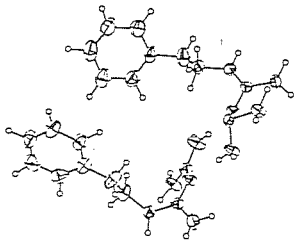
ethylamine side chain is maximally extended - a prerequisite for sympathomimetic activity. In one of the molecules the plane of the side chain was found to be nearly normal (88.41°) to the plane of the ring and therefore in very good agreement with the characteristic value, and the corresponding value obtained for the other molecule is also within the permissible range. The nitrogen atom in the maximally extended side chain of each molecule was observed to be at a distance of 5 Å from the centre of the aromatic ring and in very close agreement with that obtained for most sympathomimetic amines. This nitrogen also acquires the characteristic positive charge since the bond features clearly suggest that the positive charge due to protonation is delocalised evenly over the amino groups. The 3-D packing of the molecules clearly reveal the formation of hydrophobic and hydrophilic zones in consonence with that observed for many sympathomimetic compounds. However, the characteristic tetrahedral nitrogen is not present here. An assay of this compound for sympathomimetic activity might therefore be able to assess the role played by the tetrahedral configuration of nitrogen in a sympathomimetic drug.

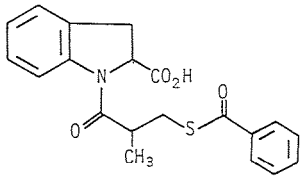


03.1–3 STRUCTURAL STUDIES OF INHIBITORS OF ANGIOTENSIN CONVERTING ENZYME. Alice Vrielink and Penelope W. Codding, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, T2N 1N4, Canada.

Angiotensin converting enzyme (ACE) is a physiologically important enzyme in the regulation of blood pressure. The enzyme converts the decapeptide, angiotensin I to the octapeptide, angiotensin II (Ang II). Ang II acts in a number of different ways to increase blood pressure. One treatment for hypertension could be to block ACE with a competitive inhibitor thus lowering levels of the hypertensive peptide, Ang II.

Based on the similarities found between ACE and the well-characterized enzyme carboxypeptidase A, Ondetti and coworkers (Science (1977) 196, 441) have postulated an active site model for ACE and have designed a therapeutic inhibitor, captopril (2-D-methyl-3-mercaptopropanoyl-L-proline). Recently, Kim and coworkers (J. Med. Chem. (1983) 26, 394) have found that the addition of a hydrophobic group to the captopril skeleton increased inhibitory potency. They suggest that the ACE active site has a hydrophobic pocket.

The structure of one of Kim's compounds, S,S-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-indoline-2-carboxylic acid (1) has been determined to probe the conformational effects of the addition of a hydrophobic group.



1

A comparison of this structure to captopril (Fujinaga and James, Acta Crystallogr (1980) B36, 3196) reveals some striking differences in conformation. In captopril the amide carbonyl points toward the carboxylic acid function while in 1 the orientation is the opposite: a trans amide. Another difference arises in the conformation of the thio-oxopropl side chain; the C-C-C-S torsion angle is -170.6° in captopril and -62.7° in 1. Therefore, in 1 the side chain is folded to bring the S atom within 3.3 Å of the amide carbonyl oxygen atom. This distance is 4.7 Å in captopril. The active site model postulates a binding site for each of these atoms (S and O) and must be reconciled with these conformational differences.

Crystal data: $C_{20}H_{19}NO_4S$, $P2_12_12_1$, a = 7.447(2), b = 11.423(2), c = 21.809(6)Å, Z = 4, ρ_X = 1.368, T = -100(5)°C.

This work was supported by the Alberta Heritage Foundation for Medical Research and the Medical Research Council of Canada (grant MA-8087 to PWC).

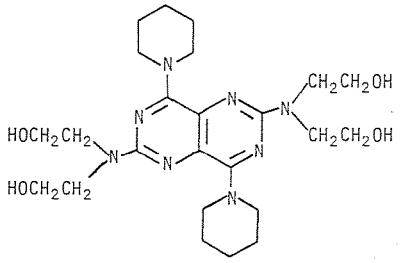
03.1–4 DIPYRIDAMOLE: A FLEXIBLE MOLECULE WITH AFFINITY FOR MORE THAN ONE RECEPTOR. Penelope W. Codding and Joanita Jakana, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, T2N 1N4, Canada.

Nucleoside transport inhibitors act to potentiate the hypotensive and vasodilatory actions of adenosine by preventing the uptake of adenosine into the cells. Molecules like dipyridamole, lidoflazine and papaverine bind competitively to the nucleoside binding site and inhibit the high-affinity uptake system. The structural analysis of dipyridamole was undertaken to identify the features in these inhibitors that are in common with adenosine. Comparisons of lidoflazine, papaverine and dipyridamole with adenosine will be presented to map out a composite nucleoside transport binding site.

Dipyridamole can also mimic another bioactive compound; it has high affinity for benzodiazepine binding sites (L.P. Davies, et al., Life Sci (1980) 26, 1089-1095). A.S. Clanachan and co-workers (Biochem Pharmacol (1983) 32, 1229-1235) have found that benzodiazepines inhibit nucleoside-transport and the binding of transport inhibitors like dipyridamole. The order of potencies of the benzodiazepines for transport inhibition differs from that for anxiolytic effect, confirming that these are two separate receptor systems. Current benzodiazepine receptor site models will be analyzed for an explanation of the affinity of dipyridamole for these receptors.

