953. *Furan and Tetrahydrofuran Compounds Analogous to Ganglion-blocking Agents of the 3-Oxapentane-1 : 5-bistrialkylammonium Series.*

By E. W. Gill and H. R. Ing.

Quaternary halides from 2 : 5-bisdialkylaminomethyl-furan and -tetrahydrofuran, analogous to 3-oxapentane-1 : 5-bis(quaternary ammonium) salts that block ganglionic transmission, have been synthesized for testing as ganglion-blocking agents. Tetrahydro-5-methylfurfuryltrimethylammonium iodide and chloroaurate, stereoisomeric with the deoxymuscarine salts, and tetrahydro-5-hydroxymethylfurfuryltrimethylammonium iodide, an isomer of muscarine, have also been prepared.

In connexion with theoretical studies on the effect of inter-quaternary distance on the ganglion-blocking activity of bis(quaternary ammonium) salts [1] it was of interest to make compounds which would have rigid structures linking the two quaternary ammonium groups but would be analogues of highly active drugs with a flexible linking chain. In compounds with a rigid system the inter-quaternary distance could be defined within close limits, whereas for flexible molecules an inter-quaternary distance–probability distribution had to be calculated.

Fakstorp *et al.*[2] prepared a large series of 3-oxapentane-1 : 5-bis(quaternary ammonium) salts of which one of the most active was the unsymmetrically alkylated compound (I; R = H), which was about 1·5 times as active as hexamethonium. Replacement of the oxapentane chain by the 2 : 5-dimethylfuran or tetrahydro-2 : 5-dimethylfuran system would provide analogues of the oxapentane compounds with a rigid structure linking the two nitrogen atoms. Such compounds, particularly the tetrahydrofuran compounds, would be approximately isosteric with branched-chain oxapentane derivatives of type (I; R = Me) which are only slightly less active than the straight-chain compounds.[2]

[1] Gill, *Proc. Roy. Soc.*, *B*, in the press.
[2] Fakstorp, Pedersen, Poulsen, and Schilling, *Acta Pharmacol. Toxicol.*, 1957, **13**, 52.

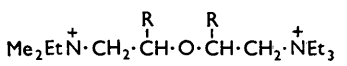
Moreover, 5-methylfurfuryltrimethylammonium is known to stimulate ganglia, being about one-quarter as effective as acetylcholine itself in the perfused superior cervical ganglion (cat),[3] so that the furan ring *per se* does not prevent the normal action of mono-quaternary trimethylammonium salts at the ganglionic synapse. Consequently any striking difference between the ganglion-blocking activity of the furan or tetrahydrofuran compounds and the oxapentane compounds could reasonably be attributed to the rigidity of the structure linking the two nitrogen atoms.

Bis(quaternary ammonium) furan compounds of the desired type were conveniently prepared from furfuryl alcohol. A Mannich condensation of furfuryl alcohol with a dialkylamine hydrochloride and paraformaldehyde gave a 5-dialkylaminomethylfurfuryl alcohol (III) which was quaternized with methyl or ethyl iodide; subsequent treatment of the corresponding quaternary chloride, first with thionyl chloride and then with a tertiary amine, gave the bisquaternary compound (II) which was isolated and purified as its 4 : 4′-diaminostilbene-2 : 2′-disulphonate [4] and then converted into the dibromide.

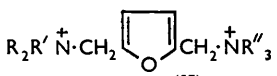
The structure of the Mannich condensation product (III) was proved by treating 5-chloromethylfurfuraldehyde,[5] of known structure,[6] with diethylamine and reducing the product with aluminium *iso*propoxide to 5-diethylaminomethylfurfuryl alcohol, identical with the Mannich condensation product when diethylamine hydrochloride was used.

Catalytic reduction of 5-dimethylaminomethylfurfuryl alcohol over Raney nickel gave 5-dimethylaminomethyltetrahydrofurfuryl alcohol (IV); a nine-stage synthesis of this compound from dibromoadipic acid has been reported recently.[7] The methiodide of (IV) is an isomer of muscarine iodide (V), but is pharmacologically inert, as is 5-hydroxymethylfurfuryltrimethylammonium iodide.[3] 5-Dimethylaminomethyltetrahydro-2-methylfuran was also prepared in a similar way from 2-methylfuran. Its methiodide, presumably the *cis*-(±)-isomer,[8] had the same R_F value as deoxymuscarine (VI), prepared from muscarine,[9] but the m. p. of the chloroaurate differed from that of deoxymuscarine.

