The Synthesis of Some Compounds related to Muscarine

By **Kenneth Bowden** † and **Brian H. Warrington,*** Smith Kline and French Research Institute, Welwyn Garden City, Herts. AL7 1EY

New compounds related to muscarine have been prepared by cyclization of some aminoacetylenic glycols rendered accessible by condensations of novel aminoacetaldehyde hemiacetal salts with substituted alkynols. Further analogues were prepared by modification of the primary products of these reactions.

ATTRACTIVE intermediates for the synthesis of analogues of muscarine (1) appeared to be aminoacetylenic glycols (4) prepared by base-catalysed condensations of alkynols (2) with aminoacetaldehyde derivatives (3). Treatment of acetylenic glycols with acid is known to result in cyclization, giving dihydrofurans.[1-13] However, difficulties were presented by the unavailability of aminoacetaldehydes. With the exception of the impure hydrochloride [14] and methiodide of dimethylaminoacetaldehyde [15] no reports of simple aminoacetaldehydes could be found in the literature. Aminoacetaldehyde dialkyl acetals (7) are readily available, however. Investigation of the report [14] of the formation of the above hydrochloride, obtained by acid hydrolysis of dimethylaminoacetaldehyde diethyl acetal (7a) showed that the

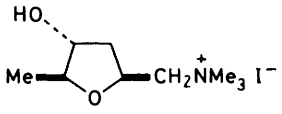
[1] V. M. Vlasov, T. A. Favorskaya, A. S. Medvedeva, and L. P. Safronova, *Zhur. Org. Khim.*, 1968, **4**, 365.
[2] S. A. Vartanyan, G.A. Chukhadzhyan, R. A. Melikyan, and Sh. A. Babanyan, *Izvest. Akad. Nauk Arm. S.S.R. Khim. Nauki*, 1962, **15**, 45.
[3] G. Dupont, *Ann. Chim. (France)*, 1913, **30**, 485; *Compt. rend.*, 1911, **152**, 1486; 1911, **153**, 275.
[4] R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis,' Butterworths, London, 1955.
[5] M. Miocque, N. M. Hung, and V. Q. Yen, *Ann. Chim. (France)*, 1963, **8**, 157.
[6] I. N. Nazarov and I. B. Torsov, *Zhur. obshchei Khim.*, 1948, **18**, 1332.
[7] W. Jasiobedzki, K. Mróz, and T. Szeromski, *Roczniki Chem.*, 1970, **44**, 2133.
[8] W. Jasiobedzki and Z. Matacz, *Roczniki Chem.*, 1968, **42**, 1599.
[9] A. S. Medvedeva, M. F. Shostakovskii, G. G. Chichkareva, T. A. Favorskaya, and V. K. Voronov, *Zhur. org. Khim.*, 1971, **7**, 641.
[10] J. A. Gautier and C. C. Farnoux, *Compt. rend.*, 1967, **264**, 224.
[11] P. P. Montijn, L. Brandsma, and J. F. Arens, *Rec. Trav. chim.*, 1967, **86**, 129.
[12] W. Jasiobedzki, W. Wawierna, and A. Zimniak, *Roczniki Chem.*, 1972, **46**, 1753.
[13] H. Tani and F. Toda, *Bull. Chem. Soc. Japan*, 1964, **37**, 470.
[14] R. Stoermer and F. Prall, *Ber.*, 1897, **30**, 1504.
[15] E. Fischer, *Ber.*, 1894, **27**, 165.

product was probably mainly the salt of the aldehyde hydrate (8a) in a crude glassy form. Only a very weak peak in its i.r. spectrum attributable to a carbonyl group could be found.

Attempts to basify this crude product resulted in decomposition, giving dimethylamine and, presumably, formose by base-catalysed polymerization of the second initial product, glycolaldehyde.[16] The enolic form of the free base is an enamine which undergoes this decomposition.[17]

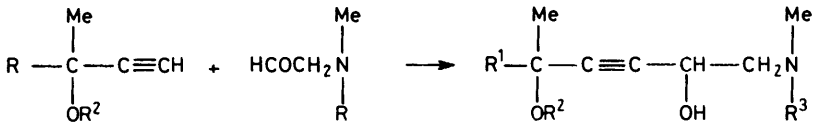
In the absence of a suitable free base, a derivative was sought from which dimethylaminoacetaldehyde (3a) could be generated *in situ* during base-catalysed condensation with an alkynide. The dialkyl acetals (7a) are known to be stable under these conditions. The crude hydrate (8a) was used with difficulty in model condensations with phenylacetylene in refluxing dioxan in the presence of lithium amide, to give traces of the product (9). Yields were too low to be of practical use.

Hemiacetals appeared to be suitable starting materials since they are known to exist in equilibrium with their parent aldehydes under basic conditions.[18] The hemiacetal (10a) was obtained by treatment of the crude glass (8a) with ethanol, followed by crystallization from the same solvent. The presence of a powerful electron-withdrawing group (protonated nitrogen) and the possibility of an intramolecular hydrogen bond explain the stability of this hemiacetal and the hydrate (8a).[19]



(1)

L—Muscarine iodide



(2)

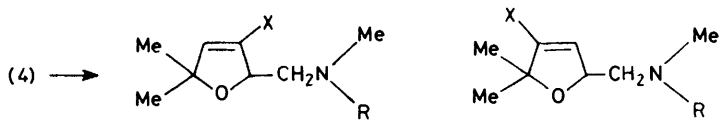
	R^1	R^2
a;	Me	$PhCH_2$
b;	Me	THP
c;	H	$PhCH_2$

(3)

	R
a;	Me
b;	H

(4)

	R^1	R^2	R^3
a;	Me	$PhCH_2$	Me
b;	Me	THP	Me
c;	H	$PhCH_2$	Me
d;	Me	THP	H
e;	Me	H	Me



(5) or (6)

THP = Tetrahydropyran-2-yl

	R
a;	Me
b;	H

Where X = OH the product exist in the ketonic form.

Methylaminoacetaldehyde dimethyl acetal (7b) also gave a stable hemiacetal (10b). The product from aminoacetaldehyde dimethyl acetal (7c) was not stable at room temperature.

Use of the hemiacetal (10a) in model condensations with phenylacetylene gave useful yields of the crude aminoalkynol (9) although there were losses during purification by sublimation. In this reaction, formation of sodium phenylacetylide gave the expected equivalent of ammonia. Addition of one equivalent of the hemiacetal hydrochloride (10a) then resulted in the evolution of a total 2—2.3 equivalents of ammonia during approximately 3 h.

Two mechanisms can be envisaged for this reaction which are compatible with the observations. (i) Neutralization and breakdown of the hemiacetal hydrochloride (10a) to give dimethylaminoacetaldehyde (3a) and 2 equivalents of ammonia, followed by reaction with sodium phenylacetylide to give the sodium salt of

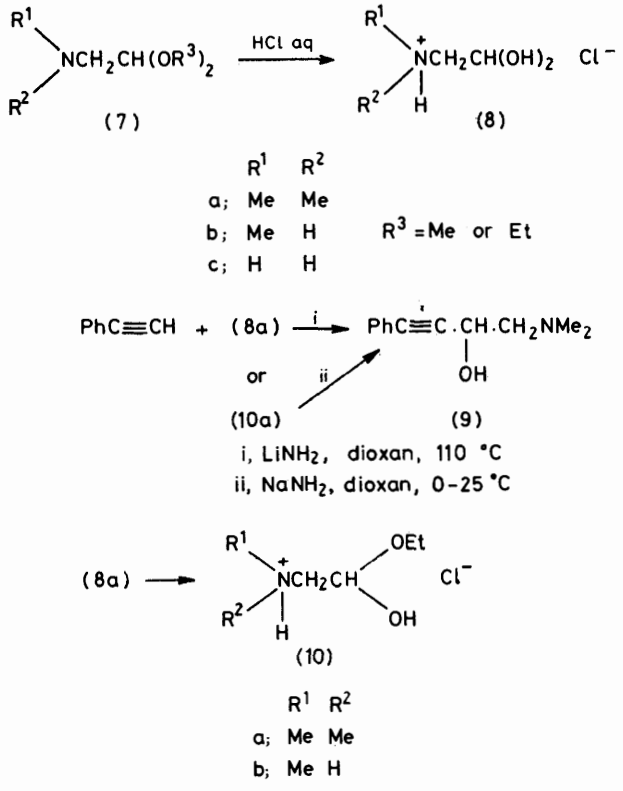
[16] A. Kuzin, *J. Gen. Chem.* (*U.S.S.R.*), 1937, **7**, 2954; E. Fischer and K. Landsteiner, *Ber.*, 1892, **25**, 2549; C. Neuberg, *ibid.*, 1902, **35**, 2626.

[17] E. J. Stamhuis, ' Enamines ' A. G. Cook, ed., Marcel Dekker, New York, 1969.

