CCA-472

547.551.5.07

Original Scientific Paper

Sulphonamide Derivatives of Heptamethylenimine.* Synthesis of Arylsulphonyl-1,1-Heptamethylenimines, *N*-[β-(1,1-Heptamethylenimino) ethyl]-arylsuphonamides and *N*-[δ-(1,1-Heptamethylensulphamyl) butyl]-arylsulphonamides

*S. Fila-Hromadko, B. Glunčić, and D. Kolbah***

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

Received June 23, 1967

Arylsulphonyl-1,1-heptamethylenimines, *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides and *N*-[δ-(1,1-heptamethylensulphamyl) butyl]-arylsulphonamides were prepared by condensation of heptamethylenimine with arylsulphonylchlorides in acetone solution. δ-(1,1-Heptamethylensulphamyl) butylamine was prepared from heptamethylenimine and 4-chlorbutansulphonylchlorid *via* δ-(1,1-heptamethylensulphamyl) butylchloride and δ-(1,1-heptamethylensulphamyl) butylphthalimide.

In the past few years numerous derivatives of heptamethylenimine have been investigated for their physiological properties. Thus, among [ω-(1,1-alkylenimino) alkyl]-guanidine[1], compounds which showed antihypertensive properties, [β-(1,1-heptamethylenimino) ethyl]-guanidine was found to be of special interest as a valuable therapeutic agent. Furthermore, a number of arylsulphonyl-(1,1-heptamethylenimino)-semicarbazides[2] has been studied on account of their strong hypoglycemic activity.

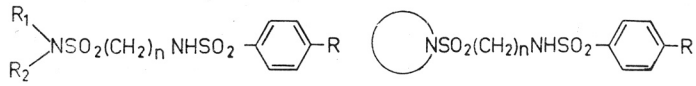
The present paper reports the synthesis of three classes of *N*-substituted sulphonamides containing in their structure heptamethylenimine. The starting material was heptamethylenimine[3–8] which condensed with arylsulphonylchlorides gave the corresponding arylsulphonyl-1,1-heptamethylenimines (I—IV, VI). The preparation was carried out at room temperature in acetone solution with an excess of heptamethylenimine as condensating agent. *p*-Aminobenzensulphonyl-1,1-heptamethylenimine (V) was obtained by alkaline hydrolysis of compounds IV and VI. A similar reaction of β-(1,1-heptamethylenimino) ethylamine[10–13] with arylsulphonylchlorides in equimolar ratios yielded the second class of sulphonamides, *i. e.* the hydrochlorides of *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides (XII—XV), which when treated with aqueous sodium hydroxide gave the corresponding free *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides (VII—X). *N*-[β-(1,1-Heptamethylenimino) ethyl]-*p*-aminobenzensulphonamide (XI) was obtained by alkaline hydrolysis of the corresponding *p*-acetylamino derivative (X). The isolated sodium salts of the last named

* The authors prefer the term »heptamethylenimine« as a more a convenient one than »octahydro-azocine« used in an earlier paper[11].

** Present address: Faculty of Pharmacy and Biochemistry, University of Zagreb.

compounds proved to be highly hygroscopic and are readily transformed by the action of air to the free sulphonamides.

The third class consisted of *N*-[δ-(1,1-heptamethylensulphamyl) butyl]--arylsulphonamides (XX—XXIV) which correspond to hitherto undescribed disulphonamides of the following general structures:



