Wesentlichen über Methylgruppen und Schwefelatome. Der kürzeste S···S-Kontakt ist nur wenig kürzer als die Summe der Van der Waals-Radien nach Pauling (1973) von 3,70 Å: S(1)···S(1^{iii}) 3,648 (3) Å [(iii) $2-x, 1-y, 1-z$].

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The Disordered Structure of Cortisol (11β,17α,21-Trihydroxy-4-pregnene-3,20-dione) and Iodocortisol (11β,17α-Dihydroxy-21-iodo-4-pregnene-3,20-dione)

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Abstract

Cortisol, $C_{21}H_{30}O_5$, and iodocortisol, $C_{21}H_{29}IO_4$, crystallize in the space group $P2_12_12_1$ as a disordered system, with an occupation number for iodocortisol of 0·18. Unit-cell parameters are $a = 6{\cdot}435\ (3)$, $b = 15{\cdot}626\ (6)$, $c = 18{\cdot}912\ (8)$ Å, $Z = 4$. The structure was solved from diffractometric data by direct methods and refined isotropically to $R = 0{\cdot}125$ for 1317 reflections. The C–I bond distance is 1·97 (1) Å with a C–C–I angle of 126·9 (6)°. The extended structure shows an unusual packing scheme in which all O atoms of iodocortisol are involved in hydrogen bonds.

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Introduction

During the course of a structural study of the enzyme Δ^5-3-ketosteroid isomerase from *P. testosterone*

(Westbrook, 1975), a series of heavy-atom isomorphous derivatives of the structure were made, using steroid competitive inhibitors of the enzyme to which heavy atoms had been covalently bonded. This method of 'rationally' introducing heavy atoms into the crystal structure has been used in a number of studies of enzymes, with significant success (Sigler, Blow, Mathews & Henderson, 1968; Arnone *et al.*, 1971). The power of this technique relies on the perfect stoichiometry of bonding between the enzyme and a good competitive inhibitor due to the specificity of the enzyme binding site. Thus, a single, well ordered heavy atom attaches to each enzyme protomer. It should be noted that such derivatives are, typically, not closely isomorphous with the native enzyme, but exhibit extremely good isomorphism with a 'blank-ligand' structure, *i.e.* the binary complex of the enzyme and a competitive inhibitor that does not contain a heavy atom but is otherwise very similar to the first inhibitor. This is the case in the steroid isomerase structure.

One such heavy-atom inhibitor which has been used is iodocortisol. Kinetic studies of this compound show it to be a strong competitive inhibitor of the enzyme, with a binding constant K_i of about $3{\cdot}6 \times 10^{-6}$ M in solution. For comparison, progesterone (4-pregnene-3,20-dione) with a poorer binding constant, $6{\cdot}4 \times 10^{-6}$ M (Talalay & Benson, 1972), has been shown to bind with one-to-one stoichiometry to the enzyme within its crystal at concentrations of $1{\cdot}5 \times 10^{-4}$ M. Although binding of iodocortisol to the enzyme in its crystal was not itself demonstrated, the success with which other competitive inhibitors bind within the enzyme crystal implied that those binding sites were fully occupied by iodocortisol as well. However, upon refinement of this derivative against an estradiol blank-ligand structure, very low occupancies of the iodine sites were observed in the enzyme crystal, of the order of 10 e. While this behavior may have been due to low occupancy of enzyme binding sites by the entire iodinated steroid, it was more likely that the iodine had dissociated from the steroid itself.

The C—I bond is known to be unstable, being β-related to a carbonyl group, making it vulnerable to hydrolysis. The consequent decay to cortisol as a result of this hydrolysis has been observed to occur readily at room temperature, with an approximate half life of one month when in a methanol solution. Commercially available iodocortisol is also heavily contaminated with cortisol for this reason.

