well as X-ray diffraction analysis of model compounds.

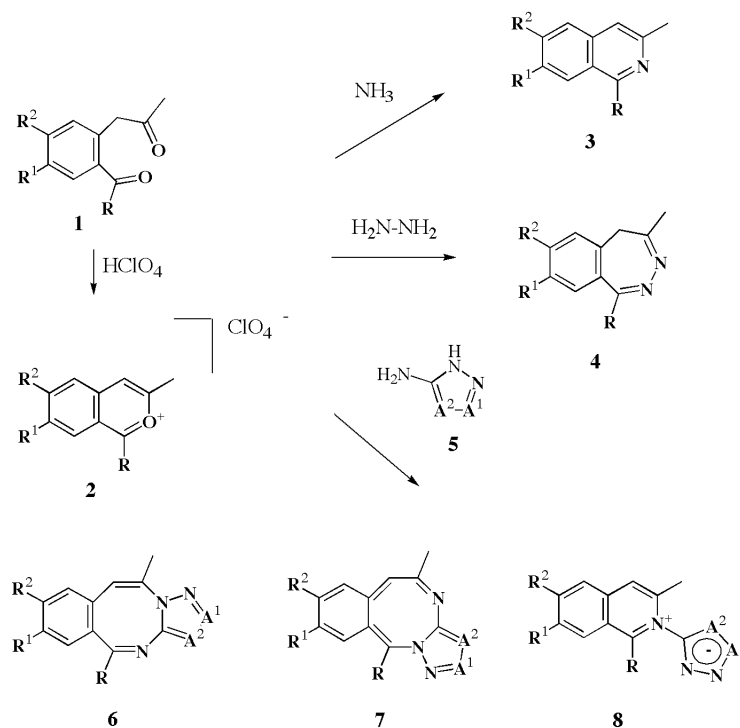
*J. Heterocyclic Chem.*, **38**, 199 (2001).

The synthesis of isoquinolines (**3**) by the reaction of ortho-acyl phenylacetones (**1**) or the pyrylium salts (**2**) with perchloric acid, and ammonia is well known from the literature [1] (Scheme 1). Carrying out the above reactions using hydrazine gives 2,3-benzodiazepines (**4**) [2]. The reactions above led us to the idea that in the reaction of amidines (**5**) with **1** or **2** either the **6** or **7** type 2,4-benzodiazocines or the **8** type isoquinolinium zwitterions should be formed.

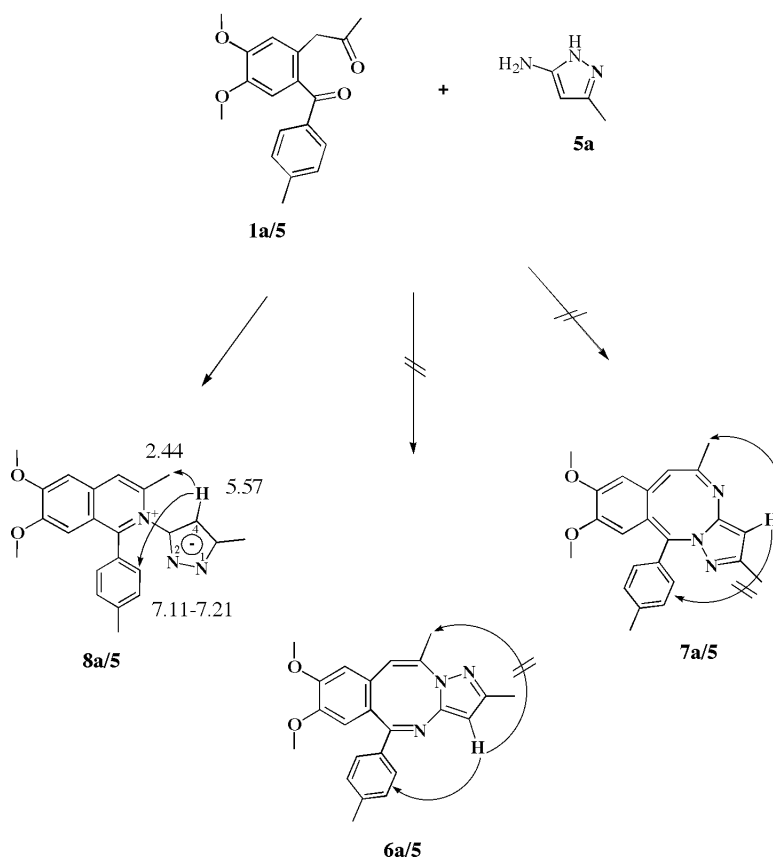
It was recently reported that some 2,4-benzodiazocines have valuable biological properties [3-4]. As Doleshall and coworkers [5-6] could have synthesised benzotriazepines only with the use of a five membered heterocyclic side ring we decided to start our synthetical work with 3-amino-pyrazoles (**5**,  $A^1$  and  $A^2 = \text{CH}$  or  $\text{CR}$ ) and 5-amino-tetrazoles (**5**,  $A^1 = A^2 = \text{N}$ ).