[18] J. D. Roberts and M. C. Caserio, ' Basic Principles of Organic Chemistry,' W. A. Benjamin, New York, 1965.

[19] C. D. Hurd, *J. Chem. Educ.*, 1966, **43**, 527.

the product (9). (ii) Neutralization of the hemiacetal (10a) to give the free base (11) and one equivalent of ammonia, then nucleophilic displacement of the ethoxide group by the alkynide. The second equivalent of



ammonia would then result from the formation of the sodium salt of the product (9).

Of these two possibilities, the former is more likely since quantitative interaction of the hemiacetal hydrochloride (10a) with sodium amide need not necessarily lead to quantitative formation of product (9). Incomplete reaction of aldehyde and alkynide (phenylacetylene was recovered from these reactions) or loss of reactant due to side reactions (see below) can account for low yields. In the second mechanism, however, the evolution of ammonia is complete only after formation of the salt of the product. Only loss of the product or salt by side reactions can explain the low yields in this case. No evidence has been found for any by-product formed from the product during the reaction.

Dimethylaminoacetamide (13) has been obtained, however, as a by-product from this type of reaction. Its formation may be rationalized as a competing reaction of sodium amide and the hemiacetal free base by nucleophilic displacement of the ethoxide group by amide with further reaction to give a carbinolamine salt (12). Addition of water during work-up would then yield the amide (13). It is unlikely that dimethylaminoacetaldehyde itself would give rise to this product by a Haller–Bauer reaction [20,21] because of the presence of an α-hydrogen.

An attempt was made to extend this reaction to condensations of alkynols (2; $R^2 = H$) but precipitation of the corresponding sodium salts prevented effective reaction. The use of protected species (2; R = $PhCH_2$, THP) overcame this difficulty. Purification of the products (4) presented difficulties and only a few were obtained pure.

It was also difficult to remove the protecting group, due to the lability of the resulting glycols. Attempts to remove the benzyl group by reduction led to the reduction of the triple bond. The presence of acid during the removal of the tetrahydropyranyl group caused a partial Meyer–Schuster [22] rearrangement of the product. An attempt was made to separate the required glycol (14) from its rearrangement product (15) by distillation, but this yielded a pyrrole (16) by thermally induced cyclization similar to that described by Ampilogova.[23] The protected glycols were found, however, to be good substrates for cyclization reactions and were used generally without further purification.

All aminoalkynols (4a—e) except (4c) gave cyclic products (6; X = OH, halogen). With (4c) no cyclic products could be formed under conditions found satisfactory for its homologue (4a). Intractable mixtures were obtained, but there was some evidence that an unstable unsaturated ketol was formed by a Meyer–Schuster rearrangement. The presence of compounds of this type in the crude products of successful cyclizations was also noted, but isolation and identification was difficult. A pure crystalline hydrochloride was obtained in the case of (15).

The literature shows differing courses for the cyclization of the glycol (17a) under differing conditions. Treatment of an aqueous suspension of the glycol with mercuric sulphate is reported to give the tetrahydrofuranone (19a) [2] while $HgSO_4$–H_2SO_4 in a biphasic system (ether–water) gave the tetrahydrofuranone (18).[1]

An attempt was made to treat the aminoalkynol (4a) with $HgSO_4$–H_2SO_4 in an analogous manner to obtain the normuscarone homologue (6; X = OX), but the only cyclic product which could be obtained under these and a variety of conditions was the tetrahydrofuranone (5a; X = OH). Other aminoalkynols behaved in the same way.

The work of Vlasov *et al.*[1] and Vartanyan *et al.*[2] was reinvestigated and the former [1] was found to be erroneous. Both sets of reaction conditions were found to give the same product, which had the physical constants identical to those given by Vlasov *et al.*[1] for compound (18), but which were shown by n.m.r. spectroscopy to have the structure (19a) assigned by Vartanyan *et al.*[2]

Within the scope of this work we have been unable to find any conditions which will allow the cyclization of aminoalkynols (4) to structures of type (6).

[20] K. E. Hamlin and A. W. Weston, *Org. Reactions*, 1937, **9**, 1.
[21] A. Haller and E. Bauer, *Ann. Chim. et Phys.*, 1909, **16**, 145.
[22] K. H. Meyer and K. Schuster, *Ber.*, 1922, **55**, 819.
[23] N. A. Ampilogova, R. A. Bogatin, M. S. Ivakhnyuk, and F. Ya. Perveev, *Zhur. obshchei Khim.*, 1973, **43**, 2749.

A similar product produced during this investigation (19b) was useful in permitting the synthesis of the tetrahydrofuranone (5a; X = OH) by an independent route (Mannich reaction) thus providing confirmation of the structure of the cyclization product of the amino-alkynol (4a).

Treatment of the tetrahydropyranyl ether (4b) or the impure glycol (4c) with $HgSO_4$–H_2SO_4 under the conditions used with the benzyl ether (4a) gave only traces of the tetrahydrofuranone (5a; X = OH). Cyclization of (4b) was best achieved by the action of a polystyrene-based sulphonic acid ion-exchange resin which had previously been impregnated with mercuric sulphate. This reagent has been described elsewhere [24] for the hydration of alkynes.

The use of a homogeneous hydration catalyst, ruthenium trichloride in 5M-hydrochloric acid,[25] was also investigated. 5-Benzyloxy-1-dimethylamino-5-methylhex-3-yn-2-ol (4a) under these conditions gave approximately equal quantities of the ketone (5a; X = OH) and a chloro-compound which was shown to have the structure (5a; X = Cl).

Treatment of the alkynols (4a, b, d, e) with hydrochloric acid alone, also gave the chloro-compound (5a; X = Cl) but accompanied by a small amount of the corresponding ketone (5a; X = OH). Separation of their hydrochlorides was achieved by crystallization. Similar results were obtained using aqueous HBr giving (5a; X = Br) and aqueous HI giving (5a; X = I).

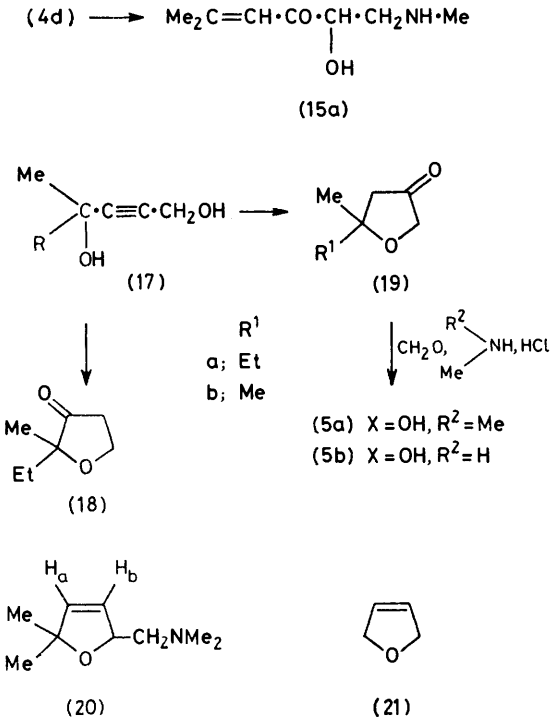
Of the two possible structures for the halogenated products (5a; X = halogen) or (6a; X = halogen) the choice of structure assigned was made mainly on the basis of the mechanism of formation, which clearly applies in these cyclization processes (see below) and by comparison with the literature.[10,12]

No satisfactory chemical means was found for establishing structures, but confirmatory evidence was obtained from n.m.r. spectroscopy using the paramagnetic shift reagent $Eu(fod)_3$ with the chloro-compound (5a; X = Cl) and the olefin (20). In compounds such as these a possible complication of this method was the presence of more than one possible co-ordination site. The measured shifts would then represent the sums of the interactions at each site with the shift reagent.

[24] J. D. Billimoria and N. F. Maclagen, *J. Chem. Soc.*, 1954, 3257.

[25] J. Halpern, B. R. James, and A. L. W. Kemp, *J. Amer. Chem. Soc.*, 1961, **83**, 4097.

However, amines are known to form much stronger co-ordination complexes than ethers [26] and when an excess of substrate was present, any contribution arising from



co-ordination at the latter group was assumed to be negligible.

N.m.r. spectra of pure samples of the above bases (20) and (5a; X = Cl) were examined in CCl_4 solution in the presence of increasing amounts of the paramagnetic shift reagent and the changes of chemical shift were plotted against the concentration of shift reagent present.

The different downfield shifts observed for the protons H_a and H_b of the olefin (20) showed that co-ordination had occurred mainly at the nitrogen atom. Examination of models showed that in any reasonable conformation the proton H_b was closer to a nitrogen-co-ordinated complex than was the proton H_a. On the assumption that the angles made by these two protons with the crystal field axis of the complex were approximately equal, as was the case in most possible conformations, H_b was taken to be the proton showing the larger shift.

