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QUATERNARY SALTS OF 1,2-BISAZOLYL- AND 1,2-BISBENZAZOLYLETHANES*

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ABSTRACT

Eleven new heterocyclic mono-and diquaternary salts have been prepared by reaction of 1,2-bisazolyl- and 1,2 bisbenzazolyl-ethanes with methyl sulfate or methyl fluorosulfonate. Their structure has been established by means of 'H and ¹³C NMR spectroscopy. Homonuclear COSY and NOESY experiments and 2D-heteronuclear correlations have been performed when necessary to assign all NMR signals.

INTRODUCTION

1,2-Bisazolyl- and 1,2-bisbenzazolyl- ethanes constitute a very interesting family of polynuclear ligands in the field of coordination chemistry (1). Syntheses and main properties of this class of compunds have been described elsewhere (2). We wish to report here their behaviour towards alkylating agents dimethyl sulfate or methyl fluorosulfonate (Magic Methyl). The structures of the azolium salts thus obtained together with the standard numbering system are gathered in Table 1.

EXPERIMENTAL

General Synthetic Procedure.- To a solution of 1,2-bisazolyl-, 1-azolyl-2-benzazolyl- or 1,2-bisbenzazolylethanes (3.0 mmoles) in 20 mL of anhydrous dichloromethane were added with external cooling (icebath), 0.7 mL (6.0 mmoles) of methyl fluorosulfonate or 0.4 mL (3.0 mmoles) of dimethyl sulfate in 10 mL of anhydrous dichloromethane, depending on the cases. The mixture was then allowed to attain room temperature and was stirred for 24 more hours. The quaternary salt, not soluble in the reaction solvent, was filtered and purified by recrystallization.

The quaternary salts have definite melting points, very high solubility in polar solvents and are hygroscopic. All the isolated compound described in this paper give correct analytical results (C,H,N) for the calculated molecular formulae (Table 2).

* Part 34 of "NMR Studies in the Heterocyclic Series"; for part 33 see reference (8).

 TABLE 1

 N-Methyl quaternary salts of 1,2-bisazolyl- and 1,2 bisbenzazolyl- ethanes.



<u>NMR Spectroscopy</u>.- NMR spectra were recorded on a BRUKER AC 200 working at 200.135 MHz in ¹H NMR and at 50.324 MHz in ¹³C NMR. Samples were dissolved in [⁺H₆] DMSO, unless specified, the deuterium signal providing field-frequency lock; the concentration was 10% (w/v). Chemical shifts (δ) are expressed in ppm from internal tetramethylsilane with an accuracy of 0.01 ppm for ¹H NMR and 0.1 ppm for ¹³C NMR. Coupling constants in Hz are given with a digital resolution of 0.2 Hz and 0.5 Hz per point for ¹H and ¹³C NMR, respectively. In all cases standard conditions and BRUKER microprograms were used for homonuclear (¹H-¹H) and heteronuclear (¹H-¹³C) correlation experiments (3).

Compound	Melting (Crystalli	Point in °C zation Solvent)	Yield (%)	Molecular Formulae	
1	78-80	(ethanol)	20	C ₉ H ₁₃ N ₄ O ₃ SF	
2	238-40	(ethanol)	60	C ₁₀ H ₁₆ N ₄ O ₂ S ₂ F ₂	
3	138-9	(ethanol)	75	C ₁₀ H ₁₆ N ₄ O ₆ S ₂ F ₂	
4	200-1	(ethanol)	65	C ₁₀ H ₁₆ N ₄ O ₄ S	
5	301-2	(ethanol)	50	C ₉ H ₁₅ N ₅ O ₆ S ₂ F ₂	
6	very hy not rec	groscopic ryst.	90	C ₈ H ₁₄ N ₆ O ₄ S	
7	145 (ac	etonitrile)	35	C ₁₂ H ₁₄ N ₅ O ₃ SF	
8	Not isolated		35ª	C ₁₃ H ₁₇ N ₅ O ₆ S ₂ F ₂	
9	211-2	(ethanol)	70	C ₁₆ H ₁₈ N ₆ O ₆ S ₂ F ₂	
10	161-2	(ethanol)	70	C ₁₆ H ₁₈ N ₆ O ₆ S ₂ F ₂	
11	> 304		65	C ₁₈ H ₂₀ N ₄ O ₆ S ₂ F ₂	

 TABLE 2

 Melting Points, yields and molecular formulae of salts 1-11

a This yield has been calculated by $^1\!H$ NMR of the reaction crude.

