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Relationship of Three-Dimensional Structure of Muscarinic Antagonists to Antimuscarinic Activity: Structure of Thiodeacylaprophen Hydrochloride

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Abstract

$C_{20}H_{28}NS^+.Cl^-$, 2-(diethylamino)ethyl 1,1-diphenylethyl sulfide hydrochloride (thiodeacylaprophen hydrochloride), $M_r = 349.9$, orthorhombic, $P2_12_12_1$, $a = 8.933$ (2), $b = 11.710$ (3), $c = 18.934$ (4) Å, $V = 1980.6$ (7) Å^3, $Z = 4$, $D_x = 1.173$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1.54178$ Å, $\mu = 26.70$ cm^{-1}, $F(000) = 752$, room temperature, final $R = 4.1\%$ for 1417 reflections with $|F_o| > 3\sigma(F)$. Thiodeacylaprophen crystallized as a tertiary amine hydrochloride salt. The S—C—C—N^+ segment adopts a *trans* configuration as does one of the C_{phenyl}—C—S—C segments. A comparison of the structure of thiodeacylaprophen with the crystal structures of potent antimuscarinic agents suggests that the relatively weak antimuscarinic activity of thiodeacylaprophen compared to atropine and aprophen may be substantially due to the short intramolecular S···N^+ distance of 4.106 (6) Å. Other contributing structural factors may include the direction of the N^+—H bond and restricted accessibility of the sulfur atom for interatomic interactions.

Introduction

Antimuscarinic agents serve as important anticholinergic and antispasmodic agents. These beneficial activities are thought to be effected by direct interaction of the antimuscarinic agent with the muscarinic cholinergic receptor. Since the three-dimensional structure of the muscarinic receptors has not been determined by protein crystallography, information on how antimuscarinic agents interact with the receptors must come from the three-dimensional structure of individual antimuscarinic agents. Input from the three-dimensional structures of both highly active and less active antimuscarinic agents is needed to further the refinement of models of the antimuscarinic binding site of the muscarinic receptor. An accurate model for the binding site of antimuscarinic agents should aid the design of antimuscarinic agents with higher activity and specificity than existing antimuscarinic agents.

Antimuscarinic agents generally contain a tertiary or quaternary amino group, an aromatic group, and an oxygen/sulfur function in the form of an ester, a thioester, an amide, an ether, a thioether, or an alcohol. Previous structural studies with ester-containing antimuscarinic agents structurally related to aprophen and atropine [compounds (II) and (V), Fig. 1] revealed that the ether oxygen is buried and cannot interact with the receptor (Karle, Karle & Chiang, 1990). The carbonyl oxygen atom is exposed and is readily accessible for hydrogen bonding or for non-bonded interactions with the receptor. The N atom of the amino group is available for hydrogen bonding or for interacting with an anionic receptor site as a positively charged tertiary amino salt. The phenyl groups may be involved in hydrophobic interactions.

Specific alterations in the chemical structure of an antimuscarinic agent do not always result in comparable changes in potency. For example, in the aprophen series [see compound (II), Fig. 1], the order of potency of the compounds substituted adjacent to the phenyl rings at the *X* position is $CH_3 > OH > H$ (Carroll, Abraham, Parham, Griffith, Ahmad, Richard, Padilla, Witkin & Chiang, 1987). However, in the thiphenamil series [see compound (IV), Fig. 1], which is identical to the aprophen series except that the ester has been converted to a thioester, the order

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of potency changes with OH > H > CH_3 (Parkes, 1955). Thioether analogs of potent thioester antimuscarinic agents in which the carbonyl group is replaced with a methylene group also demonstrate antimuscarinic activity, albeit 15 to 135 times less active than their thioester analogs (Parkes, 1955). These thioether compounds are 2.4 to 3.7 times more active than their oxygen ether analogs which demonstrate relatively low antimuscarinic activity (Parkes, 1955). Nevertheless, some oxygen ether compounds are potent antimuscarinic agents such as the oxygen ether compound (VI) (Fig. 1) which possesses 46% of the activity of atropine (Yoshida, Morita & Ogawa, 1973*a*). Thus, the relative potency of antimuscarinic agents is not dependent upon a single feature of the molecule, but the result of a combination of chemical and structural features including the chemical entity of the oxygen/sulfur group, the structure of the amino portion of the molecule, and the position and size of the aromatic or aliphatic groups.