An attempt was made to prepare bisquaternary tetrahydrofuran compounds in the



(I)



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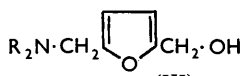

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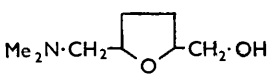

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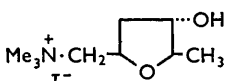

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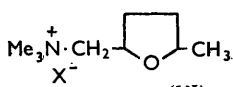

(VI)

same way as the furan compounds, by using tetrahydrohydroxymethylfurfurylamines, but this was unsuccessful. Furfurylamines, prepared from furfuraldehyde by the Leuckart reaction,[10] do not undergo the Mannich condensation under normal conditions, but 2 : 5-bisdialkylaminomethylfurans can be obtained in variable yields under more drastic conditions. Catalytic reduction and quaternization then yielded the desired bisquaternary tetrahydrofurans.

Both the furan and the tetrahydrofuran bisquaternary ammonium compounds were inactive as ganglion-blocking agents, a result which proved to be consistent with the conclusions of the theoretical studies already mentioned.[1]

[3] Ing, Kordik, and Tudor-Williams, *Brit. J. Pharmacol.*, 1952, **7**, 103.
[4] Leeds and Slack, *J.*, 1956, 3941.
[5] Fischer and Neyman, *Ber.*, 1914, **47**, 973.
[6] Fenton and Gostling, *J.*, 1901, 807.
[7] Gryszkiewicz-Trochimowski, Gryszkiewicz-Trochimowski, and Levy, *Bull. Soc. chim. France*, 1958, 603.
[8] Wiggins and Wood, *J.*, 1950, 1566.
[9] Kögl, Salemink, Schouten, and Jellinek, *Rec. Trav. chim.*, 1957, **76**, 126.
[10] Weilmuenster and Jordan, *J. Amer. Chem. Soc.*, 1945, **67**, 415.

Experimental

5-Dialkylaminofurfuryl Alcohols.—Equimolar amounts of furfuryl alcohol and dialkylamine hydrochloride in ethanol were boiled under reflux with paraformaldehyde (1·5 mol.) for 2 hr. One mol. of paraformaldehyde was then added and heating continued for 12 hr. The solvent was removed *in vacuo* and a concentrated aqueous solution of the residue made strongly alkaline with sodium hydroxide and extracted with ether. After being dried (Na_2SO_4) the ethereal extract was distilled. 5-Dimethylaminomethylfurfuryl alcohol had b. p. 125—135°/15 mm., n_D^{20} 1·4900 (yield 70%) (Found: C, 62·1; H, 8·5. Calc. for $C_8H_{13}O_2N$: C, 62·0; H, 8·4%). Its methiodide, crystallized from ethanol, had m. p. 128° as recorded by Ing *et al.*,[3] and its *ethiodide*, crystallized from ethanol–ethyl acetate, m. p. 82° (Found: C, 38·4; H, 5·8; N, 4·6. $C_{10}H_{18}O_2NI$ requires C, 38·6; H, 5·8; N, 4·5%).

5-Diethylaminomethylfurfuryl alcohol had b. p. 140—146°/15 mm. (yield 60%) (Found: C, 65·1; H, 9·0. $C_{10}H_{17}O_2N$ requires C, 65·6; H, 9·3%). Its *methiodide*, crystallized from ethanol–ethyl acetate, had m. p. 68° (Found: C, 40·3; H, 6·2; N, 4·2. $C_{11}H_{20}O_2NI$ requires C, 40·6; H, 6·2; N, 4·3%). The orientation of these compounds was proved as follows: Diethylamine (13·2 g.) was added to 5-chloromethylfurfuraldehyde [5] (13 g.) in anhydrous ether (30 ml.). The solution was chilled occasionally during 2 hr. in order to moderate the reaction, then left overnight at room temperature. Precipitated diethylamine hydrochloride was removed and 5-diethylaminomethylfurfuraldehyde (60%) isolated by distillation; this had b. p. 128—130°/15 mm. It formed a yellow oil, darkening in air and too unstable to give satisfactory analyses; its *picrate*, m. p. 101—102°, crystallized from ethanol (Found: C, 46·7; H, 4·6; N, 13·3. $C_{16}H_{18}O_9N_4$ requires C, 46·8; H, 4·4; N, 13·7%).

