CCA-647

547.541.5

Original Scientific Paper

Some Studies on the Reaction of β-(*N*,*N*-Heptamethylenimino) ethanol with Arylsulphonyl Chlorides

S. Fila-Hromadko and K. Kovačević

Research Department »Pliva«, Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

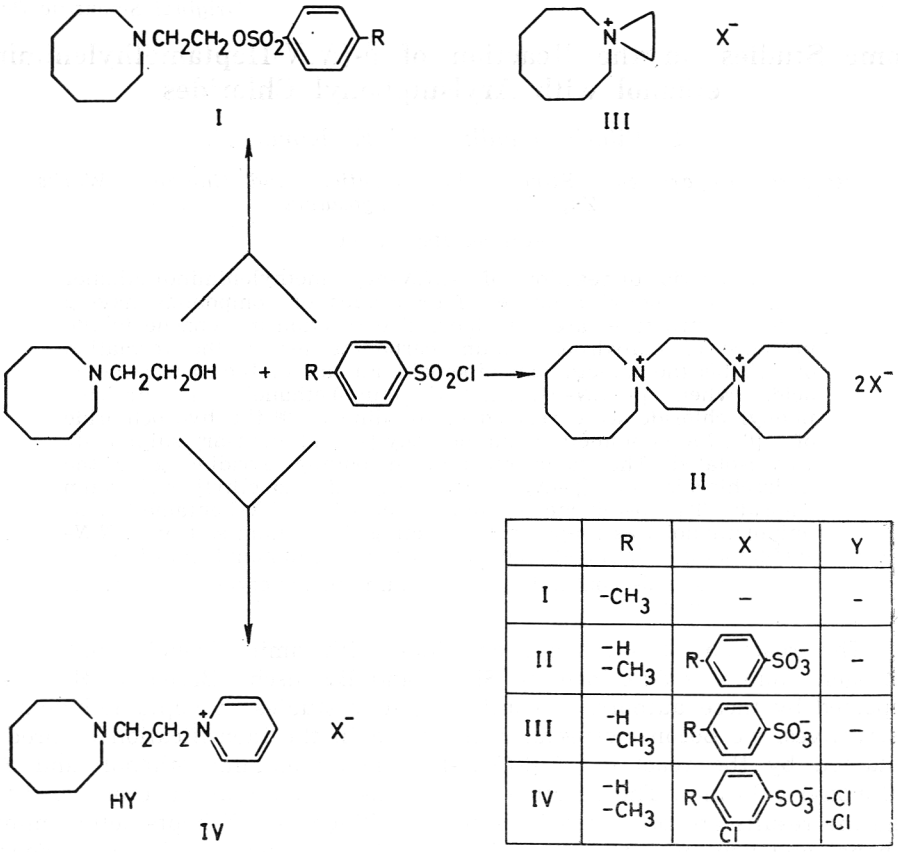
Received May 15, 1970

In a series of reactions of β-(*N*,*N*-heptamethylenimino) ethanol with arylsulphonyl chlorides, four groups of compounds having different structures are described. The reaction in benzene in the presence of anhydrous sodium carbonate led to the formation of *N*,*N*-bis (heptamethylene)piperazinium salt of the arylsulphonic acid. When β-(*N*,*N*-heptamethylenimino) ethanol and arylsulphonyl chloride were reacted in pyridine at 0° the hydrochloride of [β-(*N*,*N*-heptamethylenimino) ethyl]-pyridinium-arylsulphonate was isolated. The same reaction in boiling pyridine gave the hydrochloride of [β-(*N*,*N*-heptamethylenimino) ethyl]-pyridinium chloride. The *p*-toluenesulphonic ester of β-(*N*,*N*-heptamethylenimino)ethanol was prepared by reacting the sodium salt of β-(*N*,*N*-heptamethylenimino)ethanol and *p*-toluenesulphonyl chloride.

All compounds containing the pyridinium moiety showed strong hypotensive effect.

