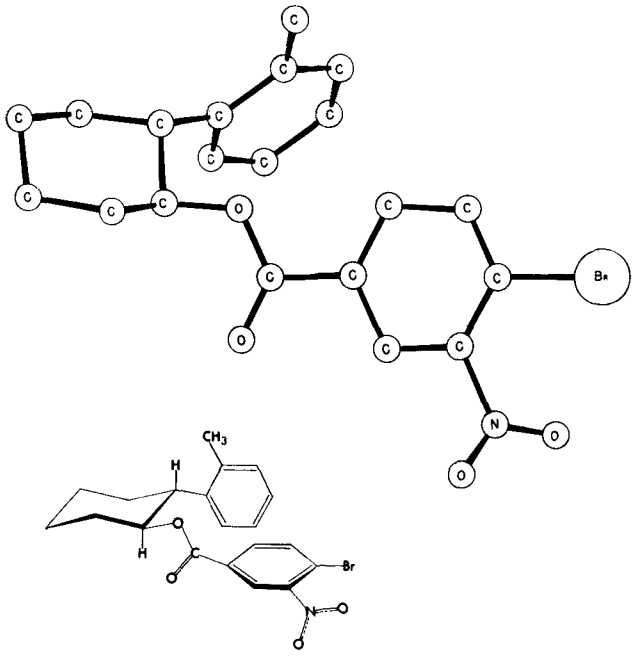

Figure 1—*(1S,2R)*−(+)-trans-*2*-o-*Tolylcyclohexyl 3-nitro-4-bromobenzoate.*

ture amplitudes were obtained from the intensities in the usual fashion. A sharpened, origin-removed, three-dimensional Patterson synthesis enabled the positions of the two unique bromine atoms to be found; the coordinates of the 50 other nonhydrogen atoms comprising the two molecules in the asymmetric unit were determined in subsequent electron-density maps based on phases calculated from the bromine positions. The positional and thermal parameters of all the atoms were refined using full matrix least squares until a discrepancy factor, R, of 0.089 was achieved.

Up to this point the normal bromine scattering curve, f_{Br}^0, was used with no correction for anomolous scattering of the X-rays by the bromine atoms. At this stage, the absolute configuration of the molecule was determined by the following method. The true bromine scattering curve, including anomolous scattering effects, $f_{Br} = f_{Br}^0 + \Delta f_{Br}' + i\Delta f_{Br}''$, was then applied; structure factors were calculated for molecules with atom coordinates x, y, and z and for molecules with atom coordinates $-x$, $-y$, and $-z$. That is, structure factors were calculated for both possible optical isomers. The discrepancy factor, $R = (\Sigma||Fo| - |Fc||)/\Sigma|Fo|$, was 0.098 for one structure and 0.086 for the other enantiomer. The difference is highly significant (3), and the absolute configuration for this structure is thus unambiguously established as the one giving the lower R. One last cycle of least-squares refinement, using the atom coordinates corresponding to the correct optical isomer but neglecting anomalous corrections to the scattering curve, brought R down to 0.079. Although hydrogen atoms could be located from a difference Fourier map, they were not included in the calculations since the additional significance does not compensate for the added cost of refinement for a structure of this size.

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Muscarinic Receptors: 4-Substituted-3-trimethylammoniumtetrahydrofuran Halides

WENDEL L. NELSON, JOHNNY K. WONG*, FRANK F. VINCENZI, PETER H. BLAKE†, and DONALD L. SMITH

Abstract □ Preparation of the *cis*- and *trans*-4-hydroxy-3-trimethylammoniumtetrahydrofuran and 4-acetoxy-3-trimethylammoniumtetrahydrofuran halides and 3-trimethylammoniumtetrahydrofuran iodide is described. Weak muscarinic activity was noted for the unsubstituted 3-trimethylammoniumtetrahydrofuran salt, being about 1000-fold less potent than acetylcholine. The *trans*-hydroxy and *trans*-acetoxy compounds showed even less activity, and the *cis*-compounds were inactive.

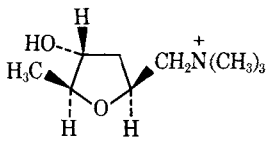
Keyphrases □ 3-Trimethylammoniumtetrahydrofuran halides, 4-substituted—muscarinic receptors, synthesis, pharmacologic testing □ Muscarinic receptors—3-trimethylammoniumtetrahydrofuran halides, 4-substituted, synthesis, pharmacologic testing

The fundamental problem of relating molecular structure to biological activity at various drug receptors becomes extremely difficult when considering small conformationally mobile molecules such as acetylcholine. Regardless of the existence of preferred conformations in the solid state and in solution (1–5), it should not be assumed that these conformations are those in the drug–receptor surface complex (6).

