smoothly from visual models to packing refinement to 'before and after' views, all within a few minutes. This would not only lead to quicker model evaluation, but would also help avoid the occasional problem of false minima that can arise when *PCK*5 is used blindly.

Thanks are due to Drs Roger Pettersen and Yeong Lin who provided many helpful suggestions. This work was supported by the National Science Foundation (GJ28286 and GJ33248X), the Robert A. Welch Foundation (A-328) and the Texas Agricultural Experiment Station.

References

Coiro, V. M., Giglio, E., Lucano, A. & Puliti, R. (1972). *Acta Cryst.* **B29**, 1404–1409.

Cullen, D. L., Hass, B., Klunk, D. G., Willoughby, T. V., Meyer, E. F., Farges, G. & Dreiding, A. S. (1975). In preparation.

Farges, G. & Dreiding, A. S. (1966). *Helv. Chim. Acta*, **49**, 552–561.

Kitaigorodskii, A. I. (1955). *Organic Chemical Crystallography*. New York: Consultants Bureau.

Stellman, S. D., Hingerty, B., Broyde, S. B., Subramanian, E., Sato, T. & Langridge, R. (1973). *Biopolymers*, **12**, 2731–2750.

Williams, D. E. (1969). *Acta Cryst.* **A25**, 464–470.

Williams, D. E. (1973*a*). *Acta Cryst.* **B29**, 96–102.

Williams, D. E. (1973*b*). Personal communication.

Willoughby, T. V., Morimoto, C. N., Sparks, R. A. & Meyer, E. F. (1974). *J. Appl. Cryst.* **7**, 430–434.

Zugenmaier, P. & Sarko, A. (1972). *Acta Cryst.* **B28**, 3158–3166.

Acta Cryst. (1975). **B31**, 1229

The Crystal and Molecular Structure of α Heteronium Bromide

By Katherine N. Coughenour[*] and Don Dennis[†]

Department of Chemistry, The University of Delaware, Newark, Delaware 19711, *U.S.A.*

(*Received* 9 *September* 1974; *accepted* 4 *December* 1974)

The crystal and molecular structure of 3-hydroxy-1,1-dimethylpyrrolidinium bromide α-phenyl-2-thiopheneglycolate (α heteronium bromide) $C_{18}H_{22}NO_3SBr$, was determined by single-crystal X-ray diffraction techniques. The crystals were orthorhombic, $D_m = 1{\cdot}5$ g cm^{-3}, space group $Pna2_1$, $Z=4$, $a=18{\cdot}596\ (1)$, $b=8{\cdot}049\ (9)$, and $c=12{\cdot}297\ (8)$ Å. The structure was solved using 1671 observed independent reflections to yield a final R value of 0·044.

Introduction

The crystal structure of the anticholinergic drug 3-hydroxy-1,1-dimethylpyrrolidinium bromide α-phenyl-2-thiopheneglycolate (heteronium bromide) has been solved. Heteronium bromide inhibits the muscarinic action of acetylcholine and thus suppresses secretory processes as well as other physiological functions (Chernish & Rosenak, 1965; Shay & Komarov, 1945). Heteronium bromide, therefore, has been therapeutically employed to reduce acid secretion in animals with duodenal ulcers (Shay & Komarov, 1945), and as a general antispasmodic agent (Ryan & Ainsworth, 1962).

The ability of heteronium bromide to elicit the responses is presumably due to its structural similarity with that portion of the acetylcholine molecule which bonds at the muscarinic receptor site. Many X-ray structural studies have been conducted in an attempt to define the three-dimensional structure of the receptor sites involved in these events (*e.g.* Meyerhöffer, 1970; Meyerhöffer & Carlström, 1969). The specific stereochemistry of the receptor site will require further investigation of the resolved isomeric compounds which function as anticholinergic agents.

