ACTA CHEMICA SCANDINAVICA 15 (1961) 1367–1371

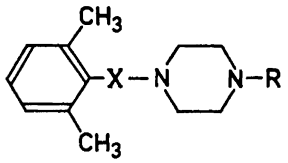
Piperazine Compounds Containing a 2,6-Dimethylphenyl Residue

RICHARD DAHLBOM* and ALFONS MISIORNY

Research Laboratories, AB Astra, Södertälje, Sweden

A number of piperazine compounds containing a 2,6-dimethylphenyl residue were prepared and tested for local anesthetic, ataractic and sedative properties. No appreciable effects were found.

In connection with investigations on local anesthetics of the aminoacylanilide type a series of compounds were prepared using an N-substituted piperazine as the amine component (type I, X = $-NHCOCH_2-$ or $-NHCOCH(C_2H_5)-$). As an extension of this work a number of compounds were prepared in which the 2,6-dimethylphenyl and piperazine residues were joined by a carbamoyl (II, X = $-NHCO-$) or a carbonyl (III, X = $-CO-$) group.



I. X = $-NHCOCH_2-$, $-NHCOCH(C_2H_5)-$

II. X = $-NHCO-$

III. X = $-CO-$

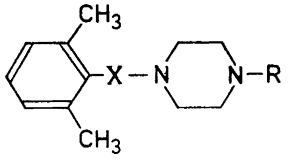
R = CH_3, $-CH_2CH=CH_2$, $-CH_2C_6H_5$, $-CH_2CH_2OH$, $-COOC_2H_5$, $-CH_2COOC_2H_5$

The new compounds were synthesized by treating an N-substituted piperazine derivative with the following: halogenoacyl-2,6-dimethylaniline (method A); 2,6-dimethylphenyl*iso*cyanate (method B); or 2,6-dimethylbenzoyl chloride (method C).

The N-methylpiperazine derivatives (R = $-CH_3$) could also be smoothly prepared from the corresponding urethanes (R = $-COOC_2H_5$) according to

* Present address: Department of Chemistry, Kungl. Farmaceutiska Institutet, Stockholm, Sweden.

Table 1. Piperazines containing a 2,6-dimethylphenyl group.

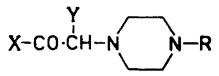


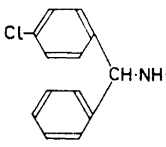
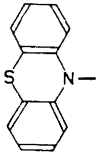
No.	X	R	Method	Yield %	Derivative	M.p. °C	Recryst. Solvent [a]	Formula	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
1	$-NHCOCH_2-$	$-COOC_2H_5$	A	92	Base	94–95	L	$C_{17}H_{25}N_3O_3$	63.9	7.89	13.2	63.9	7.82	13.3
2	»	$-CH_3$	A	70	2 HCl	267–268 (d)	E-Aq	$C_{15}H_{23}N_3O \cdot 2\,HCl$	53.9	7.54	21.2	54.0	7.54	21.0
			D	66	2 HCl	267–268 (d)	E-Aq							
3	»	$-CH_2C_6H_5$	A	73	Base	145–146	M	$C_{21}H_{27}N_3O$	74.7	8.07	12.45	74.6	7.99	12.3
4	»	$-CH_2COOC_2H_5$	A	62	Base	83– 84	L	$C_{18}H_{27}N_3O_3$	64.8	8.16	12.6	64.7	8.27	12.6
5	»	$-CH_2CH_2OH$	D	99	Base	111–112	L-B	$C_{16}H_{25}N_3O_2$	65.9	8.65	14.4	65.7	8.52	14.4
			A	84	Base	111–112	L-B							
6	»	$-CH_2CH=CH_2$	A	52	Base	88– 89	L	$C_{17}H_{25}N_3O$	71.0	8.77	14.6	71.0	8.40	14.4
7	$-NHCOCH(C_2H_5)-$	$-COOC_2H_5$	A	45	Base	127–128	L-B	$C_{19}H_{29}N_3O_3$	65.6	8.41	12.1	65.5	8.21	11.8
8	»	$-CH_2COOC_2H_5$	A	31	Base	91– 92	L	$C_{20}H_{31}N_3O_3$	66.5	8.64	11.6	66.5	8.64	11.6
9	$-NHCO-$	$-COOC_2H_5$	B	98		231–232	M	$C_{16}H_{23}N_3O_3$	62.9	7.59	13.7	63.1	7.66	13.9
10	»	$-CH_3$	D	86	Base	198–199	B	$C_{14}H_{21}N_3O$	68.0	8.56	17.0	68.0	8.32	16.8
11	»	$-CH_2C_6H_5$	B	97	Base	235–236	M	$C_{20}N_{25}N_3O$	74.3	7.79	13.0	74.6	7.77	13.2
12	»	$-CH_2COOC_2H_5$	B	91	Base	132–134	B	$C_{17}H_{25}N_3O_3$	63.9	7.89	13.2	64.2	7.68	13.2
13	»	$-CH_2CH_2OH$	D	63	Base	164–165	B	$C_{15}H_{23}N_3O_2$	64.9	8.36	15.2	65.1	8.37	15.2
			B	97	Base	164–165	B							
14	»	$-CH_2CH=CH_2$	B	89	Base	171–172	E-Aq	$C_{16}H_{23}N_3O$	70.3	8.48	15.4	70.5	8.47	15.5
15	$-CO-$	$-CH_3$	D[b]	92	HCl	267–268 (d)	E	$C_{14}H_{20}N_2O \cdot HCl$	62.6	7.88	10.4	62.2	7.83	10.3
			C	62	HCl	267–268 (d)	E							
16	»	$-CH_2C_6H_5$	C	56	HCl	257–259	E	$C_{20}H_{24}N_2O \cdot HCl$	69.6	7.30	8.12	69.6	7.63	7.98
17	»	$-CH_2COOC_2H_5$	C	93	Base	206–207	E-Et	$C_{17}H_{24}N_2O_3 \cdot HCl$	59.9	7.39	8.22	59.3	7.35	7.99
18	»	$-CH_2CH_2OH$	D	90	HCl	184–185	E-Et	$C_{15}H_{22}N_2O_2 \cdot HCl$	60.5	7.78	9.41	60.2	7.59	9.69
19	»	$-CH_2CH=CH_2$	C	69	HCl	222–224	E-Et	$C_{16}H_{22}N_2O \cdot HCl$	65.2	7.86	9.50	64.9	7.97	9.43