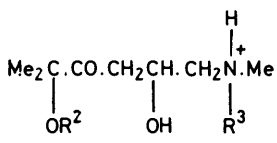
In the case of the chloro-compound (5a; X = Cl) the protons present showed a pattern of shifts similar to that shown by the corresponding protons in the olefin (20), indicating a similarity of conformation of the europium complexes of these compounds. The downfield shift shown by the single olefinic proton present in the chloro-compound (5a; X = Cl) was of similar magnitude to that of proton H_a and sufficiently different to that of proton H_b of the olefin (20) to allow the assignment of structure (5a; X = Cl) to the chloro-compound.

To check that any co-ordination with the ether groups would not affect these results, supporting work with 2,5-dihydrofuran (21) was carried out. Sizeable but equal downfield changes in shift were observed for protons in the 2- and 5-positions along with small, equal downfield changes for the olefinic protons.[27]

In attempts to obtain cyclic products of the type (6; X = OH) cyclization of aminoalkynols (4a and b) were attempted using neutral,[28,29] basic [30] and less strongly acidic [31] conditions. These gave either intractable products or, in the latter case, the ketone (5a; X = OH).

In order to establish more clearly the mechanism operating in the cyclizations described, two experiments were performed, the attempted cyclization of the unsaturated ketol (15) and the attempted conversion of the ketone (5a; X = OH) to the chloro-compound (5a; X = Cl). It was established that in the reaction conditions normally prevailing during the formation of these compounds, the above interconversions did not occur. The final products must be considered therefore to be stable with respect to their precursors and to each other.

If a conventional hydration of the triple bond were the first step in cyclizations giving tetrahydrofuranones, the electron-donating effects of the alkyl groups at C-5 and the electron-withdrawing effect of a protonated nitrogen at C-1 of the aminoalkynols (4a, b, d, e) would lead to the keto-alcohols (22a, b, c) being the predominant isomers



(22)

	R^2	R^3
a;	$PhCH_2$	Me
b;	THP	Me
c;	THP	H

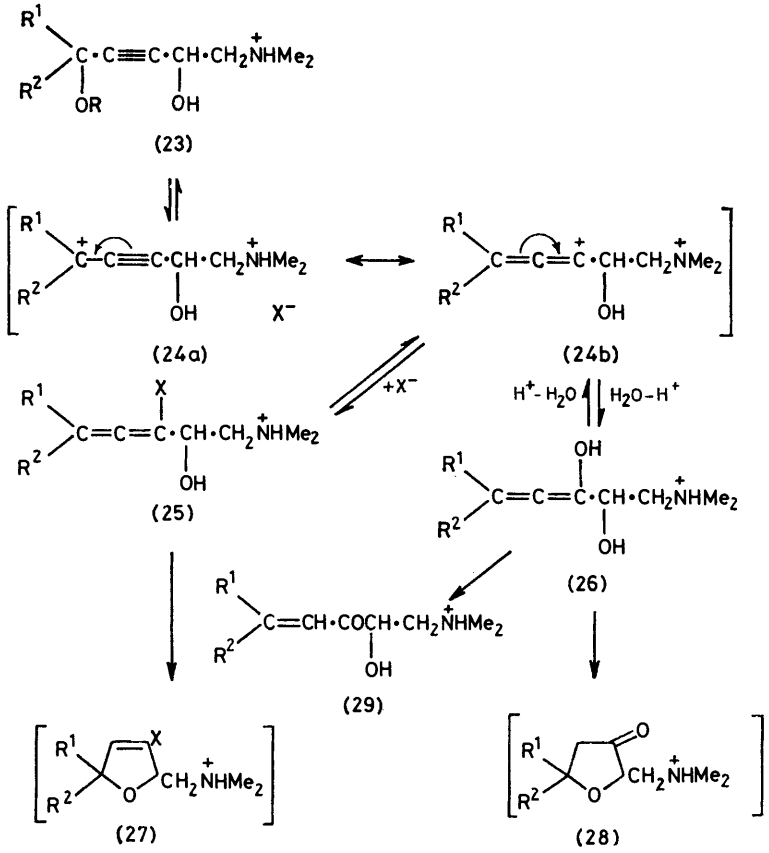
obtained and the tetrahydrofuranones (6) the final products of further reaction.[5,32] The structures found for the cyclic products isolated do not support such a mechanism. As the assigned structures of the cyclic products prepared by Vlasov *et al.*[1] were found to be wrong, it may be presumed that the mechanism of formation proposed by these workers is also erroneous.

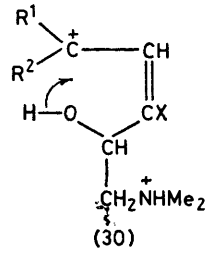
It seems likely that all cyclizations of acetylenic γ-glycols, or their protected derivatives, are not conventional hydration reactions followed by ring closures,

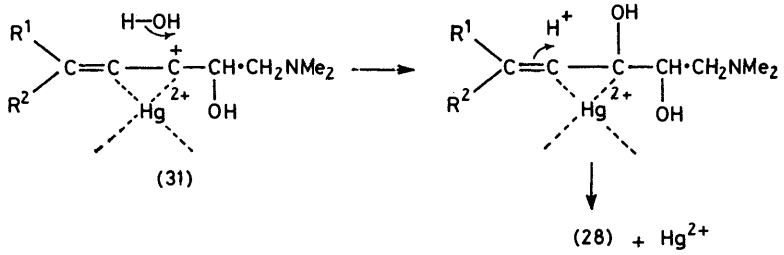
[26] J. K. M. Saunders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.
[27] This subject is more fully discussed by B. H. Warrington, Ph.D. Thesis, University of London, 1975.
[28] M. F. Shostakovskii, T. A. Favorskaya, A. S. Medvedeva, L. P. Safronova, and V. K. Voronov, *Zhur. org. Khim.*, 1970, **6**, 2377; L. I. Vereshchagin, L. G. Tikhonova, E. I. Totova, V. P. Latyshev, and L. D. Gavrilov, *Zhur. org. Khim.*, 1973, **9**, 1355.
[29] L. Ruzica, M. W. Goldberg, and F. Hunziker, *Helv. Chim. Acta*, 1939, **22**, 707.
[30] C. Moureu, *Compt. rend.*, 1903, **137**, 259; 1904, **138**, 206; *Bull. Soc. chim. France*, 1904, **31**, 493.
[31] M. S. Newman, *J. Amer. Chem. Soc.*, 1953, **75**, 4740.
[32] M. Koulkes, *Compt. rend.*, 1955, **241**, 1789.

but proceed by a mechanism similar to that of the Meyer–Schuster rearrangement.[22]

A mesomeric carbonium ion, represented by the general structure (24a, b) formed by acid-catalysed cleavage of the OR group from the starting material (23) is the key intermediate in the cyclization reaction. In the cases presently considered, a carbonium ion will form preferentially at C-5 due to the stabilization received by electron donation from a methyl group (R^1, R^2 or both) to this carbon. On the same basis, the electron-withdrawing effect of a protonated nitrogen will discourage any tendency to lose the hydroxy-group at C-2. The possible fates of the carbonium ion (24a, b) when acted upon by water or halide ion (X^-) are shown.







Where $R^1 = R^2 = Me$, structures (27), (28), and (29) have been obtained from this type of reaction. As the

conversion of (29) into (28) has been shown not to occur under the conditions of the reaction, it is likely that these compounds have a common precursor such as (26). Attack on the allenic form of the carbonium ion (24b) by halide ion will give the chloro-allene (25). Cyclization occurs *via* the carbonium ion (30), which is also stabilized by the presence of two methyl groups at C-5. Cyclization of the allenic alcohol (26) to give the ketone (28) can occur in a similar manner, but tautomerism giving the unsaturated ketol (29) can compete and the relative ease of these two reactions will determine the relative yields of the two products.

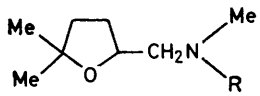
As the presence of a heavy-metal catalyst favours cyclization, it may be that at this stage the catalyst plays its role by stabilization of the tautomeric pair (26) and (29). Comparison may be made with the mercury triple-bond complex which is believed to be formed during a conventional hydration of a triple bond.[33,34] Thus a mercuriated form of the mesomeric carbonium ion (24) may be formed and during attack of the appropriate form (31) by water, the presence of mercury may result in the occurrence of preferential protonation in such a direction as to lead to cyclization rather than tautomerism. The loss of mercury and cyclization then take place. The following points support this view. (i) In preparations of the chloro-compound (5a; X = Cl), small amounts of the corresponding ketone (5a; X = OH) are also formed by interaction of the mesomeric carbonium ion (24) with solvent water. (ii) With ruthenium trichloride as catalyst, which acts in a manner similar to the mercuric ion, larger amounts of the ketone are formed despite the presence of 5M-hydrochloric acid. This is not to suggest that the catalyst makes attack of the carbonium ion by water easier, but that following attack, cyclization rather than tautomerism becomes more favoured. (iii) A difference in the mode of reaction is observed in the benzyl ether (4a) and the tetrahydropyranyl ether (4b) in that treatment of the former with $HgSO_4$–H_2SO_4 gives moderate yields of the ketone (5a; X = OH) whereas the latter gives only traces.

