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Structure of 2,4-Dioxo-1,2,3,4,6,7,8,9-octahydro-10H^+-pyrimido[4,5-*b*]quinolinium Trifluoroacetate Trifluoroacetic Acid Solvate

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Abstract. $C_{11}H_{12}N_3O_2^+.C_2F_3O_2^-.C_2HF_3O_2$, $M_r=445{\cdot}28$, monoclinic, $C2/c$, $a=24{\cdot}063$ (8), $b=8{\cdot}236$ (2), $c=18{\cdot}523$ (3) Å, $\beta=100{\cdot}39$ (2)°, $V=3610{\cdot}8$ (1) Å^3, $Z=8$, $D_x=1{\cdot}638$, $D_m=1{\cdot}620$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu=15{\cdot}047$ cm^{-1}, $F(000)=1808$, $T=296$ K, $R=0{\cdot}065$ for 2279 observed reflections. The molecule is a 2,4-disubstituted tricyclic linear system and is protonated. Associated with each cation are two trifluroacetic acid molecules, only one of which is ionized.

Introduction. As part of a research effort directed towards the synthesis of tricyclic folate antimetabolites as potential antitumor agents, we were interested in the synthesis of the linear compound 2,4-dioxo-1,2,3,4,-6,7,8,9-octahydropyrimido[4,5-*b*]quinoline. Facile syntheses of such tricyclic systems are carried out by the cyclocondensation of appropriately substituted 6-aminopyrimidines with bis electrophiles. The linear and/or angular structure of the product is predicated on the direction of ring closure (Irwin & Wibberley, 1969). Each time a new bis electrophile is utilized, the structure of the product needs to be unequivocally proved, usually by an independent synthesis. In two cases where independent synthetic proof of structure was not carried out, a reinvestigation has shown erroneous initial structure assignments (Paterson & Wood, 1972; Wood, Wrigglesworth, Yeowell, Gurney & Hurlbert, 1974; Stark & Breitmaier, 1973; Taylor & Fletcher, 1984). Our new synthesis of tricyclic analogues related to folates (Gangjee, Ohemeng, Tulachka, Lin & Katoh, 1985) required proof of the linear nature of the product and thus its crystal structure determination was undertaken.

Experimental. Crystals were grown by slow evaporation from a trifluroacetic acid–water solution; density measured by flotation in methylene chloride/methylene iodide mixture; clear rectangular needle-like crystal 0·55 × 0·58 × 0·78 mm cleaved from large needle and mounted in glass capillary; Picker FACS-I diffractometer, graphite monochromator; 12 high-angle reflections used for orientation matrix and unit-cell measurements, hkl with $h+k\neq 2n$, $h0l$ $l\neq 2n$ absent, space group $C2/c$ chosen based on density, non-chiral nature of molecule and E statistics; absorption corrections based on Howell's analytical expression for polyhedra, min. = 1·927, max. = 2·342; $2\theta_{max}=120°$, hkl range 0→26, 0→9, −20→20, three standard reflections monitored every 50 reflections, no decay, 2763 reflections measured in θ–2θ scan mode, 2682 unique, $R_{int}=0{\cdot}061$ for duplicates, 403 unobserved [$I<3\sigma(I)$]; structure solved with *MULTAN*78; all non-hydrogen atoms found from best E map, but only after 20 largest

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E's temporarily removed from data set; H positions calculated except for HN3, HN10 and HO6 which were found in difference Fourier maps; H-atom parameters unrefined, all non-hydrogen atoms refined with anisotropic thermal parameters, $\sum w||F_o|-|F_c||^2$ minimized, $R = 0{\cdot}065$, $wR = 0{\cdot}091$, $S = 1{\cdot}43$, $w = 1/\sigma^2$ with $\sigma = 0{\cdot}022F_o + 7{\cdot}11$ for $F_o < 77$, $\sigma = 0{\cdot}033F_o + 2{\cdot}839$ for $F_o > 77$, last cycle max. $\Delta/\sigma = 0{\cdot}08$, ave. $= 0{\cdot}02$; heights in final difference Fourier map: max. $= 0{\cdot}22$, min. $= -0{\cdot}31$ e Å^{-3}; isotropic secondary-extinction parameter $g = 0{\cdot}35823 \times 10^{-5}$ (unrefined); atomic scattering factors taken from *International Tables for X-ray Crystallography* (1974), no anomalous-dispersion corrections; computer programs used: data reduction Shiono (1971), Furey (1979); absorption corrections Alcock (1970); direct methods Main, Hull, Lessinger, Germain, Declercq & Woolfson (1978); refinement Furey (1984); Fourier synthesis Furey (1979); analysis Busing, Martin & Levy (1964); graphics Johnson (1970).