Experimental

Heteronium bromide was obtained from the Eli Lilly Drug Co. as a powdered racemic compound prepared by the method of Ryan & Ainsworth (1962). The α and β diastereoisomers were resolved by fractional crystallization from methanol/ethyl acetate (1:4 v/v) to yield the pure α isomer with a m.p. of 208–211 °C. Analysis of the crystalline α isomer yielded C = 52·39 %, H = 5·33 %, compared to the theoretical C = 52·43 % and H = 5·38 %. The crystals used for the X-ray analysis were grown by the vapor-diffusion method using a methanolic solution of the compound and ethyl acetate as the vapor phase. The approximate unit-cell dimensions and the space group were determined from photographs with Mo $K\alpha$ radiation. The density was obtained by the flotation method using a mixed solvent of tetrabromoethane and ether.

---

[*] Submitted in partial fulfillment of the Masters of Science Degree requirements at the University of Delaware, Newark, Delaware 19711, U.S.A.

[†] To whom correspondence should be directed.

The systematic absences are consistent with space groups *Pnma* or *Pna*2_1. Since there are four molecules per unit cell, and no mirror plane or center of inversion for heteronium bromide, the appropriate space group is *Pna*2_1.

Intensity data were collected with a Syntex *P*1 autodiffractometer using graphite-crystal monochromatized Cu *K*α radiation and a θ–2θ scan mode. The crystal had dimensions of 0·25 × 0·25 × 0·625 mm, a linear absorption coefficient of 45·77 cm^{-1}, and was oriented about the *b* axis. The intensity data were taken at a 1° min^{-1} scan rate and included background counts for $\frac{1}{3}$ scan time on each side of the peak intensity.

Data were collected for 1746 (*hkl*) and 1155 ($\bar{h}\bar{k}\bar{l}$) independent reflections. The intensity data for the 1746 positive reflections [of which 1671 were observed; $I_{\text{obs}} = 3{\cdot}0\ \sigma(I)$] were used in the structure determination. Three standard reflections were each monitored 59 times during the data collection and used to calculate the standard deviation of intensity $\sigma(I) = 1{\cdot}7\%$. No significant correction for crystal decomposition was required. The intensities were corrected for Lorentz and polarization factors. An ellipsoidal absorption correction was made to account for a 10% variation in the mean intensity, where $[F_{\text{rel}}]^2 = K(t)A^*(\theta\chi)I_o/\text{Lp}$.

Table 1. *Atomic coordinates for* $C_{18}H_{22}NO_3SBr$ (× 10^4)

Coordinates are given as fractions of cell edges. Standard deviations for the least significant digit are given in parentheses.

	x	*y*	*z*
Br	−2224 (0·4)	−1262 (0·9)	0 (0)*
S	−4668 (1)	−4004 (2)	−1808 (2)
N	−2617 (3)	−6699 (7)	1681 (5)
O(1)	−3602 (2)	−6137 (5)	−558 (4)
O(2)	−2795 (3)	−6563 (8)	−1900 (5)
O(3)	−3791 (2)	−8086 (5)	−3152 (4)
C(1)	−1929 (4)	−7122 (10)	2276 (6)
C(2)	−3147 (4)	−8065 (9)	1866 (8)
C(3)	−2465 (4)	−6472 (8)	474 (6)
C(4)	−2923 (4)	−5071 (8)	2018 (6)
C(5)	−3406 (4)	−4558 (8)	1080 (6)
C(6)	−3050 (3)	−5304 (7)	65 (6)
C(7)	−3403 (4)	−6631 (8)	−1568 (5)
C(8)	−4049 (3)	−7164 (7)	−2261 (5)
C(9)	−4571 (4)	−8260 (7)	−1648 (6)
C(10)	−4329 (4)	−9447 (8)	−896 (6)
C(11)	−4822 (6)	−10425 (10)	−360 (7)
C(12)	−5553 (5)	−10270 (11)	−585 (8)
C(13)	−5775 (5)	−9132 (12)	−1333 (9)
C(14)	−5344 (4)	−8222 (8)	−1836 (6)
C(15)	−4390 (3)	−5553 (7)	−2681 (5)
C(16)	−4475 (4)	−5129 (8)	−3749 (6)
C(17)	−4782 (4)	−3479 (9)	−3857 (8)
C(18)	−4911 (4)	−2754 (9)	−2899 (8)
H(1*a*)†‡	−1533	−6121	2143
H(1*b*)	−2040	−7242	3148
H(1*c*)	−1713	−8298	1958
H(2*a*)	−2912	−9256	1609
H(2*b*)	−3288	−8121	2733
H(2*c*)	−3638	−7821	1384
H(3*a*)	−1945	−5931	354
H(3*b*)	−2493	−7643	60
H(4*a*)	−2502	−4174	2134
H(4*b*)	−3227	−5197	2751
H(5*a*)	−3433	−3227	1018
H(5*b*)	−3938	−5046	1188
H(6)	−2814	4339	−418
H(10)	−3759	−9589	−740
H(11)	−4641	−11325	230
H(12)	−5941	−11039	−165
H(13)	−6346	−9025	−1505
H(14)	−5556	−7364	−2437
H(16)	−4331	−5924	−4428
H(17)	−4892	−2895	−4637
H(18)	−5145	−1530	−2808
H(O3)§	−3468	−7470	−2683