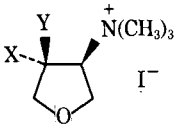
Various conformationally rigid or semirigid cholinergic agents have been prepared to aid in determination of the architectural features of the drug–receptor complex on various cholinergic sites, *e.g.*, muscarinic, nicotinic, and acetylcholinesterase (7–12). Attempts which incorporate the least number of additional atoms have generally been most successful, although comparisons of closely related compounds in higher series also seem valid (12).

In this study, various analogs of 3-trimethylammoniumtetrahydrofuran iodide were prepared. This system

offered the opportunity to look at possible analogs of muscarine, in which a conformation similar to the one in which the trimethylammonium head is directed toward C-4 of muscarine is represented by attaching this radical at C-3 in tetrahydrofuran (Structure I). In these com-



muscarine



I

1. X = Y = H
2. X = OH Y = H
3. X = OAc Y = H
4. X = H Y = OH
5. X = H Y = OAc

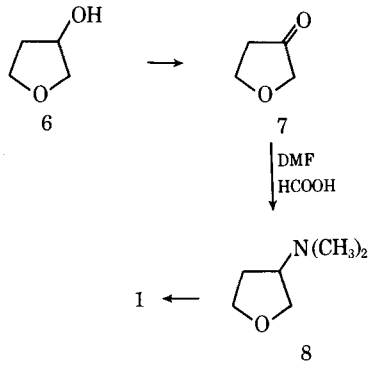
pounds, the distance of the two-carbon separation of oxygen from nitrogen is similar to that in the *transoid*-conformation of acetylcholine (ACh).

In addition, the *cis*- and *trans*-3-acetoxy (and hydroxy) analogs were prepared as conformational analogs of ACh in which the acetoxy oxygen and trimethylammonium nitrogen are fixed distances apart, similar to totally eclipsed and eclipsed conformations of ACh. These compounds can also be related to the acetyl-α,β-dimethylcholines held in fixed conformations, with the methyl groups attached to each other through an ether bridge.

Also, the 4-hydroxy compounds could show some structural analogy to muscarine, if the other speculation concerning the position of the trimethylammonium groups proved to be true.

SYNTHESIS

Preparation of Compound 1 (Scheme I) was accomplished from

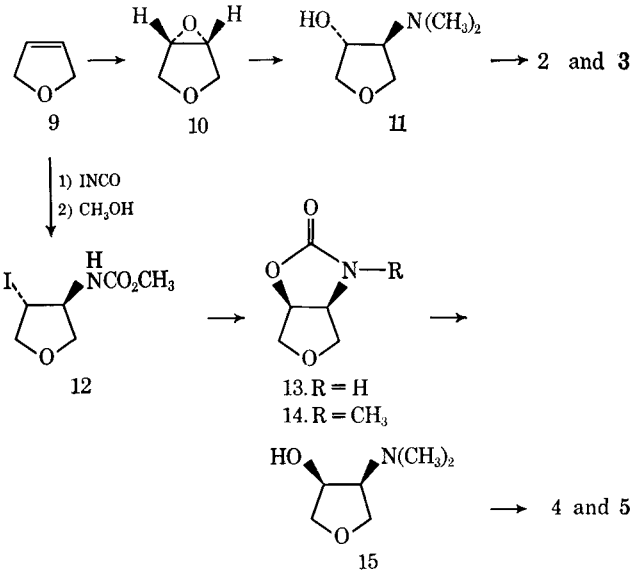


Scheme I

3-tetrahydrofuranone (Compound 7) which was readily prepared from 1,2,4-butanetriol (13). Dehydration afforded Compound 6, which was oxidized to Compound 7 (14).

Initially, it was planned to convert the oxime of ketone 7 to 3-aminotetrahydrofuran, as reported by Korobitsyna *et al.* (15). In the present study, the reported solid oxime could not be isolated, and the sodium amalgam reduction of the crude oxime failed to produce material that could be proven to be the desired amine. However, direct conversion of ketone 7 to Compound 8 was accomplished using Bach's modification (16) of the Leuckart reductive alkylation procedure, using dimethylformamide and 90% formic acid (17).