A crystal was obtained from a methanol solution known to contain both iodocortisol and cortisol, in roughly equal concentrations. This crystal was the only solid residue of the solution, even after the methanol was completely evaporated, so the crystal most probably contained both compounds. A structural study of the crystal was undertaken to elucidate the mechanism of decay of iodocortisol, and also to observe the similarity of the molecular geometry.

Experimental

Iodocortisol and cortisol were purchased from Steraloids, Inc. All organic solvents were obtained from Mallinckrodt, specified as reagent grade. Thin-layer chromatography (TLC) was performed using five 0·20 m silica-coated glass plates containing fluorescent UV (2540 Å) dye, purchased from Brinkmann. *m*-Dinitrobenzene, for the Zimmermann reaction, was purchased from Sigma, and all salts used in the Zimmermann and Tata reactions were obtained from Mallinckrodt.

20 mg of iodocortisol were dissolved in 0·1 ml chloroform, applied to a TLC plate, and run. The solvent phase used consisted of 3:1 chloroform:ethyl acetate. Two spots were observed by UV fluorescence, with R_f values 0·105 and 0·290. The Zimmermann reaction (Zimmermann, 1935) was used to show that both spots contained steroids, and the method of Tata (Tata, 1969) was used to show that the upper spot, but not the lower, contained iodine. The upper spot was scraped using a spatula into a glass centrifuge tube, and three consecutive extractions using 4 ml ethyl acetate each were made, separating the solid and liquid materials between extractions by 30 min of centrifugation at 5000 min^{-1} in a Sorval centrifuge. The collected supernatant ethyl acetate was evaporated to 0·5 ml using dry nitrogen, causing a spontaneous crystallization of thin white needles. The ethyl acetate supernatant was discarded after centrifugation; the needles were dried with nitrogen and then dissolved in 2 ml of methanol.

Under identical conditions of TLC pure cortisol produced a single spot with an R_f of 0·105. The purified iodocortisol also produced a single spot, with an R_f of 0·290. A mixture of the purchased iodocortisol and cortisol gave two spots identical to those of the purchased iodocortisol alone, but the $R_f = 0{\cdot}105$ spot was darker. A vial containing purified iodocortisol was left at room temperature for four weeks, and then examined by TLC; two spots were observed with R_f values of 0·105 and 0·290, of roughly equal intensities. This vial was kept at 273 K and the solution was allowed to slowly evaporate. After one month, a single crystal had formed in the vial, which was mounted and used for diffraction studies.

Oscillation and Weissenberg photographs showed the crystal to be orthorhombic. No systematic extinctions were observed, although all odd reflections on the three axes were weak. As it turned out the structure was solved and refined in the space group $P2_12_12_1$ and the small violations of the corresponding systematic extinctions were ascribed to the disordered occupancy of the iodine atoms (see below).

A fragment of the crystal (maximum and minimum linear dimensions of about 0·6 and 0·4 mm respectively) was mounted on an Enraf–Nonius CAD-4 diffractometer. 25 centered reflections, using least-squares refinement, produced the unit-cell dimensions and orientation matrix for the data collection.

Intensities were measured by the θ–2θ scan technique at a rate of 1·33–20·0° min^{-1} determined by a fast prescan of 20° min^{-1}.

1575 reflections were collected in the range $0° < \theta < 23°$ using graphite-monochromated Mo $K\alpha$ radiation. Of these, 1317 had $I \geq 3\sigma(I)$. Intensities of three standard reflections were essentially constant over the duration of the experiment. Data were corrected for Lorentz and polarization effects but not for absorption or extinction. The absorption factor with Mo $K\alpha$ radiation for 18% iodocortisol and 82% cortisol is 0·390 mm^{-1}. The measured and calculated densities were 1·33 and 1·30 Mg m^{-3} respectively.

Structure solution and refinement

The lack of systematic absences was initially misleading. As shown in Table 1, all axes had odd reflections with amplitudes well above their standard deviations, which were calculated by counting statistics with

$$\sigma(F) = \sigma(I)/2F = (C + R^2B)^{1/2}/2F$$

where C is the total count, R the ratio of scan time to background-counting time and B is the total background count.