Discussion. The positional and isotropic thermal parameters for non-hydrogen atoms are given in Table 1.* A view of the molecule indicating the atom-numbering scheme is given in Fig. 1 and a packing diagram viewed down the b axis is shown in Fig. 2. The crystal structure consists of alternating tricyclic and trifluroacetic acid molecules with hydrogen bonds between N10—O3, N1—O5, N3—O1 and O4—O6 of different molecules. The donor–acceptor distances are 2·734 (4), 2·861 (4), 2·875 (4) and 2·442 (4) Å respectively. Bond distances and angles for non-hydrogen atoms* are close to those commonly observed in similar structures with the exception of the C7—C8 bond which is significantly shorter than expected (1·456 *vs* 1·510 Å). The tricyclic ring system is not planar with deviations of −0·22, 0·47 Å for atoms C7, C8 from the best plane defined by the remaining atoms (neglecting oxygens). Atoms O3, O5 involved in hydrogen bonding deviate from the aforementioned plane by 0·42 and 0·49Å respectively. The short C7—C8 bond length and elevated thermal factors suggest disorder in that part of the molecule and may be indicative of conformational flexibility in the ring. Final difference electron density maps show some disorder in this region but no attempts were made to model it. Dreiding models also support this finding since alternative conformations are readily obtained by varying ring pucker parameters. If such flexibility is present in the rigid crystal structure, one would expect even greater flexibility in solution. In view of the importance of this section of the molecule in similar bicyclic 2,4-diamino systems with respect to inhibition of dihydrofolate reductase, we are currently investigating the parent tricyclic 2,4-diamino analogue along with substituents on the C ring in an attempt to reduce conformational flexibility.

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters*

Fractional coordinates × 10^4 with e.s.d.'s in the least significant digit in parentheses.

$B_{eq} = \frac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
O1	−340 (1)	6490 (3)	−1730 (1)	3·8
O2	1544 (1)	6018 (4)	−1680 (1)	4·0
N1	231 (1)	6455 (3)	−617 (1)	2·7
C2	139 (1)	6398 (2)	−1373 (2)	2·8
N3	601 (1)	6261 (4)	−1697 (1)	3·0
C4	1161 (1)	6109 (4)	−1341 (2)	2·9
C4*A*	1228 (1)	6135 (4)	−537 (2)	2·5
C5	1757 (1)	5974 (4)	−92 (2)	2·9
C5*A*	1823 (1)	6062 (4)	667 (2)	2·7
C6	2402 (1)	5928 (5)	1148 (2)	3·9
C7	2374 (2)	5826 (8)	1955 (3)	6·2
C8	1942 (2)	6838 (7)	2187 (2)	5·5
C9	1359 (2)	6506 (5)	1775 (2)	3·6
C9*A*	1349 (1)	6322 (4)	968 (2)	2·7
N10	834 (1)	6463 (3)	527 (1)	2·5
C10*A*	765 (1)	6354 (4)	−208 (2)	2·3
O3	−51 (1)	7318 (3)	1189 (2)	4·0
O4	−73 (1)	10001 (4)	997 (2)	5·4
C11	−253 (1)	8677 (5)	1197 (2)	3·3
C12	−790 (2)	8862 (5)	1506 (3)	4·2
F1	−1149 (1)	9908 (4)	1115 (2)	7·5
F2	−1078 (1)	7523 (4)	1511 (2)	8·2
F3	−689 (2)	9457 (5)	2174 (2)	9·1
O5	−840 (1)	7476 (3)	−312 (1)	3·8
O6	−915 (1)	9918 (4)	−851 (2)	5·5
C13	−1099 (1)	8640 (4)	−579 (2)	3·2
C14	−1733 (2)	8710 (5)	−614 (3)	4·4
F4	−1913 (1)	7750 (4)	−146 (2)	7·0
F5	−1913 (1)	10164 (4)	−483 (3)	9·3
F6	−1998 (1)	8257 (7)	−1260 (2)	10·9

