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Amines Related to Adrenaline Containing Nuclear Chlorine

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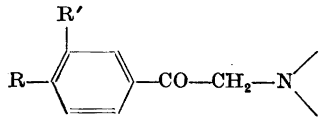
A number of amines related to adrenaline and noradrenaline containing nuclear chlorine have been prepared and tested for antiadrenaline and antinoradrenaline activity.

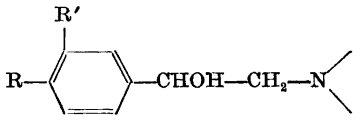
Several investigators have been interested in amines related to adrenaline and noradrenaline containing chlorine in the 3- and/or 4-position of the benzene nucleus. Thus Glynn and Linnell [1] prepared α-3,4-dichlorophenyl-β-aminoethanol from 3,4-dichloro-ω-aminoacetophenone. Edkins and Linnell [2] synthesised a number of ω-aminoacetophenones containing halogen substituents in 3- or 4-position but were unable to reduce them to the corresponding alcohols. Similar difficulties met Hansen [3] who prepared 3-chloro-4-hydroxy-ω-methylaminoacetophenone. However, the synthesis of α-(3-chloro-4-hydroxyphenyl)-β-methylaminoethanol and its ethyl analogue was performed by Fosdick, Fancher and Urbach [4] by catalytic hydrogenation of the corresponding N-benzylated acetophenones. Finally Lutz *et al.*[5] during their search for new antimalarials prepared a number of halogen substituted dialkylaminoacetophenones which were reduced to the corresponding alcohols by means of aluminium *iso*propoxide.

In the course of an investigation on drugs with potential antiadrenaline effect, a number of compounds of type I and II were synthesised. As amino components, piperidine and substituted piperazines were mainly used because of the presence of these amines in well-known adrenergic blocking drugs [6,7].



R = Cl, OH; R′ = H, Cl

I

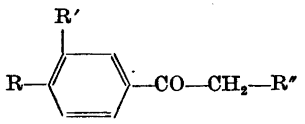


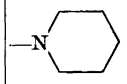
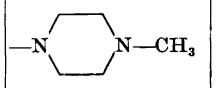
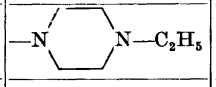
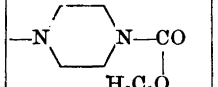
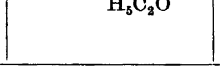
R = Cl; R′ = H, Cl

II

The compounds of type I were easily obtained from the appropriate ω-chloroacetophenone and the desired amine. The compounds of type II were prepared by the reduction of the corresponding amino ketone with lithium

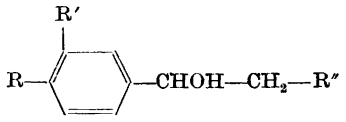
Table 1.

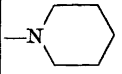
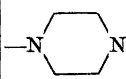


No.	R	R′	R″	Yield [a] %	Derivative analysed	M. p. °C	Recryst. solvent [b]	Formula	Analyses, %					
									Calc.			Found		
									C	H	N	C	H	N
1	Cl	H		85	Base	52— 53	P	$C_{13}H_{16}ClNO$	65.7	6.78	5.89	65.3	6.46	5.55
					HCl	222—223	A	$C_{13}H_{16}ClNO \cdot HCl$	56.9	6.25	5.11	56.5	6.33	5.39
2	OH	Cl		87	HCl	268—270 (decomp.)	A—E	$C_{13}H_{16}ClNO_2 \cdot HCl$	53.8	5.91	4.83	53.6	6.14	4.50
3	Cl	Cl		70	HCl	249—251	A—P	$C_{13}H_{15}Cl_2NO \cdot HCl$	50.6	5.23	4.54	50.6	5.53	4.57
4	Cl	H	—NH—C_2H_5	41	HCl	246—248 (decomp.)	A	$C_{10}H_{12}ClNO \cdot HCl$	51.3	5.59	5.98	51.5	5.65	5.91
5	Cl	H		55	HCl	248—249 (decomp.)	A—Aq	$C_{13}H_{17}ClN_2O$ 2 HCl · 2 H_2O	43.2	6.41	7.75	43.7	6.62	7.81
6	Cl	Cl		69	HCl	252—254 (decomp.)	A	$C_{13}H_{16}Cl_2N_2O \cdot 2$ HCl	43.4	5.04	7.78	43.4	5.09	7.66
7	Cl	H		56	HCl	266—268 (decomp.)	A—Aq	$C_{14}H_{19}ClN_2O \cdot 2$ HCl	49.5	6.23	8.25	49.3	6.26	8.24
8	Cl	H		87	HCl	196—197 (decomp.)	A—E	$C_{15}H_{19}ClN_2O_3 \cdot HCl$	51.9	5.80	8.07	52.1	5.86	8.02
9	Cl	Cl		67	Base	108—109	M	$C_{15}H_{18}Cl_2N_2O_3$	52.2	5.25	8.12	52.2	5.06	7.85
					HCl	212—214 (decomp.)	A—E	$C_{15}H_{18}Cl_2N_2O_3 \cdot HCl$				c		