The 3,4-disubstituted analogs of tetrahydrofuran were prepared by stereospecific routes from 2,5-dihydrofuran (Scheme II). Epoxi-

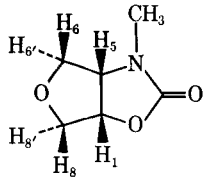


Scheme II

dation of Compound 9 at 0° provided 3,6-dioxabicyclo[3.1.0]heptane (Compound 10), which was treated with dimethylamine to yield *trans*-3-hydroxy-4-dimethylaminotetrahydrofuran (Compound 11). Compound 2 was prepared from Compound 11 by quaternization with iodomethane, and Compound 3 by acetylation followed by quaternization.

Formation of Compounds 4 and 5 was accomplished from *trans*-3-carbomethoxyamino-4-iodotetrahydrofuran (Compound 12), which was prepared by addition of iodine isocyanate to Compound 9, followed by methanolysis of the intermediate isocyanate. Pyrolysis (130°) of Compound 12 produced 2,7-dioxa-4-azabicyclo[3.3.0]-octan-2-one (Compound 13), which was alkylated by formation of the sodium salt of Compound 13 and dimethyl sulfate. Other alkylation procedures, including sodium hydride–iodomethane, and utilization of other bases, *e.g.*, sodium hydroxide and sodium carbonate, failed.

The stereochemistry of these tetrahydrofuran-fused oxazolidinones, although not in question from the synthetic scheme, is readily assigned from their NMR spectra. This is most apparent in the spectrum of the *N*-methylated derivative (Compound 14) (Structure II).



II

The signals for H-1 and H-5 are quartets at 5.05 and 4.28 δ, respectively, with $J_{1,5} = 7$ c.p.s., $J_{5,6} = J_{1,8} = 4$ c.p.s. Signals for protons H-6 and H-8 were observed as overlapping quartets at 3.42 and 3.58 δ, $J_{gem} = 10$ c.p.s. The downfield signal was assigned to H-8 on the basis of decoupling experiments. Upon irradiation at the frequency of H-1, H-8 collapsed into a doublet, showing J_{gem} only. Protons H-6′ and H-8′ apparently have almost identical chemical shifts. A slightly broadened doublet at 4.10 δ, J_{gem} = 10 c.p.s., was observed integrating for two protons.

Lithium aluminum hydride reduction of Compound 14 produced *cis*-amino alcohol (Compound 15), which was converted to Compounds 4 and 5 in steps analogous to conversion of Compound 11 to 2 and 3.

PHARMACOLOGY

Muscarinic assays were determined using strips of guinea pig ileum in oxygenated Tyrode's solution. 3-Trimethylammonium iodide (Compound 1) showed significant muscarinic activity, being

active at 1×10^{-4} *M*, equivalent to 1×10^{-7} *M* acetylcholine, or 1000-fold less potent, but $\alpha = 1.0$. The *trans*-compounds, 2 and 3, showed activity at 5×10^{-3} *M* ($\alpha = 1.0$). The *cis*-compounds, 4 and 5, were inactive at concentrations up to 10^{-2} *M*. The agonist effects were not blocked by hexamethonium, indicating the observed effects are postganglionic parasympathetic in origin. No atropinelike effects were observed for the compounds tested.

The marginal activity of the former compounds, 1, 2, and 3, can be rationalized in terms of a maximal O→N$^+$ distance, similar to the 1,3-dioxolanes (18) and calculations on muscarine (19), or the extended conformation of acetylcholine (7, 11, 12). However, the low level of activity precludes worthwhile speculation.

EXPERIMENTAL

Melting points were obtained with a calibrated Thomas-Hoover Unimelt apparatus and are corrected. IR data were recorded on Beckman IR-5A and IR-8 spectrophotometers. NMR spectra were determined with Varian A-60 and T-60 spectrometers, using tetramethylsilane (TMS) or 3-trimethylsilyl-1-propanesulfonic acid sodium salt as the internal standard. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England.

3-Tetrahydrofuranone (Compound 7)—A mixture of 100 g. (0.94 mole) of 1,2,4-butanetriol and 2.0 g. (0.01 mole) of *p*-toluenesulfonic acid monohydrate was distilled, using a water aspirator at 100–120°, to afford about 100 g. of distillate in 2–3 hr. (13). The product, a mixture of water and 3-hydroxytetrahydrofuran, was not separated but subjected to oxidation as described by Yurev *et al.* (14).

