MOLECULAR PROPERTIES OF LOCAL ANESTHETICS: THE CRYSTAL STRUCTURE OF 2-DIETHYLAMINOETHYL P-METHOXYBENZOATE HYDROCHLORIDE

by

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The crystal structure of the local anesthetic 2-diethylaminoethyl p-methoxybenzoate hydrochloride has been determined from three-dimensional X-ray diffractometer data. A detailed discussion of the molecular structure is presented.

INTRODUCTION

The local anesthetic activity of parasubstituted benzoic acid esters of 2-diethylaminoethyl alcohol varies widely depending on the substituent group. Vanderhaeghe, Kolosy and Claesen (1954) reported that the activity of para alkoxybenzoates increases regularly with the size of the alkoxy group, reaches a maximum with the hexoxy group and then falls abruptly with higher homologues. Using a variety of parasubstituted benzoates, Galinsky, Gearien, Perkins and Susina (1963) were able to relate ED_{50} values of these compounds to their carbonyl absorption frequencies, although good correlation could not be found with the Hammett (1970) sigma constants of the substituent groups. Although changes in the para substituent of benzoate esters will change the charge distribution and thus the bond order of the carbonyl portion of the molecule, other changes such as molecular conformation, hydrogen bonding and lipid solubility will also occur which could alter local anesthetic activity. In an attempt to sort out

some of these effects, we have undertaken a crystallographic study of compounds of this type. The crystal structure of procaine hydrochloride has been reported (Beall, Herdklotz and Sass, 1970). This work on the p-methoxy substituent is a continuation of this study.

EXPERIMENTAL

The compound 2-diethylaminoethyl p-methoxybenzoate hydrochloride was synthesized using the method of Galinsky, Gearien, Perkins and Susina (1963). Crystals suitable for X-ray diffraction study were obtained by recrystallization from a 2:1 ethanol to ethylacetate solution in an ether atmosphere. The crystals are orthorhombic (space group $P2_12_12_1$) with cell dimensions a = 7.10(2), b = 8.870(4) and c = 25.305(4)Å. The experimental density, measured by flotation, of 1.21g/ml compares well with the calculated value of 1.20 g/ml based on four molecules per unit cell. Three-dimensional intensity data were collected on a Phillips PAILRED diffractometer using equi-inclination geometry. Silicon monochromatized molybdenum K_α radiation was employed using a fixed counter moving crystal technique. Each scan covered 3° with a scan rate of 1°/minute. Background radiation was measured on both sides of the scan for a period of two minutes. A total of 4520 relections were measured; reducing to 2275 independent intensity measurements. The trial structure was obtained from Patterson and Fourier syntheses phased on partial structural information. Hydrogen atoms were located as refinement progressed using a series of difference maps. The structure was refined by three-dimensional least-squares techniques. Positional parameters and anisotropic temperature factors were refined for non-hydrogen atoms while only the positional parameters of the hydrogen atoms were refined (isotropic temperature factors equal to 5.0 were assumed for the hydrogen atoms). The final R index was 0.061. The resulting positional parameters of all atoms are presented in table 1.

RESULTS AND DISCUSSION

The measured bond distances and angles for 2-diethylaminoethyl

TABLE 1

POSITIONAL PARAMETERS

Atom	X	Y	Z
CL(1)	0.6375	0.5040	0.9579
N(1)	0.1992	0.4945	0.9642
O(1)	0.0839	0.7686	0.8859
O(2)	0.2645	0.9468	0.8480
O(3)	-0.4521	0.9508	0.6971
C(1)	-0.1976	0.7972	0.8127
C(2)	-0.3444	0.8095	0.7754
C(3)	-0.3275	0.9223	0.7372
C(4)	-0.1678	1.0145	0.7362
C(5)	-0.0235	0.9987	0.7729
C(6)	-0.0385	0.8883	0.8124
C(7)	0.1130	0.8751	0.8497
C(8)	0.2223	0.7532	0.9274
C(9)	0.1452	0.6554	0.9697
C(10)	0.1319	0.4077	1.0101
C(11)	0.2130	0.4624	1.0631
C(12)	0.1274	0.4263	0.9140
C(13)	0.1992	0.2713	0.9044
C(14)	-0.6064	0.8493	0.6923
H(1)	0.3695	0.4902	0.9601
H(1,1)	-0.2117	0.7140	0.8467
H(2,1)	-0.4881	0.7466	0.7802
H(4,1)	-0.1110	1.0652	0.7070
H(5,1)	0.1076	1.0774	0.7825