The reaction of sulphonyl chlorides with aminoalcohols containing a nitrogen atom was described by Slotta and Behnisch.[1] Based on the results reported by these authors, in continuing[2] our studies of heptamethylenimine derivatives, we become especially interested in the identification of products obtained by the reaction of β-(*N*,*N*-heptamethylenimino) ethanol[3] and arylsulphonyl chlorides. The reaction was studied under four different conditions and the results are presented in Scheme 1. When β-(*N*,*N*-heptamethylenimino) ethanol and benzene or toluenesulphonyl chlorides were refluxed in benzene in the presence of anhydrous sodium carbonate a crystalline product (m. p. 294°; and 300° respectively) was isolated. According to the elemental analysis, any one of the three equaly probable different structures I—III could be assigned to the product. Both reaction products when treated with boiling hydrobromic acid, were transformed into a compound corresponding by analysis either to *N*,*N*-bis(heptamethylene)piperazinium dibromide (II, X=Br) or (*N*,*N*-heptamethylene)aziridinium bromide (III, X=Br). The piperazinium ion structure was more plausible since Slotta and Behnisch[1] have isolated a tetramethylpiperazinium di-*p*-toluenesulphonate by an analogous reaction of dimethylaminoethanol with *p*-toluenesulphonyl chloride. The crystalline product did not change when treated with hydrochloric acid, which excluded structure I (m. p. 113°—116°; R=CH_3), a product of the reaction between the sodium salt of β-(*N*,*N*-heptamethylenimino) ethanol and *p*-toluenesulphonyl chloride, in ether at — 16° with subsequent introduction of gaseous hydrogen chloride at the same temperature. Later, Cope and Burg carried out an

SCHEME 1

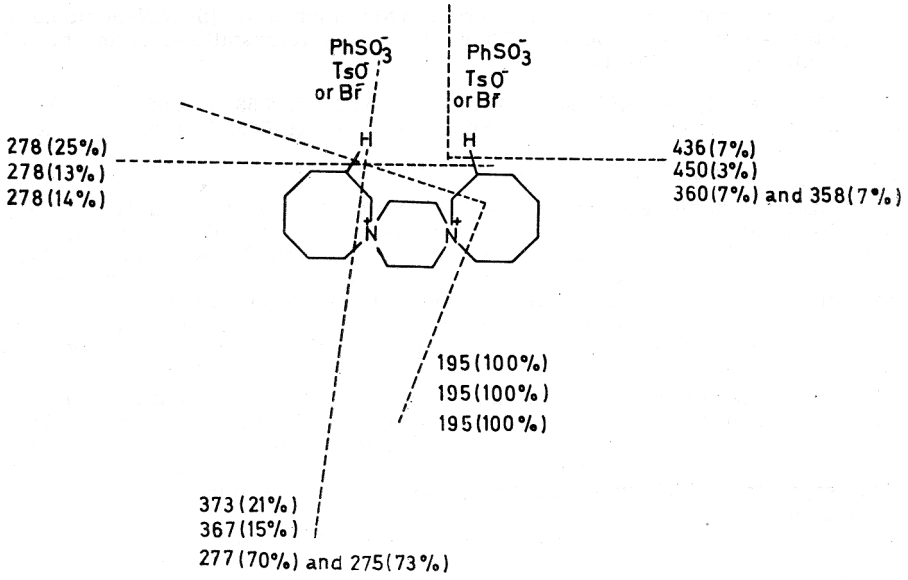


	R	X	Y
I	$-CH_3$	–	–
II	$-H$ $-CH_3$	R SO_3^-	–
III	$-H$ $-CH_3$	R SO_3^-	–
IV	$-H$ $-CH_3$	R SO_3^- Cl	-Cl -Cl

analogous reaction with methanesulphonyl chloride[4], but neither of these authors anticipated the possibility of aziridinium ion formation. In fact, Slotta and Behnisch proved the tetramethylpiperazinium di-*p*-toluenesulphonate structure preparing this compound by a different way starting from piperazine[1].