These compounds can be considered to be derived from δ-(1,1-heptamethylensulphamyl) butylamine (XIX). This previously unknown amine was prepared from heptamethylenimine which when condensed with 4-chlorbutansulphonylchloride[14] gave δ-(1,1-heptamethylensulphamyl) butylchloride (XVII). This compound was then converted by the Gabriel reaction[15] to δ-(1,1-heptamethylensulphamyl) butylphtalimide (XVIII). Hydrazynolysis of XVIII with hydrazine hydrate yielded the free δ-(1,1-heptamethylensulphamyl) butylamine (XIX). Condensation of XIX with the appropriate arylsulphonylchlorides in the presence of potassium carbonate gave the above mentioned *N*-[δ-(1,1-heptamethylensulphamyl) butyl]-arylsulphonamides (XX—XXIII). Compound XXIV was obtained by hydrolysis of XXIII with 10% aqueous sodium hydroxide. Sodium salts of the sulphonamides XX—XXIV were prepared in the same manner as the sodium salts of VII—XI (see Experimental) and also proved to be highly hygroscopic.

EXPERIMENTAL

Melting points are uncorrected.

Arylsulphonyl-1,1-heptamethylenimines (I—IV)

A solution of the corresponding arylsulphonylchloride (0.01 mole) in acetone (20 ml.) was gradually added to heptamethylenimine (0.02 mole in 20 ml. of acetone) at a temperature between 20 and 30°. The reaction mixture was kept at room temperature for 6 hr., the solvent evaporated and the residual thick brown oil washed several times with water until crystallisation occurred. The crystalline crude arylsulphonyl-1,1-heptamethylenimines were filtered off with suction, dried and recrystallised from 96% ethanol.

p-*Aminobenzensulphonyl-1,1-heptamethylenimine* (V)

Procedure A

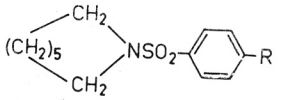
p-Acetylaminobenzensulphonyl-1,1-heptamethylenimine (1 part) and 10% aqueous sodium hydroxide (10 parts) were refluxed for 3 hr. The reaction mixture was cooled to room temperature, the water layer decanted and the residual oil successively washed with water to give a crystalline product which was recrystallised from 96% ethanol.

p,p-*bis-(1,1-Heptamethylenimine)-sulphonylcarbanilide* (VI)

A solution of carbanilide-*p,p*-disulphonic acid dichloride (0.01 mole) in methyl isobutyl ketone (40 ml.) was gradually added to heptamethylenimine (0.04 mole) in the same solvent (40 ml.). Further steps were performed essentially in the same manner as given for the preparation of compounds I—IV (see above). *p,p*-Bis-(1,1-heptamethylenimine) sulphonylcarbanilide (VI) was obtained in 100% yield. One part of VI and sodium hydroxide (10 parts) were then heated under reflux for 3 hr. to give *p*-aminobenzensulphonyl-1,1-heptamethylenimine (V).

TABLE I

Arylsulphonyl-1,1-heptamethylenimines

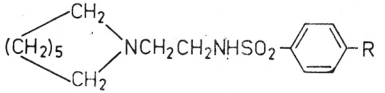


	R	Yield %	M. p. 0°	Formula	Found (%)				Calc'd. (%)			
					C	H	N	Cl	C	H	N	Cl
I	H	91	85—6	$C_{13}H_{19}NO_2S$	61.70	7.40	5.42	—	61.64	7.56	5.53	—
II	CH_3	90	84*	$C_{14}H_{21}NO_2S$	—	—	—	—	—	—	—	—
III	Cl	97	86—8	$C_{13}H_{18}ClNO_2S$	54.10	6.09	5.11	12.25	54.25	6.30	4.86	12.32
IV	$NHCOCH_3$	93	139—40	$C_{15}H_{22}N_2O_3S$	58.20	6.88	8.98	—	58.01	7.15	9.03	—
V	NH_2	98	129	$C_{13}H_{20}N_2O_2S$	58.02	7.34	10.45	—	58.19	7.51	10.44	—
VI	$NHCONH(C_6H_4)$ $—SO_2N(C_7H_{14})$	90	235—7	$C_{27}H_{38}N_4O_5S_2$	57.63	7.02	9.91	—	57.64	6.81	9.96	—

* Reported (ref. 9) 82.5°.

