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Potential Local Anaesthetics. Part II. Synthesis of Basic *N*-Benzyl-acetamides and -propionamides

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N-(Substituted benzyl)- chloroacetamides and -∝-chloropropionamides have been condensed with diethylamine, piperidine, and morpholine to yield diethylamino / piperidinyl / morpholinyl-*N*-(substituted benzyl)-acetamides and -propionamides.

Some of the basic amides prepared earlier[1] exhibited local anaesthetic activity and diethylamino-*N*-*o*-chlorobenzylacetamide was found to be significantly more potent than cocaine and xylocaine[2]. This prompted the authors to prepare basic *N*-benzylacetamides, having a variety of substituents in the benzene ring, and also the corresponding propionamides for pharmacological studies. With this object several diethylamino-piperidinyl/ morpholinyl-*N*-(substituted benzyl)- acetamides and-propionamides have been prepared. Substituted benzylamines were condensed with chloroacetyl chloride and ∝-halopropionyl chloride and the resulting halo *N*-benzylacetamides/propionamides on heating with appropriate secondary amines gave diethyl/piperidinyl/morpholinyl-*N*-(substituted benzyl)- acetamides and- propionamides.

EXPERIMENTAL

Preparation of benzylamines and their condensation with ∝-haloacyl halides were carried out as described in Part I[1]. *N*-Benzyl- ∝-halopropionamides are shown in Table II (A and B).

Condensation of Secondary Amines with N-(*Substituted benzyl*)- ∝*halo-acylamides.*— A mixture of *N*-(substituted benzyl)- ∝-halo-acylamide (0.015*M*) and secondary amine (0.03*M*) in benzene (50 ml) was refluxed for 6 hours. The benzene solution after filtration was treated with cold dilute hydrochloric acid (1 : 1) and the aqueous extract was treated in cold with excess of ammonia to liberate the base. The ether extract of the base was dried with anhydrous magnesium sulphate and gaseous hydrogen chloride was passed to convert the basic amides into hydrochlorides. The hydrochlorides crystallised as needles from acetone. The compounds prepared are shown in Tables I-V.

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1. Dalal and Trivedi, this *Journal*, 1960, **37**, 437.
2. Jindal and Patel, private communication.

TABLE I

Hydrochlorides of (N-substituted benzyl)-acetamides.

R. C_6H_4.R'.HCl

	R.	M.P.	Formula.	% Nitrogen. Found.	Reqd.
			A. Diethylamino-. R'=CH_2.NH.CO.CH_2.NEt_2.		
1.	*p*-Br	132°	$C_{13}H_{19}ON_2Br$. HCl	8.1	8.3
2.	*o*-OMe	172°	$C_{14}H_{22}O_2N_2$. HCl	7.8	7.7
3.	*p*-OMe	185°	$C_{14}H_{22}O_2N_2$. HCl	7.6	7.7
			B. Morpholino-. R'=-CH_2NH.CO.$CH_2N(CH_2)_4O$.		
*1.	*m*-Cl	116°	$C_{13}H_{17}O_2N_2Cl$. HCl	9.4	9.2
*2.	*p*-Br	156°	$C_{13}H_{17}O_2N_2Br$. HCl	7.7	7.9
*3.	3,4-DiMe	142°	$C_{15}H_{23}O_2N_2$. HCl	9.2	9.3
*4.	2,4-DiMe	148°	$C_{15}H_{23}O_2N_2$. HCl	9.3	9.3
*5.	2,5-DiMe	146°	,,	9.2	9.3
6.	*o*-OMe	115°	$C_{14}H_{20}O_3N_2$. HCl	9.0	9.1
7.	*p*-OMe	160°	,,	9.0	9.1
			C. Piperidinyl-. R'=CH_2.NH.CO. $CH_2N(CH_2)_5$.		
1.	*o*-Me	170°	$C_{15}H_{22}ON_2$·HCl	9.7	9.9
2.	*m*-Me	174°	,,	9.8	9.9
*3.	*m*-Cl	192°	$C_{14}H_{19}ON_2Cl$. HCl	9.3	9.2
*4.	*p*-Cl	142°	,,	9.2	9.2
*5.	*p*-Br	145°	$C_{14}H_{19}ON_2Br$. HCl	8.2	8.0
6.	3,4-DiMe	160°	$C_{16}H_{25}ON_2$. HCl	9.4	9.4
7.	2,4-DiMe	162°	,,	9.2	9.2
8.	2,5-DiMe	189°	,,	9.2	9.2
9.	*o*-OMe	200°	$C_{15}H_{22}O_2N_2$.HCl	9.2	9.3
10.	*p*-OMe	222°	,,	9.3	9.3

TABLE II

N-Benzyl- ∝-halo-propionamides.

R. C_6H_4.CH_2.NH.CO.CH. (∝ halo) Me.

No.	R.	M.P.	Formula.	Found.	Reqd.
			A. ∝-Chloro-.		
1.	*p*-Me	59-60°	$C_{11}H_{14}ONCl$	Cl : 16.7%	16.8%
2.	*p*-Cl	65°	$C_{10}H_{11}ONClBr$	N : 5.0	5.1
3.	2,4 DiMe	76°	$C_{12}H_{17}ONCl$	Cl : 15.4	15.6
4.	2,5-DiMe	125°	,,	Cl : 15.5	15.6
			B. ∝-Bromo-.		
1.	*o*-Me	85°	$C_{11}H_{14}ONBr$	Br : 31.0	31.2
2.	*m*-Me	Oily	,,	Br : 31.2	31.2
3.	*o*-Cl	92°	$C_{10}H_{11}ONClBr$	N : 5.2	5.1
4.	*m*-Cl	Oily	,,	N : 5.1	5.1
5.	*p*-Cl	110°	,,	N : 5.1	5.1
6.	3,4-DiMe	82°	$C_{12}H_{17}ONBr$	Br : 29.6	29.5
7.	*o*-OMe	Oily	$C_{11}H_{14}O_2NBr$	Br : 29.5	29.5
8.	*p*-OMe	,,	,,	Br. : 29.7	29.5

TABLE III

$R.C_6H_4CH_2.NH.CO.CH.CH_3$

$NEt_2.HCl$

Hydrochlorides of α-diethylamino-N-(subst. benzyl) propionamides.

