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Short Communications

Quaternary Derivatives of some Anaesthetic, Spasmolytic, Analgesic and Antihistaminic Agents

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Cholinesterase is inhibited by a great variety of drugs [1], among these atropine and other drugs with spasmolytic activity. Certain local anaesthetics [2] and some analgetics [3], like dolantin (demerol, pethidin), in larger doses antagonize cholinesterase too, but it is uncertain whether this action is of any importance for their pharmacological effects, although Thimann [4] has put forward the theory that local anaesthetics compete with acetylcholine for the receptor substances of nerve endings.

As acetylcholine is a quaternary ammonium compound it would be anticipated that quaternary ammonium compounds should inhibit cholinesterase more strongly than tertiary, at any rate if their activity is due to a drug-receptor combination. As a matter of fact it has been shown that the spasmolytic activity of scopolamine and some other spasmolytic drugs is enhanced by quaternization [5]. On the other hand Ehrlich [6] found that the methoiodide of cocaine and Löfgren and Fischer [7] that the ethochloride of xylocaine were devoid of anaesthetic activity.

On the whole very few quaternary derivatives of drugs, that are tertiary amines, have been described. For example we have not been able to find other quaternary derivatives of local anaesthetics than the two above mentioned. With a view to studying the effect of quaternization somewhat more systematically we have prepared quaternary derivatives of some of the common local anaesthetics, of the analgesic (and spasmolytic) drugs dolantin and amidone and of the antispasmodic drug trasentin.

In this connexion we have also prepared quaternary derivatives of some antihistaminic agents, although in this case there is no reason for supposing that antagonism with acetylcholine should be of any importance for their activity.

The pharmacological effects of the new quaternary compounds are being studied by Dr. Kjerulff-Jensen and Dr. Grandjean of this laboratory. The following, purely preliminary, results were obtained:

1. Quaternary compounds derived from local anaesthetics have only weak anaesthetic effect, but at any rate in the case of derivatives of nupercaine, the activity is not completely abolished.

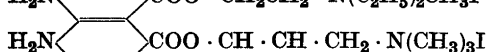
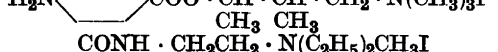
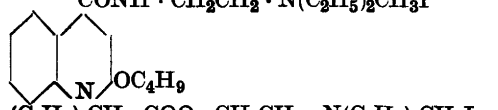
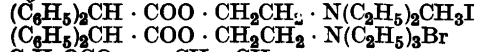
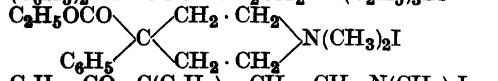
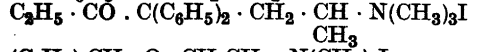
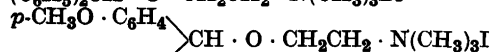
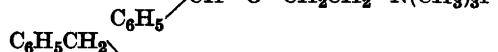
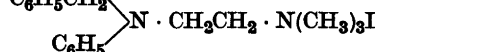
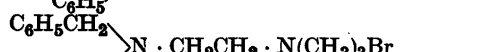
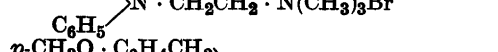
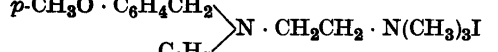
2. Quaternary compounds derived from antispasmodics retain the antispasmodic effect.

3. Quaternary derivatives of the analgesic drugs amidone and dolantin seem to be without or almost without analgesic effect.

4. Quaternary derivatives of antihistaminic drugs retain their antihistamine effect and in some cases the toxicity is lowered.

The compounds could be prepared by dissolving the tertiary compounds in ethanol and adding alkyl halogenide; in cases where the tertiary amine was on

Table 1. The melting points and analyses of the prepared compounds.

Structure	Quaternary deriv. of	M. p. °C	% N calc.	% N found	Recryst. from	Solubility in water
	Procaine	138	7.41	7.25	A	s.
	Tutocaine	170	7.15	6.92	A + E	s.
	Nupercaine	114	8.65	8.69	Ac + E	s.
	Trasentin	117-123	3.09	3.12	Ac + E	sl. s.
	Trasentin	155	3.32	3.30	A + E	v. s.
	Dolantin	196	3.60	3.55	A	s.
	Amidone	165	3.10	3.11	Ac + E	s.
	Benadryl	194	3.53	3.47	A	sl. s.
	Benadryl	197	3.99	3.93		s.
	—	144	3.28	3.18	A	sl. s.
	Antergan	158	7.07	6.93	A	sl. s.
	Antergan	196	8.02		A	v. s.
	—	184	6.58	6.57	A	sl. s.
	Pyribenzamin	d.	10.58	10.18	A	sl. s.
	Neoantergan	131	9.82	10.02	A	s.

