

almost always observed in the positions of the extra spots expected for the equilibrium structure excepting the sharp superlattice spots due to the ordering of oxygen atoms. The diffuse scattering seems to be caused by the short range order of titanium vacancies and it is thought that this transition structure would ultimately transform to the equilibrium ordered structures of $\text{TiO}_{0.9}$ and Ti_2O .

Long range order was not observed by previous workers (Andersson, Collen, Kuylenstierna & Magnéli, 1957) in oxygen rich alloys ($\text{TiO}_x, x > 1.1$) in which there is an excess of titanium vacancies relative to oxygen vacancies. In the present study, however, diffuse scattering, indicative of the presence of some short range order of vacancies, has been observed in the electron diffraction patterns of an alloy corresponding to $\text{TiO}_{1.2}$. This alloy became fully ordered after long annealing treatments below 700°C but the structure is different from that of the ordered equiatomic alloy. An analysis of this structure is now in progress.

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The Structure of the Catecholamines.

I. The Crystal Structure of Noradrenaline Hydrochloride

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Crystals of noradrenaline hydrochloride, $\text{C}_8\text{H}_{11}\text{O}_3\text{N} \cdot \text{HCl}$ are orthorhombic, space group $P2_12_12_1$ with four formula units in a cell having the dimensions $a = 8.580$, $b = 19.120$, $c = 5.775$ Å. The crystal structure has been determined by interpretation of two-dimensional Patterson projections with aid of minimum functions and refined by three-dimensional least-squares methods. The final R index for 1013 observable reflexions is 0.066. The catechol part of the molecule is planar and the bond distances and angles are close to those of tyrosine. As in most chloride salts of organic bases the amine group NH_3^+ is hydrogen bonded to Cl^- .

Introduction

Noradrenaline, often also named norepinephrine, which chemically is 1-(3,4-dihydroxyphenyl)-2-aminoethanol, is a hormone serving important physiological functions in endocrine and neural integration. It is

released locally by sympathetic nerve endings where it acts as a neurotransmitter but it is also secreted by chromaffin cells, e.g. of the adrenal medulla. Since (–)-noradrenaline is of great biological significance we thought it worth while to investigate its crystal structure. To our knowledge, none of the catechol-

amines, to which noradrenaline belongs, have been subjected to crystal structure analysis. The reason why no earlier attempts seem to have been made is probably the difficulty in obtaining pure and good crystals of these biologically active substances. The commonly used labelling system of the catecholamine nucleus [Fig. 1(a)] differs from that used in this investigation [Fig. 1(b)].

Experimental

Colorless, clear crystals of suitable size were obtained by recrystallization from distilled water of a highly purified sample of microcrystalline (-)-noradrenaline hydrochloride which was prepared by Dr B. F. Tullar. A small prism elongated along the *c* axis was used for the initial two-dimensional study, but all intensities for the three-dimensional structure determination were collected from a crystal trimmed to the dimensions $0.19 \times 0.17 \times 0.18$ mm.

Crystal data

(-)-Noradrenaline (norepinephrine) hydrochloride
 $C_8H_{11}O_3N \cdot HCl$
 M.W. 205.64

Biaxial positive, $\alpha = a$, $\beta = c$, $\gamma = b$, orthorhombic
 $a = 8.58_0$, $b = 19.12_0$, $c = 5.77_5$ Å, $V = 947.4$ Å³
 $D_m = 1.440 \pm 0.002$ g.cm⁻³, $D_x = 1.441$ g.cm⁻³, $Z = 4$
 $\mu = 34.1$ cm⁻¹ (Cu $K\alpha$)

Absent reflexions: $h00$ when h is odd
 $0k0$ when k is odd
 $00l$ when l is odd

Space group $P2_12_12_1$.

Using the usual multiple film and equi-inclination technique, integrated Weissenberg photographs were recorded with Ni-filtered Cu $K\alpha$ radiation for the 0-4 layers about the *a* axis and the 0-4 layers about the *c* axis, thereby covering 95.5 per cent of a total of 1264 independent reflexions within an effective copper sphere of $\sin \theta = 0.988$. The photographic density of 1013 independent reflexions above threshold for observation and of corresponding background was determined in a microdensitometer. The conversion of densitometer data to intensities included the evaluation of film factors, correction for the α_1 - α_2 separation, correlation of the measurements from different photographs and correction for Lorentz and polarization effects but no corrections for extinction or absorption.