TABLE II

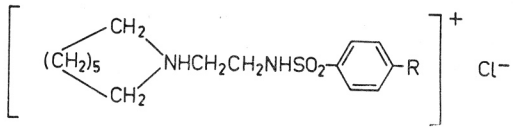
N-[*β*-*(1,1-Heptamethylenimino) ethyl*]-*arylsulphonamides*



	R	M. p. 0°	B. p. 0.2 °/mm	Formula	Found (%)				Calc'd. (%)			
					C	H	N	Cl	C	H	N	Cl
VII	H	—	172—4	$C_{15}H_{24}N_2O_2S$	60.68	8.22	9.70	—	60.79	8.16	9.45	—
VIII	CH_3	40—2	166—9	$C_{16}H_{26}N_2O_2S$	61.67	8.21	9.27	—	61.91	8.44	9.03	—
IX	Cl	69—71	180	$C_{15}H_{23}ClN_2O_2S$	54.26	6.80	8.71	10.61	54.46	7.00	8.46	10.72
X	$NHCOCH_3$	125	—	$C_{17}H_{27}N_3O_3S$	57.54	7.42	12.15	—	57.77	7.70	11.89	—
XI	NH_2	98	—	$C_{15}H_{25}N_3O_2S$	57.86	8.02	13.39	—	57.86	8.09	13.50	—

TABLE III

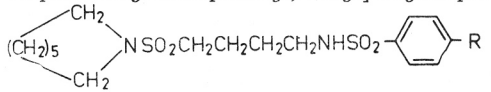
N-[β-(1,1-Heptamethylenimino) ethyl] arylsulphonamides HCl



	R	Yield %	M. p. 0° C	Formula	Found (%)					Calc'd. (%)				
					C	H	N	Cl	HCl	C	H	N	Cl	HCl
XII	H	84	156—8	$C_{15}H_{25}ClN_2O_2S$	54.24	7.40	8.34	—	10.6	54.12	7.57	8.41	—	10.90
XIII	CH_3	91	131—2	$C_{16}H_{27}ClN_2O_2S$	55.13	8.03	8.34	—	10.69	55.40	7.84	8.07	—	10.51
XIV	Cl	76	166—7	$C_{15}H_{24}Cl_2N_2O_2S$	48.77	6.55	7.91	9.88	19.13	49.05	6.58	7.62	9.92	19.31
XV	$NHCOCH_3$	89	156—9	$C_{17}H_{28}ClN_3O_3S$	52.26	7.52	11.05	—	9.45	52.36	7.23	10.77	—	9.35
XVI	NH_2	96	155—8	$C_{15}H_{26}ClN_3O_2S$	52.04	7.25	12.13	—	10.58	51.79	7.53	12.08	—	10.48

TABLE IV

N-[δ-1,1-Heptamethylensulphamyl) butyl]-arylsulphonamides



	R	Crude Yield %	M. p. 0°	Formula	Found %				Calc'd. %			
					C	H	N	Cl	C	H	N	Cl
XX	H	93	81—2	$C_{17}H_{28}N_2O_4S_2$	52.80	7.15	7.31	—	52.57	7.27	7.21	—
XXI	CH_3	75	105	$C_{18}H_{30}N_2O_4S_2$	53.69	7.30	7.21	—	53.72	7.51	6.96	—
XXII	Cl	93	121—2	$C_{17}H_{27}ClN_2O_4S_2$	48.44	6.14	6.62	8.50	48.26	6.43	6.62	8.38
XXIII	$NHCOCH_3$	88	184—5	$C_{19}H_{31}N_3O_5S_2$	50.96	6.88	9.44	—	51.23	7.01	9.43	—
XXIV	NH_2	98	127	$C_{17}H_{29}N_3O_4S_2$	50.35	7.18	10.59	—	50.61	7.25	10.42	—

N-[β-(1,1-Heptamethylenimino) ethyl]-arylsulphonamides (VII—IX), *their hydrochlorides* (XII—IV) *and sodium salts*

A solution of an arylsulphonylchloride (0.033 mole) in acetone (20 ml.) was gradually added to β-(1,1-heptamethylenimino) ethylamine (0.033 mole) in the same solvent (20 ml.) at a temperature between 20 and 30°. During the addition or shortly afterwards hydrochlorides of *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides separated. The crude crystalline product was filtered off and recrystallised from methanol or 96% ethanol.