The diversity shown in the activity of dipyridamole is also shown in the crystal structure. The compound ($C_{24}H_{40}N_8O_4$) crystallizes in space group Pc at -100(5)°C with two molecules in the asymmetric unit and a = 11.233(2), b = 11.116(1), c = 20.563(1)Å, β = 104.45(2)°. The two unique molecules differ in the conformations of

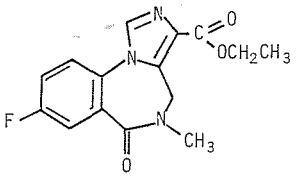
the side chains; the torsion angles vary by 5-10° in the hydroxyethyl groups. The molecular inversion center is approximately conserved.



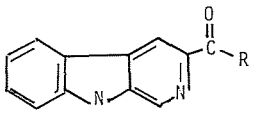
This work was supported by the Alberta Heritage Foundation for Medical Research and the Medical Research Council of Canada (grant MA-8087 to PWC).

of the orientations of the side chains.

A potential antagonist binding site that is consistent with binding data from rat cerebral cortex has been identified by superpositions of RO15-1788, MeBCC, and NCBC. This model superimposes the six membered aromatic rings, the ester and amide side chains and an aromatic nitrogen atom. This binding site model may be interpreted either as evidence of multiple receptor sites or of a dynamic receptor. RO15-1788: $P4_2/n$, a = b = 19.395(5)Å, c = 7.172(3)Å, Z = 8
MeBCC: $P2_1/c$, a = 11.4866(9), b = 5.8091(3), c = 32.147(3)Å, β = 97.111(3)°, Z = 8
NCBC: C2/c, a = 16.220(4), b = 7.728(2), c = 19.623(6)Å, β = 104.16(1)°, Z = 8



RO15-1788



MeBCC R = OCH_3
NCBC R = $NHCH_2CH_3$

This work was supported by the Alberta Heritage Foundation for Medical Research and the Medical Research Council of Canada (grant MA-8087 to PWC).

03.1–5 STRUCTURAL STUDIES OF BENZODIAZEPINE ANTAGONISTS. Alastair K.S. Muir and Penelope W. Codding, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, T2N 1N4, Canada.

A natural receptor for benzodiazepine anti-anxiety drugs like diazepam has been identified in the brain. The endogenous ligand for this receptor and its pharmacological function are being sought. Several derivatives of β-carboline have been found to have the highest affinity of the endogenous compounds; however, the actual formulation of the natural β-carboline has not been found. Some of the high affinity β-carbolines are antagonists of the action of benzodiazepines and are thus anxiety-producing compounds. These findings suggest that the natural function of the benzodiazepine receptor may be to mediate alertness and related attributes. Several compounds that are antagonists at this receptor have been studied to develop a model for the binding of antagonists to the benzodiazepine receptor.

The structures of one benzodiazepine, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a][1,4]benzodiazepine-3-carboxylate (RO15-1788), and two β-carboline, methyl β-carboline-3-carboxylate (MeBCC) and N-ethyl-3-carbamyl-β-carboline (NCBC), antagonists were determined. A comparison of the antagonist benzodiazepine to an agonist, oxazepam (Gilli, Bertolasi, Sacerdoti, and Borea, Acta Crystallogr. (1978), B34, 2826), indicates that the 1,2 annelation induces only small changes in the conformation of the azepine ring. Thus the difference in activity must be due to the relative numbers of bonding groups and their electronic character.

In each of the three antagonists the ester or amide side chain is coplanar with the ring of attachment. The formation of hydrogen bonds is an important determinant

03.1–6 THE CRYSTAL AND MOLECULAR STRUCTURE OF 21-ACETOXY-11-(*R*)-RIFAMYCINOL S.

By M.Brufani, L.Cellai, S.Cerrini, D.Lamba and A.Segre. Istituto di Strutturistica Chimica "G. Giacomello" – C.N.R. Rome, ITALY.

Rifamycins are a class of natural and semisynthetic antibiotics belonging to the family of naphthalenic ansamycins. They specifically inhibit bacterial DNA-dependent RNA polymerase (M.Brufani, The Ansamycins. Topics in Antibiotic Chemistry. Ed. P.G.Sammes, Ellis Horwood Ltd., Chichester (1977) 1, 91). The basic requirement for the biological activity of these molecules (M.Brufani, S.Cerrini, W.Fedeli and A.Vaciago, J.Mol. Biol. (1974) 87, 409) is a proper spatial relationship of the four oxygen atoms O(1), O(2), O(9), O(10). They act as acceptors and/or donors of hydrogen bond in the complex with the enzyme.
Recently a comparative study of the conformation of rifamycins in solution and in the solid state has been accomplished (L.Cellai, S.Cerrini, A.Segre, M.Brufani, W.Fedeli and A.Vaciago, J.Org.Chem. (1982) 47, 2652). It is there pointed out that, in the two states, the conformation of the molecule experiences only minor changes, which do not affect the structural features responsible for the biological activity. The crystal structure of the 21-acetoxy-11-(*R*)rifamycinol S has been determined in order to investigate the factors affecting and stabilyzing the conformation of the aliphatic ansa-chain of these molecules.