RESULTS AND DISCUSSION

Quaternization of 1,2-bisazolylethanes afforded the dimethylated salt except in compounds with a pyrazolyl group, (cf. compounds 1 and 7) thus proving the less nucleophilic character of that substituent (Table 1). These results are in agreement with our previous work on 1,2-bis(pyrazol-1'-yl) methanes (5).

The ¹H and ¹³C NMR studies have been carried out comparing the chemical shifts and coupling constants of products **1-11** with those of the neutral parent molecules, namely, 1,2-bisazolyl- and 1,2-bisbenzazolyl-ethanes (2). In order to assign all the signals to the different proton and carbon atoms (4-8), the quaternization effect on the NMR parameters on going from the <u>N</u>-methylazoles to their quaternary salts has also been considered.

As expected, the ¹H chemical shifts (Table 3) in the azolium salts appear at lower field than those of the neutral molecules. Usually the most sensitive protons are those in α -position to the nitrogen being methylated, the chemical shifts of the heterocyclic moieties being much close due to the positive charge delocalization through the ring. The coupling constants increase with quaternization. Compound 1 with two pyrazolyl rings, one neutral and the other bearing a positive charge, provides a clear example of this statement.

Compound Number	CH ₃ (a) CH ₃ (b)	CH ₂ (a) CH ₂ (b)	н ₂ н ₂ ,	Н ₃ Н ₃ ,	Н ₄ Н ₄ ,	Н ₅ Н ₅ ,	Н ₆ Н ₆ ,	Н ₇ Н ₇ ,
1	-	4.70(t)	-	7.43(d) J _{3,4} =1.6;	6.23(dd) J _{4,5} =2.1	7.68(d)		
	3.91(s)	4.93(t) J _{AB} =7.1	-	8.48(d) J _{3,4} =2.6;	6.81(dd) J _{4,5} =2.8	8.16(d)	-	-
2	4.23(s)	5.06(s)	-	8.61(d) J _{3,4} =2.7;	6.86(dd) J _{4,5} =2.8;	8.26(d) J _{3,5} =1.1	-	-
	4.23(s)	5.06(s)		8.61(d)	6.86(dd)	8.26(d)		
3	3.82(s)	4.64(s)	8.93(s)	- J _{2,4} =J _{2,5} =	7.67(ddd) J _{4,5} =1.7) 7.55(ddd)	-	-
	3.82(s)	4.64(s)	8.93(s)	-	7.67(ddd) 7.55(ddd)	-	-
4	4.21(s)	5.03(t)	-	8.59(d) J _{3,4} =2.7;	6.84(dd) J _{4,5} =2.9	8.21(d)	-	-
	3.83(s)	4.73(t) J _{A,B} =5.5	9.08(s)	- J _{2,4} =J _{2,5} =.	7.72(ddd) J _{4,5} =1.9) 7.61(ddd)		
5	4.16(s)	5.02(t)	-	8.57(d) J _{3,4} =2.9;	6.86(dd) J _{4,5} =3.0;	8.30 (dd) J _{3,5} =1.1	_	-
	3.90(s)	5.00(t)	-	9.13(s)	→	9.99(s)		
6	3.91(s)	4.97(s)	-	9.16(s)	-	10.0(s)	-	-
	3.91(s)	4.97(s)	-	9.13(s)	-	10.0(s)		
7	-	4.97(s)	-	7.30(d) J _{3,4} =1.7;	6.14(dd) J _{4,5} =2.1	7.66(d)		
	4.58(s)	5.44(t) J _{AB} =5.4	-	-	8.32(m)	7.93(m)	7.93(m)	7.93(m)
8	4.28(s)	5.28(t)	-	8.63(d) J _{3,4} =2.8;	6.83(dd) J _{4,5} =2.9;	8.36(d) J _{3,5} =1.3		
	4.62(s)	5.63(t)	-	-	8.40(m)	8.00(m)	8.00(m)	8.40(m)
9	4.55(s)	5.82(s)	-	-	8.40(m)	8.01(m)	8.01(m)	8.40(m)
	4.55(s)	5.82(s)	-	-	8.40(m)	8.01(m)	8.01(m)	8.40(m)
10 ^a	4.62(s)	5.88(m)	-	-	8.38(m)	8.02(m)	8.04(m)	8.56(m)
	4.68(s)	6.01(m)	-	-	8.26(m)	7.83(m)	8.07(m)	8.30(m)
11 ^b	4.00(s)	5.15(s)	9.26(s)	-	<	7.15-7.90(m)	>
	4.00(s)	5.15(s)	9.26(s) –	<	7.15-7.90(r	n)	>