The crystalline hydrochlorides (0.033 mole) were dissolved in hot water (100 ml.), and after treatment with charcoal and filtration, the solution was made alkaline with 10% sodium hydroxide (15 ml.). Free *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides separated as dark oils which in some cases crystallised. The reaction mixture was extracted with ether and after evaporation of the solvent crude *N*-[β-(1,1-heptamethylenimino) ethyl]-arylsulphonamides were obtained as thick oils which distilled *in vacuo* giving the pure compounds. N-[β-(1,1-Heptamethylenimino) ethyl]-*p*-aminobenzensulphonamide (XVI) was prepared by hydrolysis of *N*-[β-(1,1--heptamethylenimino) ethyl]-*p*-acetylaminobenzensulphonamide (XV) with 10% sodium hydroxide, according to the procedure A. Treatment of *N*-[β-(1,1-heptamethylenimino) ethyl]-*p*-aminobenzensulphonamide with ethanolic hydrochloric acid gave the corresponding hydrochloride which was recrystallised from absolute ethanol.

N-[β-(1,1-Heptamethylenimino) ethyl]-arylsulphonamides (0.011 mole) were dissolved in a solution of sodium (0.011 gram atome) in dry ethanol (16 ml.) and the obtained solution was poured into dry ether (150 ml.). The precipitated white sodium salts were filtered off and dried in a vacuum desiccator over anhydrous calcium chloride. On addition of water the sodium salts were converted to the corresponding free sulphonamides.

δ-(1,1-Heptamethylensulphamyl) butylchloride (XVII)

4-Chlorbutansulphonylchloride (76.4 g. 0.4 mole) in dry acetone (90 ml.) was gradually added to heptamethylenimine (90 g., 0.8 mole) in the same solvent (120 ml.) at 15—20°. The reaction mixture was stirred for 3 hr. at room temperature. The precipitated hydrochloride of heptamethylenimine was filtered off with suction and the filtrate evaporated *in vacuo* to give 140.6 g. of a thick brown oil which after shaking with water crystallised. The crude product (100 g., 94%) was recrystallised from 96% ethanol to give colourless crystals of pure δ (1,1-heptamethylensulphamyl) butylchloride (XVII), m. p. 69°.

Anal. $C_{11}H_{22}ClNO_2S$ (267.81) Calc'd.: C 49.33; H 8.28; N 5.23; Cl 13.24%
Found: C 49.08; H 8.06; N 5.42; Cl 13.18%

δ-(1,1-Heptamethylensulphamyl) butylphtalimide (XVIII)

An intimate mixture of δ-(1,1-heptamethylensulphamyl) butylchloride (106.8 g., 0.4 mole) and potassium phthalimide (81.4 g., 0.44 mole) was heated with mechanical stirring during 4 hr. at 140—150°. After cooling of the reaction mixture to 60—65°, 300 ml. of water were added. A crystalline product was obtained which was filtered off and thoroughly washed with water until the filtrate was free of chloride ions. The crude δ-(1,1-heptamethylensulphamyl) butylphthalimide (120 g., 79%) was crystallised from 96% ethanol to give colourless crystals, m. p. 140—141°.

