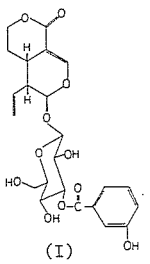
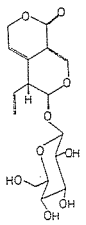
03. 3–18 STRUCTURES OF TWO SECOIRIDOID GLUCOSIDES: DECENTAPICRIN A, $C_{23}H_{25}O_{11}$ AND GENTIOPICROSIDE HEMIHYDRATE, $C_{16}H_{20}O_9 \cdot H_2O$, B.Kojić-Prodić and A.L. Spek, Vakgroep Algemene Chemie, afdeling Kristal- en Structuurchemie, University of Utrecht, 3508 TB Utrecht, The Netherlands.

The crystal and molecular structures of secoiridoid glucosides decentapicrin A(I) and gentiopicroside(II) with fungitoxic properties, isolated from plant *Centaurium littorale* [W.G. van der Sluis & R.P. Labadie, Planta medica (1981) 41,150-160]will be described.



(I)



(II)

The crystals of both compounds are orthorhombic with space group $P2_12_12_1$. Unit cells:(I), a=5.8234(6), b=12.512 (2), c=31.693(5)Å, Z=4; D_x=1.373gcm^{-3}; (II), a=8.175(2), b=12.810(2), c=31.99(1)Å, Z=8;D_x=1.449gcm^{-3}. The final R= 0.053 for 1088 reflexions [$I>1.5\sigma(I)$](I) and R=0.043 for 1789 reflexions(II) [$I>2.5\sigma(I)$].

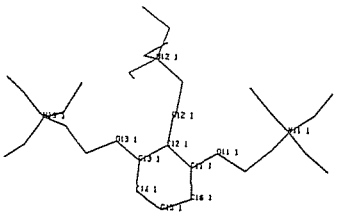
The structure of decentapicrin A reveals a non-planar secoiridoid moiety; the δ-lactone and pyran rings exhibit puckered conformation which can be approximated to an envelope type with C(6) and C(9) as the flaps. The β-D-glucose moiety is in the chair, $^4C_1$, conformation. The molecular packing is realized through intermolecular hydrogen bonds forming spiral chains in the a and b directions. These perpendicular spirals are connected by hydrogen bonds enclosing hydrofobic and hydrofilic areas.

In the crystal of gentiopicroside hemihydrate there are two conformers which have different conformations of the δ-lactone ring: nearly planar[mean value of torsion angle =5(1)°] and half-chair. Both conformers show a skew-boat conformation of pyran ring. The β-D-glucose moiety appears in the chair, $^4C_1$, conformation. Molecular packing is dominated by hydrogen bonds between the water molecule and both sugar residues, sugar-sugar, and the sugar-secoiridoid moieties (involving only conformer with non-planar δ-lactone ring). The molecules connected by hydrogen bonds form waved layers [in the (ab) plane] which are separated by ethenyl residues.

03. 3–19
X-RAY STRUCTURE AND CONFORMATIONAL FLEXIBILITY OF GALLAMINE OF BROMIDE: A POTENT NEUROMUSCULAR BLOCKER

By Jasmine Husain and Rex A. Palmer, Department of Crystallography, Birkbeck College, Malet Street, London WC1E 7HX.

The structure of the classical neuromuscular blocking agent gallamine has been determined by direct methods and difference Fourier synthesis. The crystals are triclinic space group P1, a = 14.216(1), b = 14.081(1), c = 20.895(2)Å, α = 104.9°, β = 92.6°, γ = 94.5° with 4 independent gallamine molecules per unit cell. Extensive disorder is observed amongst the bromide counterions which are distributed in 17 sites and both water and ethanol solvent molecules have been located. The gallamine molecules were refined by constrained least squares and occupancy factors were refined for the disordered bromide structure.

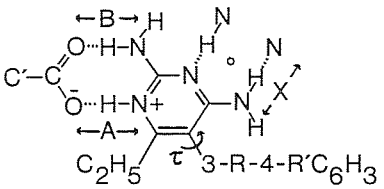


Gallamine Molecule

Stacking of 4 Gallamine Molecules

03. 3–20 GEOMETRY OF ANTIFOLATE DRUGS: EFFECT OF COUNTER IONS AND SUBSTITUENTS ON PYRIMETHAMINE SALTS. By P.K. Bryant, J. Colby, R.G. Jenks, P.R. Lowe, and C.H. Schwalbe, Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, UK.

The action of several important anti-infective and anti-cancer drugs is inhibition of the enzyme dihydrofolate reductase (DHFR). Now that the crystal structure of DHFR from eukaryotic as well as prokaryotic sources is available, it should be possible to design a selective inhibitor that is a perfect fit to DHFR of an invading organism, but a poor fit to host DHFR. However, such rational design is hampered by the relatively low precision of the protein crystallographic data. The present study supplies precise data on one type of drug: pyrimethamine and its analogues. With pyrimethamine hydrochloride (1) as a reference, structural data are reported for pyrimethamine acetate hydrate (2), pyrimethamine salicylate (3), and pyrimethamine salicylate isopropanol solvate (4), thus modeling the ionic and hydrogen bonding link between the drug and a side chain carboxylate ion of DHFR, which is believed to be of major importance for drug binding.