TABLE 3'H-NMR parameters of the quaternary salts.

a The chemical shifts of the benzo-protons have been determined by means of the $^1\mathrm{H-}^{13}\mathrm{C}$ COSY spectrum

b In D₂O

Homonuclear (¹H-¹H) NOESY correlation experiments performed in salts 1, 2, 3 and 6 allowed us to establish which heterocyclic protons were adjacent to the methyl or to the methylene groups. In pyrazole-containing molecules a NOE effect between these last two groups was also observed.

In compound 10, the assignment was made on the basis of the following results:

i) A NOESY correlation between the N-methyl protons at 4.62 and 4.68 ppm with protons H_4 at 8.38 and H_7 at 8.30 ppm, respectively.

ii) A 2D-heteronuclear (${}^{1}H{-}{}^{13}C$) correlation between the CH and CH₃ carbon atoms, unambiguously assigned (Table 4) according to the ${}^{13}C$ NMR data existing for 1,2-dimethyl- and 1,3-dimethyl-indazolium iodides 12 and 13 (9) (Figure 1), and the corresponding protons.

iii) An homonuclear ('H-'H) COSY confirmed the results obtained from i) and ii).



FIG 1. ¹³C NMR chemical shifts in [²H₆] DMSO (ppm/TMS) from reference (4).

Proton chemical shifts of salts 4, 5, 7, 8 and 9 were assigned by analogy with data for derivatives 1-3, 6 and 10. The spectrum of 1,1'-ethylene-3,3'-dimethyl-bisbenzimidazolium difluorosulfonate 11 is similar in all aspects to that of other benzimidazolium salts (6,7). Also in ¹³C NMR, quaternization effects were observed both on chemical shift and coupling constants. In Table 4 the chemical shift differences between the quaternary salt and the neutral molecule of some representative examples are given in brackets. Methylene carbons of the CH_2-CH_2 - bridge are shifted upward when the methyl group in the quaternary salt is located at the nitrogen at 2-position (c.f. compounds 2 and 10), but move downward when it is at 3-position.