Additional proof for the proposed structure of *N,N*-bis(heptamethylene)piperazinium diarylsuphonate and (*N,N*-heptamethylene)piperazinium dibromide were provided by the mass fragmentation pattern in the mass spectrometer (Scheme 2). Molecular ions were not obtained, but the fragments formed presumably resulted from a thermal β-elimination of the corresponding acids. All three compounds, *N,N*-bis(heptamethylene)piperazinium di-*p*-toluenesulphonate, -benzenesulphonate and -bromide, showed two characteristic fragments of mass 278 and 195 (See Scheme 2).

SCHEME 2



In contrast, β-(*N,N*-heptamethylenimino)ethanol reacted with arylsulphonyl chlorides in pyridine at 0° to give the hydrochloride of [β-(*N,N*-heptamethylenimino)ethyl]pyridinium arylsulphonate (IV, X = R—C_6H_4—SO_3(*p*), R = H, CH_3; Y = Cl). According to the results reported by Slotta and Behnisch for the analogous reaction of dimethylaminoethanol with *p*-toluenesulphonyl chloride,[1] IV could be expected as the product of this reaction in boiling pyridine. However, this reaction led to the formation of the hydrochloride of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium chloride (IV, X = Cl; Y = Cl). This structure was confirmed by preparing the same compound in a different way, *i. e.* quarternizing pyridine by reaction with the hydrochloride of β-(*N,N*-heptamethylenimino)ethyl chloride. All three above mentioned compounds (IV) containing the pyridinium function were transformed into the same hydrobromide of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium bromide (X = Br; Y = Br) when treated with concentrated hydrobromic acid.

The compounds described above were studied for hypotensive activity in cats by a cardiovascular test[5] and by direct measurement of blood pressure in artery carotis communis. When compared to guanethidine and bretylium tosylate, all derivatives containing the pyridinium moiety were more active than bretylium tosylate.

EXPERIMENTAL

[β-(N,N-*Heptamethylenimino)ethyl*] p-*toluenesulphonate HCl* (I)

β-(*N,N*-Heptamethylenimino) ethanol (6.28 g., 0.04 mole) was added dropwise to a stirred suspension of sodium hydride (50% suspension in oil) (2 g., 0.042 mole) in ether (75 ml.). The resulting mixture was held by external cooling at —6 to —10° and then *p*-toluenesulphonyl chloride (7.8 g., 0.041 mole) in ether (25 ml.) was added maintaining the same temperature. After cooling and stirring at —10°

to -16^0 for 2 hours, gaseous hydrogen chloride was bubbled in at the same temperature. The ethereal layer was decanted, and anhydrous ethanol (30 ml.) was added to the residue. This mixture was filtered, and the filtrate was evaporated *in vacuo*. The slightly yelow oily residue (10.3 g.), crystallised upon addition of a mixture of ethanol-ether (1 : 1). The crude hydrochloride of [β-(*N,N*-heptamethylenimino) ethyl]-*p*-toluenesulphonate (7.3 g., 48%) was recrystallised from the same solvent mixture; m. p. 113—116°.

Anal. $C_{16}H_{26}ClNO_3S$ (347.50) Calc'd.: C 55.25; H 7.53; N 4.02; HCl 10.5%
Found: C 55.50; H 7.25; N 4.29; HCl 10.4%

N,N-*bis(Heptamethylene)piperazinium Salts* (II) (Table I)

N,N-bis*(Heptamethylene)piperazinium diarylsulphonates* (IIa and IIb). — Arylsulphonyl chloride (0.15 mole) was gradually added to a stirred mixture of β-(*N,N*-heptamethylenimino)ethanol (15.7 g., 0.1 mole) and anhydrous sodium carbonate (10.6 g., 0.1 mole) in benzene (100 ml.). The reaction mixture was boiled under reflux with stirring for 8 hours. After cooling to room temperature, a crystalline product was obtained which was filtered and thoroughly washed with cold water. The crude *N,N*-bis(heptamethylene)piperazinium diarylsulphonate was recrystallised from aqueous ethanol.