Several trials with an old version of *MULTAN* (*Enraf–Nonius Structure Determination Package*) assuming space groups $P2_12_12_1$, $P222_1$, $P2_12_12$ and $P222$, including the possible rotation of axes in $P2_12_12$ and $P222_1$, gave no interpretable solution.

By that time one of us (PM) had adapted the 1978 version of *MULTAN* to our available hardware (PDP 11/45 with 48K, 16 bits word) and a trial with this system was performed. Space group $P2_12_12_1$ was assumed and an unoriented fragment of the ten atoms which form two fused six-membered rings of the steroid skeleton was input to the program. This was used to calculate normalized structure factors as described by Main (1975).

An E map computed with the phases given by the solution with the highest figure of merit showed all the non-hydrogen peaks of cortisol except the O of the hydroxyl group at C(21).

A difference map phased on these atoms showed a peak of about 10 e Å^{-3} at a distance of nearly 2 Å from C(21).

This peak was interpreted as a superposition of disordered OH groups and I atoms alternatively bonded to C(21). In order to refine the structure, this peak was treated as iodine and its occupancy was allowed to refine. Several cycles of isotropic full-matrix least squares gave a final R factor of 0·136. The occupancy of the I atom converged to 0·18. A difference map calculated at this stage was essentially flat.

Attempts to refine the structure anisotropically led systematically to non-positive-definite thermal tensors. This was probably caused by the poor quality of the data as a consequence of disorder, which is also responsible for the violations of some of the systematic extinctions corresponding to the space group $P2_12_12_1$. A constrained refinement of the occupancies of an O and an I atom located at fixed distances of 1·41 and 1·95 Å respectively from C(21) was also unsuccessful,

Table 1. *Odd axial reflections which violate the extinction rules of* $P2_12_12_1$

h	k	l	F_{obs}	$\sigma(F_{obs})$	$F_{obs}/\sigma(F_{obs})$
0	0	1	11·74	0·13	90·31
0	0	3	8·66	0·46	18·83
0	0	5	3·66	1·62	2·26
0	1	0	11·50	0·18	63·89
0	3	0	12·19	0·40	30·47
0	5	0	5·50	0·90	6·11
0	7	0	7·40	0·77	9·61
0	17	0	5·43	1·78	3·06
1	0	0	5·49	0·74	7·42
5	0	0	4·73	1·73	2·73

Table 2. *Final positional parameters and isotropic temperature factors* (Å^2) *with estimated standard deviations in parentheses*

	x	y	z	B
I	0·8780 (8)	0·4071 (3)	0·6809 (3)	4·27 (9)
O(3)	0·518 (2)	0·3299 (6)	0·0070 (5)	4·2 (2)
O(11)	0·912 (1)	0·2106 (5)	0·3263 (5)	4·2 (2)
O(17)	0·911 (2)	0·5036 (6)	0·4546 (5)	4·7 (2)
O(20)	1·256 (2)	0·3869 (7)	0·5578 (6)	6·2 (2)
C(1)	0·655 (2)	0·2589 (7)	0·1776 (6)	3·1 (2)
C(2)	0·603 (2)	0·2396 (8)	0·1017 (7)	3·7 (2)
C(3)	0·634 (2)	0·3129 (7)	0·0559 (6)	2·9 (2)
C(4)	0·817 (2)	0·3622 (8)	0·0704 (6)	3·3 (2)
C(5)	0·935 (2)	0·3531 (7)	0·1294 (6)	2·9 (2)
C(6)	1·137 (2)	0·3997 (8)	0·1352 (6)	3·4 (2)
C(7)	1·161 (2)	0·4445 (8)	0·2068 (7)	3·9 (3)
C(8)	1·113 (2)	0·3825 (7)	0·2684 (6)	2·8 (2)
C(9)	0·897 (2)	0·3411 (6)	0·2566 (6)	2·6 (2)
C(10)	0·880 (2)	0·2917 (7)	0·1872 (6)	2·7 (2)
C(11)	0·819 (2)	0·2930 (7)	0·3234 (6)	3·2 (2)
C(12)	0·850 (2)	0·3404 (8)	0·3931 (7)	3·6 (2)
C(13)	1·064 (2)	0·3792 (7)	0·4013 (6)	3·2 (2)
C(14)	1·118 (2)	0·4327 (7)	0·3364 (6)	3·0 (2)
C(15)	1·305 (2)	0·4835 (8)	0·3575 (7)	3·8 (3)
C(16)	1·291 (2)	0·4964 (8)	0·4376 (6)	3·5 (2)
C(17)	1·093 (2)	0·4478 (7)	0·4596 (6)	3·3 (2)
C(18)	1·221 (2)	0·3069 (8)	0·4163 (7)	3·8 (2)
C(19)	1·023 (2)	0·2117 (7)	0·1780 (6)	3·2 (2)
C(20)	1·095 (2)	0·4153 (9)	0·5336 (7)	4·4 (3)
C(21)	0·900 (3)	0·4132 (11)	0·5768 (9)	6·1 (4)