This aldehyde (15 g.) was reduced by slow distillation through a column of its solution in propan-2-ol (150 ml.) containing aluminium *iso*propoxide, prepared from aluminium (0·38 g.), mercuric chloride (0·05 g.), and propan-2-ol (10 ml.). When no more acetone could be detected in the distillate (24 hr.) the solvent was distilled off, the residue dissolved in water (50 ml.), and its aqueous solution basified strongly and extracted with ether. The dried extract (Na_2SO_4) gave 5-diethylaminomethylfurfuryl alcohol (11·3 g., 75%), b. p. 142—146°/15 mm., whose *α-naphthylurethane*, crystallized from light petroleum, had m. p. 104° alone or mixed with the α-naphthylurethane prepared from the Mannich condensation product (Found: C, 72·0; H, 6·6. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8%).

2 : 5-Bisdialkylaminomethylfuran Dialkylobromides.—5-Dimethylaminomethylfurfuryl alcohol methiodide (29·7 g.) in methanol (100 ml.) was heated under reflux with freshly prepared silver chloride (17·2 g.) for 2 hr. The filtrate from silver halides was evaporated to dryness *in vacuo*, and the residue covered with chloroform (20 ml.) and treated slowly with thionyl chloride (13·3 g.) in chloroform (20 ml.). Next day the solution was evaporated *in vacuo* and the dark brown residue heated with trimethylamine (40 ml.; 33% w/w in ethanol) in a pressure bottle at 100° for 4 hr. The solvent was removed *in vacuo*, and the residue taken up in water (100 ml.) and treated with sodium 4 : 4′-diaminostilbene-2 : 2′-disulphonate (41·1 g.) in water (100 ml.) at 40°. The precipitated amsonate was collected after the mixture had been stored overnight at 0° and recrystallized from water (yield 35 g., 60%). The amsonate (17·4 g.) was suspended in water (75 ml.) at 50°, treated with hydrobromic acid (7·5 ml.; *d* 1·46), stirred, and chilled. The amsonic acid was recovered and washed with warm water (20 ml.), and the filtrate evaporated to dryness *in vacuo*. Three crystallizations of the residue from ethanol–ethyl acetate gave *2 : 5-bisdimethylaminomethylfuran dimethobromide*, m. p. 238° (decomp.) (10 g., 90%) (Found: C, 39·0; H, 6·65; N, 7·5. $C_{12}H_{24}ON_2Br_2$ requires C, 38·7; H, 6·45; N, 7·5%).

Similarly were prepared: *2-Diethylaminomethyl-5-dimethylaminomethylfuran diethobromide*, m. p. 234° (decomp.) (Found: C, 44·35; H, 7·3; N, 6·4. $C_{16}H_{32}ON_2Br_2$ requires C, 44·85; H, 7·5; N, 6·55%). *2-Diethylaminomethyl-5-ethylmethylaminomethylfuran diethobromide*, m. p. 228° (decomp.) (Found: C, 46·5; H, 7·7; N, 6·4. $C_{17}H_{34}ON_2Br_2$ requires C, 46·2; H, 7·7; N, 6·4%).

2-Dimethylaminomethyltetrahydrofurfuryl Alcohol.—2-Dimethylaminomethylfurfuryl alcohol (25·2 g.) in ethanol (100 ml.) was hydrogenated over Raney nickel W7 [11] at room temperature and 100 atm. The product (21 g., 80%) had b. p. 120—122°/15 mm., n_D^{20} 1·4640 (Found: C, 60·7; H, 10·6; N, 8·7. Calc. for $C_8H_{17}O_2N$: C, 60·3; H, 10·7; N, 8·8%). The *picrate*,

[11] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

crystallized from ethanol, had m. p. 102° (Found: C, 43·0; H, 5·0. $C_{14}H_{20}O_9N_4$ requires C, 43·3; H, 5·2%). The methiodide had m. p. 85° (Gryszkiewicz-Trochimowski *et al.*[7] record m. p. 83—84°).