N,N-bis*(Heptamethylene)piperazinium dibromide* (IIc). — A solution of *N,N*-bis-(heptamethylene)piperazinium diarylsulphonate (0.01 mole) in 48% hydrobromic acid (60 ml) was boiled under reflux for 2.5 hours. The resulting mixture was cooled to room temperature. After addition of anhydrous ethanol (45 ml.) a white crystalline product separated which was filtered, washed with anhydrous ethanol and dried in a vacuum desiccator over calcium chloride. The crude *N,N*-bis(heptamethylene) piperazinium dibromide (3.95 g) was crystallised from water.

MS-Analysis

Compound IIa (400° C, 10^{-8} Torr)
Mass spectrum *m/e* (relative intensity) at: 436(7), 353(21), 278(25), 195(100), 126(14), 70(17), 55(14).

Compound IIb (380°, 10^{-8} Torr)
Mass spectrum *m/e* (relative intensity) at: 450(3), 367(3), 367(15), 298(3), 278(13), 195(100), 152(9), 126(12), 70(20), 55(14).

Compound IIc (360°, 10^{-8} Torr)
Mass spectrum *m/e* (relative intensity) at: 460(11), 360(7), 358(7), 278(7), 278(14), 275(70), 276(8), 275(73), 195(100), 24(16), 99(9), 81(7).

[β-(N,N-*Heptamethylenimino)ethyl*]-*pyridinium Salts* (IV) (Table II)

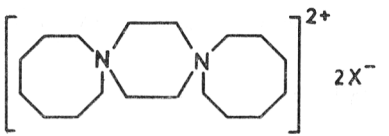
[β-(N,N-*Heptamethylenimino-ethyl*]-*pyridinium arylsulphonate HCl* (IVa and IVb). — A solution of β-(*N,N*-heptamethylenimino)ethanol (15.7 g., 0.1 mole) in pyridine (100 ml.) was cooled to 0°. Arylsulphonyl chloride (0.1 mole) was then gradually added with stirring while the reaction temperature was maintained at 0° to 2°. The reaction mixture was stirred 4 hours at 0° and 3 additional hours at room temperature. After standing 2 hours in refrigerator the crystals were filtered and dried in a vacuum desiccator over anhydrous calcium chloride. The crude hydrochloride of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium arylsulphonate was crystallised from a mixture of ethanol-ether (1 : 1).

[β-(N,N-*Heptamethylenimino)ethyl*]-*pyridinium chloride HCl* (IVc). — *p*-Toluenesulphonyl chloride (19.0 g., 0.1 mole) was gradually added to a stirred solution of β-(*N,N*-heptamethylenimino)ethanol (15.7 g., 0.1 mole) in pyridine (150 ml.). The reaction mixture was boiled under reflux with stirring for 3 hours. After cooling to room temperature the reaction mixture was kept 2 hours in a refrigerator. The crystals were filtered with suction and dried in a vacuum desiccator over anhydrous calcium chloride. The crude hydrochloride of [β-(*N,N*-heptamethylenimino) ethyl]-pyridinium chloride (12.9 g.) was crystallised from ethanol-ethyl acetate (1 : 2).

[β-(N,N-*Heptamethylenimino)ethyl*]-*pyridinium bromide HBr* (IVd). — A solution of the hydrochloride of [β-(*N,N*-heptamethylenimino)ethyl-pyridinium *p*-tolu-

TABLE I

N,N-bis*(Heptamethylene) pyperazinium salts* (II)



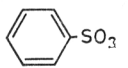
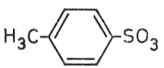
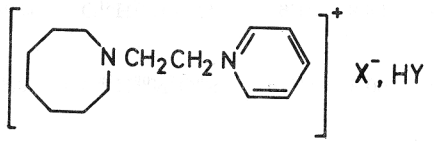
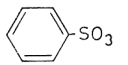
	X	yield %	M. p. 0° C	Formula	Calc'd (%)				Found (%)			
					C	H	N	Br	C	H	N	Br
IIa		61.7	294	$C_{30}H_{46}N_2O_6S_2$	60.59	7.80	4.71	—	60.08	7.60	4.54	—
IIb		56.0	300	$C_{32}H_{50}N_2O_6S_2$	61.71	8.09	4.50	—	61.43	8.21	4.27	—
IIc	Br	90.0	297° (decomp)	$C_{18}H_{36}Br_2N_2$	49.10	8.24	6.36	36.30	49.04	8.26	6.41	36.28