The title compound thiodeacylaprophen, $Ph_2C(CH_3)SCH_2CH_2N(CH_2CH_3)_2$, differs from aprophen, a potent antimuscarinic agent (Gordon, Padilla, Moore, Doctor & Chiang, 1983), by substitution of the acyloxy group (O=C—C— atoms) in aprophen with an S atom. We decided to undertake the crystal structure analysis of thiodeacylaprophen hydrochloride following the discovery of its strikingly low antimuscarinic activity in order to determine what structural features may contribute to the lack of potent antimuscarinic activity. The crystal structure of thiodeacylaprophen was compared to the crystal structure of aprophen and other potent antimuscarinic agents.

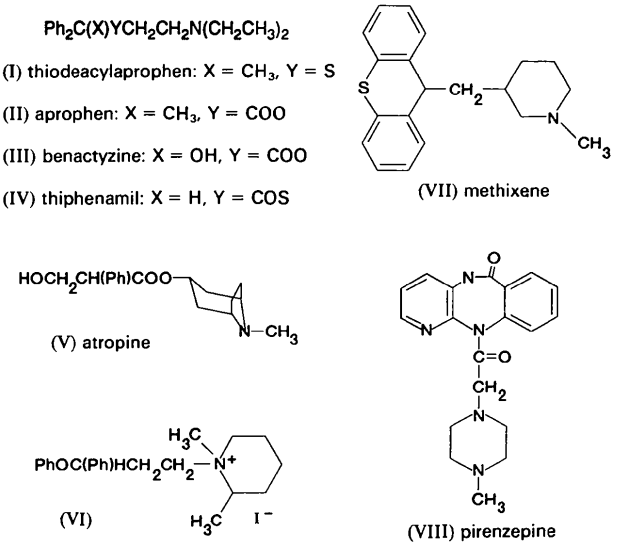

Fig. 1. Chemical structures of thiodeacylaprophen and other antimuscarinic agents.

Experimental

Thiodeacylaprophen hydrochloride was crystallized from chloroform/hexane. Diffraction data were collected from a clear prism, 0.5 × 0.12 × 0.14 mm, in the θ–2θ mode to a maximum 2θ value of 115° on an *R*3*m*/micro Nicolet four-circle diffractometer (Siemens Analytical X-ray Instruments Inc., Madison, WI) with a graphite monochromator. Range of indices: h 0→10, k 0→13 and l 0→21. The number of reflections measured was 1625, and the number of independent reflections was 1568. The standard reflections 400, 040 and 006 were monitored every 100 intensity measurements. The standards varied by up to 2.5%. The lattice parameters were based on 25 centered reflections with 2θ values between 30 and 45°. No correction for absorption or extinction was used. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). Eleven atoms were found in the first E map. The remaining non-H atoms were found in subsequent E maps. All but three of the H atoms were found in difference maps. Least-squares refinement was performed using 1417 reflections with $|F_o| > 3\sigma(F)$ ($R_{merge} = 0.012$). Coordinates for all atoms except H atoms were refined (on F) by a blocked-cascade program in the *SHELXTL* system (Sheldrick, 1985). Coordinates for the H atoms were kept in idealized positions. Anisotropic thermal parameters for the C, N, S and Cl atoms, and isotropic thermal parameters for the H atoms were refined on a total of 209 parameters. Final $R = 4.06\%$ and $wR = 4.62\%$, $w = 1/[\sigma^2(|F|) + 0.0005(F_o)^2]$. Final difference electron density $|\rho|_{max} = 0.13$ and $|\rho|_{min} = -0.13$ e Å^{-3}. $(\Delta/\sigma)_{max} = 0.13$. $S = 1.62$. Atomic scattering factors were those incorporated in *SHELXTL* (Sheldrick, 1985).*

The biological assays were performed as described previously (Gordon, Bruer, Padilla, Smejkal & Chiang, 1989; Leader, Smejkal, Payne, Padilla, Doctor, Gordon & Chiang, 1989). This research was conducted in compliance with the Animal Welfare Act and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NIH Publication 85-23 (1985).