giving an extremely low value for the occupancy of the O atom.

After locating the H atoms on stereochemical grounds (except those of the two methyl groups), assigning to them the isotropic temperature factor of the atom to which each is bonded and introducing the weighting scheme $w = (aF^2_{obs} + bF_{obs} + c)^{-1}$, with $a = 0{\cdot}014$, $b = -0{\cdot}286$ and $c = 5{\cdot}856$ on an absolute scale, three further cycles of full-matrix isotropic least squares gave a final R factor of 0·125.

The final positional parameters and isotropic temperature factors of all non-hydrogen atoms are given in Table 2.*

Discussion

The chemical formula of iodocortisol together with the numbering scheme is shown in Fig. 1. Individual bond lengths and the valency angles are listed in Tables 3 and 4 together with the corresponding values for cortisol in cortisol methanol solvate (Roberts, Coppola, Isaacs & Kennard, 1973) for direct comparison. From Tables 3 and 4 it can be seen that the molecular geometry of these compounds is essentially the same. Some minor differences in the bond distances and angles are probably not significant and can be ascribed to the poor quality of the data due to the disorder of the structure. The obvious difference is the ligand at C(21), in which the OH group at C(21) in cortisol is replaced by an I atom in iodocortisol. The C–I bond length (1·97 Å) is somewhat shorter than expected but that may be explained by the presence of the disordered OH group located at a shorter distance from C(21). We found no satisfactory explanation for the C(20)–C(21)–I angle of 126·9°, which is much greater than the expected tetrahedral angle of about 109°.

* Lists of structure factors and H atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35557 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The extended structure is completely different from that of cortisol methanol solvate in which the hydrogen-bonding pattern involves a solvent molecule. In iodocortisol, all O atoms, with the exception of the disordered OH group at C(21), are involved in hydrogen bonds with the carbonyl O(3) and O(20) atoms as donors and the hydroxyl O(11) and O(17) atoms as acceptors. Fig. 2 shows a stereoscopic drawing of the structure with the hydrogen bonds indicated by dotted lines. The relevant intermolecular O–O distances are: O(3)–O(17) = 2·82, O(11)–O(20) = 2·85 Å.

This unusual packing scheme with almost all O atoms involved in hydrogen bonds is very efficient in terms of minimizing the free energy of the crystal. It might be speculated that the rather odd disordered association of iodocortisol and cortisol, together with the distortion of the C(20)–C(21)–I angle, are steric requirements of the compact hydrogen-bond packing scheme.

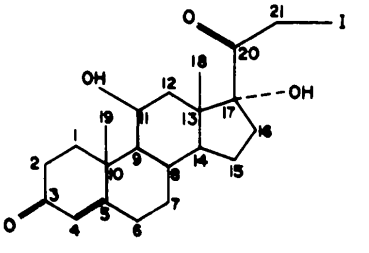

Fig. 1. Structure of iodocortisol showing the numbering scheme.

