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STUDIES ON THE STRUCTURE-ACTION RELATIONSHIPS OF PARASYMPATHOMIMETIC FURAN COMPOUNDS

BY

A. K. ARMITAGE AND H. R. ING

From the Department of Pharmacology, Oxford University

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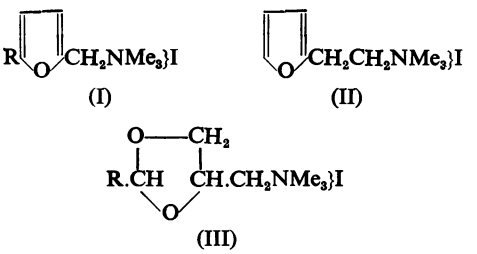
The discovery that 5-methylfurfuryltrimethylammonium iodide (I, R=CH_3) was considerably more active as a parasympathomimetic (or muscarinic) drug than furfuryltrimethylammonium iodide ("Furmethide"; I, R=H) was discussed in an earlier paper (Ing, Kordik, and Tudor Williams, 1952). Two more homologues of furmethide have now been prepared, viz. 5-ethylfurfuryltrimethylammonium iodide (I, R=C_2H_5) and β-2-furylethyltrimethylammonium iodide (II); both compounds were compared, on the same preparations, with furmethide and its 5-methyl derivative. 2249F or "Dilvasene" (III, R=H) and 2268F (III, R=CH_3) were also tested in order to compare these highly active compounds with our furan compounds.



RESULTS AND DISCUSSION

The new compounds were tested by the methods already described by Ing, Kordik, and Tudor Williams (1952), and the results are recorded in Table I. It will be noticed that the 5-ethylfurfuryl compound (I, R=C_2H_5) was considerably less active than either the furfuryl or 5-methylfurfuryl compounds. Since the 5-ethylfurfuryl compound contains the equivalent of a 6-atom acyclic chain, this result is in accordance with the empirical 5-atom rule (Alles and Knoefel, 1939; Ing, 1949) that maximal parasympathomimetic activity in homologous compounds of the type $RNMe_3\}X$ will be shown by compounds which contain a 5-atom acyclic chain or its equivalent (excluding H-atoms) attached to the quaternary N-atom; it also illustrates the astonishing dependence of parasympathomimetic properties upon detailed structure, since the 5-ethylfurfuryl compound only differs from the highly active 5-methylfurfuryl compound by the addition of a methylene group.

Unfortunately the next higher homologue of 2268F (III, R=C_2H_5) was not available, but Fourneau, Bovet, Bovet, and Montezin (1944) found it to be less active than 2268F on blood pressure (dog) and isolated intestine (rabbit).

It is worth noting that the relative parasympathomimetic activities of furmethide and its 5-methyl compound were similar to those of 2249F and 2268F; the only striking difference between these pairs of compounds was the much greater activity of 2249F and 2268F on frog rectus.

β-2-Furylethyltrimethylammonium iodide was about as active as 2249F and 2268F on frog rectus, but in its parasympathomimetic properties it was consistently less active than its lower homologue,

TABLE I

Compound	M.W.	Approx. Equipotent Molar Ratios (ACh=1)				
		Cat's B.P.	Rabbit Auricles	Guinea-pig Ileum	Frog Heart	Frog Rectus
Furfuryltrimethylammonium iodide (Furmethide) ..	267	10–30	16	12	126	505
5-Methylfurfuryltrimethylammonium iodide	281	1–3	1·2	0·34	15	7,000
5-Ethylfurfuryltrimethylammonium iodide	295	120	750	35	1,900–3,800	<2,000
β-2-Furyltrimethylammonium iodide	281	260	80	105	400	23
2249F (Dilvasene)	273	60	8	17	90	21
2268F	287	1·6	0·22	0·43	1·2	33

furmethide (I, R=H); it therefore provides an exception to the 5-atom rule.

There are two types of homologous series: (1) those in which the length of a terminal alkyl chain is varied, leaving the relative positions of functional groups in members of the series unchanged; and (2) those in which the length of a polymethylene chain connecting two functional groups is varied. 5-Alkylfurfuryltrimethylammonium salts (I) belong to the first type; β-2-furylethyltrimethylammonium iodide (II) belongs to the second type—i.e., to the series 2-furyl-$(CH_2)_n$-NMe_3}I (IV) in which only the value of *n* is altered. Furmethide itself belongs to both types, since it is a furfuryl derivative of formula I (R=H) and a 2-furyl derivative of formula IV (*n*=1).