Data from 437 observed reflexions occurring in both the zones [100] and [001] were cross-correlated so that all reflexions could be put on a common scale. In the final set of intensity data the mean values were taken from twice recorded reflexions and the 173 unobserved reflexions were given half the intensity of the threshold value. Finally the structure factors were placed approximately on an absolute scale by the method due to Wilson (1942). All these calculations were performed on an IBM 1401 computer with our program system written by Bergin and Ringertz.

Determination of the structure

The Patterson projection calculated from the initially recorded set of $hk0$ data could not be interpreted directly although it was possible to locate a Cl-Cl rotation peak. Since the chlorine atom alone would not suffice as a 'heavy atom' for phase determination ($Z_{Cl}/Z_{residue} < 0.2$) it was decided to use the Cl-Cl peak for preparing graphical minimum function maps according to Buerger (1951). Besides the heavy chlorine maximum, the $M_4(xy)$ map contained four prominent peaks which also were included in the first calculation of structure amplitudes. The signs thus obtained were applied to $|F_o|$ and the corresponding electron-density map contained additional maxima. After repetition of this procedure five times a sufficiently large number of peaks was obtained for a fairly accurate location of the molecule in the $(hk0)$ projection. At this stage the agreement index R ($R = \sum |F_o - F_c| / \sum |F_o|$) was 0.35. Four almost identical sets of atomic coordinates were now refined with an average isotropic temperature factor $B = 2.5$ Å⁻². One of these alternatives proved to be correct; after three cycles of refinement its R value had dropped to 0.12 whereas the other did not improve past $R = 0.29$. From the projected bond-lengths and bond angles as well as from the interpretation of an $(h0l)$ Patterson projection it was evident that the more or less planar catechol part of the molecule was tilted some 52° to the (001) plane. This enabled preliminary and approximately correct z coordinates to be calculated for all the non-hydrogen atoms.

Refinement procedure

The roughly determined structure was refined three-dimensionally on an IBM 7090 computer with the full matrix least-squares program by Busing, Martin &

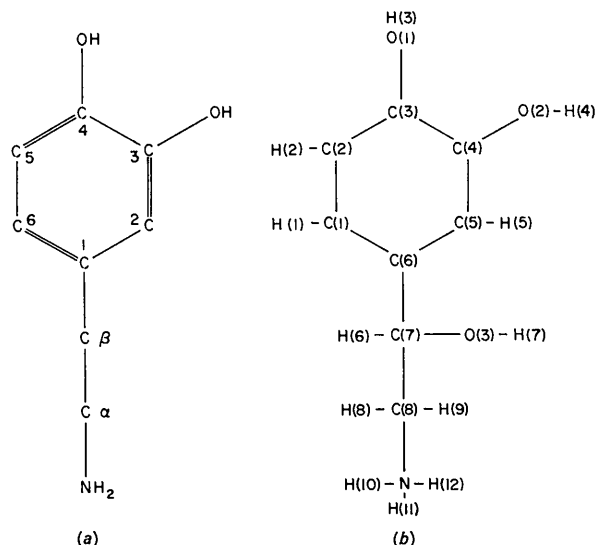


Fig. 1. The chemical labelling system of the catechol nucleus (a) compared with that used in this investigation (b).

Levy (1962). All reflexions were assigned unit weight. The atomic scattering factors for Cl^- and neutral H, C, N and O were taken from *International Tables for X-ray Crystallography* (1962) but no dispersion correction was made for the anomalous scattering of Cl^- . After four cycles of refinement using observed reflexions only, and the 13 non-hydrogen atoms which were given individual isotropic temperature factors, an R index of 0.099 was obtained. The introduction of anisotropic temperature factors caused a further drop in the R value to 0.082 after two additional cycles.

