SOME NEW SULPHONAMIDES AND DERIVATIVES OF BICYCLIC GUANIDINES[1]

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ABSTRACT

The preparations and bacteriostatic activities of some sulphonamide derivatives of the bicyclic guanidines are described. Some 1-(2-hydroxy-3-(aryloxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazoles have also been prepared.

DISCUSSION

A series of arylsulphonyl derivatives of 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole (1, 2), Δ^8-hexahydro-1,4,8-pyrimidazole (3), and Δ^9-1,4,9-triazabicyclo(5.3.0)decene (3) have been prepared for evaluation as bacteriostats. Their properties are listed in Table II. An examination of Table I shows that these compounds display bacteriostatic activity against a number of organisms. Moreover, the activity of the 1-*p*-aminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole is of the same order as 1-*p*-acetylaminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole. Both the *p*-aminobenzenesulphonyl-derivatives are fairly toxic compounds. The LD_{50} values for mice by intraperitoneal injection lie within the range of 100–150 mg./kg.

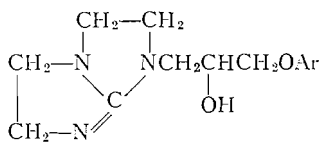
TABLE I

HIGHEST DILUTIONS OF SULPHONAMIDES (MG./ML.) PREVENTING BACTERIAL GROWTH

Test organisms	I*	II	III	IV	V	VI
Staphylococcus pyogenes (R)	4	4	6	3	6	5
Sarcina lutea	3	<2		3	4	1
Streptococcus faecalis	4	5	6	3	6	>5
Aerobacter aerogenes	4	<2	6	3	4	3
Escherichia coli No. 198	3	3	6	3	3	4
Salmonella pullorum	4	4		3	4	4
Pseudomonas aeruginosa	4	5		3	4	4
Proteus mirabilis	5	4		3	4	>5
Proteus vulgaris	3		6	3	5	3
Staphylococcus pyogenes (S)					7	>5

*I, 1-*p*-Acetylaminobenzenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0)decene.
II, 1-*p*-Toluenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0)decene.
III, 1-*p*-Toluenesulphonyl-Δ^8-hexahydro-1,4,8-pyrimidazole.
IV, 1-*p*-Acetylaminobenzenesulphonyl-Δ^8-hexahydro-1,4,8-pyrimidazole.
V, 1-*p*-Acetylaminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole.
VI, 1-*p*-Aminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole.

Some substituted 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazoles (I) were prepared by the reaction of 1,2-epoxy-3-aryloxypropanes with 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imida-



I

Ar = tolyl, *o*- or *p*-chlorophenyl, and 2,4-dichlorophenyl groups

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Contribution from the L. G. Ryan Research Laboratories of Monsanto Canada Limited, Ville LaSalle, Quebec.

TABLE II

ARYLSULPHONYL DERIVATIVES OF THE BICYCLIC GUANIDINES

Compound	Yield (%)	M.p. (° C.)	Formula	C		H		N		S	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
1-*p*-Toluenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole	99	182–184	$C_{12}H_{15}N_3O_2S$	54.31	54.36	5.70	5.63	15.84	16.13	12.08	11.84
1-*p*-Acetylaminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2,-*a*)imidazole	94.5	270–271.5	$C_{13}H_{16}N_4O_3S$	50.61	50.66	5.20	5.26	18.16	18.33	10.40	10.52
1-*p*-Toluenesulphonyl-Δ^8-hexahydro-1,4,8-pyrimidazole	99.5	174–177	$C_{13}H_{17}N_3O_2S$	55.89	56.22	6.13	6.11	15.04	15.12	11.48	11.31
1-*p*-Acetylaminobenzenesulphonyl-Δ^8-hexahydro-1,4,8-pyrimidazole	59.1	267–269	$C_{14}H_{18}N_4O_3S$	52.16	52.30	5.63	5.71	17.39	17.69	9.94	9.95
1-*p*-Toluenesulphonyl-Δ^9-1,4,9-triazabicyclo-(5.3.0)decene	86.5	110.5–111.5	$C_{14}H_{19}N_3O_2S$	57.31	57.12	6.53	6.67	14.32	14.51	10.93	11.16
1-*p*-Acetylaminobenzenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0)decene	72.0	236–238	$C_{15}H_{20}N_4O_3S$	53.55	53.33	5.99	6.13	16.66	16.52	9.54	9.43
1-*p*-Nitrobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole	97.9 67.0*	179–180 231–233 dec.	$C_{11}H_{12}N_4O_4S$ $C_{17}H_{15}N_7O_{11}S$	44.58 38.86	44.72 38.87	4.08 2.88	4.16 3.11	18.91 18.67	19.36 18.66	10.82 6.10	10.74 6.12
1-*p*-Aminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole	85.8	185–186	$C_{11}H_{14}N_4O_2S$	49.60	49.23	5.30	5.36	21.04	21.09	12.04	12.05
1-*p*-Aminobenzenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0)decene	63.0	207–208.5	$C_{13}H_{18}N_4O_2S$	53.05	53.45	6.16	6.40	19.03	18.81	10.90	10.48