2-Dimethylaminomethyltetrahydro-5-methylfuran.—2-Dimethylaminomethyl-5-methylfuran [12] was hydrogenated in the same way and the tetrahydrofuran derivative obtained in 70% yield; it had b. p. 163°/760 mm., n_D^{20} 1·4358 (Found: C, 67·3; H, 11·8; N, 9·4. Calc. for $C_8H_{17}ON$: C, 67·2; H, 11·9; N, 9·8%). The methiodide, prepared in acetone solution, had m. p. 157° and R_F 0·68 when chromatographed on Whatman No. 1 (solvent system: butanol 5, ethanol 5, water 2). Kögl *et al.*[9] report R_F 0·65—0·68 for deoxymuscarine. The methochloroaurate, crystallized from water, had m. p. 132° whereas Kögl *et al.*[9] record m. p. 108—109° for deoxymuscarine chloroaurate.

2 : 5-Bisdialkylaminomethylfurans.—*NN*-Dimethylfurfurylamine [10] (25 g.,), dimethylamine hydrochloride (20 g.), and paraformaldehyde (9 g.) in propan-1-ol (100 ml.) were boiled under reflux for 5 hr., more paraformaldehyde (6 g.) being added after 1·5 and 3 hr. The residue after removal of solvent *in vacuo* was taken up in water, and the solution made strongly alkaline and extracted with ether. Fractionation of the dried extract (Na_2SO_4) gave unchanged furfuryldimethylamine (14·4 g.; b. p. 60—130°/20 mm.) and 2 : 5-*bisdimethylaminomethylfuran*, b. p. 140—150°/20 mm. (10·5 g., 72% on unrecovered furfuryldimethylamine) (Found: C, 65·6; H, 9·75; N, 15·2. $C_{10}H_{18}ON_2$ requires C, 65·9; H, 9·9; N, 15·4%).

2-Diethylaminomethyl-5-dimethylaminomethylfuran, obtained (30%) in the same way from furfuryldiethylamine,[10] had b. p. 128—130°/15 mm. (Found: C, 68·4; H, 10·3; N, 13·1. $C_{12}H_{22}ON_2$ requires C, 68·6; H, 10·5; N, 13·3%).

2 : 5-*Bisdialkylaminomethyltetrahydrofurans and their dialkyloiodides.*

NN'-Alkylation	M. p. or b. p./mm.	Found (%) C	H	N	I	Required (%) C	H	N	I
NNN'N'-Tetramethyl	122—124°/15 mm.	64·5	11·65	14·9	—	64·5	11·8	15·1	—
,, ,, dipicrate [a]	187—188°	—	—	—	—	—	—	—	—
,, ,, dimethiodide [b]	>300°	30·8	6·1	—	54·3	30·7	6·0	—	54·1
,, ,, diethiodide [c]	165°	34·0	6·6	—	50·8	33·7	6·4	—	51·0
NN-Dimethyl-*N'N'*-diethyl	124—126°/15 mm.	67·0	12·0	12·9	—	67·4	12·1	13·1	—
,, ,, dimethiodide [c]	>300°	33·5	6·4	—	50·8	33·7	6·4	—	51·0
,, ,, diethiodide [c]	185°	36·3	6·9	—	48·4	36·5	6·8	—	48·3

Solvents for crystallization: [a] water; [b] 1 : 9 v/v aqueous methanol; [c] ethanol–ethyl acetate.

2 : 5-Bisdialkylaminomethyltetrahydrofurans.—The 2 : 5-bisdialkylaminomethylfuran (0·1 mole) in ethanol (100 ml.) was hydrogenated over Raney nickel W7 at 20°/100 atm. Hydrogen uptake ceased after about 1 hr. The catalyst was removed by centrifugation and the supernatant solution fractionated. Yields were about 70%. Analyses for these *compounds* and their *meth-* and *eth-iodides* are given in the Table.

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[12] Holdren and Hixon, *J. Amer. Chem. Soc.*, 1946, **68**, 1198.