a E, ethanol; Et. ether; Aq, water; B, benzene; M, methanol; L, ligroin.

b The starting material for this reduction, 1-(2,6-dimethylbenzoyl)-4-ethoxycarbonylpiperazine, was prepared by method C but could not be obtained in crystalline form. Therefore it was used without further purification.

Table 2. Piperazinoacylbenzhydrylamines and phenothiazines.



No.	X	Y	R	Method	Yield %	Derivative	M.p. °C	Recryst. Solvent[a]	Formula	Calc. %			Found %		
										C	H	N	C	H	N
20		H	$-COOC_2H_5$	A	90	$HClO_4$	214–216 (d)	E-Aq	$C_{22}H_{26}ClN_3O_3 \cdot HClO_4$	51.2	5.27	8.14	51.4	5.34	8.02
21	»	»	$-CH_3$	A	73	Base	143–144	M-Aq	$C_{20}H_{24}ClN_3O$	67.1	6.76	11.7	66.8	6.84	11.4
22	»	»	$-CH_2COOC_2H_5$	A	77	2 HCl	201–203 (d)	E	$C_{23}H_{28}ClN_3O_3 \cdot 2\ HCl$	54.9	6.01	8.36	55.2	6.13	8.11
23	»	»	$-CH_2CH_2OH$	A	69	2 HCl	254–256 (d)	E-Aq	$C_{21}H_{26}ClN_3O_2 \cdot 2\ HCl$	54.7	6.12	9.12	54.5	6.32	9.07
24		»	$-CH_2C_6H_5$	A	72	Base 2 HCl	141–142 227–229 (d)	E-Aq M-Et	$C_{25}H_{25}N_3OS$ $C_{25}H_{25}N_3OS \cdot 2\ HCl$	72.3 61.5	6.06 5.57	10.1 8.60	72.4 61.1	6.06 5.75	10.0 8.73
25	»	$-CH_3$	»	A	80	Base 2 HCl	135–136 213–214	E-Aq M-Et	$C_{26}H_{27}N_3OS$ $C_{26}H_{27}N_3OS \cdot 2\ HCl$	72.7 62.1	6.34 5.82	9.79 8.36	72.8 61.9	6.28 6.06	9.62 8.22

a See Table 1.

the excellent method of Dannley *et al.*[1] (method D). (This method involves preparation of methylamines from urethanes by reduction with lithium aluminium hydride). The β-hydroxyethyl compounds (R = $-CH_2CH_2OH$) were alternatively prepared by reduction of the corresponding ethoxycarbonylmethyl derivative (R = $-CH_2COOC_2H_5$).

The compounds and their properties are listed in Table 1. The new compounds were tested for local anesthetic action on rabbit cornea, using Xylocaine as standard. The observed effects were slight and it is evident that the piperazine residue decreases the anesthetic potency in the aminoacylanilide type of local anesthetics.

Toxicity tests showed some compounds to have a sedative effect; attempts were therefore made to enhance this effect by replacing the 2,6-dimethylphenyl group by a *p*-chlorobenzhydryl or a phenothiazine residue (compounds 20—25 in Table 2). However, these compounds had little or no ataractic and sedative properties in pharmacological tests.