The reaction of 4,5-dimethoxy-2-(4-methylbenzoyl)-phenylacetone (**1a/5**,  $R = 4\text{-methylphenyl}$ ,  $R^1 = R^2 = \text{methoxy}$ ) with 5-amino-3-methyl-1*H*-pyrazole (**5a**,  $A^1 = \text{CCH}_3$ ,  $A^2 = \text{CH}$ ) led in acetonitrile to a sole product easily isolable from the reaction mixture (Scheme 2) (Table I). As discussed above its structure must correspond to **6a/5**, **7a/5** or **8a/5**. The elemental analysis, ms, ir, pmr and cmr spectra of the product obtained (Table III) is consistent with any of the structures **6a/5-8a/5** however, it does not allow one to distinguish between them. Irradiation of the pmr peak corresponding to the CH proton 4 of the pyrazole ring of **8a/5** resulted in observation of DNOE on both the C-methyl group of the newly built in heteroring and the 2H protons of the 4-methylphenyl group. This is only possible in case of the **8a/5** structure as molecules corresponding to **6a/5**

Scheme 1



Scheme 2



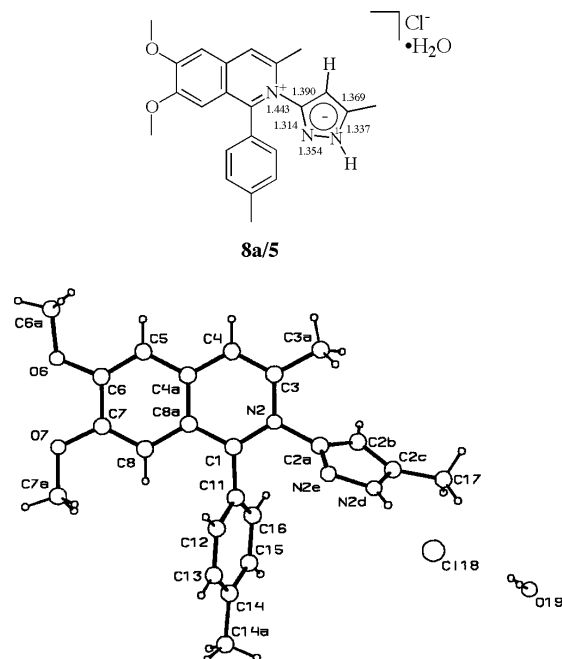
and **7a/5** have rigid bicyclic structures in which at least one of the above mentioned moieties is sterically too far from the pyrazole CH group to allow energy transfer.