A three-dimensional difference function was calculated. This allowed the location of nine out of the twelve hydrogen atoms. At the probable positions of the three remaining H atoms, H(1), H(4) and H(7), there were either low or rather elongated maxima. After a least-squares refinement with the nine located hydrogen atoms included, a new three-dimensional difference function was prepared. This enabled the remaining hydrogen atoms to be found. The refinement was con-

cluded with a least-squares cycle in which 154 parameters, *i.e.* the coordinates of all 25 atoms, the anisotropic temperature parameters of the 13 non-hydrogen atoms and one scaling factor, were adjusted. The temperature factors of the hydrogen atoms were kept constant at the isotropic values for the atoms to which the hydrogens were covalently bonded. These values, ranging from $B=1.8$ to $B=3.6 \text{ \AA}^{-3}$, were taken from the last isotropic cycle involving non-hydrogen atoms only. The final R value was 0.085 for all reflexions and 0.066 for observed reflexions only.

The positional and thermal parameters for the final structure are given in Tables 1 and 2 respectively. The observed and calculated structure factors are given in Table 3.

Discussion

The geometry of the molecule

No attempts were made to determine the absolute configuration from the anomalous dispersion of chlorine for Cu $K\alpha$ radiation. Although this effect is small it has been used successfully for the determination of the absolute configuration of L-tyrosine (Parthasarathy, 1962) but no inference can be drawn from the configuration of this biological precursor of noradrenaline as its α carbon atom is rendered symmetric in the catecholamines. However, it has been shown by chemical means that natural laevorotatory noradrenaline has the configuration of D(-)-mandelic acid (Pratesi, La Manna, Campiglio & Ghislandi, 1959). According to the 'sequence rule' (Cahn, Ingold & Prelog, 1956) (-)-noradrenaline is an (R) form. Hence the absolute configuration is that shown in Fig. 2.

The molecule is maximally extended, *i.e.* the C(8)-N bond is nearly parallel to the C(6)-C(7) bond. The catechol part is planar with bond distances and bond angles shown in Fig. 2 and Tables 4 and 5 respectively. The mean C-C distance, 1.389 Å, and the mean C-O distance, 1.379 Å, in this part of the molecule are in good agreement with corresponding values found in catechol, 1.385 and 1.372 Å respectively (Brown, 1966). The best plane through the catechol part was calculated according to Blow (1960) from the coordinates of C(1)-C(6), O(1) and O(2), all given equal weights. The

Table 1. *Final fractional atomic coordinates and their standard deviations (in parenthesis)*

	x/a	y/b	z/c
C(1)	0.5614 (9)	0.5359 (4)	0.1456 (14)
C(2)	0.5988 (9)	0.4666 (4)	0.0987 (15)
C(3)	0.5359 (8)	0.4143 (3)	0.2357 (13)
C(4)	0.4361 (9)	0.4318 (3)	0.4165 (13)
C(5)	0.4044 (8)	0.5022 (3)	0.4653 (14)
C(6)	0.4675 (8)	0.5545 (3)	0.3254 (12)
C(7)	0.4371 (9)	0.6317 (3)	0.3741 (13)
C(8)	0.5494 (8)	0.6548 (3)	0.5630 (16)
N	0.5335 (7)	0.7314 (3)	0.6083 (11)
O(1)	0.5649 (6)	0.3441 (2)	0.1907 (10)
O(2)	0.3702 (8)	0.3810 (3)	0.5521 (12)
O(3)	0.2839 (5)	0.6431 (2)	0.4656 (10)
Cl	0.7577 (2)	0.2687 (1)	0.5685 (3)
H(1)	0.605 (11)	0.569 (5)	0.013 (18)
H(2)	0.658 (11)	0.446 (4)	-0.054 (18)
H(3)	0.601 (11)	0.332 (5)	0.314 (18)
H(4)	0.318 (13)	0.383 (5)	0.714 (20)
H(5)	0.336 (10)	0.513 (5)	0.616 (18)
H(6)	0.458 (11)	0.663 (4)	0.226 (17)
H(7)	0.219 (11)	0.687 (4)	0.562 (17)
H(8)	0.496 (12)	0.630 (5)	0.748 (19)
H(9)	0.650 (11)	0.637 (5)	0.519 (19)
H(10)	0.448 (11)	0.745 (5)	0.706 (17)
H(11)	0.607 (11)	0.746 (5)	0.695 (17)
H(12)	0.556 (11)	0.756 (5)	0.461 (18)

