

THE DETERMINATION OF LOCAL ANÆSTHETICS BY EXCHANGE OF IONS

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By methods based on the use of ion exchange resins a number of groups of substances of importance in pharmacy have been determined, i.e. alkaloids^{1,2,3} sulphonamides,^{4,5} official acids and their salts, etc.^{6,7,8} It seemed possible that local anæsthetics might be determined in a similar way both as pure substances, and in the form of galenicals.

From the chemical point of view substances with local anæsthetic effect are derivatives of *p*-aminobenzoic acid or substituted amides, or substituted urethanes. Benzocaine and butesine are esters which are insoluble in water, the others are organic bases and are used in the form of salts which are soluble in water. They may be determined (1) gravimetrically,^{9,10} (2) by titrating the base, precipitated by alkali and isolated by extraction or distillation, with an acid,^{11,12} or (3) bromimetrically.^{13,14,15,16,17,18,19} Procaine or procaine-penicillin may also be determined by volumetric methods^{20,21,22}; Colorimetric or photometric determinations,^{23,24,25,26,27,28,29,30,31} and biological methods have also been worked out.^{32,33}

We have separated the bases of the commonly used local anæsthetics by chromatography on a column of the anion exchange resin Amberlite IRA-400. In this process the acid component was separated and remained in the column, and the basic component set free was determined volumetrically. The principal advantage of this procedure is that the laborious separation of the base by organic solvents is avoided.

EXPERIMENTAL

The assembly of the apparatus for chromatography, the preparation of the column, solutions used and experimental technique are the same as described by Jindra and Pohorsky.^{2,3} The addition of a stopcock to the outlet of the tube to regulate the speed of the flow, is an advantage.

Method. The samples were dried to constant weight in a desiccator over concentrated sulphuric acid and 20 to 50 mg., weighed with an accuracy of ± 0.01 mg., was dissolved in 5 ml. of distilled water in a 35-ml. beaker and 15 ml. of ethanol added. Before use the regenerated and rinsed chromatographic column was washed with 5 ml. of hot ethanol (95 per cent.). When the ethanol had drained away, the solution of the substance under examination was passed through the ion-exchange column (8 to 10 g. of Amberlite TRA-400), the speed of flow being regulated by the stopcock to 60 drops per minute. The column was then washed with 30 ml. of hot ethanol (96 per cent.). The beaker containing the collected eluate was used for the titration with 0.1N hydrochloric acid, methyl red being used as indicator, or the titration being made

A. JINDRA AND J. RENTZ

potentiometrically. The column was washed with a few ml. of distilled water and regenerated in the usual way. The results of our experiments are shown in Table I.

TABLE I

	Theoretical content of base, per cent.	Base equivalent to 1 ml. of 0.1N acid, mg.	Weight taken, mg.	0.1N (f = 0.9664) acid used, ml.	Content of base, per cent.	Deviation, per cent.
2-Diethylaminoethyl <i>p</i> -aminobenzoate hydrochloride (Procaine)	86.56	23.62	45.61	1.73	86.51	- 0.06
			35.07	1.33	86.49	- 0.10
			44.62	1.70	86.88	+ 0.38
			37.39	1.42	86.62	+ 0.06
			37.71	1.43	86.49	- 0.08
3-Diethylamino-2:2-dimethylpropyl- <i>p</i> -aminobenzoate hydrochloride (Larocaine)	88.42	27.84	45.82	1.53	89.24	+ 0.92
			33.43	1.10	88.52	+ 0.11
			21.92	0.72	88.37	- 0.17
			36.71	1.21	88.67	+ 0.29
			40.94	1.34	88.06	- 0.41
3-Dimethylamino-1:2-dimethylpropyl- <i>p</i> -aminobenzoate hydrochloride (Tutocaine)	87.28	25.03	45.30	1.63	87.05	- 0.27
			38.42	1.38	86.90	- 0.44
			28.92	1.04	87.00	- 0.33
			35.31	1.27	87.01	- 0.31
			37.34	1.35	87.47	+ 0.21
2-Butoxy-4- β -diethyl-aminoethylcarbonylquinoline hydrochloride (Nupercaine)	90.38	34.24	39.71	1.08	90.01	- 0.41
			34.76	0.95	90.44	+ 0.07
			35.10	0.95	89.57	- 0.89
			41.60	1.12	89.10	- 1.41
			33.60	0.91	89.63	- 0.83
1-Dimethylamino-2-methyl-2-butanol benzoate hydrochloride (Amylocaine)	86.58	23.53	54.12	2.06	86.51	- 0.08
			47.84	1.82	86.45	- 0.14
			37.45	1.42	86.18	- 0.47
			28.30	1.08	86.73	+ 0.17
			36.28	1.37	86.03	- 0.64
2-Dimethylaminoethyl- <i>p</i> - <i>n</i> -butylaminobenzoate hydrochloride (Amethocaine)	87.84	26.33	42.43	1.46	87.57	- 0.30
			35.05	1.21	87.86	+ 0.02
			40.07	1.37	87.01	- 0.94
			30.56	1.05	87.45	- 0.45
			33.98	1.18	88.38	- 0.61
<i>p</i> -Dialloxyethenyl-diphenylamidine hydrochloride (Diocaine)	89.85	32.30	18.72	0.54	90.05	+ 0.43
			30.50	0.87	89.05	- 0.90
			49.98	1.42	88.70	- 1.28
			35.93	1.03	89.48	- 0.39
			28.16	0.81	89.80	- 0.07

Local anesthetics in galenicals may also be determined by this method. The presence of an electrolyte is a disturbing factor as the water-ethanolic solution is more basic when the anion has been removed. As an example we describe the determination of procaine in an ointment containing 2 per cent. of procaine hydrochloride in soft paraffin.

Procedure: 2 to 3 g. of the ointment is vigorously mixed in a 50-ml. beaker with 5 ml. of boiling distilled water and 5 ml. of ethanol (96 per cent.) added. When the ointment base has settled the ethanolic solution is poured off into another beaker. The ointment base is then washed 5 times with a mixture of 5 ml. of hot water and 5 ml. of ethanol. The mixed solution and washings are then passed through the ion exchange column of Amberlite IRA-400, at 50 to 60 drops per minute. The beaker and the column are then washed quickly with 60 ml. of warm ethanol (96 per cent.). The eluate is diluted with water, 10 to 15 drops of methyl red are added and the eluate is titrated from a microburette with 0.1N

DETERMINATION OF LOCAL ANÆSTHETICS

hydrochloric acid to a distinct red colour. 1 ml. of 0·1N hydrochloric acid is equivalent to 0·027264 g. of procaine hydrochloride.

Results: 2·00 g. of ointment (40 mg. of procaine hydrochloride, required 1·44, 1·45 ml. of 0·1N acid ($f = 0·9664$) = 38·15, 38·41 mg. of procaine hydrochloride.

SUMMARY

1. Salts of local anæsthetics can be determined by separation of the base by means of the anion-exchange resin, Amberlite IRA-400, and titration with acid.

2. This method can be used for galenicals if no electrolyte is present.

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