LETTERS TO THE EDITORS

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Quaternary Derivatives of Benzoyltropine and Benzoyl-ψ-tropine with Anticholinergic and Local Anæsthetic Properties

In the course of experiments dealing with correlations between structure and effect of cholinergic-blocking (antimuscarine, antinicotinic) actions[1,2], it has been found that in the case of compounds with tropeine structure the influence exerted on the effects by different quaternary groups shows great variations. Quaternary derivatives of tropeines possessing local anæsthetic properties, for example, benzoyltropine (= benzoyl-anti-tropine)[3], as well as benzoyl-ψ-tropine (= benzoyl-syn-tropine), have been prepared and studied[5], special consideration being given to the correlations between stereo-structure and pharmacological effect. Antimuscarine, ganglionic-blocking, curare-like, as well as local anæsthetic actions have been investigated. The effects of the individual compounds are shown in the accompanying table.

	1	2	3	4	5
Benzoyltropine HCl	0·01	< 0·1	—	1·5	
,, CH_3I	0·025	2·1	0·15	0·6	
,, C_2H_5Br	0·02	3·0	0·25	1·4	
,, n-C_3H_7Br	0·02	2·8	< 0·10	1·2	
,, n-C_4H_9Br	0·005	6·0	0·25	0·6	
,, benzyl Br	0·01	3·0	0·10	1·2	
Benzoyl-ψ-tropine HCl	0·003	< 0·1	—	2·2	2·6
,, CH_3I	0·002	< 0·2*	< 0·06	0·25	0·4
,, C_2H_5Br	0·005	6·7	0·15	0·58	2·8
,, n-C_3H_7Br	0·003	6·0	0·10	0·80	3·0
,, n-C_4H_9Br	0·005	4·6	0·25	1·50	3·2
,, i-$C_5H_{11}I$	0·003	2·8	0·20	1·55	4·3
,, benzyl Br	0·005	0·5	0·10	2·20	2·0

1. Antimuscarine effect on isolated rabbit and guinea pig intestine; atropine = 1.
2. Ganglionic blocking effect on nictitating membrane of the cat; TEA = 1.
3. Curare effect in the frog; *d*-tubocurarine = 1·0.
4. Infiltration anæsthesia on the skin of the abdomen in the rat (ref. 4); procaine = 1·0.
5. Conduction anæsthesia (frog plexus anæsthesia); procaine = 1·0.

* Ganglionic stimulating effect can also be observed.

In the case of tropeines with different stereo-structures, cholinergic-blocking effects undergo entirely different changes when quaternary groups are altered. In our opinion, when measuring anæsthetic action upon conduction, it does not suffice to use methods by means of which the motor response alone can be studied in the case of substances possessing curare activity. The derivatives we used, however, show marked activity from the point of view of infiltration anæsthetic action as well. Thus the higher alkyl, as well as aralkyl, quaternaries show activities similar to those of tertiary compounds. This effect could be observed in the case of other tropeines and other aralkyl quaternaries—for example, α-naphthylmethyl, 1-4-xylylene, as well[5]. This means that the generally accepted view, according to which local anæsthetic action of amines is confined to compounds containing secondary or tertiary amino groups, is not valid. The above view gained general acceptance most probably owing to the fact that it was mainly methyl quaternary compounds that had been studied. The methyl quaternaries have proved to be relatively inactive in the present investigations.

In our opinion, the syn- or anti-position of the OH group of tropine and the aromatic ester group bound to it[3], as well as the character of the quaternary groups, interact to influence the total stereo-structure of the compound, and thus secure the optimal molecular structure required for the different pharmacological effects[5].

Local anæsthetic action of quaternary tropeines showing anticholinergic effect suggests that the local anæsthetic action (using the term in a general sense) should be considered to be an anticholinergic effect.

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[2] Gyermek, L., and Nádor, K., *Acta Physiol. Hung.*, 3/1, 183 (1952).
[3] Fodor, G., *Nature*, 170, 278 (1952).
[4] Gyermek, L., and Kisérletes, Orvostud, *Arch. Int. Pharmacodyn.* (in the press).
[5] Gyermek, L., *Acta Physiol. Hung.* (in the press).

Synthesis of Quaternary Compounds possessing Lasting Local Anæsthetic Action

It has been found that, when compounds with local anæsthetic action containing tertiary nitrogen and belonging to different types of compounds are transformed into alkyl-, but especially into aralkyl-, quaternary derivatives, then the new compounds invariably exhibit a slowly developing local anæsthetic action that, however, is of very long duration. Nádor and Gyermek have found that ganglionic blocking[1] and curare-like action[2] of quaternary compounds are to a great extent dependent upon the type of chain the nitrogen is quaternarized with; therefore alkyl- and aralkyl-quaternary compounds have been used in our experiments.

Synthesis of quaternary compounds has been carried out in the following way. The tertiary compound is brought into reaction in benzene or acetone with the proper alkyl- or aralkyl-halogenide; the reaction proceeds smoothly, but care must be taken to exclude even traces of humidity. In this way, among others, diethyl-benzyl-4-(amino-benzoyl)-β-oxyethyl-ammonium bromide, that is, procaine-brombenzylate, was obtained by the reaction of *p*-amino-benzoic acid-β-diethylaminoethylester and benzyl bromide; melting point, about 120° indefinite; markedly hygroscopic. $C_{20}H_{27}O_2N_2Br$ requires C, 59·65; H, 6·68; N, 6·87; Br, 19·62 per cent; found: C, 59·32; H, 6·66; N, 6·74; Br, 19·60 per cent.

Similar methods have been used for the preparation of pantocaine-brombenzylate from methanol-ether (melting point, 168–70°), and nupercaine-brombenzylate from ethanol-ether (melting point, 183–85°).

Methyl-quaternary derivatives were prepared in the same way. The compounds dissolve readily in water and are stable. Novocaine-brombenzylate decomposes in water, a small amount of benzyl bromide being set free when exposed to prolonged standing.

Compounds have been synthesized in other ways as well, and thus evidence has been obtained that the quaternarizing alkyl or aralkyl chain was invariably added to the β-dialkyl-aminoalkyl side-chain. For example, the *p*-nitrobenzoic acid-β-bromethylester, obtained by means of esterizing glycolbromhydrine