Cleavage of the tetrahydropyranyl ether to the mesomeric carbonium ion may occur so rapidly that co-ordination of the triple bond with the mercuric ion cannot take place to any great extent. The main direction of breakdown of the non-mercuriated carbonium ion would then be toward the unsaturated ketol. Cleavage of the benzyl ether (4a) would occur less rapidly and so allow a greater degree of co-ordination with mercury to take place.

The tetrahydropyranyl ether (4b) on treatment with strong acid ion-exchange resin impregnated with mercuric sulphate, would cleave less rapidly. Since there would be fewer ' free ' protons in solution, cleavage would occur at the surface of the resin, and the opportunity for co-ordination with mercury would be greater. Appreciable yields of the ketone (5a; X = OH) were obtained when the tetrahydropyranyl ether was treated in this manner. The reaction conditions imposed by the use of impregnated resin also agreed well with those outlined [34] as being the most favourable for the formation of a complex, that is, no excess of water or catalyst should be present in solution. (iv) Attempts to cyclize compounds bearing only one methyl group at C-5 (4c) gave ill-defined products, and when HCl was the cyclizing agent, the product contained no chlorine and was probably the unsaturated ketol (29). This may be explained by failure of the allenic compounds (25, 26; R^1 = Me, R^2 = H) to cyclize, there being insufficient stabilization to allow the formation of the necessary carbonium ions, because of reduced electron donation. Since an equilibrium between (23), (25), and (26) is proposed, then both (25) and (26) where (R^1 = Me, R^2 = H) will eventually give the only possible final product, the unsaturated ketol (29).

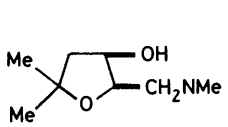
The primary products of the cyclization reactions were further modified to provide materials for biological investigations. The chloro-compound (5a; X = Cl) was both partially and fully reduced and dechlorinated to yield the olefin (20) and the tetrahydrofuran (32a). Reduction of the ketone (5a; X = OH) using potassium borohydride gave, substantially, a single product. This was assigned the *cis*-structure (33) shown, both from the method of preparation, attack by borohydride would be less hindered on the side of the molecule opposite to that of the side chain, and from i.r. spectra.

Several of the cyclic compounds (5a; X = Cl, Br, I,

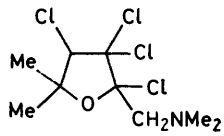


(32)

R
a; Me
b; H



(33)



(34)

H) were subjected to a nitrogen demethylation procedure [35] to yield the secondary amines (5b; X = Cl, Br, I, H) and (32b). The ketone (5b; X = OH) was not prepared by this method, but by means of a Mannich reaction using methylamine and the tetrahydrofuran (19b). Addition of chlorine to the chloro-compound (5a; X = Cl) gave the polychloro-compound (34). The methiodides of compounds (5a; X = OH, Cl, Br, I, H) and (32a) were also prepared.

[33] E. G. Rochow, D. T. Hurd, and R. N. Lewis, ' The Chemistry of Organometallic Compounds,' J. Wiley, New York, 1957, pp. 109—112.

[34] W. L. Budde and R. E. Dessey, *Tetrahedron Letters*, 1963, 651; *J. Amer. Chem. Soc.*, 1963, **85**, 3964.

[35] F. Bickelhaupt, K. Stach, and M. Theil, *Monatsh.*, 1964, **95**, 485.

The muscarinic and acetylcholinesterase-inhibitory activities of these compounds will be described elsewhere.

EXPERIMENTAL

Melting points were determined in an Electrothermal 1A6301 apparatus with thermometer corrected for stem error. I.r. spectra were recorded on Beckman IR9 and Perkin-Elmer PE157 spectrometers. N.m.r. spectra were recorded on a Varian A60 instrument. Mass spectra were obtained using an AEI MS902 spectrometer. For analytical g.l.c. a Perkin-Elmer 810 was used. Accuracy of determinations was to the normal limits of these instruments.

2-Dimethylamino-1-ethoxyethanol Hydrochloride (10a).—Dimethylaminoacetaldehyde diethyl acetal (295.5 g) was added to a stirred mixture of ice (600 g) and conc. hydrochloric acid (1.0 l) and set aside at 25 °C for 5 days. Evaporation of this solution at 35 °C/10 mmHg and finally at 40 °C/1 mmHg (over P_2O_5) gave a fawn glass (272 g) which on treatment with hot ethanol (300 ml) yielded, on cooling, *2-dimethylamino-1-ethoxyethanol hydrochloride* as prisms (252 g, 82%), m.p. 111—112 °C (Found: C, 42.55; H, 9.7; Cl, 21.05; N, 8.1. $C_6H_{16}ClNO_2$ requires C, 42.5; H, 9.5; Cl, 20.9; N, 8.25%), $\nu_{max.}$ (Nujol) 3 200vs, sh (OH bonded), 1 160s and 1 110s (O–C–O), and 1 060s cm^{-1} (C–O); $\delta(D_2O)$ 1.15 (3 H, t, J = 6 Hz, OCH_2CH_3), 2.93 [6 H, s, $\overset{+}{N}(CH_3)_2$], 3.21 (2 H, d, J = 6 Hz, $\overset{+}{N}CH_2$), 3.63 (2 H, q, J = 6 Hz, OCH_2CH_3), and 5.44 [1 H, t, J = 6 Hz, $CH(O)_2$].

1-Ethoxy-2-methylaminoethanol Hydrochloride (10b).—In a similar manner, methylaminoacetaldehyde diethyl (or dimethyl) acetal gave *1-ethoxy-2-methylaminoethanol hydrochloride*, m.p. 84—85 °C (warm ethanol–ether) in 51—71% yield (Found: C, 38.55; H, 9.05; Cl, 22.65; N, 8.8. $C_5H_{14}ClNO_2$ requires C, 38.6; H, 9.05; Cl, 22.8; N, 9.0%; $\nu_{max.}$(Nujol) 3 300 vs, sh (OH, bonded), 1 595s ($\overset{+}{N}H_2$), 1 170s, and 1 105s (O–C–O), 1 070s (C–O), and 630s cm^{-1} (OH); $\delta(D_2O)$ 1.17 (3 H, t, J = 7.2 Hz, CH_3CH_2O), 2.94 (3 H, s, $CH_3\overset{+}{N}$), 3.13 (2 H, d, J = 5.0 Hz, $CH_2\overset{+}{N}$), 3.64 (2 H, q, J = 7.5 Hz, OCH_2CH_3), and 5.38 [1 H, t, J = 5.2 Hz, $CH(O)_2$]. The product was prone to aerial oxidation and unstable in hydroxylic solvents above 50 °C.

4-Dimethylamino-1-phenylbut-1-yn-3-ol (9).—Freshly distilled phenylacetylene (30.4 g) was slowly added to a stirred suspension of sodium amide (42.0 g) in dry dioxan (500 ml) and stirring was continued until one equivalent of ammonia (entrained in a stream of dry nitrogen into known amounts of dilute sulphuric acid containing an indicator) was evolved (*ca.* 2 h). Finely ground 2-dimethylamino-1-ethoxyethanol hydrochloride (28.4 g) was added to the stirred mixture at 0 °C from a flask connected by a tube to the reaction vessel, to avoid loss of ammonia. Stirring was continued until the evolution of 2 equivalents of ammonia was complete. Ammonium chloride (50 g), water, and finally dilute sulphuric acid were added to the reaction mixture at 25 °C to form an acidic mixture which separated into two layers. The organic layer gave, on evaporation, neutral material, mainly phenylacetylene (*ca.* 18 g). The aqueous acidic layer was basified with 40% sodium hydroxide solution and extracted with ether. Evaporation of the dried ($MgSO_4$) extract gave the crude product (15 g, 47%), m.p. 60—61 °C, sublimation of which gave pure *4-dimethylamino-1-phenylbut-1-yn-3-ol* (3.0 g, 9.5%) as needles, m.p. 67—68 °C (Found: C, 75.9; H, 8.3; N, 7.4. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%); $\nu_{max.}$(KBr disc) 3 090m and 3 070m (CH, arom.), 2 790m and 2 730m (CH_3N), and 760s, 690s (monosub. phenyl); (CCl_4 soln.) 3 450m,br (OH, bonded); (thin film) 2 200w cm^{-1} (C≡C); $\delta(CDCl_3)$ 2.36 [6 H, s, $N(CH_3)_2$], *ca.* 2.60 (2 H, AB of ABX, CH_2N), 3.83 (1 H, s, O*H*), 4.63 (1 H, X of ABX, ≡C*H*), and 7.30 (5 H, m, *Ph*). Treatment of the base with an excess of iodomethane in acetone gave the *methiodide* as needles, m.p. 146 °C (ethanol–ether) (Found: C, 46.85; H, 5.55; I, 38.35; N, 4.35. $C_{13}H_{18}INO$ requires C, 47.15; H, 5.55; I, 38.3; N, 4.25%).