To a cold solution (−10°) of 100 g. of the crude distillate of Compound 6 in 150 ml. of ether was added dropwise a cold (0°) solution containing 100 g. (0.33 mole) of sodium dichromate dihydrate, 120 g. (0.12 mole) of concentrated sulfuric acid, and 150 ml. of water. The stirred solution was kept cold (−10 to 0°) for 5–6 hr. and then overnight at room temperature. The mixture was partitioned between ether and water, and the aqueous layer was extracted four additional times with ether. The combined ether layers were dried ($MgSO_4$), and solvent was removed, affording 42.1 g. (52% in two steps) of a slightly yellow oil; IR, 3.37, 3.47 (C—H stretching), 5.72 μ (C=O stretching); NMR ($CDCl_3$) δ: 4.23 (triplet, $J = 7$ c.p.s., C-5 protons), 3.83 (singlet, C-2 protons), 2.47 (triplet, $J = 7$ c.p.s., C-4 protons).

3-Dimethylaminotetrahydrofuran (Compound 8)—In a glass-lined autoclave were placed 6.00 g. (70 mmoles) of Compound 7, 10.0 g. (210 mmoles) of 90.9% formic acid, and 15.3 g. (210 mmoles) of dimethylformamide. The autoclave was sealed and heated at 185° for 16 hr., cooled to room temperature, and opened; the contents were then removed. The crude reaction mixture was acidified with 40 ml. of aqueous 10% HCl and washed with several portions of ether. The aqueous acid extract was made alkaline with aqueous 2 *N* NaOH and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated, affording a colorless oil which was converted to the quaternary ammonium salt without further purification.

3-Trimethylammoniumtetrahydrofuran Iodide (Compound 1)—To a cold (0°) solution of 2.88 g. (25 mmoles) of crude Compound 8 in 10 ml. of acetone was added 9.90 g. (70 mmoles) of iodomethane. After 12 hr., the slightly yellow crystalline solid was collected and recrystallized from methanol–ether, affording 1.50 g. (23% of theory) of Compound 1, m.p. 235–236°, NMR (CD_3OD) δ: 3.06 [singlet, $\overset{+}{N}(CH_3)_3$ protons], overlapping multiplets centered at 3.65, 4.20, and 4.37 integrating for the five aliphatic protons, 2.43 (multiplet, $W_h = 14$ c.p.s., C-4 methine protons).

Anal.—Calcd. for $C_7H_{16}INO$: C, 32.70; H, 6.27; N, 5.45. Found: C, 32.86; H, 6.33; N, 5.66.

3,6-Dioxabicyclo[3.1.0]heptane (Compound 10)—To a cold (0°) solution of 34.0 g. (0.186 mole) of *m*-chloroperbenzoic acid in 400 ml. of chloroform was added carefully 12.6 g. (0.18 mole) of 2,5-dihydrofuran (Compound 9) in 100 ml. of chloroform. The solution was maintained at 0° for 18 hr. with constant stirring; it was then extracted with cold aqueous 5% NaOH, washed with H_2O, and dried ($MgSO_4$). The solvent was removed utilizing a rotary evaporator, affording 10.0 g. (65%) of a slightly yellow, thin oil which was used without further purification.

***trans*-4-Hydroxy-3-dimethylaminotetrahydrofuran (Compound 11)**—To a cold (0°) 150-ml. capacity, steel autoclave chamber were added 5.0 g. (0.058 mole) of Compound 10 and 26.2 g. (0.58 mole) of anhydrous dimethylamine; 50 ml. of benzene was also added as solvent. The autoclave was sealed and heated at 100° overnight. Initial pressure on the gauge was 100 p.s.i. After cooling to 0°, the autoclave was opened and the contents were removed. The solvent was evaporated and the residual oil distilled, affording 6.08 g. (80%) of a slightly yellow oil, b.p. 82° (1.2 mm.). The product was carried to the next reaction without further purification.

***trans*-4-Hydroxy-3-trimethylammoniumtetrahydrofuran Iodide (Compound 2)**—This compound was prepared by a method similar to that used with Compound 1, using ethyl acetate as solvent. An analytical sample was prepared by crystallization from methanol–ethyl acetate, m.p. 194–195°; NMR (D_2O) δ: 3.22 [singlet, $\overset{+}{N}(CH_3)_3$], 3.60 (quartet, $J = 6$ c.p.s., C-3 methine proton), 4.25 (multiplet, W_h about 18 c.p.s., five protons).