**Picrate.*

zole. 1,2-Epoxy-3-(*o*- or *p*-chlorophenoxy)propane gave the expected derivative I (Ar = *o*- or *p*-chlorophenyl) and a small amount (3.8%) of a by-product. The by-product was identified as a di-(2-hydroxy-3-(*o*- or *p*-chlorophenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazolium chloride by analysis. It gave a test for chloride ion and it formed a picrate whose analysis also agreed with this structure. This indicates that the 1,2-epoxy-3-(*o*- or *p*-chlorophenoxy)propane was contaminated with at least 3.8% of the corresponding chlorohydrin derivative, which was most likely used in the preparation of the epoxy compound.

1-(2-Hydroxy-3-(*m*-methylphenoxy)propyl)- and 1-(2-hydroxy-3-(*o*- or *p*-chlorophenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazoles gave LD_{50} values of 125–150 mg./kg. and 150–200 mg./kg. respectively on intraperitoneal injection in mice. These compounds produced convulsions at the toxic level.

EXPERIMENTAL[2]

Preparation of the Arylsulphonyl Derivatives of the Bicyclic Guanidines

Since all of the arylsulphonyl derivatives of the bicyclic guanidines were prepared in the same manner, only the preparation of 1-*p*-toluenesulphonyl-Δ^8-hexahydro-1,4,8-pyrimidazole is described in detail. The properties of the arylsulphonyl derivatives are described in Table II.

To a stirred solution of Δ^8-hexahydro-1,4,8-pyrimidazole (5.0 g., 0.04 mole) and *p*-toluenesulphonyl chloride (7.60 g., 0.04 mole) in water (25 ml.) covered with ether (20 ml.) was added a solution of sodium hydroxide (11 ml. of 3.65 *N* sodium hydroxide solution). After the dropwise addition of the sodium hydroxide solution, which required 20 minutes, the reaction mixture was stirred for an additional 40 minutes at room temperature. The product (11.06 g.) was recovered by filtration and then crystallized from ethyl acetate.

1-p-Aminobenzenesulphonyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

A mixture of 1-(*p*-acetylaminobenzenesulphonyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)-imidazole (9 g., 0.03 mole), ethanol (200 ml.), and 5 *N* sodium hydroxide solution (50 ml.) was heated under reflux for 15 minutes. The solution on cooling and dilution with water deposited crystals, yield 6.7 g. (85.5%). The crude product (m.p. 181°–184°C.) was purified by crystallizing from an acetone–hexane (4:1) solution. 1-*p*-Aminobenzenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0.)decene (Table II) was prepared in a similar manner from 1-*p*-acetylaminobenzenesulphonyl-Δ^9-1,4,9-triazabicyclo(5.3.0)decene.

1-(2-Hydroxy-3-(m-methylphenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

2,3,5,6-Tetrahydro-1-imidaz(1,2-*a*)imidazole (4.44 g., 0.04 mole) and 1,2-epoxy-3-(*m*-methylphenoxy)propane (6.57 g., 0.04 mole) in absolute methanol (30 ml.) were refluxed for $3\frac{1}{2}$ hours. After the solvent was removed *in vacuo* under nitrogen, a yellow oil was obtained, yield 11.05 g. (99.7%). This oil slowly crystallized over a period of several days. Recrystallization from acetone–hexane gave a 57% yield of pure product (m.p. 102.5°–104° C.). Anal. Calc. for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.27. Found: C, 65.09; H, 7.70; N, 15.42%.

A paper chromatogram of the product on No. 1 Whatman paper developed with butanol – acetic acid – water (40:10:50) gave an R_f value of 0.72 ± 0.01.

Its picrate formed in the usual manner from water melted at 127°–132° C., yield

[2]*All melting points are uncorrected. The microanalyses were determined by Micro-Tech Laboratories, Skokie, Illinois.*

85.8%. One crystallization from absolute ethanol raised the melting point to 143.5°–144° C. Anal. Calc. for $C_{21}H_{24}N_6O_9$: C, 50.00; H, 4.79; N, 16.66. Found: C, 50.10; H, 4.67; N, 16.92%.

