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The Structure of Muscarine

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(*Received* 24 *December* 1956)

The structure of the alkaloid muscarine has been determined by X-ray analysis of the iodide and confirmed by chemical degradation. Muscarine iodide is orthorhombic with $a = 6{\cdot}81$ Å, $b = 11{\cdot}75$ Å, $c = 15{\cdot}40$ Å; space group $P2_12_12_1$; 4 molecules of $C_9H_{20}O_2NI$ per unit cell. Atomic parameters were determined by heavy-atom techniques and refined by two-dimensional difference syntheses. Muscarine iodide is found to be trimethyl-(2-methyl-3-hydroxy-tetrahydrofuryl-5-) methyl ammonium iodide. A hydrogen bond of 3·57 Å is found between iodine and the hydroxyl oxygen. The tetrahydrofuran ring is not planar.

1. Introduction

Muscarine, a poisonous substance isolated from the fly agaric, has been the subject of numerous investigations for over a century (for a survey see Kögl, Duisberg & Erxleben (1931), Balenović, Cerar, Gašpert & Galijan (1955), Schouten (1956)). It was found that muscarine is a saturated quarternary ammonium base of probable molecular formula $C_9H_{20}O_2N^+OH^-$, containing one free hydroxyl group. A definite elucidation of the structure, however, was not achieved (Eugster & Waser, 1954; Kuehl, Lebel & Richter, 1955; Schouten, 1956).

Some years ago Kögl and coworkers started a new investigation of the muscarine problem. Relatively large quantities of the alkaloid could be isolated by chromatographic methods (Kögl, Salemink, Schouten & Jellinek, 1957). Towards the end of 1955 X-ray analysis was included in the investigation methods. The combination of chemical and diffraction methods proved to be fruitful: (1) Some degradation products of muscarine could be identified by powder photographs (for details see Kögl *et al.*, 1957). (2) Single-crystal methods led to the derivation of the muscarine structure.

Muscarine tetrachloroaurate was found to be triclinic

$$(a = 7{\cdot}83\text{ Å},\ b = 8{\cdot}98\text{ Å},\ c = 12{\cdot}01\text{ Å};\ \alpha = 92{\cdot}2^\circ,\ \beta = 101{\cdot}5^\circ,\ \gamma = 91{\cdot}9^\circ)$$

with two molecules in the unit cell. As muscarine is optically active the space group must be $P1$ and the two molecules in the cell must be crystallographically independent. No attempt was made to continue the investigation of this compound. The X-ray analysis of muscarine iodide, however, was successful. It was found that muscarine iodide is the quarternary trimethyl-ammonium salt of 2-methyl-3-hydroxy-5-(amino-methyl)-tetrahydrofuran; this formula could be confirmed by chemical degradation (Kögl *et al.*, 1957).

At the same time as this structure was found, Eugster (1956) proposed two hypothetical formulas for muscarine which have some features in common with the formula found in our investigation.

2. Structure determination of muscarine iodide

(*a*) *Experiments*

Muscarine iodide is orthorhombic with cell dimensions

$$a = 6{\cdot}81\text{ Å};\quad b = 11{\cdot}75\text{ Å};\quad c = 15{\cdot}40\text{ Å}\,.$$

With four molecules of $C_9H_{20}O_2NI$ per unit cell, the calculated density is 1·62 g.cm.$^{-3}$. From missing spectra the space group $P2_12_12_1$ is derived.

The intensities of the reflexions $hk0$, $h0l$, $0kl$, and $1kl$ were measured photometrically (Smits & Wiebenga, 1953) on integrated Weissenberg photographs (Wiebenga & Smits, 1950). The exposures were taken with Cu $K\alpha$ radiation, using the multiple-film technique. After correction for Lorentz, polarization and absorption factors and for the α_1–α_2 splitting as a function of the glancing angle, relative $|F_o|$ values were obtained.

(*b*) *Derivation of the muscarine skeleton*

The iodine parameters were determined from Patterson projections along the a and b axes. Although space group $P2_12_12_1$ does not possess a centre of symmetry, the projections along the orthorhombic axes are centrosymmetric. The signs of most structure amplitudes could be determined from the iodine contributions, and Fourier projections along the a, b and c axes were calculated. In the projection along the a axis some ten resolved atomic peaks were found. The projections along the b and c axes were poorly resolved, but it was possible to derive rough atomic positions, which were used in the structure-factor calculations.