Table 2. *Anisotropic parameters and standard deviations (in parenthesis)*

β_{ij} are the coefficients in the expression: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$

	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	0.0099 (11)	0.0018 (2)	0.0166 (23)	0.0008 (4)	0.0051 (15)	0.0005 (6)
C(2)	0.0090 (10)	0.0018 (2)	0.0200 (25)	0.0001 (4)	0.0051 (16)	0.0012 (6)
C(3)	0.0062 (8)	0.0011 (1)	0.0170 (21)	-0.0001 (3)	-0.0021 (14)	0.0004 (5)
C(4)	0.0094 (10)	0.0015 (2)	0.0151 (20)	-0.0009 (4)	0.0060 (16)	0.0006 (6)
C(5)	0.0080 (9)	0.0014 (2)	0.0162 (21)	-0.0004 (3)	0.0022 (14)	-0.0001 (5)
C(6)	0.0057 (8)	0.0011 (2)	0.0158 (20)	0.0001 (3)	-0.0021 (13)	-0.0002 (5)
C(7)	0.0071 (9)	0.0012 (2)	0.0204 (24)	0.0002 (3)	-0.0001 (14)	-0.0003 (5)
C(8)	0.0074 (9)	0.0012 (2)	0.0240 (25)	0.0001 (3)	-0.0043 (17)	-0.0008 (6)
N	0.0076 (7)	0.0012 (1)	0.0196 (20)	-0.0006 (3)	-0.0012 (12)	-0.0005 (5)
O(1)	0.0088 (7)	0.0012 (1)	0.0195 (17)	0.0005 (2)	0.0009 (11)	-0.0010 (4)
O(2)	0.0221 (12)	0.0014 (1)	0.0343 (23)	-0.0018 (3)	0.0204 (17)	0.0002 (5)
O(3)	0.0056 (6)	0.0017 (1)	0.0262 (19)	0.0005 (2)	-0.0017 (10)	-0.0024 (4)
Cl	0.0088 (2)	0.0016 (0)	0.0198 (5)	0.0003 (1)	0.0019 (4)	0.0008 (1)

THE STRUCTURE OF THE CATECHOLAMINES. I.

Table 3. Observed and calculated structure factors

Within each area are values of h, k, F_o, F_c, and α. Asterisks indicate unobserved reflexions.

A large table with multiple columns containing numerical data for structure factors. The table is organized into several sections labeled L, L', L'', and L'''.

deviation of the atoms from this plane having the equation: $0.7893x + 0.0463y + 0.6122z = 4.810$, are shown in Table 6. This plane is nearly parallel to the (201) plane (the dihedral angle between these planes being 2.93°) a feature which amply accounts for the high structure amplitude of the 201 reflexion. The bond distances and bond angles in the rest of the molecule compare favourably with corresponding bonds and angles in tyrosine (Srinivasan, 1959). The C–N bond (1.493 Å) is significantly longer than the normal C–N single bond, but agrees well with the average value for the C–NH₃ single bond (Hahn, 1957).

There are two short intramolecular distances in the molecule. The O(1)–O(2) distance, 2.774 Å, indicates

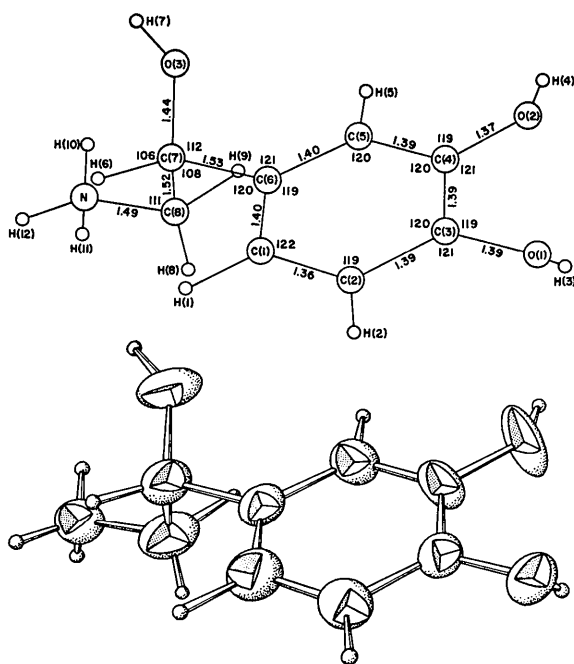


Fig. 2. Bond distances and angles (top) and a perspective drawing of the noradrenaline molecule showing the ellipsoids of thermal motion with a probability of 74% (bottom).