General Method for the Preparation of the Aminoalkynols (4).—To a stirred suspension of sodium amide (120 g) in purified dioxan (1.0 l) was slowly added the protected butynol (2) (0.8 mol). After a further 2 h the mixture was cooled in ice and finely ground 2-dimethylamino-1-ethoxyethanol hydrochloride (180 g) was added at a rate which maintained a reaction temperature of 23—35 °C. Stirring was continued at room temperature for 16 h and then ice followed by water was added to the reaction mixture at 25 °C until two clear layers formed. The dioxan layer was separated and further extractions were made with the same solvent. The combined extracts were dried ($MgSO_4$) and evaporated to give a brown oil which was taken up in ether and filtered. Evaporation of the filtrate gave the crude aminoalkynol (4) which was generally used in cyclization reactions without further purification. In this manner the following compounds were prepared.

5-Benzyloxy-1-dimethylamino-5-methylhex-3-yn-2-ol (4a).—Using 3-benzyloxy-3-methylbut-1-yne [36] as starting material, a crude product was obtained which was purified by crystallization from acetone at −10 °C followed by recrystallization from light petroleum (b.p. 40—60 °C) to give the pure *product* as bronze needles, m.p. 55 °C (13—16%) (Found: C, 73.25; H, 9.0; N, 5.3. $C_{16}H_{23}NO$ requires C, 73.55; H, 8.85; N, 5.35%); $\nu_{max.}$ (Nujol) 3 200m,br (OH, bonded), 2 850m and 2 800m (CH_3N), 1 160s and 1 060s (C–O), and 780s and 690s cm^{-1} (monosub. phenyl); $\delta(CDCl_3)$ 1.52 [6 H, s, $C(CH_3)_2$], 2.30 [6 H, s, $N(CH_3)_2$], 2.5 (2 H, AB of ABX, CH_2N), 3.68 (1 H, s, O*H*), 4.46 (1 H, X of ABX, =C*H*–CH_2), 4.62 (2 H, s, $PhCH_2$), and 7.31 (5 H, s, *Ph*). Distillation of the accumulated filtrates gave dimethylaminoacetamide (13), b.p. 80 °C/0.5 mmHg, m.p. 96—97 °C (needles). The literature [37] gives the melting point as 96.5 °C.

1-Dimethylamino-5-methyl-5-tetrahydropyran-2-yloxyhex-3-yn-2-ol (4b).—By the use of 3-methyl-3-tetrahydropyran-2-yloxybut-1-yne [38] (2b) as starting material and distillation of the crude product through a short column a fraction was obtained, with much decomposition, b.p. 120—140 °C/0.5 mmHg. This distillate was then purified by chromatography through a column of silica gel, the product being obtained by elution with ethanol. Separation of minor impurities was achieved on a second column using light petroleum (b.p. 40—60 °C) as the eluant, giving the pure *product* (Found: C, 65.9; H, 10.0; N, 5.7. $C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.85; N, 5.45%); $\nu_{max.}$(film) 3 380m,br (OH), 2 850m and 2 760m (CH_3N), 2 200w (C≡C), 1 130s (C–O–C), and 1 080 cm^{-1} (C–O–C, ring); $\delta(CDCl_3)$ 1.48 and 1.52 [6 H, 2s, $C(CH_3)_2$], 1.6 (6 H, m, $CH_2CH_2CH_2$), 2.33 [6 H, s, $N(CH_3)_2$], 2.51, 2.62 (2 H, m, CH_2N), 3.75 (1 H, s, O*H*),

[36] J. P. Guermont, *Bull. Soc. chim. France*, 1953, 386.
[37] R. A. Turner, *J. Amer. Chem. Soc.*, 1946, **68**, 1607.
[38] D. N. Robertson, *J. Org. Chem.*, 1960, **25**, 931.

3.8 (2 H, m, OCH_2), 4.44 (1 H, m, $\equiv CH$), and 5.05br (s, $O_2CH{\cdot}CH_2$).

5-Benzyloxy-1-dimethylaminohex-3-yn-2-ol (4c).—By use of 3-benzyloxybut-1-yne,[36] a crude product was obtained for which no satisfactory method of purification could be found. Neutral materials could be removed by extraction of a solution in dichloromethane with 5% (w/v) H_2SO_4. Basification (2N-NaOH) and extraction into dichloromethane, followed by evaporation of the extract gave an oil, $\nu_{max.}$(film) 3 300s,br (OH, bonded), 2 800vs and 2 750vs (CH_3N), 2 200w (C≡C), and 735s and 700s cm^{-1} (monosub. phenyl). Impurity peaks due to the corresponding unsaturated keto-alcohol (15c) were at 1 680 (C=O) and 1 600 cm^{-1} (C=C).

5-Methyl-1-methylamino-5-tetrahydropyran-2-yloxyhex-3-yn-2-ol (4d).—By use of (2b) and with (10b) in place of (10a), a very unstable product was obtained. Unchanged (2b) was removed from the crude product by distillation (b.p. 33 °C/0.05 mmHg) to give an oil, which was used immediately for the preparation of cyclic products, $\nu_{max.}$(film) 3 350m,br (OH), 2 800m (CH_3N), 1 160s (C–O–C), and 1 080s cm^{-1} (C–O–C, ring). An impurity gave a peak at 1 680m cm^{-1}.

1-Dimethylamino-5-methylhex-3-yne-2,5-diol (4e).—A solution of crude 1-dimethylamino-5-methyl-5-tetrahydropyran-2-yloxyhex-3-yn-2-ol (4b) (160 g) in dichloromethane was treated dropwise with a quantity of 5% (w/v) sulphuric acid such that, after agitation, a slightly acidic aqueous layer was obtained. From this, by basification and extraction with dichloromethane, was obtained the crude product (46.1 g), $\nu_{max.}$(film) 3 350s,br (OH), 2 800s and 2 750s (CH_3N), 1 170s (C–O–C), and 1 700mbr and 1 600m,br cm^{-1} (impurities). Distillation of this material (6.7 g) gave a viscous yellow oil (2.0 g), b.p. 100—105 °C/0.33 mmHg, which solidified on cooling. This was identified as *2-(2-hydroxypropyl)-1-methylpyrrole*, m.p. 112 °C (acetone–light petroleum b.p. 60—80 °C) (Found: C, 69.1; H, 9.7; N, 10.3. $C_8H_{13}NO$ requires C, 69.05; H, 9.4; N, 10.05%); $\nu_{max.}$ (Nujol) 3 200s cm^{-1} (OH); δ($CDCl_3$) 1.61 [6 H, s, $C(CH_3)_2$], 1.72 (1 H, s, OH), 3.81 (3 H, s, CH_3N), and 5.99, 6.54 (3 H, *ca.* d, *ca.* t, =CH–CH=CH).