1-(2-Hydroxy-3-(o- or p-chlorophenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

To a solution of 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole (4.44 g., 0.04 mole) in absolute methanol (35 ml.) was added 1,2-epoxy-3-(*o*- or *p*-chlorophenoxy)propane (7.35 g., 0.04 mole) and the mixture was refluxed for 3 hours. Evaporation of the solution *in vacuo* gave 11.7 g. (99%) of semicrystalline solid. A paper chromatogram on No. 1 Whatman paper, which was developed with butanol–acetic acid–water (40:10:50) solvent, gave two spots on spraying with bromcresol green solution with R_f values of 0.77±0.01 and 0.88. The two components were separated by crystallization from acetone. An acetone-insoluble fraction was obtained with an R_f value of 0.88, yield 0.78 g. (3.8%). Two crystallizations from methanol – ethyl acetate (1:5) solution raised the melting point from 183°–189° C. to a constant value of 190°–191° C. These crystals gave a positive test for chloride ion with silver nitrate solution. The analytical values agreed with those calculated for a di-(2-hydroxy-3-(*o*- or *p*-chlorophenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz-(1,2,-*a*)imidazolium chloride. Anal. Calc. for $C_{23}H_{28}Cl_3N_3O_4$: C, 53.46; H, 5.46; Cl, 20.58; N, 8.13. Found: C, 53.53; H, 5.53; Cl, 20.83; N, 8.01%.

A picrate (m.p. 162.5°–164° C.) was formed in 80% yield in the usual manner from water. The melting point was not changed by further crystallization. Anal. Calc. for $C_{29}H_{30}Cl_2N_6O_{11}$: C, 49.09; H, 4.26; Cl, 9.99; N, 11.85. Found: C, 49.01; H, 4.32; Cl, 10.06; N, 11.89%.

The acetone filtrate from above on cooling deposited 8.37 g. (71.2%) of crystals melting at 149°–153° C. Three crystallizations from acetone raised the melting point to 153.5°–154° C. (R_f, 0.77±0.01). Anal. Calc. for $C_{14}H_{18}ClN_3O_2$: C, 56.86; H, 6.13; Cl, 11.99; N, 14.21. Found: C, 57.32; H, 6.02; Cl, 12.12; N, 14.52%.

A picrate (m.p. 127°–128° C.) was formed in the usual manner from water, yield 86.2%. Two crystallizations from methanol–ether (1:1) solution raised the melting point to 129°–130° C. Anal. Calc. for $C_{20}H_{21}ClN_6O_9$: C, 45.77; H, 4.03; Cl, 6.76; N, 16.02. Found: C, 46.12; H, 4.19; Cl, 6.95; N, 16.14%.

1-(2-Hydroxy-3-(2,4-dichlorophenoxy)propyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

A solution of 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole (4.44 g., 0.04 mole) and 1,2-epoxy-3-(2,4-dichlorophenoxy)propane (8.79 g., 0.04 mole) in absolute methanol (35 ml.) was refluxed for 3 hours. Evaporation of the solution gave 13.04 g. (98.7%) of dark viscous oil. A paper chromatogram prepared as described above gave two basic spots with R_f values of 0.77 and 0.46. The latter value indicated the presence of unchanged 2,3,5,6-tetrahydro-1-imidaz(1,2-*a*)imidazole.

The crude oil (11.04 g.) was refluxed with water (25 ml.) and the aqueous phase was removed by decantation. This process was repeated twice to remove the unchanged starting material from the product. After the sticky residue was triturated with acetone (50 ml.), crystallization occurred, yield 2.36 g. (17.9%). The melting point of these crystals was raised from 154°–156.5° C. to 155°–156.5° C. (R_f, 0.77) by crystallizing from ethanol–water (2:3) solution. Anal. Calc. for $C_{14}H_{17}Cl_2N_3O_2$: C, 50.92; H, 5.19; Cl, 21.48; N, 12.73. Found: C, 50.96; H, 5.23; Cl, 21.83; N, 12.34%.

The picrate was prepared by dissolving a sample of the crystals in the minimum amount of methanol and adding saturated aqueous picric acid solution. The picrate (m.p. 144°–146° C.) was obtained in 66% yield. It was purified to a constant melting point

of 146°–147° C. by crystallizing from methanol–ether (2:1) solution. Anal. Calc. for $C_{20}H_{20}Cl_2N_6O_9$: C, 42.95; H, 3.61; Cl, 12.68; N, 15.03. Found: C, 42.84; H, 3.59; Cl, 13.03; N, 14.85%.

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