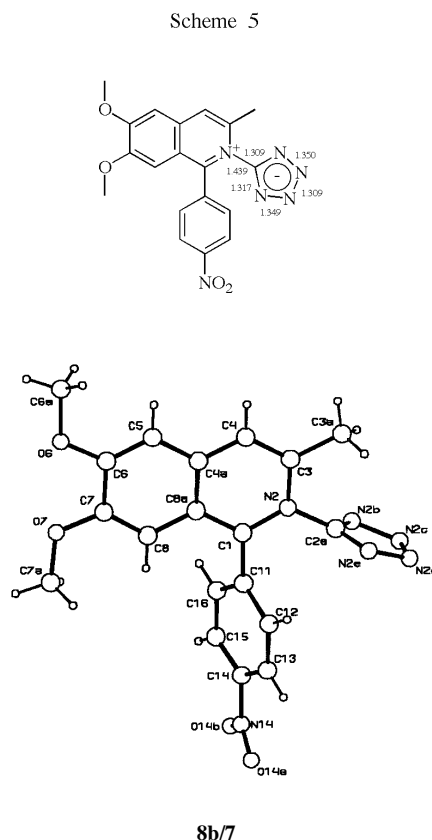
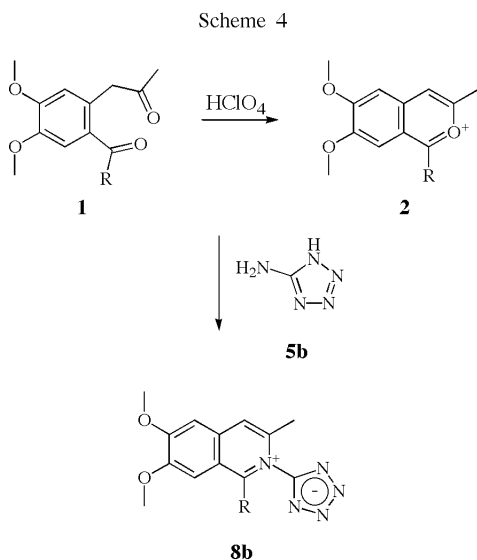
The synthetic, analytical and spectral data, of all other derivatives **8a**, it is compounds **8a/1-8a/8** obtained through analogous reactions of derivatives **1** or **2** and **5a** ( $A^1 = CCH_3$ ,  $A^2 = CH$  and  $A^1 = A^2 = CH$ , respectively) (Tables I and III), are in agreement with the model compound **8a/5**. Thus, pointing out that their structures are analogous to that of **8a/5** above.

The structure **8a** represents a zwitterion having the positive charge on the isoquinolinium nitrogen atom, while its negative charge is either delocalised throughout the pyrazole ring or more or less fixed to one of its nitrogen atoms.

Structure **8a** deduced from DNOE measurements was corroborated by X-ray diffraction analysis [7] of **8a/5.HCl**, as well (Scheme 3), proving the presence of the pyrazolo-isoquinolinium structure. It can be deduced from the measured pyrazole bond lengths as well as from the site of protonation of the pyrazole nitrogen atom 1 that the negative charge is preferably localised on nitrogen atom 1. As expected, both, the pyrazole and the 1-phenyl rings are

Scheme 3





strongly shifted out (nearly perpendicular) from the plane of the isoquinolinium ring system. This causes the close proximity of the pyrazole CH proton and the methyl group 3 as well as that of the ortho proton of the phenyl ring, resulting in the observed DNOE.

After the successful synthesis of **8a** ( $A^1 = \text{CCH}_3$ ,  $A^2 = \text{CH}$  and  $A^1 = A^2 = \text{CH}$ ) type (pyrazol-3-yl)isoquinolinium zwitterions the reactions with 5-amino-tetrazole (**5b**,  $A^1 = A^2 = \text{N}$ ) were carried out (Scheme 4). As expected, again zwitterions **8b** were obtained (Table II)

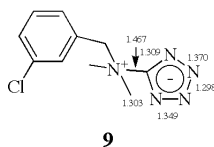
Table I  
Analytical Data of the Hydrochloride Salts of Pyrazol-3-yl-isoquinolinium Zwitterions