At this stage it was not known which peaks were caused by C atoms, which by O or N, while some peaks might be entirely spurious. It was provisionally assumed that all peaks were caused by atoms with the scattering power of C. The scattering factors of C—and in the final stage of the analysis also those of N and O—were interpolated from the values given by Hoerni & Ibers (1954). For I Thomas–Fermi scattering factors (*Internationale Tabellen*, 1935) were used after correction for dispersion and anomalous scattering (Dauben & Templeton, 1955).

Inclusion in the structure-factor calculations of the atoms located gave the signs of all observed structure amplitudes. New projections of the electron density were computed. Although there was still some overlapping of atoms in all projections, the rough structure of the muscarine ion was now clearly evident. The model found was furthermore confirmed by generalized projections $1kl$ (Cochran & Dyer, 1952), in which the phases of the structure amplitudes were calculated from the iodine contributions alone.

Most atomic parameters could be read directly from the Fourier projections; for the determination of a few parameters, which could not be easily derived

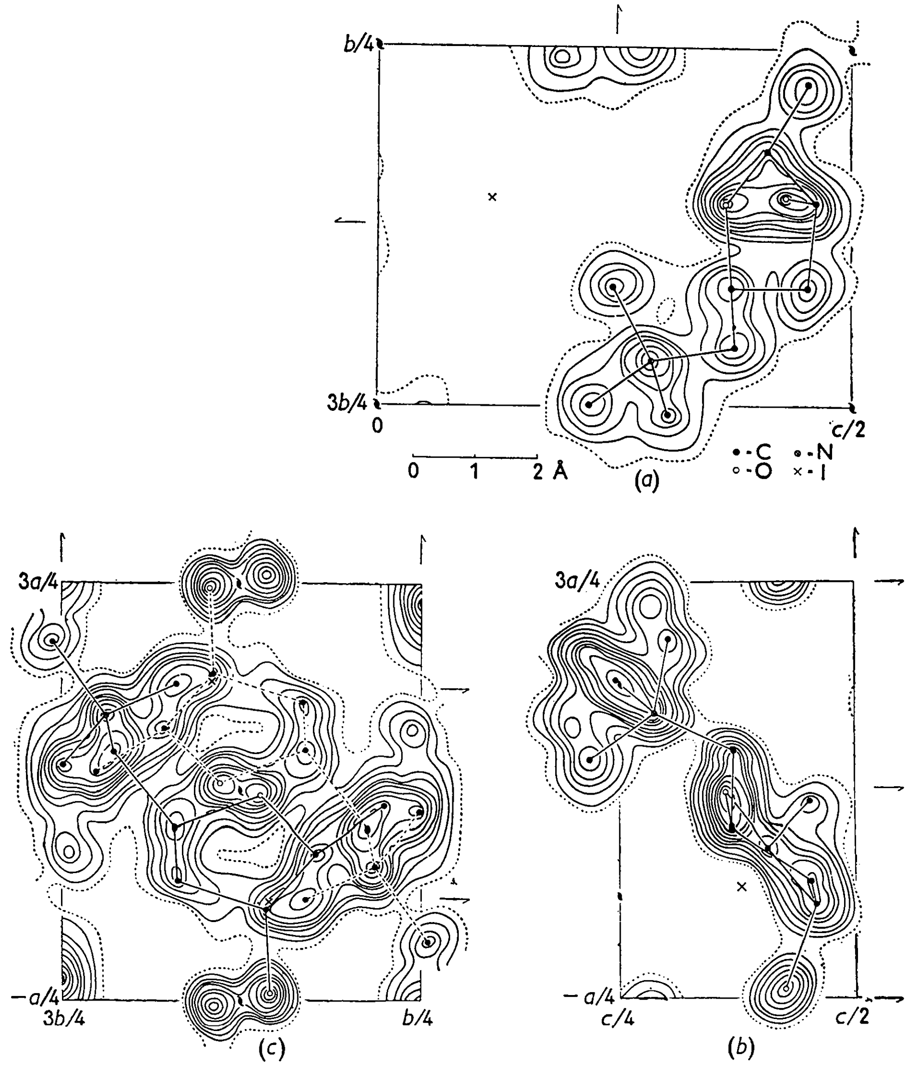


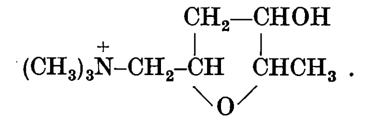
Fig. 1. Projection of the electron density of the muscarine ion on (a) (100), (b) (010) and (c) (001). The iodine contributions are subtracted from the structure amplitudes. Contours are at intervals of approximately 1 e.Å^{-2}; the 2 e.Å^{-2} contour is broken. Iodine positions are indicated by a cross.

in this way, because of overlapping, use was made of the molecular model. Finally the parameters were refined by difference syntheses.