Results

Table 1 lists the coordinates and U_{eq} values for the non-H atoms. Table 2 lists bond lengths, bond angles and selected torsion angles. The bond length of the H atoms attached to the C and N atoms was

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54677 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0350]

Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and thermal parameters* U_{eq} ($Å^2 \times 10^3$) *with e.s.d.'s in parentheses*

$$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
S	10729 (1)	3593 (1)	7180 (1)	73 (1)
N	13911 (4)	3813 (3)	5621 (2)	70 (1)
C(1)	16410 (6)	3744 (5)	6218 (3)	105 (2)
C(2)	15493 (5)	4281 (4)	5670 (3)	94 (2)
C(3)	13711 (7)	3932 (4)	4304 (3)	104 (2)
C(4)	13090 (6)	4318 (4)	4992 (2)	88 (2)
C(5)	13073 (5)	4048 (3)	6288 (2)	71 (1)
C(6)	11651 (5)	3379 (4)	6335 (2)	72 (1)
C(7)	11322 (4)	2349 (3)	7709 (2)	56 (1)
C(8)	10731 (5)	1261 (4)	7357 (2)	83 (2)
C(9)	10564 (4)	2469 (3)	8443 (2)	57 (1)
C(10)	10804 (5)	1598 (4)	8929 (2)	83 (2)
C(11)	10096 (6)	1624 (5)	9589 (3)	96 (2)
C(12)	9166 (5)	2510 (4)	9764 (2)	84 (2)
C(13)	8917 (5)	3365 (4)	9291 (2)	76 (2)
C(14)	9620 (5)	3345 (4)	8634 (2)	65 (1)
C(15)	13011 (4)	2340 (3)	7799 (2)	57 (1)
C(16)	13711 (5)	3172 (4)	8204 (2)	79 (2)
C(17)	15262 (6)	3160 (6)	8293 (3)	99 (2)
C(18)	16100 (6)	2339 (5)	7985 (3)	103 (2)
C(19)	15446 (6)	1512 (5)	7579 (3)	102 (2)
C(20)	13908 (5)	1519 (4)	7480 (2)	77 (2)
Cl	13919 (1)	1205 (1)	5449 (1)	90 (1)

Table 2. *Bond lengths* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

S—C(6)	1.816 (4)	S—C(7)	1.846 (4)
N—C(2)	1.518 (6)	N—C(4)	1.519 (6)
N—C(5)	1.493 (5)	C(1)—C(2)	1.464 (7)
C(3)—C(4)	1.486 (7)	C(5)—C(6)	1.495 (6)
C(7)—C(8)	1.531 (6)	C(7)—C(9)	1.553 (5)
C(7)—C(15)	1.518 (5)	C(9)—C(10)	1.390 (6)
C(9)—C(14)	1.377 (6)	C(10)—C(11)	1.402 (7)
C(11)—C(12)	1.369 (8)	C(12)—C(13)	1.362 (6)
C(13)—C(14)	1.394 (6)	C(15)—C(16)	1.389 (6)
C(15)—C(20)	1.390 (6)	C(16)—C(17)	1.396 (7)
C(17)—C(18)	1.351 (8)	C(18)—C(19)	1.367 (8)
C(19)—C(20)	1.386 (7)		