5,5-Dimethyl-2-dimethylaminomethyl-3-oxotetrahydrofuran (5a; X = OH).—*Method A.* Zeo-Carb 225, impregnated with mercuric sulphate [24] (80 g), was added to a stirred, refluxing solution of 1-dimethylamino-5-methyl-5-tetrahydropyran-2-yloxyhex-3-yn-2-ol (20.33 g; purity 80%) in methanol (450 ml) and water (150 ml). The cooled reaction mixture was filtered and the separated resin was washed on a column with 8N-hydrochloric acid (400 ml). The eluate was evaporated to dryness, the residue basified with 2N-sodium hydroxide, and the mixture extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract gave a brown oil which was treated with an excess of hydrochloric acid and evaporated to dryness. The crude mass was extracted with chloroform, evaporation of which gave a solid from which, by repeated crystallization from acetone, was obtained *5,5-dimethyl-2-dimethylaminomethyl-3-oxotetrahydrofuran hydrochloride* (2.3 g, 16.5%), m.p. 172 °C (Found: C, 51.95; H, 8.85; Cl, 17.25; N, 6.9. $C_9H_{18}ClNO_2$ requires C, 52.05; H, 8.75; Cl, 17.05; N, 6.75%); $\nu_{max.}$ (Nujol) 2 600vs,br and 2 740vs,br ($\overset{+}{N}H$), 1 765s (C=O), 1 440m ($\overset{+}{N}H$), and 1 115s cm^{-1} (C–O–C, ring); δ($CDCl_3$) 1.34 and 1.47 [6 H, 2 s, $C(CH_3)_2$], 2.42 (2 H, s, CH_2CO), 2.95 [6 H, 2 d, $\overset{+}{N}H(CH_3)_2$], 3.40 (2 H, m, $=CH{\cdot}CH_2\overset{+}{N}$), and 4.71 (1 H, q, $=CH{\cdot}CH_2\overset{+}{N}$), and 12.67br (1 H, $\overset{+}{N}H$). The *methiodide* had m.p. 215 °C (decomp.) (Found: C, 38.1; H, 6.55; I, 40.45; N, 4.45. $C_{10}H_{20}INO_2$ requires C, 38.35; H, 6.45; I, 40.5; N, 4.45%). Yields of the ketone (5a; X = OH) from this preparation ranged from 4.5—20% (5 experiments) and appeared to correlate with the age of the impregnated resin used. Freshly prepared resin gave the best result. In preparations in which old resin was used, in addition to the ketone (5a) there was obtained, on concentration of the filtrate, *1-dimethylamino-2-hydroxy-5-methyl-3-oxohex-4-ene hydrochloride*, m.p. 147 °C (decomp.). This material was unstable in air (Found: C, 51.3; H, 9.0; N, 6.6. $C_9H_{18}ClNO_2$ requires C, 52.05; H, 8.75; N, 6.75%); $\nu_{max.}$ (Nujol) 3 230s (OH, bonded), 2 500m,br ($\overset{+}{N}H$), 1 695s (C=O, conj.), and 1 640s cm^{-1} (C=C, conj.); δ(D_2O) 1.42 [6 H, s, $C(CH_3)_2$], 2.94 [6 H, s, $\overset{+}{N}(CH_3)_3$], 4.02 (2 H, d, $CH{\cdot}CH_2\overset{+}{N}$), and 7.0 (2 H, m, C=CH and $CH{\cdot}CH_2\overset{+}{N}$).

Attempts to cyclize this material with sulphuric acid (20%) at 55 °C failed. After 1 h a black tar was produced, the only easily identifiable feature in the i.r. spectrum of which was an acetylenic band at 2 200 cm^{-1}. The presence of mercuric sulphate catalyst did not alter this result.

Method B. 5-Benzyloxy-1-dimethylamino-5-methylhex-3-yn-2-ol (10.0 g) was added to a stirred solution of mercuric sulphate (10.0 g) in sulphuric acid (20%, 400 ml). The temperature of the stirred mixture was gradually raised to 55 °C during 3 h and then maintained at 60 °C for 4 h. The cooled acidic solution was thoroughly extracted with ether to remove the benzyl alcohol, basified (4N-NaOH), and filtered to remove the precipitated inorganic material. The filter cake was washed and the filtrate extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) extract gave a brown oil (9.0 g) from which 5,5-dimethyl-2-dimethylaminomethyl-3-oxotetrahydrofuran (1.0 g, 15%), b.p. 44 °C/0.8 mmHg, was obtained.

Method C. Aqueous dimethylamine (28% w/v; 1.6 ml) was mixed with aqueous formaldehyde (38% w/v; 0.79 ml) and, when the exothermic reaction had subsided, was rendered acidic (pH 2) with concentrated hydrochloric acid. 5,5-Dimethyl-3-oxotetrahydrofuran [2] (0.98 g) was added and the mixture refluxed until all material was in solution (4 h). The cooled reaction mixture was extracted with ether to remove unchanged starting material (0.5 g) and the aqueous layer was basified, extracted with dichloromethane, and the dried ($MgSO_4$) extract evaporated to give a basic oil (0.59 g) which was treated with dilute hydrochloric acid and evaporated to dryness. By repeated recrystallization of the resinous residue from acetone was obtained *5,5-dimethyl-2-dimethylaminomethyl-3-oxotetrahydrofuran hydrochloride* (120 mg, 6.5%), m.p. 172 °C.

5,5-Dimethyl-2-methylaminomethyl-3-oxotetrahydrofuran (5b; X = OH).—A mixture of 5,5-dimethyl-3-oxotetrahydrofuran [2] (10.0 g), methylammonium chloride (30.0 g), aqueous formaldehyde (38% w/v; 8.2 ml), and concentrated hydrochloric acid (5.0 ml) was refluxed for 8 h. The cooled mixture was extracted with ether to remove unchanged starting ketone (5 g), basified, and again extracted. The latter extract was dried ($MgSO_4$) and evaporated to give an oil which was distilled under reduced pressure and the fraction (4.6 g), b.p. 100—104 °C/12 mmHg, was collected. This was acidified with dilute hydrochloric acid and evaporated to dryness. The residue was extracted with acetone and the concentrated extract was fractionally crystallized.

Early fractions consisted mainly of a resinous gum but later fractions gave *5,5-dimethyl-2-methylaminomethyl-3-oxotetrahydrofuran hydrochloride* (450 mg, 2.8%) as needles, m.p. 133—134 °C (Found: C, 49.6; H, 8.1; N, 6.95. $C_8H_{16}ClNO_2$ requires C, 49.6; H, 8.35; N, 7.25%), $\nu_{max.}$ (Nujol) 3 200m ($\overset{+}{N}H_2$), 2 700m,br ($CH_3\overset{+}{N}$), and 1 770s cm^{-1} (C=O); δ(D_2O) 1.39 and 1.50 [6 H, 2s, C(CH_3)$_2$], 2.66 (2 H, s, CH_2CO), 2.78 [3 H, s, $D\overset{+}{N}(CH_3)$], 3.6 (2 H, AB of ABX, $CH_2\overset{+}{N}$), and 4.48 (1 H, X of ABX, $CH{\cdot}CH_2\overset{+}{N}$).

3-Chloro-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran (5a; X = Cl).—1-Dimethylamino-5-methyl-5-(2-tetrahydropyranyloxy)hex-3-yn-2-ol (50 g, purity 80%) was slowly added to concentrated hydrochloric acid (500 ml) at 25 °C and set aside at room temperature for 2 days. The diluted reaction mixture was thoroughly extracted with ether to remove neutral material, then evaporated to dryness and the crude glassy mixture of hydrochlorides obtained was extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract gave a solid which was fractionally crystallized to give *3-chloro-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran hydrochloride* (16.95 g, 48%), m.p. 198 °C (Found: C, 48.0; H, 7.8; Cl, 15.4; N, 6.25. $C_9H_{17}ClNO$ requires C, 47.8; H, 7.6; Cl, 15.7; N, 6.2%), $\nu_{max.}$ (Nujol) 2 800—2 200s,br ($\overset{+}{N}H$) and 1 640s cm^{-1} (C=C); δ(D_2O) 1.31 and 1.38 [6 H, 2s, C(CH_3)$_2$], 2.95 [3 H, s, $\overset{+}{N}(CH_3)_2$], 3.40 (2 H, m, $CH{\cdot}CH_2\overset{+}{N}$), 5.15 (1 H, m, CH=C·C*H*), and 6.18 (1 H, d, J = 2 Hz, *H*C=C·CH). The by-product separated from this crystallization was identified as the hydrochloride of the ketone (5a; X = OH). Some degree of useful separation of these hydrochlorides could also be achieved by continuous (3 days) extraction of a solution of the mixture in concentrated hydrochloric acid with chloroform. The chloro-compound (5a; X = Cl) was extracted preferentially into the organic layer, evaporation of which gave almost pure material. The enrichment of the aqueous phase with the ketone (5a; X = OH) allowed easier isolation of this compound. There was no evidence of conversion of the ketone into the chloro-compound during this process.

(3-Chloro-5,5-dimethyl-2,5-dihydrofurfuryl)trimethylammonium Iodide.—Treatment of the free base (5a; X = Cl) with an excess of iodomethane in acetone and recrystallization of the precipitated product from the same solvent gave the *methiodide* in quantitative yield, m.p. 265 °C (decomp.) (Found: C, 36.65; H, 5.9; I, 38.15; N, 4.25; total halide, 48.8. $C_{10}H_{19}ClINO$ requires C, 36.2; H, 5.75; I, 38.25; N, 4.2; total halide, 48.95%).

3-Bromo-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran (5a; X = Br).—The compound was prepared in a manner similar to the chloro-analogue by the action of concentrated hydrobromic acid (30%) on 1-dimethylamino-5-methyl-5-(2-tetrahydropyranyloxy)hex-3-yn-2-ol. The *hydrobromide* was obtained in 38—42% yield, m.p. 185 °C (needles from acetone) (Found: C, 34.45; H, 5.55; Br, 50.45; N, 4.35. $C_9H_{17}Br_2NO$ requires C, 34.3; H, 5.45; Br, 50.75; N, 4.45%), $\nu_{max.}$ (Nujol) 3 050m (=CH), 1 625s (C=C), and 1 100s, 1 000s, and 975s cm^{-1} (ring modes); δ($CDCl_3$) 1.36 and 1.44 [6 H, 2s, C(CH_3)$_2$], 3.0 [6 H, m, $\overset{+}{N}(CH_3)_2$], 3.68br (2 H, d, $CH{\cdot}CH_2\overset{+}{N}$), 5.41 ($CH{\cdot}CH_2\overset{+}{N}$), and 6.12 (1 H, d, 4-H). Treatment of the free base with an excess of iodomethane in acetone gave a quantitative yield of the *methiodide*, m.p. 258 °C (decomp.), as needles (Found: C, 32.2; H, 5.25; N, 3.75; I, 33.5; total halide, 55.1. $C_{10}H_{19}BrINO$ requires C, 31.95; H, 5.1; N, 3.7; I, 33.75; total halide, 55.0%).