(*c*) *The final structure*

The final Fourier syntheses are shown in Fig. 1. The iodine contributions are subtracted from the structure amplitudes in order to suppress series-termination effects and to bring out some peaks which are otherwise hidden behind the iodine maximum.

The maximum electron densities of three atomic peaks are considerably higher than that of the other peaks, which are very nearly of equal height. One of the heavy peaks—the lowest of the three—could be readily ascribed to the N atom. The second high peak was assumed to be caused by the hydroxyl group; this hypothesis was further strengthened by the short distance to iodine, which indicated an OH · · · I bond. The third heavy peak, situated in the five-membered ring, was ascribed to the second O atom. So the structure of the muscarine ion was found to be:



$$\begin{array}{l} \qquad\qquad\qquad CH_2\text{—}CHOH \\ \qquad\quad\;\; + \qquad\quad | \qquad\;\; | \\ (CH_3)_3N\text{-}CH_2\text{-}CH \quad CHCH_3\ . \\ \qquad\qquad\qquad\quad \diagdown O \diagup \end{array}$$

This structure could be confirmed by chemical and infra-red methods (Kögl *et al.*, 1957).

The final atomic parameters are given in Table 1; all atoms lie in the fourfold position:

$$x, y, z;\ \tfrac{1}{2}-x,\ -y,\ \tfrac{1}{2}+z;\ \tfrac{1}{2}+x,\ \tfrac{1}{2}-y,\ -z;\ -x,\ \tfrac{1}{2}+y,\ \tfrac{1}{2}-z.$$

The final structure factors for $hk0$, $h0l$ and $0kl$ reflexions were calculated—applying a temperature factor with $B = 4{\cdot}4$ Å^2 for all atoms and in all directions—and compared with the observed structure factors, which were brought on an absolute scale (for a complete list of observed and calculated structure factors see Jellinek, 1957).

Although the absolute value of the disagreement factor R is not a good measure for the accuracy of a structure determination if a heavy atom is present, the decline of R in subsequent stages of the analysis gives an indication of the reliability of the atomic positions adopted. In our case R dropped from 23·9% (23·0% for $hk0$, 24·2% for $h0l$, 23·2% for $0kl$ reflexions) when all atoms but iodine are neglected, to 7·8% (7·5% for $hk0$, 7·6% for $h0l$, 8·1% for $0kl$) by inclusion of the C, N and O atoms. (In these calculations unobserved reflexions were included only when the calculated structure factors were larger than corresponds with the limit of observation.) More detailed temperature factors—and also the inclusion of hydrogen—would give a still lower value of R, but it seemed dubious whether the anisotropies derived would be real, as systematic errors up to 3–5% may be present in the $|F_o|$ values because of the strong absorption.

3. Discussion of the structure

(*a*) *The muscarine ion*

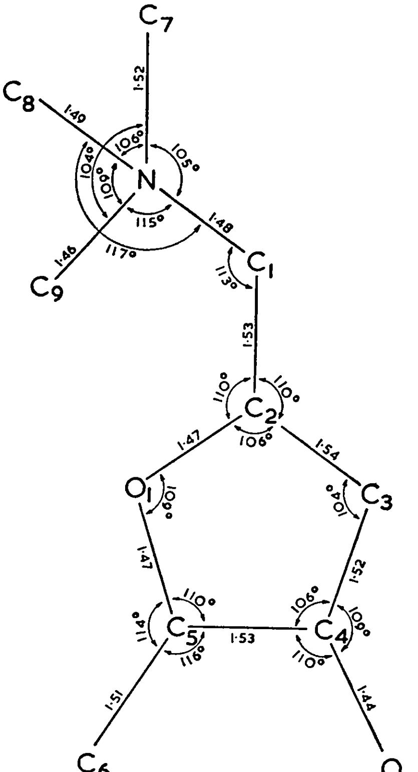


Fig. 2. Bond distances (in Å) and angles within the muscarine ion.