C(6)—S—C(7)	103.8 (2)	C(2)—N—C(4)	110.9 (3)
C(2)—N—C(5)	110.4 (3)	C(4)—N—C(5)	110.4 (3)
N—C(2)—C(1)	114.1 (4)	N—C(4)—C(3)	112.9 (4)
N—C(5)—C(6)	112.3 (3)	S—C(6)—C(5)	111.4 (3)
S—C(7)—C(8)	108.8 (3)	S—C(7)—C(9)	106.8 (2)
C(8)—C(7)—C(9)	108.3 (3)	S—C(7)—C(15)	110.6 (2)
C(8)—C(7)—C(15)	112.7 (3)	C(9)—C(7)—C(15)	109.5 (3)
C(7)—C(9)—C(10)	117.4 (3)	C(7)—C(9)—C(14)	124.7 (3)
C(10)—C(9)—C(14)	117.9 (4)	C(9)—C(10)—C(11)	120.3 (4)
C(10)—C(11)—C(12)	120.4 (5)	C(11)—C(12)—C(13)	119.8 (4)
C(12)—C(13)—C(14)	120.0 (4)	C(9)—C(14)—C(13)	121.5 (4)
C(7)—C(15)—C(16)	120.3 (3)	C(7)—C(15)—C(20)	122.0 (3)
C(16)—C(15)—C(20)	117.8 (4)	C(15)—C(16)—C(17)	120.4 (5)
C(16)—C(17)—C(18)	120.4 (5)	C(17)—C(18)—C(19)	120.6 (5)
C(18)—C(19)—C(20)	119.7 (5)	C(15)—C(20)—C(19)	121.4 (4)

C(7)—S—C(6)—C(5)	−97.3 (3)	C(6)—S—C(7)—C(8)	−62.9 (3)
C(6)—S—C(7)—C(9)	−179.7 (3)	C(6)—S—C(7)—C(15)	61.3 (3)
C(4)—N—C(2)—C(1)	−173.8 (4)	C(5)—N—C(2)—C(1)	63.5 (5)
C(2)—N—C(4)—C(3)	68.0 (5)	C(2)—N—C(5)—C(6)	−166.7 (4)
C(4)—N—C(5)—C(6)	70.3 (4)	N—C(5)—C(6)—S	175.4 (3)
S—C(7)—C(9)—C(10)	177.6 (3)	S—C(7)—C(9)—C(14)	0.8 (5)
C(8)—C(7)—C(9)—C(10)	60.6 (5)	C(8)—C(7)—C(9)—C(14)	−116.2 (4)
C(15)—C(7)—C(9)—C(10)	−62.6 (4)	C(15)—C(7)—C(9)—C(14)	120.7 (4)
S—C(7)—C(15)—C(16)	68.0 (4)	S—C(7)—C(15)—C(20)	−111.3 (4)
C(8)—C(7)—C(15)—C(16)	−170.0 (4)	C(8)—C(7)—C(15)—C(20)	10.7 (5)
C(9)—C(7)—C(15)—C(20)	131.2 (4)	C(7)—C(9)—C(10)—C(11)	−176.9 (4)
C(7)—C(9)—C(14)—C(13)	176.6 (4)	C(7)—C(15)—C(16)—C(17)	179.5 (4)
C(7)—C(15)—C(20)—C(19)	−178.8 (4)	C(9)—C(7)—C(15)—C(16)	−49.4 (5)

kept fixed at 0.96 Å throughout the refinement procedure.