Anal. $C_{19}H_{26}N_2O_2S$ (378.41) Calc'd.: C 60.30; H 6.93; N 7.40%
Found: C 60.05; H 6.69; N 7.65%

δ-(1,1-Heptamethylensulphamyl) butylamine (XIX)

A mixture of δ-(1,1-heptamethylensulphamyl) butylphthalimide (152.2 g., 0.4 mole); dry ethanol (1530 ml.) and *N* ethanolic solution of hydrazine hydrate (1170 ml.) was boiled under reflux during 4 hr. The reaction mixture was then evaporated to dryness, acidified with 10% hydrochloric acid and the separated crystals filtered off with suction. The filtrate was made alkaline with a 40% aqueous sodium hydroxide and the separated oily layer extracted with ether. After drying and evaporation of the solvent δ-(1,1-heptamethylensulphamyl) butylamine (89 g., 89%) was obtained as

a bright yellow oil which distilled at 162°/0.2 mm. The so obtained colourless oil crystallised after staying at room temperature, m. p. 105—106°.

Anal. $C_{11}H_{24}N_2O_2S$ (248.37) Calc'd.: C 53.20; H 9.74; N 11.28%
Found: C 53.49; H 9.78; N 11.27%

N-[*δ-(1,1-Heptamethylensulphamyl) butyl*]-*arylsulphonamides* (XX—XXIII)

A solution of an arylsulphonylchloride (0.02 mole) in acetone (10 ml.) was gradually added to a stirred mixture of δ-(1,1-heptamethylensulphamyl) butylamine (4.96 g., 0.02 mole) and anhydrous potassium carbonate (2.76 g., 0.02 mole) in the same solvent (20 ml.) at a temperature between 25 and 30°. The stirring was continued for 24 hr. at room temperature and two additional hours under reflux.. The potassium chloride formed and the unreacted potassium carbonate were filtered off and the acetone from the filtrate removed under reduced pressure. *N*-[δ-(1,1-Heptamethylensulphamyl) butyl]-arylsulphonamides (XX—XIII) were left behind as thick brown oils which crystallised after addition of water. Ethanol (96%) was used for recrystallisation.

N-[*δ-(1,1-Heptamethylensulphamyl) butyl*]-p-*aminobenzensulphonamide* (XXIV)

A mixture of XXIII (8.9 g., 0.02 mole) and 10% aqueous sodium hydroxide (89 ml.) were boiled under reflux for 3 hr. The reaction mixture was cooled to room temperature and the separated crystalline *N*-[δ-(1,1-heptamethylensulphamyl) butyl]--*p*-aminobenzensulphonamide (XXIV) filtered off and recrystallised from 96% ethanol.

Sodium salt of the above described *N*-[δ-(1,1-heptamethylensulphamyl) butyl]--arylsulphonamides were prepared by dissolving the free sulphonamide (0.01 mole) in a solution of sodium (0.23 g., 0.01 gram atome) in dry ethanol (36 ml.). After keeping at room temperature or in an ice box for a short time crystallisation usually set in. In case that no crystallisation occurred the ethanolic solution of the sulphonamide was poured into dry ether (300 ml.) to precipitate the corresponding sodium salts. The obtained sodium salts were sucked off and dried in a vacuum desiccator over anhydrous calcium chloride.

Acknowledgment. Thanks are due to Mr. Eugen Guštak for helpful discussion of the problem.