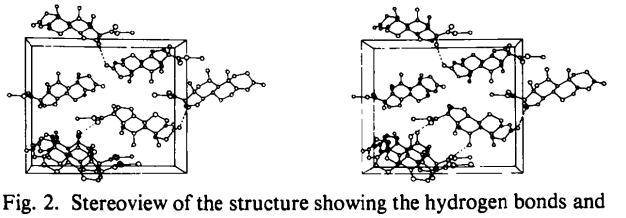

Fig. 2. Stereoview of the structure showing the hydrogen bonds and packing scheme.

Table 3. *Interatomic distances* (Å) *with e.s.d.'s in parentheses*

	(a)	(b)		(a)	(b)		(a)	(b)
C(1)–C(2)	1·523 (5)	1·505 (8)	C(8)–C(9)	1·545 (5)	1·553 (7)	C(13)–C(18)	1·534 (5)	1·539 (8)
C(1)–C(10)	1·534 (5)	1·550 (8)	C(8)–C(14)	1·567 (4)	1·505 (7)	C(14)–C(15)	1·506 (5)	1·497 (8)
C(2)–C(3)	1·490 (8)	1·448 (8)	C(9)–C(10)	1·573 (4)	1·525 (7)	C(15)–C(16)	1·553 (5)	1·530 (8)
C(3)–C(4)	1·453 (5)	1·438 (8)	C(9)–C(11)	1·541 (4)	1·552 (7)	C(16)–C(17)	1·548 (5)	1·546 (8)
C(3)–O(3)	1·235 (4)	1·217 (6)	C(10)–C(19)	1·552 (4)	1·560 (7)	C(17)–C(20)	1·533 (5)	1·489 (8)
C(4)–C(5)	1·355 (4)	1·354 (8)	C(11)–C(12)	1·543 (5)	1·524 (8)	C(17)–O(17)	1·430 (4)	1·461 (7)
C(5)–C(6)	1·498 (5)	1·497 (8)	C(11)–O(11)	1·423 (4)	1·419 (7)	C(20)–C(21)	1·505 (5)	1·503 (10)
C(5)–C(10)	1·527 (4)	1·494 (7)	C(12)–C(13)	1·530 (5)	1·517 (8)	C(20)–O(20)	1·210 (4)	1·215 (8)
C(6)–C(7)	1·519 (5)	1·531 (8)	C(13)–C(14)	1·501 (4)	1·525 (7)	C(21)–O(21)	1·410 (4)	
C(7)–C(8)	1·535 (5)	1·544 (8)	C(13)–C(17)	1·563 (4)	1·547 (8)	C(21)–I		1·975 (8)

(*a*) Cortisol (Roberts *et al.*, 1973); (*b*) iodocortisol (this work).