Anal.—Calcd. for $C_7H_{16}INO_2$: C, 30.78; H, 5.90; N, 5.13. Found: C, 30.79; H, 5.86; N, 5.15.

***trans*-4-Acetoxy-3-trimethylammoniumtetrahydrofuran Iodide (Compound 3)**—To 2.00 g. (0.015 mole) of *trans*-4-hydroxy-3-dimethylaminotetrahydrofuran (Compound 11) was added 20 ml. of acetic anhydride. After heating the mixture at reflux for 1 hr., excess acetic anhydride and the by-product acetic acid were removed. Aqueous 3% HCl, 100 ml., was added to the residual oil and allowed to stand for 1 hr. The aqueous mixture was washed with ether, made alkaline with aqueous 10% NaOH, and extracted four times with ether. The combined ether extracts were dried ($MgSO_4$) and the solvent removed, affording 1.95 g. (75%) of a light-yellow oil.

A solution of 1.00 g. (5.7 mmoles) of the crude amino ester in 75 ml. of ethyl acetate and 5 ml. of iodomethane was stoppered and shaken occasionally for 1 hr. A white precipitate formed and was removed by filtration, affording 1.82 g. (100%) slightly yellow solid. An analytical sample was prepared by crystallization from methanol–ethyl acetate, m.p. 231°.

Anal.—Calcd. for $C_9H_{18}INO_3$: C, 34.29; H, 5.71. Found: C, 34.73; H, 5.71.

The chloride salt of Compound 3 was prepared from the quaternary ammonium salt, Compound 2, which was first converted to the chloride salt by ion exchange, followed by acetylation, m.p. 185°.

Anal.—Calcd. for $C_9H_{18}ClNO_3$: C, 48.78; H, 8.11. Found: C, 48.49; H, 8.17.

***trans*-3-Iodo-4-carbomethoxyaminotetrahydrofuran (Compound 12)**—To a cold (−15°) solution of 12.6 g. (0.18 mole) of 2,5-dihydrofuran in 540 ml. of anhydrous ether were added 59.9 g. (0.40 mole) of freshly prepared silver cyanate and 45.7 g. (0.18 mole) of iodine. The stirred mixture was allowed to warm to room temperature over a period of 6 hr. After this time, the initially red solution had become a yellow slurry. The inorganic salts (silver iodide and excess silver cyanate) were removed by filtration. Anhydrous methanol, 50 ml., was added to the filtrate, and the resulting mixture was refluxed overnight. After removing the organic solvents utilizing a rotary evaporator, the residual dark-brown oil was dissolved in ether, washed with 10% aqueous sodium bisulfite, with water, dried ($MgSO_4$), and evaporated, affording 24.4 g. (50% in two steps) of a yellow solid. An analytical sample was prepared by crystallization from ether, m.p. 107–108°; IR (potassium bromide), 3.08 (N—H), 3.40, 3.50 (C—H stretching), 5.98 (C=O stretching).

Anal.—Calcd. for $C_6H_{10}INO_3$: C, 26.59; H, 3.72; N, 5.17. Found: C, 26.65; H, 3.75; N, 5.14.

2,7-Dioxa-4-azabicyclo[3.3.0]octan-3-one (Compound 13)—A stream of dry nitrogen was passed over 5.0 g. (18.4 mmoles) of *trans*-3-iodo-4-carbomethoxyaminotetrahydrofuran and bubbled through a mixture of benzene and pyridine while heating the solid in an oil bath at a temperature of 130°. When no additional pyridine methiodide formed, the reaction was stopped (about 45 min.), affording 2.0 g. (83.3%) of a brown oil which solidified at room temperature. An analytical sample was prepared by crystallization from methanol–ethyl acetate, m.p. 116–117°, IR (potassium bromide), 3.08 (N—H), 3.35, 3.50 (C—H stretching), 5.77 (C=O). NMR (CD_3OD) δ: 5.17 (quartet, $J = 4$ and 7 c.p.s., methine proton at C-1), 4.33 (quartet, $J = 4$ and 7 c.p.s., methine proton at C-5), 4.40 (broad multiplet, N—H proton), 3.93 (doublet, $J_{gem} = 11$ c.p.s., one proton at C-6 and at C-8), 3.53 and 3.47 (overlapping quartets giving the appearance of a doublet of triplets, $J = 4$ and 11 c.p.s. in each case, one proton at C-6 and at C-8).