Compound	R	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup>	A <sup>2</sup>	Yield %	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis %			
									Calcd./Found			
									C	H	N	Cl
<b>8a/1</b>	4-Methyl-phenyl	Methoxy	Methoxy	CH	CH	61 [1]	231-234 (EtOH)	C <sub>22</sub> H <sub>22</sub> ClN <sub>3</sub> O <sub>2</sub> (395.89)	66.75 66.61	5.60 5.58	10.61 10.56	8.96 8.98
<b>8a/2</b>	4-Chloro-phenyl	Methoxy	Methoxy	CH	CH	58 [1] 68 [2]	220-224 (2-PrOH)	C <sub>21</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> (416.31)	60.59 60.42	4.60 4.62	10.09 10.04	17.03 17.11
<b>8a/3</b>	4-Methoxy-phenyl	Methoxy	Methoxy	CH	CH	57 [1]	241-244 (EtOH)	C <sub>22</sub> H <sub>22</sub> ClN <sub>3</sub> O <sub>3</sub> (411.89)	64.15 63.95	5.38 5.40	10.20 10.16	8.61 8.58
<b>8a/4</b>	4-Nitrophenyl	Methoxy	Methoxy	CH	CH	62 [1]	228-230 (EtOH)	C <sub>21</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>4</sub> (426.86)	59.09 58.86	4.49 4.48	13.13 13.07	8.31 8.35
<b>8a/5</b>	4-Methyl-phenyl	Methoxy	Methoxy	CCH <sub>3</sub>	CH	61 [1]	217-219 (HCl/H <sub>2</sub> O)	C <sub>23</sub> H <sub>24</sub> ClN <sub>3</sub> O <sub>2</sub> •H <sub>2</sub> O (427.94)	64.56 64.32	6.12 6.15	9.82 9.86	8.28 8.25
<b>8a/6</b>	3-Chloro-phenyl	Methylenedioxy		CCH <sub>3</sub>	CH	60 [1]	239-242 (EtOAc/2-PrOH)	C <sub>21</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> (414.31)	60.88 60.74	4.14 4.12	10.14 10.19	17.11 17.18
<b>8a/7</b>	4-Chloro-phenyl	Methoxy	Methoxy	CCH <sub>3</sub>	CH	69 [1]	206-209 (Acetone)	C <sub>22</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> (430.34)	61.40 61.24	4.92 4.90	9.76 9.72	16.48 16.53
<b>8a/8</b>	4-Nitrophenyl	Methoxy	Methoxy	CCH <sub>3</sub>	CH	71 [1]	219-222 (HCl/H <sub>2</sub> O)	C <sub>22</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>4</sub> (440.89)	59.93 59.87	4.80 4.81	12.71 12.77	8.04 8.07

[1] Starting from the corresponding phenylacetone (**1**).

[2] Starting from the corresponding pyrylium salt (**2**).

Scheme 6



9

the pmr and cmr spectra of which are again in agreement with the proposed structures (Tables IV) but do not proved them. Thus again single crystal X-ray diffraction analysis of 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-2-(tetrazol-5-yl)-isoquinolinium salt (**8b/7**) [7] (Scheme 5) was performed as model. As can be seen from the perspective view of **8b/7** the 1-(4-nitrophenyl) and the 2-(tetrazol-5-yl) rings are again nearly perpendicular to the plane of the isoquinolinium moiety. However, in this case the tetrazol-5-yl ring is totally symmetrical (see the bond lengths on Scheme 5) proving the full delocalisation of the negative charge through this heteroring. A similar situation was observed by G. B. Ansell [8] when single crystal X-ray diffraction analysis of 5-[(3-chlorobenzyl)dimethylammonium]tetrazolate (**9**) was carried out (Scheme 6 - see the analogous tetrazolyl bond lengths).

The spectral data of all other **8b** type isoquinolinium zwitterions **8b/1-8b/7** obtained in the reactions of derivatives **1** or **2** and **5b** were again in agreement with those of the corresponding model compound **8b/7** (see Tables II and IV), proving their analogous structure.

## EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The ms spectra were recorded on a Kratos MS25RFA instrument using a direct inlet probe in EI or CI mode. The pmr and cmr measurements were performed using Varian Gemini-2000 and Varian Unity Inova instruments. Standard Varian HSQC and HMBC programs were used. The stationary phase for chromatography was Kieselgel 60H (Merck 7736 for thin layer chromatography), for the eluents different mixtures of chloroform and methanol were used.

General Method for the Synthesis of Pyrazol-3-yl-isoquinolinium hydrochloride Zwitterions (**8a**).

A mixture of 0.02 mole of the corresponding 5-amino-1H-pyrazole derivative (**5**) ( $A^1 = \text{CH}$  and  $\text{CCH}_3$ , respectively,  $A^2 = \text{CH}$ ) (Fluka), 0.02 mole of the corresponding phenylacetone (**1**) [9] or the pyrylium salt (**2**) [9], respectively, 30 ml of acetonitrile and 2 ml of concentrated hydrochloric acid was refluxed with stirring for 3 hours. After cooling the crystals that precipitated were filtered off, washed with a small amount of acetonitrile, and recrystallised from an appropriate solvent (Table I).