a hydrogen bond suggested to occur in catechol (Pauling, 1960). However, this bond is not present in crystalline catechol (Brown, 1966) or in the present structure. Thus, neither of the hydrogen atoms H(3) and H(4) covalently bound to O(1) and O(2) respectively is directed towards an adjacent oxygen atom. Both are instead involved in intermolecular hydrogen bonds (see below). The other short distance, O(3)–N (2.851 Å), is within the range for a hydrogen bond but in this case too the angles involved are quite unfavourable and the distance between H(7) and N is 2.44 Å. Provided that the H(7) position is correct it seems improbable that an O(3)–H(7)···N hydrogen bond is present.

Packing of the molecules

The arrangement of the molecules in the crystal is illustrated in Fig. 3, which likewise shows the network of hydrogen bonds stabilizing the structure. The O(2)–H(4)···O(3) distance of 2.77 Å is indicative of a rather strong intermolecular hydrogen bond, especially as the bond angles involved are quite favourable. The intermolecular O(1)–Cl distance of 3.097 Å and O(2)–Cl ($x - 0.5, 0.5 - x, 1.0 - z$) distance of 3.100 Å are nearly the same, but only O(1) seems to form a hydrogen bond with Cl, since the H(3)–Cl distance is 2.33 Å whereas the H(4)–Cl distance is 3.37 Å. The distances of the three hydrogen atoms H(10), H(11) and H(12) from the nitrogen (Table 4) clearly indicate that they are covalently bonded to nitrogen and that chlorine occurs as a negative ion in the structure. All the hydrogen atoms of the NH₃ group seem to be involved in hydrogen bonds. Thus the distances N–Cl ($1.5 - x, 1.0 - y, 0.5 + z$) and N–Cl, ($1 - x, 0.5 + y, 1.5 - z$), 3.208 and 3.203 Å respectively, are those expected for hydrogen bonding between N and Cl⁻. The hydrogen atoms involved are H(10) and H(11), the distances of which to the chloride ions are 2.24 and 2.47 Å respectively, whereas the third hydrogen atom H(12) does not come closer than 3.84 Å to any chlorine atom. This hydrogen atom is on the other hand directed towards O(1) ($1 - x, 0.5 + y, 0.5 - z$), which is at a distance of 2.889 Å from N, thus forming a weak N–H···O

Table 4. Interatomic distances and standard deviations (in parenthesis)

C(1)–C(2)	1.391 (10) Å	C(6)–C(7)	1.525 (9) Å
C(2)–C(3)	1.386 (10)	C(7)–C(8)	1.523 (10)
C(3)–C(4)	1.393 (10)	C(8)–N	1.493 (8)
C(4)–C(5)	1.403 (9)	C(3)–O(1)	1.388 (7)
C(5)–C(6)	1.395 (9)	C(4)–O(2)	1.370 (8)
C(6)–C(1)	1.363 (10)	C(7)–O(3)	1.435 (9)
C(1)–H(1)	1.06 (10)	N–H(10)	0.96 (10)
C(2)–H(2)	1.09 (10)	N–H(11)	0.85 (9)
C(5)–H(5)	1.07 (10)	N–H(12)	0.99 (10)
C(7)–H(6)	1.06 (10)	O(1)–H(3)	0.81 (10)
C(8)–H(8)	1.26 (10)	O(2)–H(4)	1.04 (12)
C(8)–H(9)	0.96 (9)	O(3)–H(7)	1.15 (9)
O(2)–H(4)···O(3)	2.770 (8)	Cl·····H(3)	2.33 (10)
N–H(12)···O(1)	2.889 (8)	Cl·····H(10)	2.24 (10)
O(1)–H(3)···Cl	3.097 (6)	Cl·····H(11)	2.47 (10)
N–H(11)···Cl	3.208 (7)	O(1)···H(12)	2.17 (9)
N–H(10)···Cl	3.203 (7)	O(3)···H(4)	1.78 (12)

