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SEARCH FOR NEW LOCAL ANAESTHETICS. PART III

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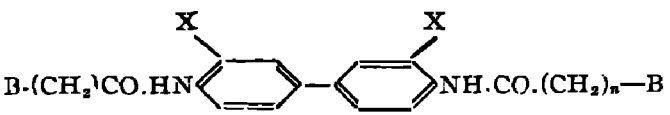
Several *bis*-diethylamino-, piperidino- and morpholino-acetyl and -propionyl derivatives of benzidine, tolidine and dianisidine have been synthesised and their local anaesthetic activity studied.

A series of local anaesthetics containing diphenyl nucleus have been reported by Braker and Christiansen (*J. Amer. Pharm. Assoc.*, 1935, **24**, 358) and some of these compounds have been found more active than procaine and cocaine. Strong local anaesthetic activity has also been reported in the case of dibasic esters containing diphenyl nucleus (Case and Koft, *J. Amer. Chem. Soc.*, 1941, **63**, 508 ; Roberts and Johnson, *ibid.*, 1925, **47**, 1396). 2 : 2′-Diaminodiphenyl also shows local anaesthetic activity, about quarter the activity of cocaine (Chierici, *Ann. chim. farmac.*, 1938, 48). The present work was undertaken to synthesise dibasic anilides of the general formula (I), containing diphenyl nucleus as lipolytic moiety.



(I)

B = Diethylamino, piperidino, and morpholino.
n = 1 or 2.
X = H, Me and MeO.

These compounds have two anaesthesiophoric groups attached to two benzene nuclei in diphenyl. The presence of methyl or methoxy group, *ortho* to the aneasthesiophoric group, is conducive to local anaesthetic potency (Lofgren, *Chem. Abs.*, 1937, **31**, 7854).

For the synthesis of these compounds, the chloro-acylated derivatives of benzidine, *o*-tolidine and *o*-dianisidine were prepared by treating the base with chloroacetyl chloride or β-chloropropionyl chloride. The resulting compound was condensed with the secondary amine. The bases were smoothly converted into their hydrochlorides.

Experimental

1. NN′-bis-*Chloroacetylbenzidine*.—Chloroacetyl chloride (22.6 g.) in dry benzene (50 c.c.) was added in small lots to a cooled solution of benzidine (28.4 g.), finely suspended in dry benzene (150 c.c.). The reaction mixture was thoroughly shaken. It was refluxed for 3 hours on a water-bath. Benzene was distilled off and the residue decomposed with ice-cold water. A yellow powdery mass was obtained which was washed with HCl (dil.) and then several times with water. It was crystallised from alcohol, yield 39.6 g., m.p. 330°. (Found : N, 8.5. $C_{16}H_{14}O_2N_2Cl_2$ requires N, 8.3 %).

TABLE I

[B, T and D stand respectively for benzidine, *o*-tolidine and *o*-dianisidine].