* Bromine has its *z* coordinate assigned a value of 0·0000.

† Hydrogen positions have been calculated as described in text.

‡ The number after the 'H' is the number of the carbon to which the hydrogen is connected.

§ Hydroxyl hydrogen.

Determination of the structure and refinement

The location of the heavy atom (Br) was determined by a three-dimensional Patterson technique. The Fourier synthesis obtained by using the structure factors phased on the bromine yielded all of the positional parameters for the non-hydrogen atoms. With these positional parameters and isotropic temperature factors of $B = 4{\cdot}0$ for carbon, 3·0 for oxygen, 3·5 for nitrogen, and 2·5 for sulfur, a value of $R = 0{\cdot}23$ was calculated. One cycle of an isotropic full-matrix least-squares calculation on the non-hydrogen atoms gave an R value = 0·10.

The non-hydrogens were then subjected to a series of full-matrix anisotropic least-squares calculations. In the final cycles non-unit-weights were introduced, where $w = 1/A^2\overline{F_o^2} + 2AB\overline{F_o} + B^2$; final value $A = 0{\cdot}024$, $B = 0{\cdot}8$ (Patterson, 1963). An anomalous dispersion correction was made using the formula $F_o^2 = S_o - 2\Delta f'(AG + BH) - [(\Delta f')^2 + (\Delta f'')^2]\,[H^2 + G^2]$ where $f' = -0{\cdot}765$ and $f'' = 1{\cdot}283$ according to Cromer & Liberman (1970).

Hydrogen positional and thermal parameters were not refined, but positional parameters were recalculated to position them with reference to shifts in the non-hydrogen atoms. It was not possible to locate the six methyl hydrogen atoms [C(1) + C(2)] or the hydroxyl hydrogen of O(3) from a difference Fourier map.

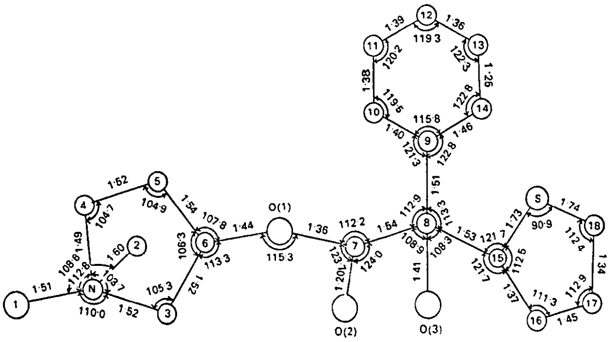


Fig. 1. Numbering, bond angles and distances for non-hydrogen atoms in α heteronium bromide.