(1)–(4) R=H,R'=Cl

(5) $R=NO_2$, $R'=C_5H_{10}N$; Cl^- salt

While ethanesulphonate salts of antifolate drugs crystallize well and have been extensively studied, carboxylate salts have not. Trimethoprim acetate (TA; R.C. Haltiwanger Jr., MSc Thesis, University of Virginia, 1971) is presented for comparison. Introduction of a polar group into the 5-substituent will perturb the binding to DHFR; structure (5) was examined for changes in packing relative to (1)-(4).

	a	b	c(Å)	α	β	γ°	Z	S.Gp.
1	11.103	8.398	14.652	90	100.30	90	4	$P2_1/c$
2	26.247	10.254	14.562	90	120.69	90	8	$C2/c$
3	11.723	13.186	13.899	79.35	66.29	86.34	4	$P\bar{1}$
4	9.101	9.539	14.979	84.05	74.81	74.45	2	$P\bar{1}$
5	18.213	12.385	19.179	90	116.41	90	8	C2/c

	A	B	X	C2-N2	C4-N4(Å)	τ	ω*(°)
1**			3.095	1.320	1.315	63	
2	2.670	2.773	3.054	1.323	1.322	76	38
3a	2.708	2.860	2.980	1.325	1.340	70	12
3b	2.668	2.847	2.964	1.337	1.331	76	7
4	2.72	2.75	3.06	1.38	1.37	79	27
TA	2.60	2.78	3.04	1.33	1.34		11
5**			3.030	1.324	1.325	57	

*Angle between C'COO and pyrimidine ring planes.
**Chloride salt.

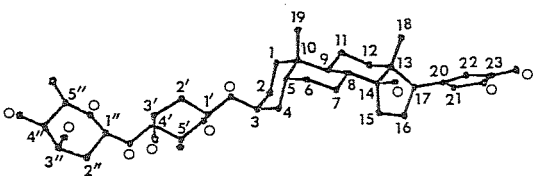
The interaction of protonated ring and carboxylate ion is uniformly strong. It does not impose coplanarity, but the consistency in distance should serve as a useful anchor point for model-building.

We thank the S.E.R.C. for studentship No. 83700621 to P.K.B. and studentship No. 82314925 to J.C.

03.3–21 STRUCTURE OF DIGITOXIGENIN BISDIGITOXOSIDE, $C_{35}H_{54}O_{10}$. Kuantee Go and Gopinath Kartha, Biophysics Department, Roswell Park Memorial Institute, Buffalo, New York 14263, U.S.A.

Digitoxigenin bisdigitoxoside recrystallized from ethyl acetate and hexane is orthorhombic, $P2_12_12_1$, a=11.419(2), b=14.310(2), c=23.959(3)Å, V=3915 Å^3, Z=4.

The structure was solved by multisolution methods and refined by block diagonal least-squares to an R index of 10.4%. An ORTEP sketch of the molecule is shown below. The D-ring has a 13α,14β-half-chair conformation. The torsion angle C(13)-C(17)-C(20)-C(22) is -116°, C(21)...O(14) distance is 2.943Å. Unlike digoxin and digoxigenin bisdigitoxoside, there is no intramolecular H-bond between the OH at C(3') and the ring oxygen of the adjacent sugar; this distance is 3.982Å (longer than 3.269Å in gitoxin). There is a disordered solvent, presumably a molecule of ethyl acetate; this solvent molecule along with the OH of the cardiac steroid and those of the sugars formed H-bonds in stabilizing the structure.



03.3–22 THE CRYSTAL AND MOLECULAR STRUCTURE OF CINCHONINIUM TETRACHLOROCUPRATE 1.5-HYDRATE, $(C_{19}H_{24}N_2O)^{2+}[CuCl_4]^{2-}.1.5H_2O$. By B. J. Oleksyn and S. A. Hodorowicz, Faculty of Chemistry, Jagiellonian University, Krakow, Poland.

Cinchona alkaloids - metal ions interactions are important as factors which could modify processes undergoing in living organisms. In reaction of MCl_2, where M=Zn, Co, Cd, Hg and Cu, with cinchoninium chloride, $CinCl_2$, tetrachloro-salts of general formula: $(Cin)^{2+}[MCl_4]^{2-}.nH_2O$ were obtained (Dyrek, Polish J. Chem.(1976) 50, 2027). Preliminary crystallographic investigation showed that only the Cu^{2+} compound is not isomorphous with the others (Chojnacki, Oleksyn, Hodorowicz, Polish J. Chem. (1975) 49, 429; Oleksyn, Stadnicka , Hodorowicz, ibid. (1976) 50, 1645). To explain this we have undertaken the crystal structure determination, which was carried out for 4426 independent reflections (3335 with $|F_o| > 3\sigma(F_o)$) measured on a CAD-4 diffractometer. The positions of Cu^{2+} ions were found with Patterson method, while those of other atoms were obtained from Fourier and difference Fourier syntheses. The current R value after anisotropic refinement of non-hydrogen atoms (513 parameters) with H atoms in fixed positions, is 0.077.

The main difference between this structure and the group of isomorphous structures of $(Cin)^{2+}[MCl_4]^{2-}.nH_2O$, where M≠Cu and n=2, are the packing conditions resulting from the fact that the asymmetric unit consists of 2 salt and 3 water molecules. The N and O atoms of Cin^{2+}, Cl^- ions, and H_2O molecules form a complicated net of hydrogen bonds (10 bond kinds of length 2.72 - 3.31Å). The geometry of $[CuCl_4]^{2-}$ tetrahedrons and Cin^{2+} cations is comparable to that described for Cd salt (Oleksyn, Stadnicka, Hodorowicz, Acta Cryst. (1978) B34, 811).

This investigation received financial support from World Health Organization.