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Substituted 1,3-Diamino-2-propanols

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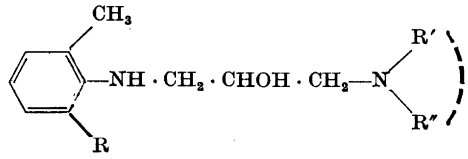
A series of 1,3-diamino-2-propanols of the general formula $R-CH_2 \cdot CHOH \cdot CH_2-Am$ where R is a 2,6-disubstituted anilino residue and Am is an alkylamino group were synthesised. Some compounds were also made with R a benzhydrylamino or 10-phenothiazinyl group.

1,3-Diamino-2-propanols of the general formula $R-CH_2 \cdot CHOH \cdot CH_2-Am$, where R is an unsubstituted or monosubstituted anilino residue and Am is a lower mono- or dialkylamino group were first prepared by Fourneau *et al.*[1,2] in connection with their investigations on antimalarial drugs. Further compounds of this type have been described by Ludwig, West and Farnsworth [3], who stated that these compounds possessed striking convulsant properties.

In connection with work on local anesthetics it was of interest to prepare and study compounds of this type containing a 2,6-disubstituted anilino residue. A number of compounds were synthesised with the general formula



in which R is methyl or chlorine and R′ and R″ are hydrogen, alkyl groups or two connected alkyl groups forming a heterocyclic ring. These compounds were prepared by two methods:

(*A*) Condensation of a 2,6-disubstituted aniline with an N-(2,3-epoxypropyl)-dialkylamine in the presence of lithium amide. Attempts to effect this condensation without a condensing agent gave very poor yields even at elevated temperatures.

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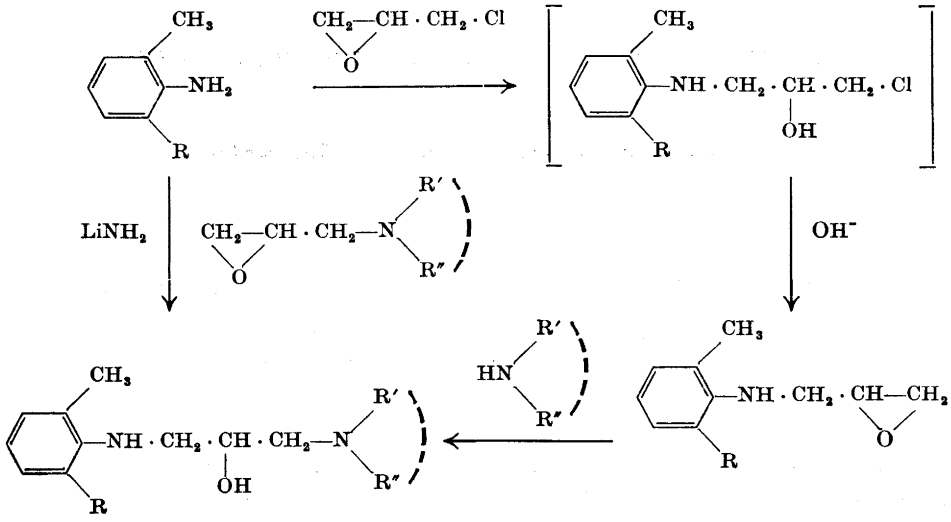
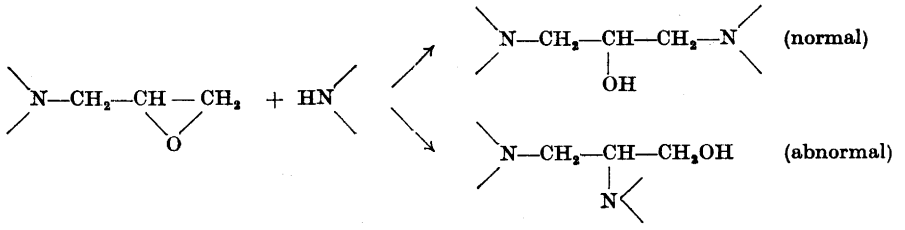
(*B*) Treatment of a 2,6-disubstituted aniline with epichlorohydrin giving a 1-anilino-3-chloro-2-propanol, followed by treatment of the product, without isolation, with a large excess of alkali in order to reform an epoxide ring and reaction of the N-(2,3-epoxypropyl)-aniline obtained with a primary or secondary amine.