The conformation and numbering scheme of thiodeacylaprophen is displayed in Fig. 2. The S···N^+ interatomic distance is 4.106 (6) Å which is comparable to the S···N^+ distance of 4.117 (6) Å in thiphenamil hydrochloride [compound (IV), Fig. 1] (Guy & Hamor, 1974). Thiodeacylaprophen assumes a *trans* configuration for the N^+—C(5)—C(6)—S bonds with a torsion angle of 175.4 (3)°. This configuration is similar to the thioesters thiphenamil hydrochloride and acetylthiocholine bromide (Shefter & Mautner, 1969) which possess an N^+—C—C—S torsion angle of 174.4 (5) and 171 (4)°, respectively. In contrast, the ester-containing aprophen assumes a staggered *gauche* conformation with an N^+—C—C—O torsion angle of 81.3 (5)° (Karle, Karle & Chiang, 1990). The *gauche* conformation is typical of ester-containing antimuscarinic agents with diethylamine groups (Guy & Hamor, 1973; Petcher, 1974; Karle, Karle & Chiang, 1990). One of the phenyl rings of thiodeacylaprophen is *trans* to the backbone of the molecule as illustrated by the C(6)—S—C(7)—C(9) torsion angle of −179.7 (3)°. However, this segment and the N^+—C—C—S segment are twisted from each other by 97.3 (3)°. Unlike the ester-containing aprophen-like compounds in which the ether O atom is buried inside the molecule, the S atom of thiodeacylaprophen is partially exposed to the surface of the molecule (Fig. 3). If thiodeacylaprophen is viewed perpendicular to the plane defined by the atoms C(6), S and C(7), one phenyl group is on the same side of the plane defined by these three atoms as the N atom. This geometric feature is common to antimuscarinic agents containing an ester or a thioester group (Guy & Hamor, 1974; Karle, Karle & Chiang, 1990).

The packing of thiodeacylaprophen hydrochloride is illustrated in a stereodiagram with a view down the *a* axis (Fig. 4). The cationic N atom is hydrogen

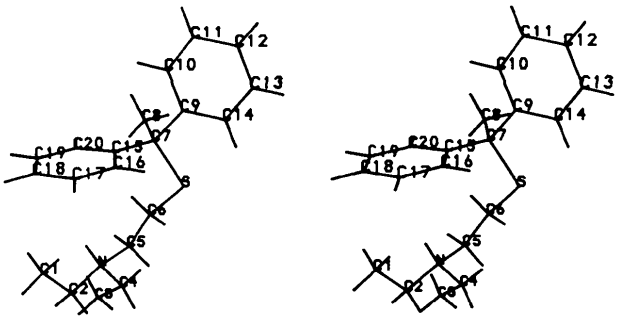

Fig. 2. Conformation and numbering scheme fo thiodeacylaprophen. The figure was drawn using the *MOGLI* program (Evans & Sutherland, 1989).

bonded to the chloride ion with an $N^+\cdots Cl$ distance of 3.070 (5) Å, an H···Cl distance of 2.113 (5) Å and an N^+—H···Cl angle of 175.1 (5)°. The hydrogen bond is essentially parallel to the *b* axis. The phenyl rings from two neighboring molecules along the *c* axis are almost orthogonal to each other with an angle of 95.5° between the least-squares planes defined by each ring. The closest approach of the phenyl rings between neighboring molecules is between two H atoms at 2.897 (5) Å. Although thiodeacylaprophen does not contain an asymmetric center, the conformation of thiodeacylaprophen prevents its mirror images from superimposing. An arbitrarily chosen crystal in space group $P2_12_12_1$ contains only one hand of the enantiomeric pair.

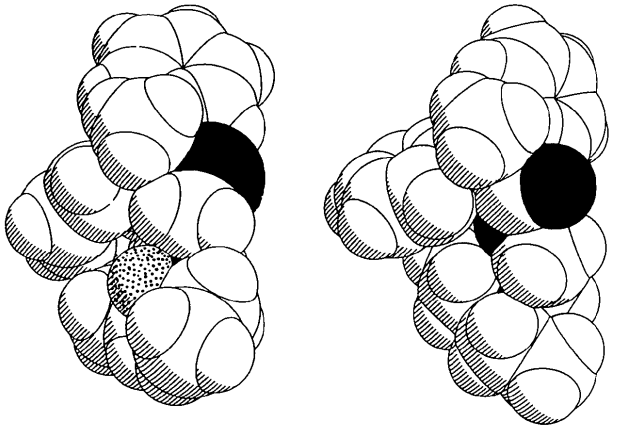

Fig. 3. Space-filling diagram of thiodeacylaprophen (left) and aprophen (right). The S, O and N^+ atoms are colored black, and the H atom attached to the N^+ atom in thiodeacylaprophen is dotted. The corresponding H atom in aprophen is at the back of the figure. The radii of the spheres are 100% of the van der Waals radii. The figure was drawn using the *SHELXTL* program package (Siemens Analytical X-ray Instruments Inc., 1986).