a Calc. on the crude products.
b A, ethanol; Aq, water; E, ether; M, methanol; P, petroleum ether.
c Calc. Cl 27.9; found 27.9.

Table 2.



No.	R	R′	R″	Yield [a] %	Derivative analysed	M. p. (B. p.) °C	Recryst. solvent [b]	Formula	Analyses, %					
									Calc.			Found		
									C	H	N	C	H	N
10	Cl	H		71	Base	68.5—70	A—Aq	$C_{13}H_{18}ClNO$	65.1	7.56	5.84	65.1	7.46	5.61
11	Cl	Cl		72	Base	89—90	M	$C_{13}H_{17}Cl_2NO$	56.9	6.25	5.11	57.4	6.37	5.05
12	Cl	H	—NH—C_2H_5	37	Base	190/0.8 mm Hg 87—88 [c]		$C_{10}H_{14}ClNO$	60.1	7.07	7.02	59.9	6.84	7.06
13	Cl	H		55	Base	85—85.5	M—Aq	$C_{13}H_{19}ClN_2O$	61.3	7.52	11.0	61.2	7.45	10.7
					HCl	236—237 (decomp.)	A	$C_{13}H_{19}ClN_2O \cdot 2\,HCl$			8.55	*d*		8.42
14	Cl	Cl		49	Base	121—122	A—Aq	$C_{13}H_{18}Cl_2N_2O$	54.0	6.27	9.69	53.8	6.20	9.49

a, *b* See Table 1.
c M. p. of solidified distillate.
d Calc. Cl 32.5; found 32.3.

aluminium hydride. The new compounds are listed in Tables 1 and 2. They have been tested for antiadrenaline and antinoradrenaline activity by Professor U.S. von Euler, Department of Physiology, Karolinska Institutet, Stockholm. In experiments on the blood pressure of cats, a weak antagonism towards adrenaline and noradrenaline was shown by the piperidino compounds 1, 10, and 11.

EXPERIMENTAL

Preparation of the amino ketones. The halogen substituted ω-chloroacetophenones required as starting material were prepared according to procedures described in literature [1,3,8].

The amino ketones were all prepared in essentially the same way. The appropriate ω-chloroacetophenone (0.025 mole) and the amine (0.065 mole) were dissolved in toluene (usually 25 ml) and the reaction mixture was kept at room temperature overnight. The amine hydrochloride was removed by filtration and the toluene solution was washed with water and then extracted with 2 N hydrochloric acid. The extract was made alkaline with sodium carbonate solution and the precipitated base was extracted with ether. The ether was dried over sodium sulphate and the amino ketone was then isolated as the hydrochloride by the addition of ethereal hydrogen chloride and recrystallised. The physical properties of these compounds are listed in Table 1.

Preparation of the amino alcohols. A solution of the free amino ketone (0.02 mole) in ether (100 ml) was prepared from the pure hydrochloride and was added, with mechanical stirring, to a suspension of lithium aluminium hydride (0.015 mole) in ether (100 ml). The mixture was stirred under reflux for 15 min. Excess hydride was destroyed with water and the mixture was made alkaline with 2 ml of 5 N sodium hydroxide. The ethereal layer was then decanted and dried over sodium sulphate. Evaporation of the solvent yielded the almost pure crystalline amino alcohol. In one case (compound 12), an oily product was obtained which was purified by distillation. The physical properties of the amino alcohols are listed in Table 2.

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