TABLE II

[β-(N,N-*Heptamethylenimino)ethyl*] *pyridinium X, HX* (IV)



	X	Y	yield %	M. p. 0° C	Formula	Calc'd (%)					Found (%)				
						C	H	N	HCl	HBr	C	H	N	HCl	HBr
IVa		Cl	93	134	$C_{20}H_{29}ClN_2O_3S$	58.16	7.07	6.78	8.85	—	58.30	7.25	6.51	8.50	
IVb		Cl	78	160	$C_{21}H_{31}ClN_2O_3S$	59.80	7.31	6.56	8.54	—	59.59	7.25	6.34	8.52	
IVc	Cl	Cl	90	238	$C_{14}H_{24}Cl_2N_2$*	57.75	8.30	9.62	12.52	—	58.02	8.01	9.63	12.40	
IVd	Br	Br	47.5	242	$C_{14}H_{24}Br_2N_2$**	44.23	6.36	7.36		20	44.45	6.19	7.38		21.1

* Calcd.: 24.35% Cl, Found: 24.10% Cl; ** Calcd.: 42.04% Br, Found: 42.50% Br.

enesulphonate (0.01 mole) in 48% hydrobromic acid (42 ml) was refluxed for 3 hours. The dark solution obtained was filtered, and the filtrate was evaporated *in vacuo* to dryness. The crude hydrobromide of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium bromide (1.8 g.) was crystallised from ethanol.

This compound also was obtained by the method above starting with the hydrobromide of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium *p*-toluenesulphonate (0.01 mole) or the hydrochloride of [β-(*N,N*-heptamethylenimino)ethyl]-pyridinium chloride (0.01 mole).

REFERENCES

1. K. H. Slotta and R. Behnisch, *Ann.* **197** (1932) 170.
2. S. Fila-Hromadko, B. Glunčić, and D. Kolbah, *Croat. Chem. Acta* **39** (1967) 207; S. Fila-Hromadko, *Ibid.* **39** (1967) 289.
3. F. F. Blicke and N. J. Doorenbos, *J. Am. Chem. Soc.* **76** (1954) 2317; R. P. Mull, U. S. Pat. 2928829 (1960).
4. A. C. Cope and M. Burg, *J. Am. Chem. Soc.* **74** (1952) 611.
5. O. Nieschulz, I. Hoffmann, and K. Popendiker, *Arzneim. Forsch.* **6** (1956) 651.

IZVOD

Studija reakcije β-(*N,N*-heptametilenimino)etanola s arilsulfokloridima

S. Fila-Hromadko i K. Kovačević

Reakcijom β-(*N,N*-heptametilenimino)etanola sa arilsulfokloridmia u prisutnosti bezvodnog natrijevog karbonata u benzenu dobiven je *N,N*-bis-heptametilen-piperazinium-diarilsulfonat. Provođenjem reakcije u piridinu kod 0° dobiven je hidroklorid [β-(*N,N*-heptametilenimino)etil]-piridinium-arilsulfonat, a u vrijućem piridinu nastaje hidroklorid [β-(*N,N*-heptametilenimino)etil]-piridinium klorida. Obradom gore navedenih spojeva sa bromovodičnom kiselinom dobiveni su odgovarajući *N,N*-bis-heptametilen-piperaziniumdibromid i hidrobromid [β-(*N,N*-heptametilenimino)-etil]-piridiniumbromid. Reakcijom natrijske soli β-(*N,N*-heptametilenimino)-etanola sa *p*-toluensulfokloridom u eteru kod —16° dobiven je β-(*N,N*-heptametilenimino) etilni ester *p*-toluensulfonske kiseline.

Svi opisani spojevi koji odgovaraju kvarternim solima piridina pokazuju jako izraženo hipotenzivno djelovanje.

»PLIVA«, TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 15. svibnja 1970.