Theoretically the opening of an unsymmetrically substituted epoxide ring can give rise to two structural isomers:



However, there is considerable evidence [4-6] that if the reaction as in this case is a nucleophilic displacement on carbon, the nucleophilic reagent entirely or predominantly attacks the least substituted carbon atom ("normal" ring-opening). We have therefore presumed that the compounds described in this paper are 1,3-diamino-2-propanols and not the isomeric 2,3-diamino-1-propanols which would be the products, if the ring-opening were "abnormal". The compounds (1—20) and their properties are listed in Table 1.

The new compounds were tested for local anesthetic action on rabbit cornea, using Xylocaine as standard. They all had a marked anesthetic effect (usually 1—5 times that of Xylocaine). The *cyclo*hexylamino compounds 7 and 15 were about 15—20 times as active as Xylocaine. The lowest activity

was shown by the compounds containing a morpholino or piperazine residue as amino component. The compounds were usually somewhat more toxic than Xylocaine and moreover had convulsant properties. Some of them had a favourable therapeutic index, but their usefulness as local anesthetics was precluded by the strong irritating properties displayed by all compounds in this series.

Several of the compounds had hypnotic or sedative effects. Attempts were therefore made to enhance this effect by replacing the anilino group by a benzhydrylamino, *p*-chlorobenzhydrylamino or a 10-phenothiazinyl residue (compounds 21—27 in Table 1). Compounds 23 and 27 are of special interest as these compounds bear a certain structural resemblance to hydroxyzine, N-(*p*-chlorobenzhydryl)-N'-[2-(2-hydroxyethoxy)-ethyl]-piperazine, and perphenazine, N-[3-(2-chloro-10-phenothiazinyl)-propyl]-N'-(2-hydroxyethyl)-piperazine, respectively, which are used clinically as ataraxic agents. However, compounds 21—27 had very little or no ataraxic properties in pharmacological tests.

EXPERIMENTAL

2,3-Epoxypropylamines

N-(2,3-Epoxypropyl)-diethylamine and *N-(2,3-epoxypropyl)-piperidine* were prepared from diethylamine and piperidine, respectively, by reaction with epichlorohydrin according to the method of Gilman *et al.*[7]

N-(2,3-Epoxypropyl)-morpholine was prepared in the same way but with some small modifications owing to the greater solubility of the morpholino compound in water. Yield 50 %. B. p. 89—90°/10 mm; n_D^{25} 1.4670. (Found: C 58.8; H 9.07; N 9.86. Calc. for $C_7H_{13}NO_2$: C 58.7; H 9.15; N 9.78.)

N-Methyl-N'-(2,3-epoxypropyl)-piperazine was prepared by the same method from N-methylpiperazine and epichlorohydrin. Yield 22 %. B. p. 95—96°/12 mm; n_D^{25} 1.4727. (Found: C 61.5; H 10.3; N 17.9. Calc. for $C_8H_{16}N_2O$: C 61.3; H 10.4; N 18.1.)

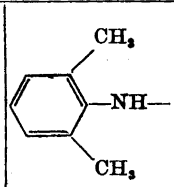
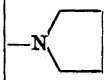
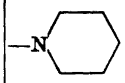
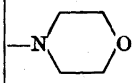
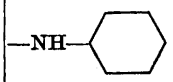
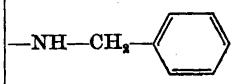
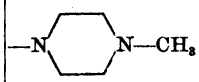
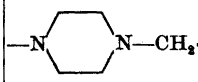
N-(2,3-Epoxypropyl)-2,6-dimethylaniline. A solution of 2,6-dimethylaniline (121 g, 1.0 mole) and epichlorohydrin (102 g, 1.1 mole) in toluene (150 ml) was refluxed for 6 h. After cooling to room temperature, powdered sodium hydroxide (75 g) was added in small portions with stirring and external cooling. After half an hour water (300 ml) was added, the stirring was continued for a further half hour. The toluene layer was separated, washed with water and dried over sodium sulphate. The solvent was evaporated *in vacuo* and the residue distilled giving a colourless oil (76 g, 43 %), b. p. 90—92°/0.3 mm; n_D^{20} 1.5415. (Found: C 74.2; H 8.43; N 8.20. Calc. for $C_{11}H_{15}NO$: C 74.5; H 8.53; N 7.90.)