The weighting function used in the final least-squares cycle was $w=1/[\Delta F]^2$; where $[\Delta F]=A+B[\bar{F}_{\text{obs}}]$ and A and B are obtained from a plot of $\Delta \bar{F}$ *vs* $[\Delta \bar{F}_{\text{obs}}]$ where 18 groups each containing an approximately equal number of reflections were used. The linear plots gave a volume of 0·024 for A and 0·8 for B.

The final cycle of least-squares calculations gave an R value of 0·044 and a weighted R value of 0·061.

The shift to error ratio in the final cycle was 0·30 for the positional parameters, and the final difference Fourier synthesis showed no electron density in excess of 1 e Å^{-3}.*

The atomic coordinates and the thermal parameters are listed in Tables 1 and 2. The X-RAY 70 system of programs (Stewart, Kundell & Baldwin, 1970) was used.

Description of the structure

The molecular structure of heteronium bromide is shown in Fig. 1 which also includes the bond lengths and angles. Fig. 2 gives the stereoscopic *ORTEP*-generated view of the molecule showing 50% probability thermal ellipsoids (Johnson, 1970). The gross molecular geometry includes a puckered pyrrolidinium ring connected through an ester (glycolate) linkage to planar thiophene and benzene rings. The conformation of the pyrrolidinium ring is shown in Fig. 3 giving deviations from a least-squares plane through the ring. The bond lengths in the ring are normal with an average N$^+$–C bond length of 1·504 Å and an average C–C distance of 1·527 Å. The glycolate bridge, including the atoms $\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}$–C–O–C, shows deviations of up to 0·09 Å from planarity. Similar deviations were found in a previous structure containing a quinuclidine ring with a quaternary nitrogen connected by a glycolate bridge to two

Table 2. *Anisotropic temperature factors for* $C_{18}H_{22}NO_3SBr$

Values of temperature parameters given are $U_{ij}\times 10^{-2}$, expressed in terms of root-mean-square amplitude of vibration in Å. Standard deviations of the least significant digits are given in parentheses.
Isotropic temperature factors for hydrogen atoms were uniformly set at $U=5{\cdot}07\times 10^{-2}$ ($B=4{\cdot}0$).

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br	6·7 (1)	5·0 (1)	4·6 (1)	−0·4 (3)	−1·5 (4)	−0·0 (4)
S	6·5 (1)	4·3 (1)	5·0 (1)	1·0 (8)	0·3 (9)	−0·3 (9)
N	3·3 (2)	3·0 (2)	3·0 (3)	0·3 (3)	0·6 (2)	0·0 (2)
O(1)	4·2 (2)	3·4 (2)	2·9 (2)	−0·3 (1)	−0·3 (1)	−0·4 (1)
O(2)	4·0 (3)	5·8 (3)	3·6 (3)	−0·2 (2)	0·3 (2)	−0·4 (2)
O(3)	5·0 (2)	3·4 (2)	3·3 (2)	0·5 (1)	0·6 (2)	−0·8 (1)
C(1)	4·6 (3)	6·5 (4)	4·1 (3)	0·6 (3)	−0·9 (3)	0·6 (3)
C(2)	4·9 (3)	4·0 (3)	6·9 (5)	−0·8 (2)	0·8 (3)	−0·0 (3)
C(3)	3·5 (3)	4·1 (3)	2·9 (3)	0·5 (2)	0·5 (2)	−0·1 (2)
C(4)	4·2 (3)	4·0 (3)	3·3 (3)	0·8 (2)	−0·2 (2)	−0·8 (2)
C(5)	5·0 (3)	3·8 (3)	3·6 (3)	0·2 (2)	−0·6 (3)	−1·0 (2)
C(6)	4·0 (3)	3·5 (2)	3·4 (3)	0·0 (2)	−0·8 (3)	−0·1 (3)
C(7)	4·3 (3)	3·2 (3)	2·7 (3)	−0·0 (2)	0·1 (2)	0·5 (2)
C(8)	4·2 (3)	2·6 (2)	2·5 (2)	0·3 (2)	−0·2 (2)	−0·8 (2)
C(0)	4·8 (3)	2·6 (3)	3·7 (3)	−0·4 (2)	0·0 (2)	−0·7 (2)
C(10)	6·2 (4)	3·2 (3)	4·1 (3)	−0·0 (3)	−0·0 (3)	−0·6 (3)
C(11)	11·7 (8)	3·8 (4)	4·6 (4)	−0·4 (4)	1·2 (4)	0·4 (3)
C(12)	7·6 (5)	4·9 (4)	6·5 (5)	−1·4 (4)	3·0 (4)	−0·8 (4)
C(13)	6·8 (5)	6·2 (4)	7·2 (6)	1·0 (4)	0·0 (4)	−1·5 (4)
C(14)	4·8 (3)	4·1 (3)	3·8 (3)	1·1 (2)	0·0 (2)	−0·5 (3)
C(15)	3·4 (3)	2·7 (2)	3·2 (3)	0·1 (2)	−0·1 (2)	−0·7 (2)
C(16)	3·5 (3)	3·8 (3)	5·0 (3)	0·2 (2)	−0·1 (2)	0·2 (2)
C(17)	5·1 (4)	4·6 (3)	6·4 (5)	−0·3 (3)	−1·6 (4)	1·1 (3)
C(18)	5·1 (3)	3·6 (3)	8·6 (5)	0·6 (2)	0·0 (4)	0·2 (3)