5,5-Dimethyl-2-dimethylaminomethyl-3-iodo-2,5-dihydrofuran (5a; X = I).—In a similar manner to that described in the preceding experiment, the action of hydriodic acid (55%) on 1-dimethylamino-5-methyl-5-(tetrahydropyran-2-yloxy)hex-3-yn-2-ol gave the *hydroiodide* in 19—27% yield, m.p. 233 °C (prisms from acetone) (Found: C, 26.3; H, 4.25; I, 62.35; N, 3.35. $C_9H_{17}I_2NO$ requires C, 26.45; H, 4.2; I, 62.05; N, 3.4%), $\nu_{max.}$ (Nujol) 2 900—2 000s—w,br, 2 810s—w,br, and 2 725s—w,br ($\overset{+}{N}H$), 1 625s (C=C), and 1 100s, 1 000s, and 970s cm^{-1} (ring modes); δ[$(CD_3)_2SO$] 1.32 and 1.40 [6 H, 2s, C(CH_3)$_2$], 3.0 [6 H, m, $\overset{+}{N}(CH_3)_2$], 3.6 (2 H, m, $CH{\cdot}CH_2\overset{+}{N}$), 5.1 (1 H, m, $CH{\cdot}CH_2\overset{+}{N}$), and 6.42 (1 H, d, 4-H). The *methiodide* obtained in the usual way (55% yield) had m.p. 256 °C (decomp.) (Found: C, 28.55; H, 4.5; I, 59.7; N, 3.2. $C_{10}H_{19}I_2NO$ requires C, 28.4; H, 4.55; I, 60.0; N, 3.3%).

2,2-Dimethyl-5-dimethylaminomethyl-2,5-dihydrofuran (5a; X = H) and *2,2-Dimethyl-5-dimethylaminomethyltetrahydrofuran* (32a).—3-Chloro-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran hydrochloride (3.0 g) in ethanol (40 ml) and 1M-sodium hydroxide solution (26.4 ml, 2 equiv.) was added to presaturated 5% palladium on carbon (100 mg) in ethanol (5 ml) and hydrogenated at 1 atm until 296 ml of hydrogen had been absorbed (*ca.* 10 min). The catalyst was filtered off and the acidified (HCl) filtrate evaporated to dryness. The solid residue was extracted with chloroform, filtered, and the extract dried ($MgSO_4$) and evaporated to give the crude product (2.55 g). Fractional crystallization from acetone gave *2,2-dimethyl-5-dimethylaminomethyl-2,5-dihydrofuran hydrochloride* as prisms (1.0 g, 39.6%), m.p. 181 °C (Found: C, 56.55; H, 9.75; Cl, 18.45; N, 7.35. $C_9H_{18}ClNO$ requires C, 56.4; H, 9.45; Cl, 18.5; N, 7.3%), $\nu_{max.}$ (Nujol or HCBD) 3 080m and 3 010m (=CH), 1 105s, C–O–C), and 749s cm^{-1} (ring mode); δ(CDCl) 1.36 and 1.30 [6 H, 2s, C(CH_3)$_2$], 2.13 [6 H, s, $\overset{+}{N}(CH_3)_2$], 3.12, 3.17 (2 H, 2q, $CH{\cdot}CH_2\overset{+}{N}$), 5.48 (1 H, 2q, $CH{\cdot}CH_2\overset{+}{N}$), and 5.83 and 5.82 (2 H, 2q, $CH{\cdot}CH{\cdot}CH{\cdot}CH_2$).

(5,5-Dimethyl-2,5-dihydrofurfuryl)trimethylammonium Iodide.—The *methiodide* was obtained in 74% yield, as plates, m.p. 227 °C (decomp.) (acetone) (Found: C, 40.35; H, 6.85; I, 42.7; N, 6.85. $C_{10}H_{20}INO$ requires C, 40.4; H, 6.8; I, 42.7; N, 4.7%).

The combined filtrates from the crystallization of the hydrochloride of (5a; X = H) gave on evaporation a mixture of the hydrochlorides of this base, the chloro-compound (5a; X = Cl) and the fully saturated compound (32a). Basification of this mixture, followed by complete hydrogenation over 5% Pd/C catalyst gave good yields of *2,2-dimethyl-5-dimethylaminomethyltetrahydrofuran hydrochloride*, m.p. 168 °C (needles from acetone) (Found: C, 55.65; H, 10.6; Cl, 18.35; N, 7.2. $C_9H_{20}ClNO$ requires C, 55.8; H, 10.4; Cl, 18.3; N, 7.25%), δ($CDCl_3$) 1.27 [6 H, s, C(CH_3)$_2$], 1.80 (4 H, s, CH_2CH_2), 2.90 and 2.95 [6 H, 2d, $\overset{+}{N}H(CH_3)_2$], 3.2 (2 H, m, =CH·$CH_2\overset{+}{N}$), and 4.5 (1 H, m, =$CH{\cdot}CH_2\overset{+}{N}$). The compound was also obtained pure in 75% yield by complete reduction of the chloro-compound (5a; X = Cl) in a single step.

(5,5-Dimethyltetrahydrofurfuryl)trimethylammonium Iodide.—The *compound* was obtained in 68% yield, as

needles, m.p. 186 °C (acetone) (Found: C, 40.55; H, 7.45; I, 42.3; N, 4.6. $C_{10}H_{22}INO$ requires C, 40.15; H, 7.4; I, 41.4; N, 4.7%).

5,5-Dimethyl-2-dimethylaminomethyl-3-hydroxytetrahydrofuran (33).—5,5-Dimethyl-2-dimethylaminomethyl-3-oxotetrahydrofuran (0.5 g) in methanol (10 ml) was added dropwise during 1 h to a solution of potassium borohydride (0.25 g) in water (1.5 ml) and trimethylamine (0.6 ml) at 3—6 °C. The solution was allowed to warm to room temperature, then heated at 50 °C for 15 min to drive off the trimethylamine. Water (1.0 ml) was added and the solution was extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract gave the crude product as an oil (0.5 g). G.l.c. (10% SE30 on Chromasorb G at 200 °C isothermal) showed a single product peak. Carefully controlled cooling of the oil led to the formation of large crystals which were separated by hand, dried on filter paper, and crystallized from light petroleum (b.p. 40—60 °C) to give *5,5-dimethyl-2-dimethylaminomethyl-3-hydroxytetrahydrofuran* (160 mg, 32%), m.p. 58 °C (prisms) (Found: C, 62.1; H, 11.1; N, 7.95. $C_9H_{19}NO_2$ requires C, 62.4; H, 11.05; N, 8.1%). G.l.c. using the above conditions showed the purity to be >99%; $\nu_{max.}$ (Nujol) 3 070s,br (OH, bonded), 2 800s (CH_3N), 1 115, and 1 055s, and 925s cm^{-1} (ring modes). In CCl_4 all solutions showed a broad band at 3 445 cm^{-1} with unchanged intensity on dilution; this indicated an intramolecularly bonded OH which suggested that the product was the *cis*-isomer. Fuller discussion of this is given elsewhere,[27] $\delta(CDCl_3)$ 1.24 and 1.34 [6 H, 2s, $C(CH_3)_2$], 2.30 [6 H, s, $N(CH_3)_2$], 1.8—2.6 (4 H, m, $CH_2CH{\cdot}CH{\cdot}CH_2$), 3.80 (1 H, s, OH), and 3.9 (2 H, m, $CH_2CH{\cdot}CH{\cdot}CH_2$).

Demethylation of Amines (5a; X = Cl), (5a; X = Br), (5a; X = I), *and* (5a; X = H).—A procedure based on that of Bickelhaupt *et al.*[35] was used. The tertiary amine (0.004 mol) in benzene (2.0 ml) was treated with ethyl chloroformate (0.009 mol) in benzene (2.0 mol) and the mixture was refluxed for 5 h. Filtration removed a small amount of solid by-product (quaternary compound) and evaporation gave the carbamate ester having a characteristic peak in the i.r. region at *ca.* 1 710 cm^{-1}. The crude carbamate ester was treated with a solution of potassium hydroxide (0.035 mol) in aqueous ethanol (95%, 10 ml) and the mixture was refluxed for several hours (times given in examples below). The crude mixture was acidified with dilute hydrochloric acid and extracted with ether to remove unchanged carbamate ester, which could be recycled. The aqueous layer was basified (5M-sodium hydroxide) and extracted with chloroform, evaporation of which gave the required secondary amine. Treatment with hydrochloric acid, evaporation of the solution and recrystallization of the residue from acetone gave the pure secondary amine hydrochloride.