Anal.—Calcd. for $C_5H_7NO_3$: C, 46.51; H, 5.47; N, 10.86. Found: C, 46.61; H, 5.64; N, 11.10.

4-Methyl-2,7-dioxa-4-azabicyclo[3.3.0]octan-3-one (Compound 14)—A solution of sodium methoxide was prepared from 2.0 g. (0.087 g. atom) of sodium and 150 ml. of anhydrous methanol. After the addition of 5.0 g. (0.04 mole) of Compound 13, the mixture was evaporated to dryness *in vacuo*. The residue was suspended in 200 ml. of dry toluene, and 10 ml. of freshly distilled dimethyl sulfate was added dropwise with stirring and cooling. The reaction was then heated at 100° for 1 hr. An equal amount of H_2O was added to the toluene solution to destroy any excess dimethyl sulfate, and the mixture was partitioned. The aqueous solution was then extracted with five portions of chloroform. The combined chloroform and toluene extracts were dried ($MgSO_4$) and evaporated, affording 4.67 g. (85%) of a slightly yellow oil which solidified on cooling. An analytical sample was prepared by crystallization from chloroform–hexane, m.p. 80°. NMR ($CDCl_3$); δ 2.88 (N—CH_3, singlet), 3.42 and 3.58 (two overlapping quartets, J = 4 and 10 c.p.s. integrating for two protons tentatively assigned to one proton at C-8 and one proton at C-6). The downfield quartet was assigned to the C-8 proton, because upon irradiation of the C-5 proton the 3.58 δ signal collapsed into a doublet, J_{gem} = 10 c.p.s. Similarly upon irradiation in the 3.4–3.5 region, the C-1 proton collapsed into a singlet $J_{1,5}$ = 7 c.p.s., 4.10 (broadened doublet, J_{gem} = about 10 c.p.s., assigned to one proton at C-8 and one at C-6 which show coupling constants with protons at C-1 and C-5, respectively, approaching zero), 4.28 (quartet partially obscured by doublet, J = 4 and 7 c.p.s. assigned to other protons at C-6 and C-8), 5.05 (quartet, J = 4 and 7 c.p.s., assigned to proton at C-1).

Anal.—Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.78. Found: C, 49.97; H, 6.36; N, 9.99.

***cis*-4-Hydroxy-3-dimethylaminotetrahydrofuran (Compound 15)**—All equipment was dried at 120° overnight. A stream of dry nitrogen was passed over a suspension of 2.0 g. (52 mmoles) of lithium aluminum hydride in 200 ml. of anhydrous tetrahydrofuran. Two grams (14 mmoles) of Compound 14 in 50 ml. of tetrahydrofuran was added dropwise over a period of 10 min., and the resulting slurry was refluxed overnight. Excess hydride was destroyed by addition of aqueous 40% Rochelle salt, and the mixture was filtered with suction through a diatomaceous earth[1] pad. The filter cake was extracted four times with ethyl acetate. The combined tetrahydrofuran and ethyl acetate portions were evaporated, affording 1.18 g. (65%) of a slightly yellow oil which turned into a solid upon cooling. An analytical sample was prepared by crystallization from ethyl acetate, m.p. 51°.

Anal.—Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.90; N, 10.68. Found: C, 54.87; H, 9.68; N, 10.92.

***cis*-4-Hydroxy-3-trimethylammoniumtetrahydrofuran Iodide (Compound 4)**—This compound was prepared by a method similar to that used with Compound 1 using ethyl acetate as solvent. An analytical sample was prepared by crystallization from methanol–ethyl acetate, m.p. 162°.

Anal.—Calcd. for $C_7H_{16}INO_2$: C, 30.78; H, 5.90; N, 5.13. Found: C, 31.00; H, 5.78; N, 5.19.

[1] Celite, Johns-Manville, N. Y.

***cis*-4-Acetoxy-3-trimethylammoniumtetrahydrofuran Iodide (Compound 5)**—This compound was prepared from Compound 15 by a method similar to the conversion of Compound 11 to Compound 3. An analytical sample was prepared by crystallization from methanol–ethyl acetate, m.p. 193°.

Anal.—Calcd. for $C_9H_{18}INO_3$: C, 34.29; N, 4.44; H, 5.71. Found: C, 34.48; N, 4.38; H, 5.71.

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