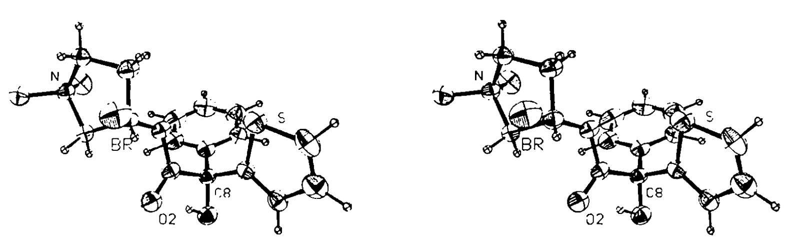
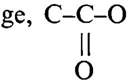


Fig. 2. Stereo view of α heteronium bromide.

---

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30817 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

benzene rings (Meyerhöffer & Carlström, 1969). Considering only four atoms of the ester bridge,  $\mathrm{C{-}\underset{\underset{O}{\|}}{C}{-}O}$ gives a nearly planar configuration at the 0·01 level of significance. The carbonyl carbon lies furthest from the plane, its positive partial charge perhaps being attracted by the bromine's charge. The hydroxyl oxygen lies 0·41 Å below this plane while the carbon connected to the ester oxygen, O(6), lies 0·26 Å above this plane.

Various 2-substituted thiophene rings have been reported (Nardelli, Fava & Giraldi, 1962; Block, Filippakis & Schmidt, 1967; Meyerhöffer, 1970). The ring in the present structure at the 0·1 level of significance is planar and symmetric as opposed to the asymmetric rings reported in Meyerhöffer's (1970) structure. The sulfur lies only 0·008 Å out of the plane of the other four atoms. The average C=C length in the ring is 1·352 Å and the average C–S length is 1·731 longer than Meyerhoffer's value of 1·709 Å. A short contact distance of 3·04 Å between the sulfur and ester oxygen is supportive of a van der Waals radius of 1·60 Å as reported previously (Nardelli *et al.*, 1962; Block *et al.*, 1967; Meyerhöffer, 1970).

The main significant deviations from normal bond lengths and angles occur in the benzene ring, with one short bond length of 1·249 Å midway between double and triple bond length and one longer adjacent bond of 1·458 Å. No short van der Waals distances are present that would indicate interaction with the faulty carbon C(14).