Table 1 - continued

Atom	X	Y	Z
H(8,1)	0.2941	0.7358	0.9161
H(8,2)	0.1802	0.8455	0.9373
H(9,1)	0.1934	0.6821	0.9982
H(9,2)	0.0004	0.6616	0.9626
H(10,1)	0.0038	0.4258	1.0124
H(10,2)	0.1730	0.3109	1.0086
H(11,1)	0.2371	0.3534	1.0735
H(11,2)	0.3503	0.4625	1.0597
H(11,3)	0.2281	0.5438	1.0712
H(12,1)	-0.0131	0.4303	0.9184
H(12,2)	0.1042	0.4737	0.8886
H(13,1)	0.1396	0.2380	0.8656
H(13,2)	0.3330	0.2678	0.8971
H(13,3)	0.0848	0.1929	0.9234
H(14,1)	-0.6912	0.8963	0.6703
H(14,2)	-0.5893	0.7786	0.7035
H(14,3)	-0.6751	0.8743	0.7303

p-methoxybenzoate (excluding all hydrogen atoms except H(1)) are shown in figure 1. The estimated standard deviations of the non-hydrogen bond distances are all equal to or less than $\pm$ 0.01Å and of the bond angles are all less than $\pm$ 1°. All bond distances and angles fall within acceptable ranges of expected values.

Similar to many molecules of interest in the cholinergic system, 2-diethylaminoethyl p-methoxybenzoate is in the trans-gauche configuration. The torsion angle C(7)-O(1)-C(8)-C(9) of 167.1° is in agreement with the value of 172.8° observed in procaine hydrochloride. The torsion angle

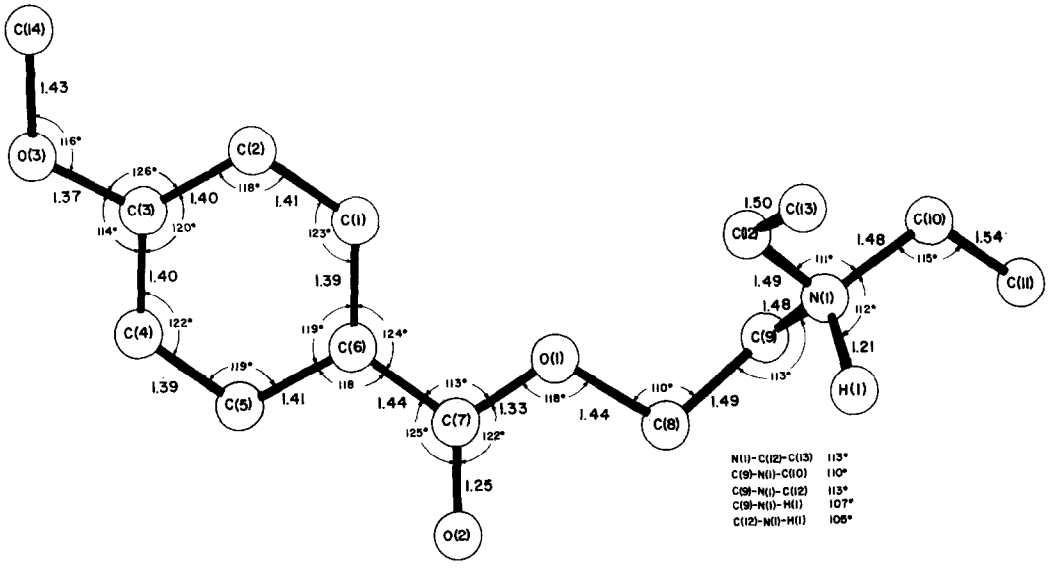
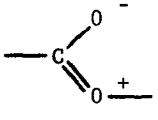


Figure 1: Molecular Dimensions of
2-Diethylaminoethyl
P-Methoxybenzoate Hydrochloride

O(1)-C(8)-C(9)-N(1) is 85.9°, again similar to the value of 70.4° obtained for procaine hydrochloride. Because of the somewhat larger torsion angle in the para methoxy compound, the N(1)···O(1) distance is somewhat longer (3.24Å) than the procaine value (3.07Å). Such a difference could be interpreted as a weaker coulombic interaction between the two atoms indicating that the negative charge on O(1) is less than that found in procaine. This argument is supported by the shorter C(7)-O(1) distance of 1.33Å compared to 1.36Å measured in procaine, and the somewhat longer C(7)-O(2) distance of 1.25Å compared to 1.22Å observed in procaine. In terms of resonance, the interpretation is that the structure



is more important in this compound than in procaine. The orientation of the tertiary amine grouping is related to that in procaine by a rotation of about 120° around the C(9)-N(2) axis, resulting in a C(12)···O(1) distance of 3.13Å.

The only hydrogen bonding in the crystal is between the tertiary nitrogen and the chlorine atom through H(1); the bond angle N(1)-H(1)-Cl(1) being 179°. The interatomic distance N(1)···Cl(1) of 3.12Å is that expected for hydrogen bonding (Pimentel and McClellan, 1960). The only other non-hydrogen intermolecular contact less than 3.5Å is between O(2) and C(13) (x,1 + y,z) and is equal to 3.24Å.

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