General Method for the Synthesis of Tetrazol-5-yl-isoquinolinium Zwitterions (**8b**).

A mixture of 0.02 mole of the corresponding phenylacetone (**1**), 0.025 mole of 5-amino-tetrazole (**5b**) (Fluka) and 20 ml of acetic acid was refluxed with stirring for 4 hours. After cooling 50 ml of water was added to the reaction mixture. The crystals that precipitated were filtered off, washed with water and recrystallised from an appropriate solvent (Table II).

Table II  
Analytical Data of the Tetrazol-5-yl-isoquinolinium Zwitterions

Compound	R	R <sup>1</sup>	R <sup>2</sup>	A <sup>1</sup>	A <sup>2</sup>	Yield %	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis %			
									Calcd./Found	C	H	N
<b>8b/1</b>	2-Chloro-phenyl	Methoxy	Methoxy	N	N	60	238-241 (DMF)	C <sub>19</sub> H <sub>16</sub> ClN <sub>5</sub> O <sub>2</sub> •H <sub>2</sub> O (399.84)	57.08	4.54	17.52	8.87
									56.88	4.52	17.60	8.91
<b>8b/2</b>	3-Chloro-phenyl	Methylenedioxy		N	N	46	289-291 (AcOH)	C <sub>18</sub> H <sub>12</sub> ClN <sub>5</sub> O <sub>2</sub> •H <sub>2</sub> O (383.80)	56.33	3.68	18.25	9.24
									56.17	3.67	18.31	9.28
<b>8b/3</b>	4-Chloro-phenyl	Methoxy	Methoxy	N	N	75	248-251 (DMF)	C <sub>19</sub> H <sub>16</sub> ClN <sub>5</sub> O <sub>2</sub> (381.83)	59.77	4.22	18.34	9.29
									59.63	4.23	18.38	9.26
<b>8b/4</b>	3,4-Dichloro-phenyl	Methoxy	Methoxy	N	N	56	224-227 (MeOH)	C <sub>19</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>2</sub> (416.27)	54.82	3.63	16.82	17.03
<b>8b/5</b>	4-Methoxy-phenyl	Methoxy	Methoxy	N	N	79	240-243 (AcOH)	C <sub>20</sub> H <sub>19</sub> N <sub>5</sub> O <sub>3</sub> •H <sub>2</sub> O (395.42)	60.75	5.35	17.71	
									60.61	5.38	17.80	
<b>8b/6</b>	4-Nitrophenyl	Methoxy	Methoxy	N	N	64	248-251 (AcOH)	C <sub>19</sub> H <sub>16</sub> N <sub>6</sub> O <sub>4</sub> •H <sub>2</sub> O (410.39)	55.61	4.42	20.48	
									55.47	4.41	20.38	
<b>8b/7</b>	4-Nitrophenyl	Methoxy	Methoxy	N	N	77	300-301 (DMF)	C <sub>18</sub> H <sub>12</sub> N <sub>6</sub> O <sub>4</sub> (376.33)	57.45	3.21	22.33	
									57.29	3.22	22.41	