The angle between the normals of the benzene ring and the thiophene ring is 79·3°. The angles between the best planes of the glycolate bridge and the phenyl and thiophene rings are respectively 64·7 and 75·4°. Significant distances with respect to definition of a receptor site are N^+–C(8), 5·54 Å; N^+–O(3), 6·43 Å; N^+–O(2), 4·42 Å; N^+–O(1), 3·34 Å, and N^+–C(7), 4·25 Å. A short intramolecular contact distance of 2·703 Å is indicative of hydrogen bonding between the hydroxyl hydrogen and the carbonyl oxygen, as assumed in Meyerhöffer & Carlström's (1969) similar structure.

Two asymmetric centers are present in heteronium bromide, one at C(8) and one at C(6). Determination was made that the configuration about these carbons was the same, either *R,R* or *S,S*. Since the α crystal contained both enantiomers, no further information could be obtained. According to the studies of Ellenbrock (1965) and Ariens & Simonis (1967) the ratio of activities of diastereoisomeric compounds similar to the present compound is dependent upon the configuration of the asymmetric carbon at the acyl end of the molecule as opposed to the asymmetric carbon at the choline or nitrogen-containing end of the molecule. This leads to the prediction that the configuration around C(8) of the present compound would be significant.

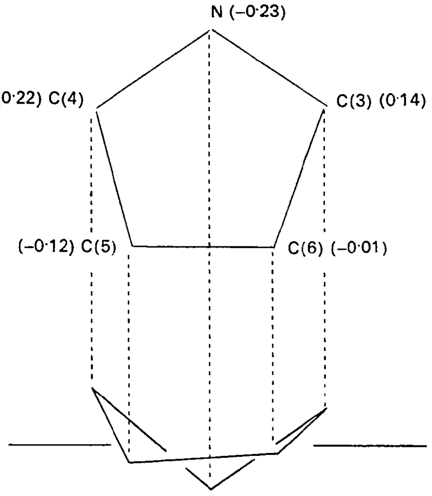


Fig. 3. Conformation of the pyrrolidinium ring, distances from the best least-squares plane of the five atoms are given in Å.

The authors wish to thank Dr J. Glusker of the Institute for Cancer Research for the use of the Syntex autodiffractometer. We also gratefully acknowledge the helpful suggestions and advice of Drs R. Gearhart, R. Wood, and A. Kossiakoff.

References

Ainsworth, C. & Ryan, C. W. (1962). *U.S. Pat. Bull.* #23 #3, **138**, 614.

Ariens, E. J. & Simonis, A. M. (1967). *Ann. N.Y. Acad Sci.* **144**, 842–853.

Block, S., Filippakis, S. E. & Schmidt, G. M. (1967). *J. Chem. Soc.* (*B*), pp. 233–238.

Chernish, S. M. & Rosenak, B. D. (1965). *Amer. J. Dig. Diseases*, **10**(8), 697–704.

Cromer, D. T. & Liberman, P. A. (1970). *J. Chem. Phys.* **53**, 1891–1898.

Ellenbrock, W. J. (1969). *J. Pharm. Pharmacol.* **17**, 393–404.

Johnson, C. K. (1970). *ORTEP* (second revision). Oak Ridge National Laboratory Report ORNL-3794.

Meyerhöffer, A. (1970). *Acta Cryst.* **B26**, 341–351.

Meyerhöffer, A. & Carlström, D. (1969). *Acta Cryst.* **B25**, 1119–1126.

Nardelli, M., Fava, G. & Giraldi, G. (1962). *Acta Cryst.* **15**, 737–746.

Patterson, A. L. (1963). *Acta Cryst.* **16**, 1255–1256.

Ryan, C. W. & Ainsworth, C. (1962). *J. Org. Chem.* **27**, 2901–2905.

Shay, H. & Komarov, S. A. (1945). *Gastroenterology*, **5**, 43–61.

Stewart, J. M., Kundell, F. A. & Baldwin, J. C. (1970). X-RAY System of Crystallographic Programs. Computer Science Center, Univ. of Maryland. Cybernet Service Control Data Corporation.