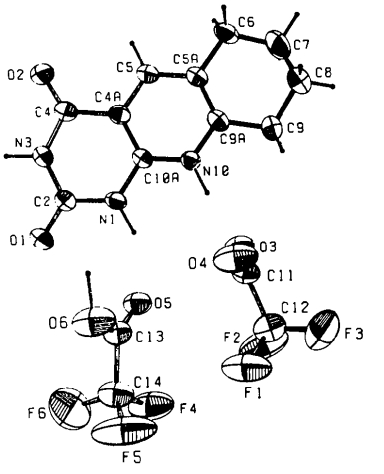

Fig. 1. An *ORTEP* (Johnson, 1970) drawing of the title compound indicating the atom-numbering scheme. Thermal ellipsoids drawn at the 50% probability level.

* Lists of structure factors, anisotropical thermal parameters, bond lengths, angles and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43799 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

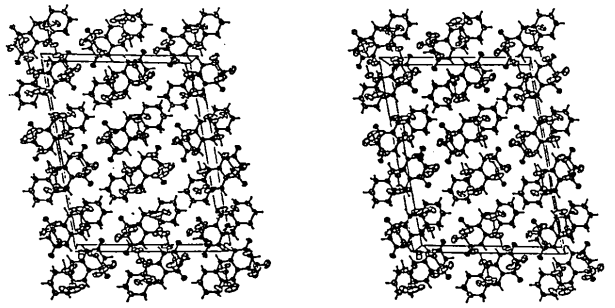

Fig. 2. An *ORTEP* (Johnson, 1970) stereodrawing showing the crystal packing. View is down the *b* axis.

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Structure of Cryptosin* Monohydrate – a New Cardioactive Glycoside

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Abstract. $C_{29}H_{40}O_{11}.H_2O$, $M_r = 582{\cdot}7$, orthorhombic, $P2_12_12_1$, $a = 9{\cdot}663\ (5)$, $b = 11{\cdot}723\ (1)$, $c = 25{\cdot}626\ (3)$ Å, $Z = 4$, $V = 2902{\cdot}9$ Å^3, $D_x = 1{\cdot}33$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 0{\cdot}9$ mm^{-1}, $F(000) = 1248$, $T = 295$ K, final R for 2273 observed reflections is 0·077. Cryptosin contains deoxyglucose, a steroid group and a lactone ring. The glucopyranose ring assumes a chair conformation. The steroid group shows the presence of an epoxy group unlike in other cardioactive compounds such as strophanthidin and digitoxigenin. The *A*/*B* and *C*/*D* ring junctions are *cis* as in other cardioactive steroids. The molecules pack in a network which contains three distinct hydrogen bonds.

*IUPAC name: 3β-(D-deoxyglucopyranosyloxy)-11β,14β-dihydroxy-7,8-epoxy-12-oxo-5β-card-20(22)-enolide.

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Introduction. Cryptosin – a new glycoside – was isolated from the leaves and *in vitro* cultured cells of the milkweed, *Cryptolepis buchanani* Roem. & Schult. at the Department of Biochemistry in our Institute. The compound demonstrates cardioactive properties (Venkateswara, Sankara Rao & Vaidyanathan, 1985).

The X-ray analysis was undertaken in view of its medicinal importance and also because there was some uncertainty regarding its actual chemical structure, particularly in the number of oxygens present (Fig. 1).

Experimental. Needle-shaped crystals were grown by evaporation of acetone solutions. Unit-cell parameters and space group were obtained from rotation and Weissenberg photographs. The cell parameters were refined by least-squares calculations from 21 high-angle reflections collected on a CAD-4 diffractometer. Cu $K\alpha$