Compound Number	CH ₃ (a) CH ₃ (b)	CH ₂ (a) CH ₂ (b)	C ₂ C ₂ ,	C ₃ C ₃ ,	C ₄ C ₄ ,
1 ^a	-	49.5 ¹ J:148	_	139.6 ¹ J:185	105.8 ¹ J:175
	36.3 ¹ J:148	49.3[-2.3] ¹ J:151	-	138.3[-1.3] J:205	107.2[+1.4] ¹ J:188
2 ^ª	37.0 ¹ J:151	47.1[-4.5] ¹ J:151	-	139.3[-0.6] ¹ J:208	107.4[+1.6] ¹ J:188
	37.0	47.1	-	139.3	107.4
3ª	35.9 ¹ J:144	48.4[+0.5] ¹ J:148	137.1[0] ¹ J:223	-	124.0[-6.4] ¹ J:204
	35.9	48.4	137.1	-	124.0
4	37.3	47.1	-	139.6	107.8
	36.2	49.0	137.9	-	124.0
5	37.0	47.9[-2.9]	-	139.2	107.6
	34.3	49.5[+0.3]	-	144.6	-
6 ^a	34.0 ¹ J:145	49.6[+1.2] ¹ J:149	_	144.2[-7.8] ¹ J:230	-
	34.0	49.6	-	144.2	-
7	-	50.2	-	139.6	105.9
	38.0	51.6	-	-	113.4
8	37.3	47.5	-	139.4	107.7
	38.0	49.0	-	-	113.6
9	38.1	49.0[+1.9]	-	-	113.9[-5.1]
	38.1	49.0	-	-	113.9
10 ^a	38.2 ¹ J:146	47.6[+0.3] ¹ J:151	-	-	114.0[-5.0] ¹ J:176
	36.4 ¹ J:147	53.1[-2.2] ¹ J:151	-	-	120.0[+2.3] ¹ J:175
11 ^b	34.4 ¹ J:145	47.6[+3.0] ¹ J:147	143.0[+0.5] ¹ J:221	-	114.7[-6.3] ¹ J:163
	34.4	47.6	143.0	-	114.7

 TABLE 4

 ¹³C-NMR parameters of the quaternary salts. Representative quaternization effects on chemical shifts in ppm are expressed in brackets.

a 2D-Heteronuclear $({}^{1}\mathrm{H}-{}^{13}\mathrm{C})$ correlations have been carried out to ascertain the ${}^{13}\mathrm{C}$ NMR chemical shifts assignment.

b In D₂O

- Compou Number	nd C ₅ C ₅ ,	С ₆ С ₆ ,	C ₇ C ₇ ,	C _{3a} C C _{3'a} C	7a ''a
1 ^a	130.8 ¹ J:185	-	-	-	-
	137.5[+6.7] ¹ J:201	-	-	-	-
2 ^a	137.9[+7.8] ¹ J:201	-	-	-	_
	137.9	-	-	-	-
3 ^a	122.3[+3.8] ¹ J:207	-	-	-	-
	122.3	-	-	-	-
4	137.9	-	-	-	-
_	122.3	-	-	-	
5	138.3	_	-	_	-
	145.9	-	-	-	-
6 ⁸	145.8[+1.8] ¹ J:227	_	-	-	-
_	145.8	-	-	-	
7	130.9	-	-	-	-
_	131.1	131.2	114.1	134.8	134.9
8	138.5	-	-	-	-
	131.1	131.4	114.3	135.0	135.2
9	131.1[+7.2]	131.3[+4.1]	114.2[+4.4]	134.9[-10.1]	135.1(+2.3
	131.1	131.3	114.2	134.9	135.1
10 ^a	130.9[+7.0] ¹ J:167	131.2[+4.1] J:167	114.2[+4.1] ¹ J:176	135.0[-9.9]	135.1[+2.4]
	130.2[+3.7] ¹ J:166	134.3[+7.8] J:167	112.6[-5.1] ¹ J:175	140.8[-2.9]	134.8[-8.9]
11 ^b	128.7[+5.9] ¹ J:167	128.7[+5.1] ¹ J:167	112.6[+4.0] ¹ J:162	132.0[-11.9]	133.0[0]
_	128.7	128.7	112.6	132.0	133.0

 TABLE 4 (Cont.)

 ¹³C-NMR parameters of the quaternary salts. Representative quaternization effects on chemical shifts in ppm are expressed in brackets.

a 2D-Heteronuclear $({}^{1}\mathrm{H}-{}^{13}\mathrm{C})$ correlations have been carried out to ascertain the ${}^{13}\mathrm{C}$ NMR chemical shifts assignment.

b In D₂O