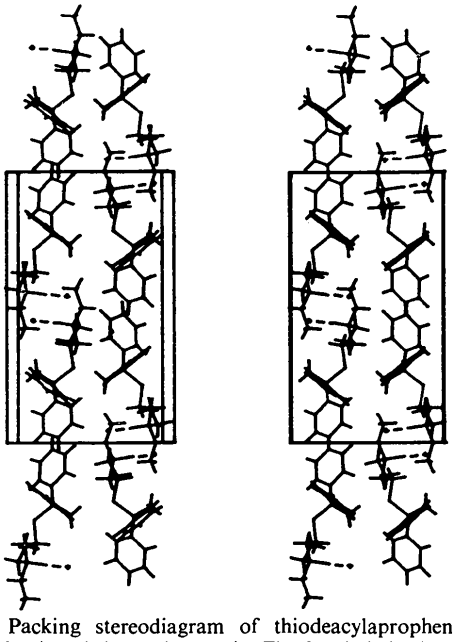

Fig. 4. Packing stereodiagram of thiodeacylaprophen hydrochloride viewed down the *a* axis. The *b* axis is horizontal, and the *c* axis is vertical. The hydrogen bonds are depicted by the dotted lines. The small crosses represent the location of the chloride ions. The figure was drawn using the *SYBYL* programs (Tripos Associates Inc., 1991).

Table 3. *Antimuscarinic activity of the title compound and standard compounds*

Values represent mean ± standard error of 3–6 separate determinations.

	Ileum contraction*		Pancreatic acini α-amylase release†	[*N-Methyl*-^{3}H]-scopolamine binding‡
	pA_2	K_B (*M*)	K_i (*M*)	K_i (*M*)
Thiodeacylaprophen	6.0±0.2	1.1×10^{-6}	$3.8\times10^{-8}\pm0.9$	$2.8\times10^{-6}\pm0.8$
Aprophen	8.5±0.1	3.1×10^{-9}	$1.7\times10^{-9}\pm0.2$	$5.1\times10^{-8}\pm0.8$
Atropine	8.7±0.1	2.0×10^{-9}	$1.6\times10^{-9}\pm1.1$	$2.4\times10^{-9}\pm0.8$
Pirenzepine	4.3±0.4	5.0×10^{-5}	$1.2\times10^{-7}\pm0.2$	$1.7\times10^{-7}\pm0.7$

* The ability of the test compound to block acetylcholine-induced contraction of male albino guinea-pig ileum. pA_2 is the negative logarithm of the concentration (K_B) of the test compound in molar units for which the addition of twice the concentration of acetylcholine is required in order to produce the same extent of contraction observed in the absence of the test compound. These values were calculated using computer programs for the Schild plot (Tallarida, Cowan & Adler, 1979).

† K_i is the equilibrium dissociation constant for the test compound. The K_i was determined by first calculating the concentration of the test compound required for 50% inhibition (I_{50}) of carbachol-stimulated release of α-amylase from Sprague–Dawley rat pancreatic acinar cells using the computer program *ALLFIT*. The K_i was then determined by the method of Cheng & Prusoff (1973).

‡ K_i is the equilibrium displacement constant for the test compound. The K_i was determined as described for the α-amylase assay except that the I_{50} is the concentration of the test compound required for 50% inhibition of binding of [*N-methyl*-^{3}H]scopolamine to N4TG1 neuroblastoma cells.