3-Chloro-5,5-dimethyl-2-methylaminomethyl-2,5-dihydrofuran Hydrochloride (5b; X = Cl).—The carbamate ester from 3-chloro-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran, after hydrolysis lasting 5 h gave *3-chloro-5,5-dimethyl-2-methylaminomethyl-2,5-dihydrofuran hydrochloride*, m.p. 137 °C, in 20% yield (Found: C, 45.25; H, 7.05; N, 6.35. $C_8H_{15}Cl_2NO$ requires C, 45.3; H, 7.15; N, 6.6%), $\nu_{max.}$ (Nujol) 1 640s (C=C) and 795s cm^{-1} (ring mode); $\delta(D_2O)$ 1.42 [6 H, 2s, $C(CH_3)_2$], 2.82 [3 H, s, $D\overset{+}{N}(CH_3)$], 3.4 (2 H, 2q, $CH_2\overset{+}{N}$), 5.10 (1 H, m, $CH{\cdot}CH_2\overset{+}{N}$), and 6.24 (1 H, d, 4-H). This compound could also be prepared in very poor yield by cyclization of the unstable aminoalkynol (4d) by treatment with concentrated hydrochloric acid.

3-Bromo-5,5-dimethyl-2-methylaminomethyl-2,5-dihydrofuran Hydrochloride (5b; X = Br).—The carbamate ester from 3-bromo-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran, after hydrolysis lasting 5 h gave the *hydrochloride*, m.p. 159 °C, as needles in 25% yield (Found: C, 37.3; H, 5.85; N, 5.4; total halogen, 45.15. $C_8H_{15}BrClNO$ requires C, 37.45; H, 5.9; N, 5.45; total halogen, 44.95%), $\nu_{max.}$ (Nujol) 1 630s (C=C) and 815m and 795m cm^{-1} (ring modes); $\delta(CDCl_3)$ 1.33, 1.45 [6 H, 2s, $C(CH_3)_2$], 2.85 [3 H, s, $D\overset{+}{N}(CH_3)$], 3.4 (2 H, 2q, $CH_2\overset{+}{N}$), 5.28 (1 H, m, $CH{\cdot}CH_2\overset{+}{N}$), and 6.10 (1 H, d, 4-H).

3-Iodo-5,5-dimethyl-2-methylaminomethyl-2,5-dihydrofuran Hydrochloride (5b; X = I).—The carbamate ester from 3-iodo-5,5-dimethyl-2-dimethylaminomethyl-2,5-dihydrofuran, after prolonged hydrolysis (3 days) and recycling of unchanged carbamate ester, gave *3-iodo-5,5-dimethyl-2-methylaminomethyl-2,5-dihydrofuran hydrochloride*, m.p. 136—137 °C, as prisms in 15% yield (Found: C, 31.85; H, 4.95; Cl, 11.4; N, 4.4. $C_8H_{15}ClINO$ requires C, 31.65; H, 5.0; Cl, 11.7; N, 4.6%), $\nu_{max.}$ (Nujol) 1 625m (C=C) and 810m and 795m cm^{-1} (ring modes).

2,2-Dimethyl-5-methylaminomethyl-2,5-dihydrofuran Hydrochloride (5b; X = H).—Hydrolysis of the carbamate ester of 2,2-dimethyl-5-dimethylaminomethyl-2,5-dihydrofuran lasting 5 h gave *2,2-dimethyl-5-methylaminomethyl-2,5-dihydrofuran hydrochloride*, m.p. 118 °C, as hygroscopic prisms in 37% yield (Found: C, 53.9; H, 9.1; Cl, 19.55; N, 7.9. $C_8H_{16}ClNO$ requires C, 54.1; H, 9.1; Cl, 19.95; N, 7.9%), $\nu_{max.}$ (Nujol) 805, and 785 m cm^{-1} (ring modes); $\delta(CDCl_3)$ 1.33 and 1.39 [6 H, 2s, $C(CH_3)_2$], 2.84 [3 H, s, $\overset{+}{N}(CH_3)$], 3.09 (2 H, 2q, $CH_2\overset{+}{N}$), 5.32 (1 H, m, $CH{\cdot}CH_2\overset{+}{N}$), 5.88 (2 H, 2q, CH=CH), and 9.33 (2 H, s, $\overset{+}{N}H$,HCl).

2,3,3,4-Tetrachloro-5,5-dimethyl-2-dimethylaminomethyltetrahydrofuran (34).—Treatment of (5a; X = Cl) with an excess of chlorine in carbon tetrachloride gave an almost quantitative yield of *5,5-dimethyl-2,3,3,4-tetrachlorotetrahydrofuran hydrochloride*, m.p. 136 °C (decomp.) (from ethanol–ether) (Found: C, 32.9; H, 5.0; N, 4.1. $C_{10}H_{16}Cl_5NO$ requires C, 32.6; H, 4.85; N, 4.25%), $\nu_{max.}$ (Nujol) 1 060s (C–O–C, ring) and 695s cm^{-1} (C–C); $\delta(D_2O)$ 1.42 and 1.50 [6 H, 2s, $C(CH_3)_2$], 3.07 [6 H, s, $\overset{+}{N}(CH_3)_2$], 3.81 (2 H, s, $CH_2\overset{+}{N}$), and 5.02 (1 H, s, 4- or 3-H).

A Re-investigation of the Work of V. M. Vlasov et al.[1]—*Cyclization of 4-methylhex-2-yne-1,4-diol.* To a solution of mercuric sulphate [HgO (1.0 g), conc. H_2SO_4 (1.0 ml), and H_2O (6.0 ml)] was added ether (150 ml) and, during 2 h, an ethereal solution of 4-methylhex-2-yne-1,4-diol [39] (15.0 g). The mixture was stirred a further 2 h and then the layers were separated. The organic layer was dried (K_2CO_3), filtered, and evaporated. The residual oil was fractionally distilled to give a fraction (6.7 g), b.p. 50—55 °C/7 mmHg, consisting mainly of the cyclic ketone. Higher-boiling material, b.p. 73—80 °C/7 mmHg (0.8 g), contained mainly an unsaturated ketol which could not be purified further. The lower-boiling fraction was distilled repeatedly at atmospheric pressure to yield a product free from contamination. This was found to be 5-ethyl-5-methyl-3-oxotetrahydrofuran, b.p. 168 °C/760 mmHg, n_D^{20} 1.4380. G.l.c. [3% OV17 on Gaschrom Q, programmed 60—200 °C/10 °C

[39] V. M. Vlasov, A. A. Vasil'eva, and E. F. Semenova, *Zhur. org. Khim.*, 1966, **2**, 595.

min^{-1}, major peak (98%) at 3.0 min]; $\nu_{max.}$(thin film) 2 980vs, 2 940s, 2 880s, 1 770vs, 1 470s, 1 445s, 1 410s, 1 385s, 1 320m, 1 278s, 1 195vs, 1 180vs, 1 135w, 1 103m, 1 070vs, 1 000w, 945m, 880s, 833m, 783m, and 764s cm^{-1}; $\delta(CDCl_3)$ 0.97 (3 H, t, CH_3CH_2), 1.32 (3 H, s, CH_3C–O), 1.7 (2 H, q, CH_3CH_2), 2.27, 2.38 (2 H, q, J = 18 Hz, CH_2O), and 4.0 (2 H, s, CH_2CO). Vlasov *et al.*[1] claimed that 2-ethyl-2-methyl-3-oxotetrahydrofuran (18) had the following properties: b.p. 52—55 °C/8 mmHg; n_D^{20} 1.4386; $\nu_{max.}$(thin film) 2 980vs, 2 940s, 2 885s, 1 770vs, 1 470s, 1 440s, 1 410s, 1 382s, 1 316m, 1 276s, 1 195vs, 1 180vs, 1 133w, 1 103m, 1 068vs, 1 003w, 950m, 880s, 834m, 780m, and 764s cm^{-1}. The preparation described above was carried out exactly as in the paper by Vlasov *et al.*[1] Higher yields of cyclic product were obtained if further amounts of catalyst were added during the early stages of the reaction. The higher boiling fraction obtained, an unsaturated ketol, did not give any cyclic product on further treatment with catalyst.

We thank Mr. M. J. Graham and staff for the microanalytical results and Dr. E. S. Pepper for n.m.r. data and help with its interpretation. We record our thanks to Professor A. H. Beckett for help and interest throughout the work.

[8/258 *Received*, 14*th February*, 1978]