N-(2,3-Epoxypropyl)-2-chloro-6-methylaniline was prepared in the same way. However, 2-chloro-6-methylaniline reacted rather sluggishly with epichlorohydrin and the reaction was therefore carried out by heating the components in diethylbenzene (mixture of isomers of b.p. 175—181°) at 160—170° for 6 h. Yield 38 %. B. p. 109—111°/1.0 mm; n_D^{20} 1.5562. (Found: C 61.3; H 6.24; N 6.89. Calc. for $C_{10}H_{12}ClNO$: C 60.8; H 6.12; N 7.09.)

N-(2,3-Epoxypropyl)-benzhydrylamine. Benzhydrylamine (216 g, 1.18 mole) was added with stirring in small portions during one hour to epichlorohydrin (111.2 g, 1.20 mole) to which had been added some water (3.6 ml). During the addition the temperature rose to 28°. Stirring was continued for 8 h, during which time the temperature rose slowly to 35° and then decreased.

The reaction product separated gradually as a thick oil. The reaction mixture was allowed to stand overnight and then benzene (150 ml) was added followed by a solution of sodium hydroxide (56 g) in water (90 ml) added with stirring over half an hour. Stirring

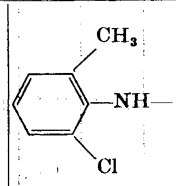
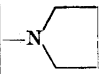
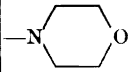
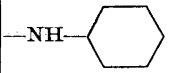
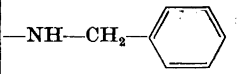
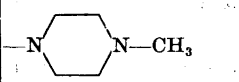
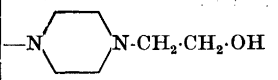
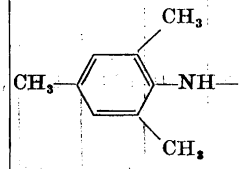
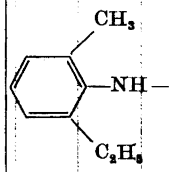
Table 1. 1,3-Diamino-2-propanols.

No.	R	Am	Method	Yield %	Derivative	Recryst. solvent[a]
1		$-N(C_2H_5)_2$	A B	69 58	Base $2\,HClO_4$	— E
2	»		B	73	Base	—
3	»		A	70	Base 2 HCl	— E
4	»		A	73	Base 2 HCl	— E
5	»	$-NH-CH_2\cdot CH_2\cdot CH_3$	B	63	Base	—
6	»	$-NH-CH(CH_3)_2$	B	37	Base	L
7	»		B	78	Base	L
8	»		B	50	2 HCl	E—Et
9	»		B	86	Base	—
10	»		B	82	3 HCl	E—Aq