In the ileum contraction and [*N-methyl*-^{3}H]-scopolamine binding assays (Table 3), thiodeacylaprophen is several orders of magnitude less active than the standard antimuscarinic agents atropine and aprophen, but in the pancreatic α-amylase release assay, thiodeacylaprophen is only approximately 20-fold less potent than aprophen or atropine. The substitution of a S atom for an O atom in an antimuscarinic agent by itself does not necessarily cause the observed decrease in activity since this substitution can result in increased antimuscarinic activity. Parkes (1955) found that the thioester analog of benactyzine displays an antispasmodic activity in a guinea-pig ileum assay 12% higher than atropine and approximately twofold higher than benactyzine [compound (III), Fig. 1]. As mentioned earlier, Parkes also found thioether compounds to have higher activity than their oxygen ether analogs. Although the antimuscarinic activity of thiodeacylaprophen is less than atropine or aprophen, thiodeacylaprophen is a more potent antimuscarinic than the standard M1 muscarinic receptor subtype antagonist pirenzepine [compound (VIII), Fig. 1] (Hammer, Berrie, Birdsall, Burgen & Hulme, 1980)

in the guinea-pig ileum assay and the pancreatic acini α-amylase release assay, but not in the [*N-methyl*-^{3}H]scopolamine binding assay.

While thiodeacylaprophen yields equipotent inhibition constants in the ileum tissue and the N4TG1 cells, it is approximately 100-fold more potent in the pancreatic tissue assay. Since the tissues used in the three assays contain different muscarinic receptor subtypes (Peralta, Ashkenazi, Winslow, Smith, Ramachandran & Capon, 1987), thiodeacylaprophen is more selective for the muscarinic receptor subtype found in the pancreatic tissue. Whether an antagonist can attain the necessary conformation to interact with subtypes of muscarinic receptors may be due in part to their rigidity or flexibility (Flavin, Lu, Thompson & Bhargava, 1987).

Discussion

The potency of an antimuscarinic agent appears to be dependent upon the proper combination of several structural features. These structural features include the distance between the cationic center (usually a quaternary amino group or a tertiary amino salt) and the oxygen/sulfur group, the accessibility of the oxygen/sulfur group for interaction with the receptor, and the position and size of the aromatic and aliphatic groups. Gordon, Breuer, Padilla, Smejkal & Chiang (1989) have proposed that the optimal distances between the cationic center and the carbonyl O atom for 2,2-diphenylpropionate antimuscarinic agents is 4.9 to 5.4 Å. Atropine hydrobromide and aprophen hydrochloride fall into this range with intramolecular $N^+\cdots O$(carbonyl) distances of 5.31 (7) and 5.072 (9) Å, respectively (Kussäther & Haase, 1972; Karle, Karle & Chiang, 1990). This distance may also be optimal for any antimuscarinic agent. The oxygen ether compound (VI) (Fig. 1) and its *o*-methyl derivative which are 46% and 67% as active as atropine, respectively (Yoshida, Morita & Ogawa, 1973*a*,*b*), have $N^+\cdots O$ distances of 4.869 (15) and 4.824 (20) Å, respectively (Guy & Hamor, 1975; Hamor, 1976). The thioester thiphenamil hydrochloride which is 20% as active as atropine in the guinea-pig ileum assay (Parkes, 1955) has an $N^+\cdots O$ distance of 4.399 (6) Å (Guy & Hamor, 1974), somewhat shorter than the proposed optimal distance. The $N^+\cdots S$ distance is a lengthy 7.198 (7) Å in methixene hydrochloride monohydrate [compound (VII), Fig. 1] (Chu, 1972), a compound around 15 times less potent than atropine in preventing acetylcholine-induced spasms (Caviezel, Eichenberger, Kidder, Lauener & Stille, 1963). The $N^+\cdots S$ distance of 4.106 (6) Å in thiodeacylaprophen hydrochloride is considerably shorter than optimal.