The schematical structure of the muscarine ion with bond distances and angles is shown in Fig. 2. The standard deviations are estimated at 0·08 Å and 6° respectively, so all distances and angles can be said to have normal values. Actually the agreement would seem to be even better than expected, as the root-mean-square deviation of the distances from their accepted values is only 0·03 Å and that of the valence angles from the tetrahedral angle is 4°. These low values, however, will be partially due to the fact that

Table 1. *Atomic parameters*

	I	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	O_1	O_2	N
x	−0·022	0·336	0·164	0·039	−0·033	0·111	0·225	0·606	0·308	0·511	0·236	−0·228	0·428
y	0·464	0·672	0·589	0·589	0·467	0·394	0·306	0·764	0·750	0·586	0·472	0·458	0·689
z	0·120	0·372	0·369	0·453	0·461	0·408	0·458	0·303	0·219	0·247	0·358	0·425	0·286

a model (with theoretical distances) was used in the determination of parameters of some overlapping atoms.

The tetrahydrofuran ring is not planar. C_2, O_1, C_5 and C_4 lie in the plane

$$4{\cdot}438x+1{\cdot}188y+11{\cdot}578z-5{\cdot}724 = 0$$

(mean distance from this plane 0·03 Å), but the distance of C_3 to this plane is 0·39 Å, which is highly significant. Analogous deviations from planarity were found in other tetrahydrofuran derivatives, e.g. sucrose (Beevers & Cochran, 1947) and cytidine (Furberg, 1950). The atoms C_1 and C_6 lie on the same side of the ring plane as C_3; O_2 is situated on the other side. C_9 lies almost in the ring plane (distance 0·10 Å) and it approaches O_1 to only 2·87 Å. This short distance has probably to be ascribed to sterical reasons and not to a hydrogen bond (the angles N–C_9–O_1 and C_2–O_1–C_9 are 84° and 82° respectively). Nevertheless, this short approach of a positive group will give O_1 somewhat of oxonium character.

It is remarkable that the chain C_7–N–C_1–C_2–C_3 is virtually flat: the mean distance of these atoms to the plane

$$3{\cdot}809x-9{\cdot}464y+3{\cdot}014z+3{\cdot}973 = 0$$

is 0·06 Å. O_2 lies at a distance of only 0·05 Å from this plane.

(*b*) *The packing*

Every muscarine ion is surrounded by seven I and by eight other muscarine ions. The contacts of I with surrounding C, O and N atoms can be divided into three groups:

(1) The distance $O_2-I = 3{\cdot}57$ Å indicates a hydrogen bond between these atoms (for $OH \cdots I$ expected distance 3·5–3·6 Å). This bond gives the muscarine ion somewhat the character of a zwitterion. The angle C_4–O_2–I is 95°.

(2) Contacts with distances of 3·9–4·0 Å; these short distances may be ascribed to electrostatic interaction of I with the $-CH_2-N(CH_3)_3^+$ group. C_1 has one I neighbour at 4·04 Å, C_8 lies at 4·03 Å of the same I, C_7 at 3·87 Å of another I and C_9 at 4·00 Å of a third I. Probably the contact of O_1 with a fourth I of 4·07 Å also belongs to this group; this again would indicate a certain oxonium character of O_1.

(3) Furthermore I is surrounded by some sixteen atoms at distances of 4·2–4·6 Å, corresponding to normal van der Waals contacts.

Sixteen of the contacts that atoms of a muscarine ion make with atoms of other ions, have distances in the range of 3·6–3·9 Å and are regarded as normal van der Waals contacts. The distances O_2–$C_{8'}$ and C_8–$O_{2'}$ are much shorter (3·35 Å), another indication of the zwitterion character of the muscarine ions, which causes mutual electrostatic attraction.

The author wishes to thank Prof. J. M. Bijvoet for encouragement and advice in the course of this study, Prof. F. Kögl and Dr C. A. Salemink for discussions on the chemical problems concerning muscarine, Dr H. Schouten for supplying the sample of muscarine iodide and Mr A. Kreuger for his ingenious technical help. The assistance of Dr H. F. van Sprang and the chem. cand. A. de Vries, D. Feil and A. Schuijff, who carried out the intensity measurements and helped with many of the calculations, is gratefully acknowledged.

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