Table III  
Pmr and Cmr Spectral Data of Derivatives **8a**

Compound	H-4	H-5	H-8	H-3'	H-4'	ArH	C-1	C-3	C-4	C-5 C-6	C-7 C-8	C-3'	C-4'	C-5'	ArC	other
<b>8a/1</b>	8.57 s [1]	8.00 s	6.79 s	5.86 t (1.9 Hz)	7.59 t (1.8 Hz)	7.02-7.13 m (4H)	156.9	144.7	123.5	106.5 158.8	152.6 106.1	145.4	101.3	131.1	127.0 129.2 129.5 141.0	20.9, 21.4 56.1, 57.8 122.8, 138.6
<b>8a/2</b>	8.41 s [2]	7.79 s	6.73 s	6.41 d (2.4 Hz)	7.86 d (2.4 Hz)	7.54 m (4H)	155.6	144.3	122.4	106.4 158.6	152.3 105.7	146.4	103.7	131.5	128.5 129.3 132.2 135.4	20.5, 56.1 57.4, 138.1 123.0
<b>8a/3</b>	8.37 s [2]	7.79 s	6.81 s	6.38 d (2.4 Hz)	7.84 d (2.4 Hz)	7.00 d (8.9 Hz) 7.38 bs	157.2	144.2	122.8	106.9 158.4	152.1 105.6	146.7	103.6	131.4	113.7 122.5 131.9 160.5	20.6, 55.5 56.0, 57.3 122.4, 137.9
<b>8a/4</b>	8.51 s [2]	7.86 s	6.66 s	6.49 t (2.1 Hz)	7.85 t (2.1 Hz)	7.85 b 8.33 dd (9.2 and 1.5 Hz)	154.4	144.5	123.3	106.2 158.7	152.5 105.7	146.2	103.9	131.7	123.3 132.1 136.7 148.4	20.4, 57.4 56.3, 122.3 138.3
<b>8a/5</b>	8.56 s [1]	8.04 s	6.76 s	5.57 s	5.57 s	7.11-7.21 m (4H)	156.9	144.8	123.6	106.3 158.8	152.7 106.5	142.4	100.3	145.4	127.1 129.5 129.7 141.0	11.1, 20.1, 21.4, 56.1, 57.9, 122.8, 138.6
<b>8a/6</b>	8.44 s [2]	7.78 s	6.79 s	6.21 s	6.21 s	7.45-7.61 m (4H)	155.2	144.8	123.8	104.6 157.0	151.4 104.0	141.3	102.5	146.3	129.0 130.1 130.5 132.3	10.7, 20.3 102.7 124.3, 140.3
<b>8a/7</b>	8.44 s [2]	7.83 s	6.71 s	6.21 s	6.21 s	7.57 m (4H)	155.5	144.3	122.9	105.6 158.5	152.3 106.4	141.2	102.5	146.4	128.4 129.3 132.2 135.3	10.5, 20.1, 56.0, 57.1, 122.1, 137.9
<b>8a/8</b>	8.47 s [2]	7.84 s	6.65 s	6.24 s	6.24 s	7.80 bs (2H) 8.33 d (2H, 9.0 Hz)	156.3	144.2	123.1	105.4 158.4	152.3 105.9	141.2	102.5	145.9	123.1 131.9 136.5 148.2	10.7, 20.4, 56.1, 57.3, 122.5, 138.0

[1] Taken in deuteriochloroform.

[2] Taken in DMSO-d<sub>6</sub>

Table IV  
Pmr and Cmr Spectral Data of Derivatives **8b** Taken in a Mixture of Deuteriochloroform and Trifluoroacetic Acid

Compound	H-4	H-5	H-8	ArH	C-1	C-3	C-4	C-5 C-6	C-7 C-8	C-5'	ArC	other
<b>8b/1</b>	8.16 s	7.54 s	6.76 s	7.35-7.55 m (4 H)	153.8	144.6	123.3	105.3 160.6	153.7 105.6	157.2	127.3, 127.8 130.1, 131.3 133.2, 133.5	20.2, 56.4 57.5, 123.0 139.4
<b>8b/2</b>	7.92 s	7.33 s	6.90 s	7.26-7.39 m (4H)	156.2	144.8	124.4	105.4 158.8	153.9 103.8	160.3	128.2, 130.2 131.1, 133.0, 136.8	19.9, 105.3 125.3, 143.6
<b>8b/3</b>	8.16 s	7.52 s	6.98 s	7.35 d (8.4 Hz) 7.53 d (8.4 Hz)	158.6	146.3	125.3	107.4 160.7	155.8 109.0	163.1	128.5, 131.9 133.0, 141.4	20.1, 58.3 59.2, 125.3 142.5
<b>8b/4</b>	8.17 s	7.53 s	6.95 s	7.25 dd (8.2 and 2.2 Hz) 7.54 d (2.1 Hz) 7.63 d (8.2 Hz)	155.0	144.8	123.8	105.7 158.9	154.4 106.8	161.8	128.0, 129.1 131.9, 132.0 135.0	19.8, 56.7 57.6, 123.6 138.2
<b>8b/5</b>	8.06 s	7.50 s	6.94 s	6.84 d (8.6 Hz) 7.31 d (8.6 Hz)	157.2	144.8	122.1	105.1 158.7	152.5 106.9	158.2	113.7, 122.8 132.4, 161.0	20.2, 56.1 57.2, 121.3 138.1
<b>8b/6</b>	8.20 s	7.54 s	6.80 s	7.67 d (8.6 Hz) 8.37 d (8.6 Hz)	154.5	145.0	123.3	105.7 158.8	154.4 106.2	161.9	124.7, 131.8, 134.9, 149.8	19.8, 56.5 57.6, 124.0 141.0
<b>8b/7</b>	8.12 s	7.47 s	6.78 s	7.56 d (8.8 Hz) 8.29 d (8.8 Hz)	154.7	145.1	123.0	105.0 158.1	153.2 103.5	159.9	124.4, 131.4, 134.3, 149.6	19.8, 104.1 124.7, 142.7