A superposition of the crystal structures of thiodeacylaprophen and aprophen shows that the two structures are not that dissimilar (Fig. 5). Chemically both structures contain a diphenylmethyl group and a diethylamine group. With a rotation about the S—C(7) bond, the phenyl and methyl groups would superimpose. However, there are several major structural differences between the two compounds. When the S atom of thiodeacylaprophen is aligned with the carbonyl O atom of aprophen, the N^+—H group points in different directions. The distance between the N^+ and S (or carbonyl O) atoms differ in their crystalline hydrochloride salt forms by 0.96 Å. Finally, although the S atom of thiodeacylaprophen is exposed to the surface of the molecule, the carbonyl O atom of aprophen appears to reside further out of the surface of the molecule than the S atom of thiodeacylaprophen and is therefore more accessible to intermolecular interactions (Fig. 3).

In summary, the *trans* conformation of the S—C—C—N^+ segment of thiodeacylaprophen is similar to other antimuscarinic agents containing this segment. The weak antimuscarinic activity of

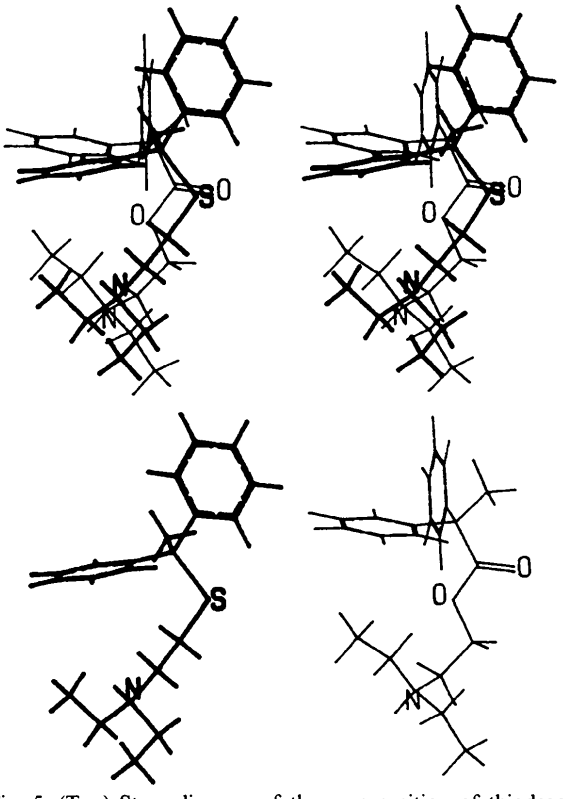

Fig. 5. (Top) Stereodiagram of the superposition of thiodeacylaprophen (thick lines) with aprophen (thin lines). (Bottom) The figures of thiodeacylaprophen and aprophen which were superimposed above. All figures were drawn using the *SYBYL* programs (Tripos Associates Inc., 1991).

thiodeacylaprophen may be due to its short S···N^+ distance, the more shielded nature of its S atom relative to the carbonyl O atom of aprophen, the differing position of the N^+—H group, and the greater hydrophobicity of a thioether group *versus* an ester group since these features constitute the major structural and chemical differences between thiodeacylaprophen and aprophen. Since thiodeacylaprophen is selective for the muscarinic receptor subtype found in pancreatic tissue, the three-dimensional structure of thiodeacylaprophen should aid modeling the structure of muscarinic receptor subtypes and modeling the interaction of antimuscarinic agents with the muscarinic receptor subtypes.

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X-ray Studies on Anti-Tumour Triazenes. Structures of 1-(4-Carbamoylphenyl)-3,3-dimethyltriazene 1-Oxide and 3,3-Dimethyl-1-(4-nitrophenyl)triazene

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Abstract

The molecular structures of the title compounds have been determined by X-ray crystallographic methods. The analyses revealed differences in the geometry, and by inference the bond delocalization in these two triazenes owing to the presence in the 1-oxide structure of an N—O bond. The geometries are compared to the crystal structures of the isomeric 3-oxides [Kuroda & Wilman (1985). *Acta Cryst.* C**41**, 1543–1545; Neidle, Webster, Kuroda & Wilman (1987).

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