Table 5. *Interatomic angles and standard deviations (in parenthesis)*

C(1)—C(2)—C(3)	119.2 (7)°	C(6)—C(7)—C(8)	107.8 (6)°
C(2)—C(3)—C(4)	119.7 (6)	C(7)—C(8)—N	110.6 (6)
C(3)—C(4)—C(5)	120.0 (6)	C(2)—C(3)—O(1)	121.4 (7)
C(4)—C(5)—C(6)	119.8 (7)	C(4)—C(3)—O(1)	118.9 (6)
C(5)—C(6)—C(1)	119.0 (6)	C(3)—C(4)—O(2)	120.9 (6)
C(6)—C(1)—C(2)	122.3 (7)	C(5)—C(4)—O(2)	119.1 (7)
C(1)—C(6)—C(7)	119.6 (6)	C(6)—C(7)—O(3)	111.8 (5)
C(5)—C(6)—C(7)	121.3 (6)	C(8)—C(7)—O(3)	105.8 (6)
C(6)—C(1)—H(1)	127 (5)	C(7)—O(3)—H(7)	137 (4)
C(2)—C(1)—H(1)	110 (5)	C(7)—C(8)—H(8)	106 (5)
C(1)—C(2)—H(2)	127 (5)	N—C(8)—H(8)	101 (4)
C(3)—C(2)—H(2)	113 (5)	H(9)—C(8)—H(8)	114 (8)
C(3)—O(1)—H(3)	100 (6)	C(7)—C(8)—H(9)	106 (6)
C(4)—O(2)—H(4)	132 (6)	N—C(8)—H(9)	119 (5)
C(4)—C(5)—H(5)	117 (5)	C(8)—N—H(10)	115 (5)
C(6)—C(5)—H(5)	123 (5)	C(8)—N—H(11)	110 (6)
C(6)—C(7)—H(6)	112 (5)	C(8)—N—H(12)	107 (5)
C(8)—C(7)—H(6)	108 (5)	H(10)—N—H(11)	98 (7)
O(3)—C(7)—H(6)	111 (5)	H(11)—N—H(12)	102 (8)
		H(12)—N—H(10)	122 (7)
N—H(10)···Cl	176 (8)	O(1)—H(3)···Cl	157 (9)
N—H(11)···Cl	146 (8)	O(2)—H(4)···O(3)	161 (9)
N—H(12)···O(1)	128 (7)		

Table 6. *Deviations from the best plane through the catechol part of the molecule*

C(1)	-0.019 Å
C(2)	+0.007
C(3)	+0.019
C(4)	-0.002
C(5)	+0.018
C(6)	-0.003
O(1)	-0.006
O(2)	-0.014

hydrogen bond. Apart from the short distances already mentioned, all packing distances seem to correspond to normal van der Waals separation.

The temperature factors

The thermal parameters presented in Table 2 corresponding to probability ellipsoids of thermal motion

are depicted in Fig. 2. This picture is calculated with the program by Johnson (1965) and drawn on a Calcomp 580 plotter. The only atoms exhibiting a marked anisotropy are the oxygen atoms [especially pronounced in O(2)] with the maximal thermal movement perpendicular to their bonds.