Abbreviations: A = alcohol, E = ether, Ac = acetone, sl. s. = slightly soluble (< 1 : 50), s. = soluble (1 : 10—1 : 50), v. s. = very soluble (> 1 : 10). The analyses were performed by the micro-Kjeldahl method. Micro-Dumas determinations consistently gave too high values, presumably due to the formation of methane (resp. ethane) which is not completely oxidized. We are indebted to Mr. O. Rosenlund Hansen for carrying out the analyses.

hand as hydrochloride, this was decomposed by sodium hydroxide, the amine extracted with ether and after drying with sodium sulphate the alkyl halogenide was added to the ethereal solution. After standing for from 24 hours to several days at ordinary temperature or in the refrigerator a crystalline precipitate had generally formed. The ethobromide of trasentin was prepared by heating a benzene solution of trasentin and ethyl bromide in a closed vessel at 100° for 8 hours.

Paper Chromatography of Primary Aromatic Amines

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The method of Consden, Gordon and Martin [1] for the analysis of amino acids by paper chromatography has been applied for the separation, identification and quantitative determination of various other substances, for instance sugars (Partridge [2], Flood, Hirst and Jones [3]), organic acids (Lugg and Overell [4]), adrenaline and associated compounds (James [5]), flavin nucleotides (Crammer [6]).

We have used this method for the analysis of primary aromatic amines. The procedure and the apparatus have been in principle the same as that of Consden *et al.*[1]. For the development of the spots we have diazotized the amines with sodium nitrite in acid solution. By coupling the resulting diazonium salts with ethyl-α-naphtylamine a characteristic red-violet colour is developed. Mixtures of benzene, amyl and methyl alcohol saturated with water have been found most suitable as solvents with regard to the differentiation of various amines and have the advantage of a short running time (4—6 hours at room temperature).

Procedure. Spots comprising the samples and containing 10—20 γ of the amines no. 1—13 and 100—200 γ of no. 14—17 in Table 1. are placed in the usual way on the paper. According to Edman [7] we have used the quick-filtering paper no. OB (50 × 50 cm), supplied by J. H. Munktells Pappersfabriksaktiebolag, Grycksbo, Sweden. After running the paper, it is dried at about 80° C till most of the organic solvents have disappeared. The paper is then sprayed with a 0.2 % sodium nitrite solution in 0.1 *N* HCl. After drying for some minutes at 50—80°, the paper is sprayed with a solution of 0.2 % ethyl-α-naphtylaminehydrochloride in conc. ethyl alcohol. The spots generally turn coloured immediately and are not influenced by heating. It is, however, easier to observe spots only faintly coloured, if the paper is dry.

Results. The R_F values for 17 primary aromatic amines run in various combinations of benzene, amyl and methyl alcohol, with or without the addition of hydrochloric acid or ammonia, are given in Table 1. Mixtures of amines are easily separated.

The compounds were as a rule recrystallized from ethanol. The compounds derived from tutocaine, trasentin, amidone and nupercaine were purified by dissolving in ethanol, resp. acetone and precipitating with ether.

The quaternary compounds are white, beautifully crystalline compounds, slightly soluble in alcohol and almost insoluble in ether and benzene. The bromides are easily soluble in water, the iodides, however, are slightly soluble also in water.

The methoiodide of trasentin is unstable when moist: It rapidly turns brown and deliquesces. When pure and dry it is quite stable.

The melting points and analyses of the quaternary derivatives are presented in Table 1.

1. Bernheim, F. *The interaction of drugs and cell catalysts* Minneapolis (1942).
2. Ammon, I., and Zipf, K. *Klin. Wochschr.* **20** (1941) 1176; Adriani, J., and Rovenstine, E. A. *Anesthesia & Analgesia* **20** (1941) 109.
3. Bernheim, F. *(l. c.)*
4. Thimann, K. V. *Arch. Biochem.* **2** (1943) 87.
5. Nyman, E. *Acta Physiol. Scand.* Suppl. X (1942).
6. Fränkel, S. *Arzneimittelsynthese* 5. Aufl. Berlin (1921) p. 337.
7. Löfgren, N., and Fischer, I. *Svensk Kem. Tid.* **58** (1946) 219.

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