Table 4. *Intramolecular angles* (°) *with e.s.d.'s in parentheses*

	(a)	(b)		(a)	(b)		(a)	(b)
C(2)–C(1)–C(10)	113·0 (3)	112·8 (5)	C(1)–C(10)–C(5)	109·7 (2)	110·2 (5)	C(8)–C(14)–C(13)	113·5 (2)	113·4 (4)
C(1)–C(2)–C(3)	112·0 (3)	112·3 (5)	C(1)–C(10)–C(9)	108·9 (2)	109·3 (4)	C(8)–C(14)–C(15)	117·3 (3)	121·5 (5)
C(2)–C(3)–C(4)	117·4 (3)	115·0 (5)	C(1)–C(10)–C(19)	110·1 (3)	106·0 (4)	C(13)–C(14)–C(15)	106·9 (2)	105·0 (5)
C(2)–C(3)–O(3)	122·1 (3)	122·7 (5)	C(5)–C(10)–C(9)	107·2 (2)	106·8 (4)	C(14)–C(15)–C(16)	102·8 (3)	106·7 (5)
C(4)–C(3)–O(3)	120·5 (3)	122·3 (5)	C(5)–C(10)–C(19)	107·1 (2)	107·1 (4)	C(15)–C(16)–C(17)	106·5 (3)	104·5 (5)
C(3)–C(4)–C(5)	123·4 (3)	124·1 (5)	C(9)–C(10)–C(19)	113·8 (2)	117·4 (4)	C(13)–C(17)–C(16)	102·4 (3)	104·2 (5)
C(4)–C(5)–C(6)	120·4 (3)	119·8 (5)	C(9)–C(11)–C(12)	113·0 (2)	115·3 (4)	C(13)–C(17)–C(20)	113·7 (2)	115·7 (5)
C(4)–C(5)–C(10)	121·9 (3)	122·5 (5)	C(9)–C(11)–O(11)	110·2 (2)	109·5 (4)	C(13)–C(17)–O(17)	107·2 (2)	105·8 (4)
C(6)–C(5)–C(10)	117·4 (2)	117·4 (5)	C(12)–C(11)–O(11)	111·4 (2)	110·6 (5)	C(16)–C(17)–C(20)	113·2 (3)	114·2 (5)
C(5)–C(6)–C(7)	112·9 (3)	112·1 (5)	C(11)–C(12)–C(13)	112·9 (2)	113·6 (5)	C(16)–C(17)–O(17)	112·0 (2)	110·7 (4)
C(6)–C(7)–C(8)	112·5 (4)	111·1 (4)	C(12)–C(13)–C(14)	109·3 (2)	110·1 (5)	C(20)–C(17)–O(17)	108·1 (2)	105·9 (5)
C(7)–C(8)–C(9)	108·6 (2)	109·4 (4)	C(12)–C(13)–C(17)	116·1 (2)	117·2 (5)	C(17)–C(20)–C(21)	117·4 (3)	120·4 (6)
C(7)–C(8)–C(14)	110·5 (2)	108·4 (4)	C(12)–C(13)–C(18)	111·8 (3)	108·9 (4)	C(17)–C(20)–O(20)	121·7 (3)	119·2 (6)
C(9)–C(8)–C(14)	109·5 (2)	111·1 (4)	C(14)–C(13)–C(17)	98·7 (2)	99·6 (4)	C(21)–C(20)–O(20)	120·9 (3)	120·3 (6)
C(8)–C(9)–C(10)	112·7 (2)	113·3 (4)	C(14)–C(13)–C(18)	110·9 (3)	113·6 (5)	C(20)–C(21)–O(21)	108·9 (3)	
C(8)–C(9)–C(11)	115·3 (2)	111·9 (4)	C(17)–C(13)–C(18)	109·3 (2)	107·4 (5)	C(20)–C(21)–I		126·9 (6)
C(10)–C(9)–C(11)	113·9 (2)	115·7 (4)						

(*a*) Cortisol (Roberts *et al.*, 1973); (*b*) iodocortisol (this work).

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The Structures of *cis*- and *trans*-4-*tert*-Butyl-1-phenyl-1,2-epoxycyclohexane

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Abstract

The crystal structures of the title compounds, (2) and (3), have been determined by three-dimensional diffraction methods. Crystals of (3) are triclinic, space group $P\bar{1}$, with $Z = 2$, and $a = 10{\cdot}802\ (1)$, $b = 8{\cdot}362\ (1)$, $c = 8{\cdot}297\ (1)$ Å, $\alpha = 75{\cdot}0\ (1)$, $\beta = 103{\cdot}9\ (1)$, $\gamma = 101{\cdot}2\ (1)°$. Crystals of (2) are monoclinic, space group $P2_1/c$, with $Z = 4$, and $a = 6{\cdot}159\ (2)$, $b = 25{\cdot}193\ (10)$, $c = 9{\cdot}853\ (10)$ Å, $\beta = 115{\cdot}8\ (1)°$. The structures have

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