1-(4-Chlorophenyl)-6,7-dimethoxy-3-methylisoquinolinium *N*-(Tetrazole-5-ide) (**8b/3**).

A mixture of 0.015 mole of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methylpyrylium perchlorate (**2b/3**) (R = 4-chlorophenyl) [9], 0.015 mole of the 5-amino-tetrazole (**5b**) (Fluka), 30 ml of acetonitrile and 2 ml of concentrated hydrochloric acid was refluxed with stirring for 5 hours. After cooling the crystals that precipitated were filtered off, washed with a small amount of acetonitrile, to yield 4.96 g of a mixture of the hydrochloride and perchlorate (mp 198-202°). This was dissolved in 20 ml of water and 15 ml of 1 *N* sodium-hydroxide was added to the solution. The crystals that precipitated were collected by filtration and washed with a small amount of water, to yield 3.32 g (58 %) of 1-(4-chlorophenyl)-6,7-dimethoxy-3-methylisoquinolinium *N*-(tetrazole-5-ide) (**8b/3**), mp 249-252°. The product is identical with that of **8b/3** obtained previously (Table II).

Acknowledgement.

The authors wish to express thanks to Dr. Sándorné Sólyom for recording the ir spectra, to Dr. Éva Szabó and Dr. Péter Slégel for recording the ms spectra. They also wish to thank Mr. Attila Fürjes, Mrs. Magdolna Nagy and Dr. István Kövesdi for recording the nmr spectra and their help with the

interpretation. Also, thanks to Mrs. Hirkóné Magdolna Csík for performing the elemental analysis and to Mrs. Lászlóné Berei for technical help.

#### REFERENCES AND NOTES

- [1] E. V. Kuznetsov, I. V. Shcherbakova and A. T. Balaban: "Benzo[c]Pyrylium Salts: Syntheses, Reactions, and Physical Properties" in *Advances in Heterocyclic Chemistry*, Vol. **50**, p 190, Edited by A. R. Katritzky, Academic Press 1990.
- [2] E. V. Kuznetsov, I. V. Shcherbakova and A. T. Balaban, "Benzo[c]Pyrylium Salts: Syntheses, Reactions, and Physical Properties" in *Advances in Heterocyclic Chemistry*, Vol. **50**, p 203, Edited by A. R. Katritzky, Academic Press 1990.
- [3] R. Ed. Johnson, D. Ch. Schlegel, and A. M. Ezrin, European Patent 597,540, *Chem. Abstr.*, **121**, 280683s (1994).
- [4] R. Ed. Johnson and D. Ch. Schlegel, European Patent 475,527, *Chem. Abstr.*, **117**, 90333x (1992).
- [5] G. Doleshall, Gy. Hornyák, B. Ágai, Gy. Simig, J. Fetter and K. Lempert, *Tetrahedron Letters*, 5069 (1973).
- [6] G. Doleshall, Gy. Hornyák, B. Ágai, Gy. Simig, J. Fetter and K. Lempert, *Tetrahedron*, **32**, 57 (1976).
- [7] Gy. Argay and A. Kálmán, *Acta Cryst. B* (to be published).
- [8] G. B. Ansell, *J. Chem. Soc. Perkin Trans 2*, 1200 (1991).
- [9] E. V. Kuznetsov, I. V. Shcherbakova and A. T. Balaban, "Benzo[c]Pyrylium Salts: Syntheses, Reactions, and Physical Properties" in *Advances in Heterocyclic Chemistry*, Vol. **50**, p 161, Edited by A. R. Katritzky, Academic Press 1990.