No.	Compounds.	Solvent for crystallisation.	M. P. of the (compound).	M. P. of the (hydrochloride).	Mol. formula of the compound.	Analysis of the compound. Found.	Calc.
3.	NN'-*bis*-(N-piperidinoacetyl)-B	* Pet. ether	208°	278-80°	$C_{26}H_{34}O_2N_4$	N: 12.8%	12.9%
4.	,, (N-morpholinoacetyl)-B	EtOH	208°	270°	$C_{24}H_{30}O_4N_4$	N: 12.4	12.7
5	,, (β-chloropropionyl)-B	,,	265°	...	$C_{18}H_{18}O_2N_2Cl_2$	N: 7.82	7.67
6.	,, (β-diethylaminopropionyl)-B	Pet. ether (40°-60°)	186°	298°	$C_{26}H_{38}O_2N_4$	N: 13.5	13.0
7.	,, (β-N-piperidino- ,,)-B	*Pet. ether	223°	325°	$C_{28}H_{38}O_2N_4$	C: 72.85 H: 7.95 N: 11.8	72.72 8.28 12.11
8.	,, (β-N-morpholinopropionyl)-B	EtOH	235°	330°	$C_{25}H_{34}O_4N_4$	N: 11.4	12.01
9.	,, (chloroacetyl)-T	,,	285°	...	$C_{18}H_{18}O_2N_2Cl_2$	N: 7.6	7.67
10	,, (diethylaminoacetyl)-T	,,	160°	281°	$C_{28}H_{38}O_2N_4$	N: 12.3	12.78
11.	,, (N-piperidino ,,)-T	,,	197°	235°	$C_{28}H_{38}O_4N_4$	C: 72.4 H: 8.0 N: 12.1	72.7 8.28 12.11
12.	,, (N-morpholinoacetyl)-T	,,	228°	268°	$C_{24}H_{34}O_4N_4$	N: 12.23	12.66
13.	,, (β-chloropropionyl)-T	,,	228°	...	$C_{20}H_{22}O_2N_2Cl_2$	N: 6.9	7.12
14.	,, (β-diethylaminopropionyl)-T	,,	156°	305°	$C_{28}H_{42}O_2N_4$	N: 11.9	12.01
15.	,, (β-N-piperidino ,,)-T	,,	177°	290°	$C_{30}H_{42}O_2N_4$	N: 11.4	11.42
16.	,, (β-N-morpholino ,,)-T	*Pet. ether	222°	265°	$C_{28}H_{38}O_4N_4$	N: 11.3	11.35
17.	,, (chloroacetyl)-D	Dilute alcohol	214°	...	$C_{18}H_{18}O_4N_2Cl_2$	N: 6.99 Cl: 17.3	7.05 17.80
18.	,, (diethylamino-acetyl)-D	Benzene	149°	213°d	$C_{26}H_{38}O_4N_4$	N: 12.2	12.12
19.	,, (N-piperidino- ,,)-D	,,	210°	267°d	$C_{28}H_{38}O_4N_4$	N: 11.3	11.33
20.	,, (N-morpholino- ,,)-D	*Pet. ether	262°	> 300°	$C_{26}H_{34}O_6N_4$	N: 11.49	11.24
21.	,, (β-chloropropionyl)-D	EtOH	223°	...	$C_{20}H_{22}O_4N_2Cl_2$	N: 6.42	6.50
22.	,, (β-diethylaminopropionyl)-D	,,	165°	210°	$C_{28}H_{42}O_4N_4$	N: 11.2	11.24
23.	,, (β-N-piperidino- ,,)-D	Benzene	190°	232°	$C_{30}H_{42}O_4N_4$	C: 68.3 H: 7.8	68.9 8.0
24.	,, (β-N-morpholino- ,,)-D	,,	223°	252°	$C_{28}H_{38}O_6N_4$	N: 10.8	10.64

* Pet ether refers to petroleum ether of b. p. 80°-100°.

2. NN'-bis-(*diethylaminoacetyl*)-*benzidine*.—A mixture of diethylamine (2.92 g., 0.04 *M*) and the above chloro compound (4.37 g., 0.01 *M*) in absolute alcohol (30 c.c.) was refluxed for 5 hours. Alcohol was distilled off and the residue washed with sodium bicarbonate solution, followed several times with water. The product was dried and crystallised from petroleum ether (80°-100°), m.p. 131-32°, yield 2.8 g. (Found : C, 70.2 ; H, 8.04 ; N, 13.9. $C_{24}H_{34}O_2N_4$ requires C, 70.23 ; H, 8.26 ; N, 13.68 %).

Hydrochloride of the above base was prepared by passing dry HCl gas in absolute alcoholic solution of the base. Alcohol was distilled off and the hydrochloride was crystallised from acetone, m.p. 274-75°.

The other analogues prepared similarly are shown in Table I.

Compounds No. 10, 11 and 16 have been tested for local anaesthetic activity at the Central Drug Research Institute, Lucknow. These showed no surface anaesthesia when applied to the cornea of guinea pigs in 3% solution. For intradermal anaesthesia, in 2% solution in normal saline, the action of these compounds started after one minute in each case and lasted for 75, 35 and 50 minutes respectively. The diethylamino compound (No. 10) shows a better activity than piperidino analogue (No. 11). The compounds in the series are being further studied for their pharmacological activity.

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