REFERENCES

1. R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.* **25** (1960) 1953.
2. Fr. 1,335,993 (1963), *cf. CA* **60**, 1720*g*.
3. R. Takamato, *J. Pharm. Soc. Japan* **48** 94; *cf. C.* 1928 II 1328.
4. A. Müller and P. Bleier, *Monatsh.* **56** (193) 391.
5. Su-Ying, Cheng, Yi-Cheng, Yu, Chi-Cho, Wang, Yun-hua, Cheng, Chai-sheng, Chang, and Su-dran, Ren, *Acta Pharm. Sinica* **11** (1964) 281; *cf. Intern. Pharm. Abstr.* **1** No. 16 (1964) 1015.
6. L. Ružička, M. Kobelt, O. Häflinger, and V. Prelog, *Helv. Chim. Acta* **32** (1949) 545.
7. A. E. Finholt, A. C. Bond, and H. J. Schlesinger, *J. Am. Chem. Soc.* **69** (1947) 1199.
8. F. F. Blicke and N. J. Doorenbos, *J. Am. Chem. Soc.* **76** (1954) 2317.
9. A. Müller, E. Šrepel, E. Funder-Fritzche, and F. Dicher, *Monatsh.* **83** (1952) 386; *cf. CA* **47**, 7511*g*.
10. R. P. Mull, Swiss. 365079 (1959).
11. S. Fila-Hromadko, *Croat. Chem. Acta* **36** (1964) 99; Youg. pat. 157 (1963),
12. R. B. Margerison and A. C. Shabica, Fr. 1,336,403 (1963); *cf. CA* **60**, 2917*e*.
13. E. Robertson, Fr. 1.320,255 (1963); *cf. CA* **59**, 10010*b*.
14. B. Helferich and G. Kleb, *Ann.* **635** (1960) 91.
15. S. Gabriel, *Ber.* **20** (1887) 224.

IZVOD

Sulfonamidski derivati heptametilenimina. Sinteza arilsulfonil-1,1-heptametilenimina, *N*-[β-(1,1-heptametilenimino)etil]-arilsulfonamida i *N*-[δ-(1,1-heptametilensulfamil) butil]-arilsulfonamida

S. Fila-Hromadko, B. Glunčić i D. Kolbah

Kondenzacijom arilsulfonilklorida s heptametileniminom odnosno β-(1,1-heptametilenimino) etilaminom dobiveni su odgovarajući arilsulfonil-1,1-heptametilenimini (I—IV, VI) odnosno hidrokloridi *N*-[β-(1,1-heptametilenimino) etil]-arilsulfonamida (XII—XV). Obradom vodene otopine navedenih hidroklorida s 10%-om natrijevom lužinom dobiveni su slobodni *N*-[β-(1,1-heptametilenimino) etil]-arilsulfonamidi (VII—X). Hidrolizom *p*-acetilaminobenzensulfonil-1,1-heptametilenimina (IV) i *p,p*-bis-(1,1-heptametilenimino)-sulfonil-karbanilida (VI) odnosno *N*-[β-(1,1-heptametilenimino) etil]-*p*-acetilaminobenzensulfonamida (XV) u baznom mediju dobiveni su odgovarajući *p*-aminobenzensulfonil derivati (V, XI). Natrijske soli sulfonamida (VII—XI) koje su dobivene taloženjem s eterom iz otopine natrijskog etilata, izrazito su higroskopne tako da pod utjecajem vlage iz zraka ponovo prelaze u odgovarajuće slobodne *N*-[β-(1,1-heptametilenimino) etil]-arilsulfonamide.

Kondenzacijom heptametilenimina sa 4-klorbutansulfonilkloridom dobiven je δ-(1,1-heptametilensulfamil) butilklorid (XVII) iz kojeg je Gabrielovom sintezom pripravljen δ-(1,1-heptametilensulfamil) butilftalimid (XVIII) a njegovom hidrazinolizom odgovarajući δ-(1,1-heptametilensulfamil) butilamin (XIX). Reakcijom δ-(1,1-heptametilensulfamil) butilamina i arilsulfonilklorida dobiveni su odgovarajući *N*-[δ 1,1-heptametilensulfamil) butil]-arilsulfonamidi (XX—XXIII). *N*-[δ-(1,1-heptametilensulfamil) butil]-*p*-aminobenzensulfonamid (XXIV) je pripravljen hidrolizom *N*-[δ-(1,1-heptametilensulfamil) butil]-*p*-acetilaminobenzensulfonamida u lužnatom mediju. Natrijske soli spomenutih sulfonamida izolirane su iz otopina natrijskog etilata.

»PLIVA«, TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 23. lipnja 1967.