J. Pharm. Pharmac., 1972, **24**, 324

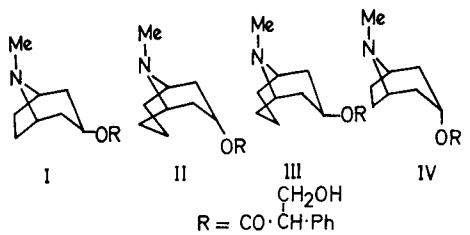
LETTERS TO THE EDITOR

Analogues and homologues of atropine: anti-acetylcholine activities

In a previous paper (Hunt & Robinson, 1970), the preparation and characterization of tropoyltropan-3β-ol (I), tropoylgranatan-3α-ol, (II) and tropoylgranatan-3β-ol (III) was reported.

Although these compounds have been previously reported (Lieberman & Limpach, 1892; Werner, 1918), they did not appear to have been adequately characterized. Additionally, despite the welter of pharmacological data available for atropine (IV), pharmacological data on these compounds, which are geometrical isomers or homologues of atropine (or both), are sparse and frequently conflicting.

Early studies employing the isomeric tropanes report only atropine to possess mydriatic activity (Liebrich O, unpublished results quoted by Lieberman & Limpach, 1892), whereas a more recent study suggests some slight mydriatic activity for tropoyltropan-3β-ol (Zipf, Dittman & Marquardt, 1963).



Werner (1918) prepared the isomeric granatanol esters (II and III) together with the mandelate esters (II, III, R = CO.CH(OH).Ph) and compared the mydriatic activity displayed by these compounds with the activity of atropine. He found that, in addition to atropine, only the esters of granatan-3β-ol showed any mydriatic activity. The opposite conclusion however has been drawn from later studies using the mandelate esters of the isomeric granatanols (Hartung & Gadekar, 1953).

It will be noted that none of the above compounds (I, II, III) have been tested as spasmolytic agents and the present paper now reports the activities of these compounds in their ability to block the acetylcholine induced contractions of guinea-pig ileum, using atropine (IV) as a standard.

Log dose-response curves were prepared for acetylcholine and for acetylcholine in the presence of each of the antagonists, employing a 35 min equilibration time for each of the antagonists. The concentrations of antagonist employed was such that a response varying between 20 and 80% of the maximum was obtained.

In the presence of each antagonist, the log dose-response curves for acetylcholine were parallel, suggesting the antagonisms were of a competitive nature. This was also inferred from the fact that, even at the highest concentration of antagonist employed the initial maximum response of the tissue could be obtained by giving a sufficiently large dose of acetylcholine. The pA_2 and pA_{10} values for each antagonist, obtained from a log (Dose ratio-1) vs $-$log molar antagonist concentration plot are given in Table 1. (These plots were linear, each point on the plot being the mean of three determinations and the best straight line calculated by the method of least squares.)

Table 1. pA_2 *and* pA_{10} *values for tropoyl derivatives.*

Compound		pA_2	pA_{10}	pA_2-pA_{10}	Slope
Tropoyltropan-3β-ol*	(I)	6·55	5·78	0·77	1·30
Tropoylgranatan-3α-ol*	(II)	9·75	8·95	0·80	1·24
Tropoylgranatan-3β-ol*	(III)	6·96	6·09	0·87	1·14
Tropoyltropan-3α-ol† (Atropine)	(IV)	9·79	8·70	1·09	0·90

* Hydrobromide salt. † Sulphate salt.

From the above data, atropine (IV) and tropoylgranatan-3α-ol (II) display approximately equal activity and are about 1000 times more potent as acetylcholine antagonists than the β-isomers (I and III). The close similarity in the dissociation constants of the above compounds does not account for this large difference in activities (Aaron & Rader, 1964).

It has been previously suggested (Long, Luduena & others, 1956), that atropine interacts with the muscarinic receptor in a conformation in which the tropane ring is in an unstable boat conformation. It is difficult to reconcile the present results with such a theory. The internuclear distance of the N to the ether O of the ester group with tropane ring of atropine in the boat conformation is about 4Å—the same as the distance in tropoyltropan-3β-ol (I) with the tropane ring in the more stable chair conformation. In addition the hydroxymethyl and phenyl groups can be related to approximately the same spatial positions in both models (Mertes & Gisvold, 1961), Thus, if the above theory were correct one would expect atropine and tropoyltropan-3β-ol to display similar potencies in their anti-acetylcholine activities. It is not possible from the compounds reported here to comment upon an alternative presentation of the conformation of receptor-bound atropine which postulates an involvement of the ether oxygen of the ester group in the drug-receptor complex. (Bowman, Rand & West, 1968).

Dept. of Pharmacy,
University of Manchester,
Manchester 13, U.K.

R. J. HUNT*
J. B. ROBINSON**

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* Present address: Eli Lilly & Co., Basingstoke, Hants, U.K.
** Present address: Faculty of Pharmacy, University of Toronto, Toronto, Canada.

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