It may well be that the empirical 5-atom rule applies only to homologous series of type 1; this would not be surprising, since there is good evidence that the activities of parasympathomimetic compounds depend not only upon the length of the chain attached to the N-atom but also upon the relative positions of the N-atom and some functional group containing oxygen. For example, both the methyl ether of homocholine, $CH_3OCH_2CH_2CH_2NMe_3$}I, and the propyl ether of formocholine, $CH_3CH_2CH_2OCH_2NMe_3$}I, are less active, as parasympathomimetic drugs, than the isomeric ethyl ether of choline, $CH_3CH_2OCH_2CH_2NMe_3$}I (Ing, Kordik, and Tudor Williams, 1952); similarly betaine ethyl ester, $CH_3CH_2OCOCH_2NMe_3$}I (Hunt and Renshaw, 1925, 1926), is less active than the isomeric methyl ester of propionic betaine, $CH_3OCOCH_2CH_2NMe_3$}I (Bass, Schueler, Featherstone, and Gross, 1950; Schueler and Keasling, 1951). The observation that the 2-furyl compound (II) is less active than the isomeric 5-methylfurfuryl compound (I, R=CH_3) provides another example. It seems, therefore, that in parasympathomimetic cations containing an oxygen function the distance between the oxygen function and the quaternary N-atom is of fundamental importance and may outweigh the effect of chain length. Maximal parasympathomimetic activity appears to be associated with the unit : oxygen function-$(C)_2$-$\overset{+}{N}Me_3$, and when this unit is present there is good evidence that cations containing a 5-atom chain (excluding H-atoms) will show greater parasympathomimetic activity than cations containing a shorter or longer chain. If, however, the oxygen function and the quaternary N-atom are separated by less or more than two C-atoms, the most active cation will not necessarily contain a 5-atom chain. This qualification of the 5-atom rule is at present hypothetical; it could only be established by the direct comparison of carefully selected compounds, which we have not yet had an opportunity of testing.

Chemical Section

(All melting points uncorrected. Analyses by Drs. Weiler and Strauss.)

5-Ethylfurfuryltrimethylammonium Iodide.—2-Acetylfuran was prepared from furan and acetic anhydride with either hydriodic acid or iodine as catalyst (Hartough and Kosak, 1949). It was reduced to 2-ethylfuran by heating it under reflux with excess of hydrazine hydrate and caustic soda in ethylene glycol for 3 hr. (11 g. acetylfuran+10 ml. 85% hydrazine hydrate+10 g. NaOH in 80 ml. ethylene glycol). The reaction mixture was distilled and the fraction boiling below 120° C. saturated with salt and extracted with ether. Evaporation of the ether and two fractional distillations of the residual oil gave a 20% yield of 2-ethylfuran, b.p. 92–95° C., which was converted into *5-ethylfurfuryltrimethylammonium iodide* in the same way as its 5-methyl homologue had been prepared from 2-methylfuran (Ing, Kordik, and Tudor Williams, 1952). The quaternary iodide was recrystallized from methyl ethyl ketone; it melted over 9° C. (89–98° C.), but analysed correctly (Found: C, 40.7; H, 6.1; N, 4.5. $C_{10}H_{18}ONI$ requires C, 40.7; H, 6.1; N, 4.7%) and behaved as a single homogeneous substance on a paper chromatogram. The *picrate*, prepared from the iodide and a saturated aqueous solution of calcium picrate, crystallized from its solution in hot water; m.p. 106–107.5° C. (Found: C, 48.8; H, 5.4; N, 14.1. $C_{16}H_{20}N_4O_8$ requires C, 48.5; H, 5.2; N, 14.1%).

β-2-Furylethyltrimethylammonium Iodide. — Furfural was condensed with nitromethane by the method of Thiele and Landers (1909) to give α-2-furyl-β-nitroethylene, m.p. 74–75° C. after recrystallization from ligroin. The latter substance (7 g.), dissolved in dry ether, was added to an ethereal solution of lithium aluminium hydride (7.6 g.) at such a rate as to keep the reaction solution boiling gently; stirring was continued for 1 hr. after addition of the nitro-compound. Excess lithium aluminium hydride was decomposed by the cautious addition of water and the solution acidified. The aqueous layer was separated, treated with 200 ml. of a saturated solution of sodium potassium tartrate and excess caustic potash, and extracted with ether after centrifugation of the colloidal precipitate; the latter was also extracted with ether. The combined ether extracts, after being dried with sodium sulphate, yielded 1.9 g. β-furylethylamine, b.p. 162° C./760 mm. The amine, dissolved in dry acetone (10 ml.), was cooled in ice and treated with a saturated solution of the theoretical amount of caustic soda (2 mols.) and excess of methyl iodide (4 mols.). The quaternary iodide separated rapidly, but in order to ensure complete reaction the solution was boiled for half an hour. The product was recrystallized from ethanol, m.p. 253° C. decomp. (Found: C, 38.3; H, 5.6. $C_9H_{16}ONI$ requires C, 38.4; H, 5.7%.)

SUMMARY

1. Two new furan derivatives, viz. 5-ethylfurfuryltrimethylammonium iodide and β-2-furylethyltrimethylammonium iodide, have been synthesized and tested as parasympathomimetic compounds.

2. The parasympathomimetic activity of the former is in accordance with the "5-atom rule"; that of the latter is not.

3. The theoretical implications of these divergent results are discussed.

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