$R-CH_2-CHOH-CH_2-Am$

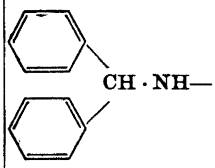
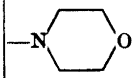
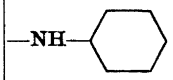
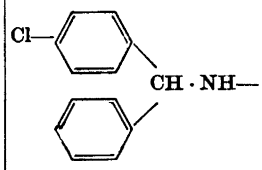
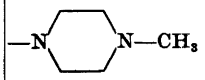
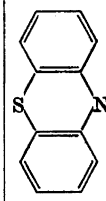
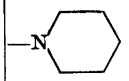
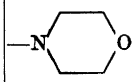
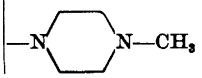
M. p. °C	B. p. °C/mm Hg	n_D^{20}	Formula	Calc. %			Found %		
				C	H	N	C	H	N
—	138—140/0.6	1.5194	$C_{15}H_{26}N_2O$	71.95	10.5	11.2	71.7	10.3	11.1
05—206	—	—	$C_{15}H_{26}N_2O \cdot 2HClO_4$	39.9	6.25	—	40.0	6.51	—
44— 45 [b]	141—143/0.3	1.5424	$C_{15}H_{24}N_2O$	72.5	9.74	11.3	72.8	9.69	11.1
—	161—162/0.8	1.5371	$C_{16}H_{26}N_2O$	73.2	9.99	10.7	72.6	9.77	10.4
48—250 (dec.)	—	—	$C_{16}H_{26}N_2O \cdot 2HCl$	—	—	21.2[c]	—	—	21.2[c]
—	175—178/0.8	1.5415	$C_{15}H_{24}N_2O_2$	68.15	9.15	10.6	68.3	9.02	10.6
37—239	—	—	$C_{15}H_{24}N_2O_2 \cdot 2HCl$	—	—	21.1[c]	—	—	21.3[c]
51— 52 [b]	134—136/0.3	—	$C_{14}H_{24}N_2O$	71.1	10.2	11.85	70.6	10.0	11.8
78— 80	146—147/0.7	—	$C_{14}H_{24}N_2O$	71.1	10.2	11.85	71.0	10.3	11.8
39— 70	—	—	$C_{17}H_{28}N_2O$	73.8	10.2	10.1	73.3	10.0	10.4
20—222	—	—	$C_{18}H_{24}N_2O \cdot 2HCl$	60.5	7.34	7.84	60.6	7.36	7.90
—	149—150/0.1	1.5412	$C_{16}H_{27}N_3O$	69.3	9.81	15.15	68.8	9.82	14.9
17—219 (dec.)	—	—	$C_{17}H_{29}N_3O_2 \cdot 3HCl$	49.0	7.74	10.1	48.4	7.99	10.0

Table 1, (continued).

No.	R	Am	Method	Yield %	Derivative	Recryst. solvent[a]
11		$-N(C_2H_2)_5$	A	62	Base	—
12	»		B	75	Base	—
13	»		A	67	Base	—
14	»	$-NH\text{-}CH_2\cdot CH_2\cdot CH_3$	B	71	Base	—
15	»		B	74	Base	L
16	»		B	81	2 HCl	E—Et
17	»		B	93	Base	—
					2 HCl	E—Aq
18	»		B	79	Base	—
19		$-N(C_2H_5)_2$	A	43	Base	—
20		»	A	62	Base	—

M. p. °C	B. p. °C/mm Hg	n_D^{20}	Formula	Calc. %			Found %		
				C	H	N	C	H	N
—	153–154/0.5	1.5311	$C_{14}H_{23}ClN_2O$	62.2	8.55	10.3	62.0	8.35	10.3
—	143–145/0.1	1.5558	$C_{14}H_{21}ClN_2O$	62.55	7.88	10.4	62.1	8.02	10.6
—	173–174/0.5	1.5534	$C_{14}H_{21}ClN_2O_2$	59.0	7.43	9.84	59.4	7.36	9.85
53– 54 [b]	141–142/0.15	—	$C_{13}H_{21}ClN_2O$	60.8	8.24	10.9	60.9	8.21	10.8
52– 53	168–170/0.1	—	$C_{16}H_{25}ClN_2O$	64.7	8.49	9.44	64.4	8.44	9.62
184–186	—	—	$C_{17}H_{21}ClN_2O \cdot 2HCl$	54.05	6.14	7.42	53.8	6.01	7.71
—	160–163/0.3	—	$C_{15}H_{24}ClN_3O$	60.5	8.12	14.1	60.5	8.19	13.8
239–240	—	—	$C_{15}H_{24}ClN_3O \cdot 2HCl$	48.6	7.07	11.2	48.8	7.21	10.9
—	220–223/0.2	—	$C_{16}H_{26}ClN_3O_2$	58.6	7.99	12.8	58.7	8.04	12.7
—	133–135/0.2	1.5169	$C_{16}H_{28}N_2O$	72.7	10.7	10.6	72.4	10.3	10.9
—	146–148/0.4	1.5174	$C_{16}H_{28}N_2O$	72.7	10.7	10.6	72.5	10.3	10.9

Table 1, (continued).