EXPERIMENTAL

The melting points were determined in an electrically heated metal block using calibrated Anschütz thermometers.

All compounds were dried at 50°/0.01 mm for 4 h before analysis.

1-Methylpiperazine and *1-(β-hydroxyethyl)-piperazine* are commercially available. *1-(Ethoxycarbonyl)-piperazine* [2], *1-benzylpiperazine* [3] and *ethyl 1-piperazineacetate* [4] were prepared by published methods. *1-Allylpiperazine* was prepared in 35 % yield from allylchloride and piperazine hexahydrate following the method for preparation of 1-benzylpiperazine given by Baltzly *et al.*[3]; b.p. 62—64°/11 mm.

α-Chloro-2,6-dimethylacetanilide [5], *α-bromo-2,6-dimethylbutyranilide* [6], *10-chloroacetylphenothiazine* [7], *10-(α-bromopropionylphenothiazine* [7], *2,6-dimethylphenylisocyanate* [8] and *2,6-dimethylbenzoylchloride* [9] were prepared according to procedures described in the literature.

N-(Chloroacetyl)-p-chlorobenzhydrylamine was prepared from chloroacetyl chloride and *p*-chlorobenzhydrylamine [10] in 64 % yield according to the method of Löfgren [5] for the chloroacetylation of amines. M.p. 116—117° after recrystallisation form ligroin-benzene. (Found: C 61.7; H 4.66; N 4.99. Calc. for $C_{15}H_{13}Cl_2NO$: C 61.2; H 4.45; N 4.76).

Piperazinoacylamines (*Method A*). A solution of the appropriate piperazine compound (0.125 mole) and a halogenoacylamine (0.05 mole) in benzene (50 ml) was refluxed. The reflux time was 2 h for compounds 1—4 and 5—6 h for compounds 5—8 and 20—25. Toluene was used as solvent in the preparation of compounds 24 and 25. After cooling to room temperature the amine hydrohalogenide was filtered and the filtrate extracted thoroughly with 2 N hydrochloric acid. The extract was made alkaline with 5 N sodium hydroxide. The reaction product usually separated as an oil which soon crystallised and was purified by recrystallisation. When the base failed to crystallize, it was extracted with ether and converted to the *hydrochloride* by the addition of an ethereal solution of hydrogen chloride.

2,6-Dimethylphenylcarbamoylpiperazines (*Method B*). A solution of 2,6-dimethylphenyl-*iso*cyanate (0.1 mole) and the appropriate piperazine derivative (0.12 mole) in benzene (50 ml) was refluxed for 2 h. On cooling, the reaction product separated in practically pure form.

2,6-Dimethylbensoylpiperazines (*Method C*). A solution of 2,6-dimethylbenzoyl chloride (0.05 mole) and the appropriate piperazine derivative (0.12 mole) in benzene (100 ml) was refluxed for 2 h. The reaction mixture was then worked up as described for method A.

Reductions of ethoxycarbonyl- and ethoxycarbonylmethylpiperazines by lithium aluminium hydride (*Method D*). The piperazine compound (0.02 mole) was added in small portions to a solution of lithium aluminium hydride (0.05 mole) in ether (200 ml). The mixture was

refluxed for 2 h and 2 N sodium hydroxide (10 ml) was added. The ether layer was separated, dried over sodium sulphate and evaporated. The residue was recrystallised or converted to the hydrochloride.

Physical constants and analytical data are collected in Tables 1 and 2.

REFERENCES

1. Dannley, R. L., Lukin, M. and Shapiro, J. *J. Org. Chem.* **20** (1955) 92.
2. More, T. S., Boyle, M. and Thorn, V. M. *J. Chem. Soc.* **1929** 39.
3. Baltzly, R., Buck, J. S., Lorz, E. and Schön, W. *J. Am. Chem. Soc.* **66** (1944) 263.
4. Braker, W. and Christiansen, W. G. *J. Am. Pharm. Assoc.* **22** (1933) 1950.
5. Löfgren, N. *Studies on Local Anesthetics.* (Diss.) Stockholm 1948, p. 25.
6. Dahlbom, R., Tegner, C., Willman, N.-E. and Löfgren, N. *To be published.*
7. Dahlbom, R. and Ekstrand, T. *Acta Chem. Scand.* **5** (1951) 102.
8. Dahlbom, R. and Österberg, L.-E. *Acta Chem. Scand.* **9** (1955) 1553.
9. Lock, G. and Schmidt, K. *J. prakt. Chem.* **140** (1934) 229.
10. Clemo, G. R., Gardner, C. and Raper, R. *J. Chem. Soc.* **1939** 1958.

Received February 20, 1961.