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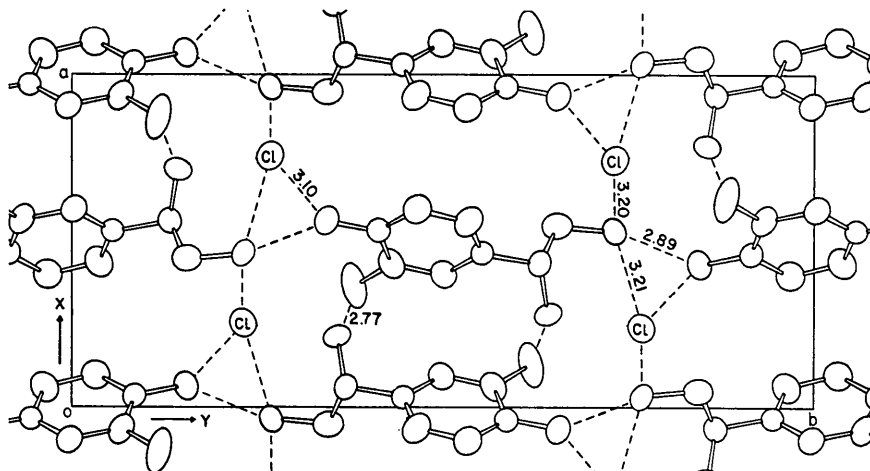


Fig. 3. Noradrenaline hydrochloride. Projection of the structure along the *c* axis showing intermolecular hydrogen bonds (Å.)

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The Crystal Structure of 5-Acetoxy-6-methoxy-8-nitroquinoline

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The structure of 5-acetoxy-6-methoxy-8-nitroquinoline was determined from three-dimensional equi-inclination Weissenberg data by a direct method. The compound crystallizes in the monoclinic system with space group $P2_1/c$. The cell data are: $a = 7.923 \pm 0.003$, $b = 9.056 \pm 0.003$, $c = 16.694 \pm 0.006$ Å, $\beta = 97.40 \pm 0.02^\circ$, $D_x = 1.466$ g.cm⁻³. The bond lengths are in agreement with those calculated by the valence bond theory. A comparison of the observed with the calculated exocyclic bond lengths indicates that only a small amount of resonance interaction occurs between the quinoline ring and the substituent groups. However, the bond lengths of the ring are unaffected by the resonance interaction with the substituent groups in that the observed values agree with theoretical bond distances of the unsubstituted molecule obtained in a recent self-consistent-field molecular-orbital type calculation. The exocyclic COC bond angles average 117° instead of the normal tetrahedral value owing to steric repulsions between some atoms in the methoxy and acetoxy groups and some of those in the ring. Packing and intramolecular steric requirements force the nitro and acetoxy groups to rotate out of the plane of the ring by 59° and 79° respectively. The resonance energy of the acetoxy group is sufficient to maintain its planarity in the overcrowded environment. On the contrary the quinoline ring deviates slightly but significantly from planarity.

Introduction

5-Acetoxy-6-methoxy-8-nitroquinoline (Fig. 1) is a synthetic intermediate in the preparation of 5-hydroxy-6-methoxyquinoline, a reference compound for use in a study of 6-methoxyquinoline metabolites (Sax & Lynch, 1966). Its spectral and chemical properties and those of 5-hydroxy-6-methoxy-8-nitroquinoline have been determined (Griffin, Byrne, Sax & Lynch, 1966). The differences in the properties of these compounds suggest a greater diversity in their molecular structures than is implied by the mere replacement of an acetoxy by a hydroxy group. In order to ascertain the structural dissimilarities in these two molecules, both were selected for crystal structure analysis, but only the structure of the acetoxy compound is considered in this paper.

Crystal data

5-Acetoxy-6-methoxy-8-nitroquinoline, C₁₂H₁₀O₅N₂,
 M.W. 262.23
 Monoclinic, space group $P2_1/c$
 $a = 7.923 \pm 0.003$, $b = 9.056 \pm 0.003$, $c = 16.694 \pm 0.006$ Å
 $\beta = 97.40 \pm 0.02^\circ$
 $D_x = 1.466$ g.cm⁻³, $D_m = 1.472$ g.cm⁻³
 $Z = 4$

Experimental

Crystals of the acetoxy compound were provided by Dr S. M. Sax of the Department of Pathology, Western Pennsylvania Hospital, Pittsburgh, Pa. The unit-cell dimensions were measured on a Picker full circle diffractometer with Cu $K\alpha$ radiation (1.5418 Å). The X-ray intensity data were collected on multifilm equi-inclination Weissenberg photographs with nickel-filtered Cu $K\alpha$ radiation from crystals rotated about the a and b axes. Both crystals were cut to approximate a

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