No.	R	Am	Method	Yield %	Derivative	Recryst. solvent[a]
21			B	68	2 HCl	E—Et
22	»		B	69	2 HCl · H_2O	E—Aq
23			A	64	3 HCl	E
24		$-N(C_2H_5)_2$	A	86	Base	E
25	»		A	94	Base	E
26	»		A	86	Base	Et
					HCl	E
27	»		A	64	2 HCl	E—Et

a E, ethanol; Et, ether; Aq, water; L, ligroin.
b M. p. of solidified distillate.
c Chlorine analysis.

M.p. °C	B. p. °C/mm Hg	n_D^{20}	Formula	Calc. %			Found %		
				C	H	N	C	H	N
224–226	–	–	$C_{20}H_{26}N_2O_2 \cdot 2HCl$	60.1	7.07	7.02	59.9	7.12	7.01
268–270	–	–	$C_{22}H_{28}N_2O \cdot 2HCl \cdot H_2O$	61.5	7.98	6.53	61.4	7.95	6.59
262–264 (dec.)	–	–	$C_{21}H_{28}ClN_3O \cdot 3HCl$	52.2	6.47	8.69	51.7	6.43	8.44
139–140	–	–	$C_{19}H_{24}N_2OS$	69.5	7.36	8.53	69.4	7.28	8.58
153–154	–	–	$C_{20}H_{24}N_2OS$	70.5	7.10	8.23	70.6	7.23	7.83
95– 97	–	–	$C_{19}H_{22}N_2O_2S$	66.6	6.48	8.18	66.5	6.41	8.12
206–207	–	–	$C_{19}H_{22}N_2O_2S \cdot HCl$	60.2	6.12	7.39	60.7	6.31	7.63
242–244 (dec.)	–	–	$C_{20}H_{25}N_3OS \cdot 2HCl$	56.1	6.35	9.81	56.4	6.70	9.51

was continued for one hour. Ether (100 ml) was then added and the organic layer was separated and dried over sodium sulphate. The solvent was evaporated under reduced pressure and the residue, a viscous oil (280 g) which did not crystallise was used as starting material for syntheses without further purification. Attempts to distill the oil led to decomposition.

1,3-Diamino-2-propanols

Method A. Lithium amide (0.11 mole) was added to a solution of the aromatic amine (0.1 mole of 2,6-dimethylaniline, 2-chloro-6-methylaniline, phenothiazine, *etc.*) in benzene (150 ml) and the reaction mixture was refluxed with stirring for 1.5 h. After cooling the appropriate N-(2,3-epoxypropyl)-dialkylamine (0.1 mole) was added, and the mixture was refluxed with stirring for a further 2.5 h. After cooling the benzene solution was washed with water and extracted with 2 N hydrochloric acid. The acid extract was then made alkaline with conc. ammonium hydroxide. The reaction product usually separated as an oil that soon crystallised and was purified by recrystallisation. When it was impossible to obtain the product in crystalline form, it was extracted with ether, the ether was evaporated and the residue distilled *in vacuo*. Some of the compounds were converted to a salt and purified by recrystallisation.

In the preparation of the phenothiazine compounds 24—27 the reaction time after the addition of the epoxide was prolonged to 5 h.

Compound 23 was prepared by condensation of *p*-chlorobenzhydrylamine and N-methyl-N′-(2,3-epoxypropyl)-piperazine in boiling xylene for 6 h and it was therefore not necessary to use lithium amide as condensing agent in this case. Compound 23 contains two asymmetric carbon atoms and should be able to give two racemates. No attempts were made to separate these racemates. Method *A* was used for compounds 1, 3, 4, 11, 13, 19, 20 and 23—27.

Method B. A solution of the appropriate N-(2,3-epoxypropyl)-aniline (0.1 mole) and a mono- or dialkylamine (0.2 mole of diethylamine, *n*-propylamine, pyrrolidine, *etc.*) in xylene (50 ml, mixture of isomers of b.p. 138—142°) was refluxed for 6 h. The xylene was washed with water and extracted with 2 N hydrochloric acid. The reaction product was then isolated as described for method A. Method *B* was used for compounds 1, 2, 5—10, 12, 14—18, 21 and 22.

Physical constants and analytical data are collected in Table 1.

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