No.	R.	M.P.	Formula.	% Nitrogen. Found.	Reqd.
1.	*o*-Me	184°	$C_{15}H_{24}ON_2$. HCl	9.0	9.8
2.	*m*-Me	171°	,,	9.7	9.8
3.	*p*-Me	195°	,,	9.8	9.8
4.	*o*-Cl	190°	$C_{14}H_{21}ON_2Cl$. HCl	9.2	9.2
5.	*m*-Cl	180°	$C_{14}H_{21}ON_2Cl$.HCl	9.4	9.2
*6.	*p*-Cl	186°	,,	9.2	9.2
7.	*p*-Br	180°	$C_{14}H_{21}ON_2$.Br.HCl	7.7	7.9
8.	3,4-DiMe	202°	$C_{16}H_{27}ON_2$.HCl	9.4	9.3
*9.	2,4- ,,	180°	,,	9.4	9.3
10.	2,5- ,,	193°	,,	9.2	9.3
11.	*o*-OMe	162°	$C_{15}H_{24}O_2N_2$. HCl	9.2	9.3
*12.	*p*-OMe	230°	,,	9.3	9.3

TABLE IV

$R.C_6H_4.CH_2NH.CO.CH.CH_3$

$N(CH_2)_4$ O.HCl

Hydrochlorides of α-morpholinyl-N (subst. benzyl)-propionamides.

No.	R.	M.P.	Formula.	% Nitrogen. Found.	Reqd.
1.	*o*-Me	198°	$C_{15}H_{22}O_2N_2$.HCl	9.3	9.3
2.	*m*-Me	154°	,,	9.4	9.3
3.	*p*-Me	180°	,,	9.4	9.3
4.	*o*-Cl	152°	$C_{14}H_{19}O_2N_2Cl$.HCl	8.9	8.9
5.	*m*-Cl	148°	,,	9.0	8.9
*6.	*p*-Cl	160°	,,	9.0	8.9
7.	*p*-Br	160°	$C_{14}H_{19}O_2N_2Br$.HCl	7.9	7.7
8.	3,4-DiMe	198°	$C_{16}H_{25}O_2N_2$.HCl	8.9	8.9
9.	2,4- ,,	190°	,,	8.7	8.9
10.	2,5- ,,	201°	,,	9.0	8.9
11.	*o*-OMe	158°	$C_{15}H_{22}O_2N_2$.HCl	9.0	8.9
12.	*p*-OMe	205°	,,	9.0	8.9

TABLE V

$R.C_6H_4.CH_2NH.CO.CH.CH_3$

$N(CH_2)_5.HCl$

Hydrochlorides of ∝-piperidinyl-N-(subst. benzyl)-propionamides.

No.	M.P.	Formula.	% Nitrogen. Found.	Reqd.
1.	165°	$C_{16}H_{24}ON_2.HCl$	9.3	9.4
2.	162°	,,	9.3	9.4
*3.	160°	,,	9.2	9.4
4.	140°	$C_{15}H_{21}ON_2Cl.HCl$	8.6	8.8
5.	185°	,,	8.8	8.8
6.	180°	,,	8.6	8.8
7.	175°	$C_{15}H_{21}ON_2Br.HCl.$	7.7	7.7
8.	170°	$C_{17}H_{27}ON_2.HCl$	9.2	9.0
*9.	182°	,,	9.0	9.0
*10.	170°	,,	9.0	9.0
11.	167°	$C_{16}H_{24}O_2N_2.HCl$	9.2	9.0
12.	189°	,,	9.2	9.0

R—same as in Table III.

The compounds shown with asterisk in the tables were examined for local anaesthetic activity and the activity was in the following order (descending). The roman figures in the bracket indicate the number of Table. 9(V), 4, 3(IC), 5 (IC), 4(IC), 10(V), 5*,3(V), 5(IB), 9(III), 6 (IV), (4(IB), 12(III), 3(IB), 1(IB) 2(IB), 6 (III)

Among the compounds tested for local anaesthetic activity, following six were studied more intensively. The results are shown in Table VI.

TABLE VI

Hydrochloride.	Surface. Xylocaine.	Surface. Cocaine as 1.	Indradermal. Xylocaine.	Indradermal. Procaine as 1.
∝-Piperidinyl-*N*-(2,4-dimethylbenzyl)-propionamide	4	2	4	8
Diethylamino-*N*-(*o*-chlorobenzyl)-acetamide	2	2	2	4
Piperidinyl-*N*-(*m*-chlorobenzyl)-acetamide	1	1/2	1	2
∝-Diethylamino-*N*-(2,4-dimethylbenzyl)-propionamide	1/3	1/6	1/3	2/3
∝-Morpholinyl-*N*-(*p*-Cl-benzyl)-propionamide	1/3	1/6	1/3	2/3
Morpholinyl-*N*-(3,4-dimethylbenzyl)-acetamide	1/2	1/4	1/2	1

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