The Crystal Structure Determination of Aldosterone

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Summary The structure of aldosterone in a monohydrated crystalline form has been determined by *X*-ray analysis to be the 18-acetal-20-hemiacetal structural isomer.

IN aqueous solution an equilibrium mixture of the three forms of aldosterone shown in Figure 1 was predicted by

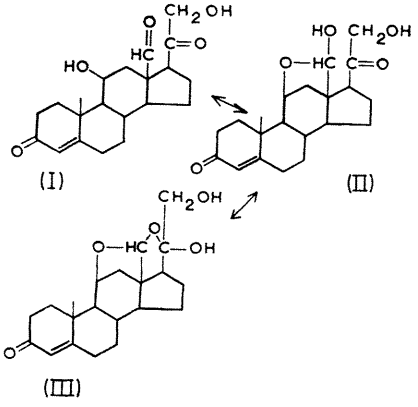

FIGURE 1. *Structural isomers of aldosterone*: (I) 18-*aldehyde*; (II) 18-*hemiacetal*; (III) 18-*acetal*-20-*hemiacetal*.

Ham *et al.*[1] The structure in solution is often referred to as an equilibrium mixture of (I) and (II) only.[2,3] The ability of aldosterone readily to form C(20), C(21) cyclic acetals suggests a predominance of the 18-acetal-20-hemiacetal form (III).[4] Because of uncertainty as to the relative stability of these forms, the strain introduced into the molecule by formation of the acetal, and the primary importance of this steroid hormone in numerous biological functions including maintenance of Na^+–K^+ electrolyte balance, the structure was undertaken as part of a programme investigating steroid structure and structural functional relationships.

Two crystalline modifications of aldosterone were obtained. Modification A was determined to be in the orthorhombic space group $P2_12_12_1$, [a = 25·6, b = 5·8, c = 24·1 Å] with two molecules in the asymmetric unit, and modification B was determined to be in the monoclinic space group $P2_1$ [a = 12·199(4), b = 6·0345(8), c = 13·181(8) Å, β = 107·31 ± 0·03°] with one molecule in the asymmetric unit. Crystals of modification B suitable for *X*-ray structure analysis were obtained and intensities of 2016 reflections were measured on a General Electric XRD-5 diffractometer using Cu-K_α radiation monochromatized by balanced nickel and cobalt filters. Lorentz and polarization corrections were applied to the data.

The structure was solved by application of the modified tangent formula[5] which was used to generate phases for the 350 strongest reflections. Atomic positions for 18 atoms were obtained from an E map and a Fourier difference synthesis clearly revealed the remaining 9 atoms of the aldosterone hydrate. After 6 cycles of anisotropic refinement of all non-hydrogen atoms by block-diagonal least-squares the reliability factor (R) is 10·5% for 1571 observed reflections.

The molecule is observed in the 18-acetal-20-hemiacetal form (Figure 2) which was favoured by Gardi.[4] The high

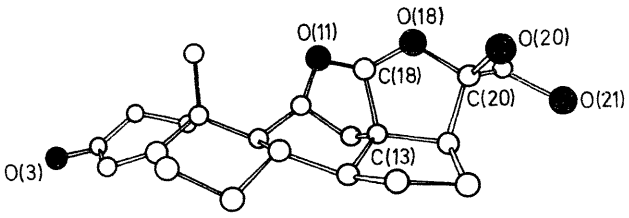

FIGURE 2. *Aldosterone structure observed in the monohydrated crystalline form.*

degree of strain introduced into the c-ring by the presence of the 18-acetal is exemplified by the C(11)–C(12)–C(13) angle of 97 ± 1° and the unusually large torsional angles C(9)–C(11)–C(12)–C(13) = 73° and C(11)–C(12)–C(13)–C(14) = 74°. The bonds in the c-ring are all of reasonable length, ranging from 1·50 to 1·57 Å with standard deviations of ±0·02 Å. The torsional angles shown in the C(18)–C(13) Newman projection (Figure 3) also illustrate the bonding strain in the acetal-hemiacetal form. The hydroxy-groups are *gauche* with O(21) taking up the most favourable

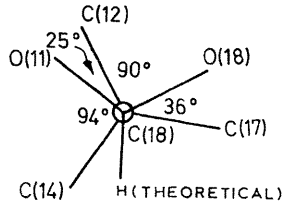

FIGURE 3. *Newman projection along* C(18)–C(13) *bond.*

conformation avoiding either interaction with H(12) or *gauche* interactions with both O(18) and O(20) as would occur in the other most probable positions. The hydrogen bonding network in the structure [O(20 · · · O(3) = 2·84 Å, O(20) · · · O(water) = 2·85 Å and O(water) · · · O(20 = 2·68 and 2·75 Å] results in a very stable crystalline hydrate.

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