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The Conformation of 3,20-Diethylenedioxy-9β,11β-oxido-11α-acetoxy-9,11-seco-11,19-cyclo-5α,14β,17α-pregnane

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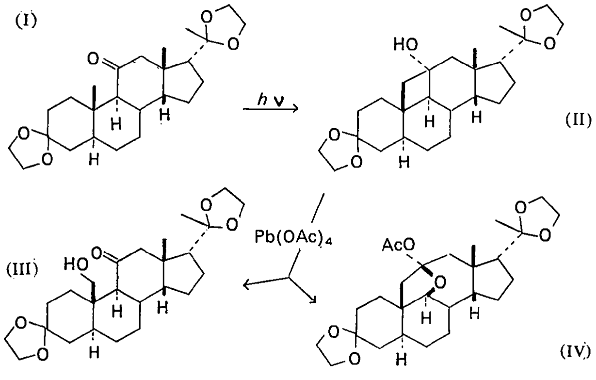
(*Received* 29 *October* 1974; *accepted* 22 *January* 1975)

The title compound, $C_{27}H_{40}O_7$, has been derived by photocyclization of a pregnane derivative and fragmentation with $Pb(OAc)_4$. It crystallizes in space group $P2_12_12_1$ with $a = 13{\cdot}833$ (7), $b = 25{\cdot}375$ (20) and $c = 7{\cdot}289$ (4) Å. The structure has been derived by using a combination of direct phase determination and a translation function. Introduction of an oxygen bridge between C(9) and C(11) and ring formation by the bonding of C(11) to C(19) have created strains in the molecule which are reflected in several CCC angles with values of 118° to 122° rather than near the more usual 111° in rings *A*, *B* and *C*. The seven-membered ring *C* has the boat conformation. Disorder in the two extreme five-membered rings limited the number of observable data. The final *R* is 11·4% for 1500 data.

The ultraviolet irradiation of various derivatives of pregnane can lead to a product in which cyclization has occurred between C(11) and the methyl group at C(19) to make a four-membered ring (see *e.g.* Gull, Saito, Wehrli & Jeger, 1974). Fragmentation of the new cyclo-product (II) by $Pb(OAc)_4$ yields (IV) as the main product rather than the expected product (III). An X-ray diffraction analysis of the structure of (IV) confirmed the formula and stereo configuration.



The stereoid nucleus undergoes a considerable conformational change with the ring closure between C(11) and C(19) and the introduction of an oxygen atom between C(9) and C(11). Therefore, it was considered desirable to obtain detailed structural information for this region where considerable strain must be relieved by changes in bond angles as well as torsional angles.

Experimental

Colorless crystals, somewhat opaque, in the form of elongated prisms were provided by Drs H. Wehrli and O. Jeger of the ETH, Zürich. The crystal data are: space group $P2_12_12_1$; $Z = 4$; $a = 13{\cdot}833(7)$, $b = 25{\cdot}375(20)$, $c = 7{\cdot}289$ (4) Å; $V = 2558{\cdot}5$ Å^3; $C_{27}H_{40}O_7$; M.W. = 476·62; $D_{\text{calc}} = 1{\cdot}237$ g cm^{-3}; size 0·20 × 0·15 × 0·9 mm; $\mu = 7{\cdot}31$ cm^{-1}. Intensity data were collected with Cu radiation ($\lambda = 1{\cdot}54178$ Å) on a four-circle automatic diffractometer with the θ–2θ scan mode, a scan width of 2·1° and a scan rate of 2° min^{-1}. The background was counted for 10 s at either end of the scan. Three reflections used as standards were monitored every hour and indicated a gradual deterioration of the crystal. The experimental I_{hkl} were scaled to compensate for the loss of scattering power up to a final factor of 1·09. Data were collected to a scattering angle of $2\theta = 120°$ although the data with $2\theta > 90°$ were very weak with only a few reflections of moderate size. For the least-squares refinement, only those data with $2\theta < 100°$ were used.

Phases were determined directly from the normalized structure factors $|E_{\mathbf{h}}|$ by means of the symbolic addition procedure. The best of four E maps showed a 13-atom fragment that did not develop more atoms when used as a partial structure in the tangent formula (Karle, 1968). The strongest peaks in a translation function (Karle, 1972).

$$\sum (|E_{\text{obs}}|^2-1)\,(|E_{\text{calc}}|^2-1)\cos 2\pi\mathbf{h}\,.\,r\,,$$

computed with the $(|E_{\text{calc}}|^2-1)$ factors based on the coordinates for the 13-atom fragment, indicated a one-dimensional shift of $\Delta 2y=\pm 0{\cdot}09$. The use of the 13-atom fragment moved by $-0{\cdot}045$ in the y direction as a partial structure for the refinement and expansion of phases by the tangent formula yielded the complete structure in the next E map. As initial phases for the tangent formula, only those terms were used for which $|E_{\mathbf{h}}|>1{\cdot}5$ and $|F_{\mathbf{h}}|_{\text{calc}}>0{\cdot}35|F_{\mathbf{h}}|_{\text{obs}}$. Subsequently phases were developed for all $|E_{\mathbf{h}}|>1{\cdot}1$. Fig. 1 shows the relationship between the 13-atom fragment and the correct placement of the molecule. It should be noted that even though three of the atoms in the fragment were spurious and a fourth one was misplaced by 1·0 Å from the correct position, neither the translation function nor the partial structure procedure were affected adversely. After translation, the remaining nine atoms were within 0·3 Å of the correct positions. The shift from the incorrect to the correct position corresponds to the spacing for the 0,22,0 reflection, $|E|=1{\cdot}90$, with no change in phase.

Full-matrix anisotropic least-squares refinement on the 34 carbon and oxygen atoms with 1502 F data, with $2\theta<100°$, and weights based on counting statistics (Gilardi, 1973) resulted in an R of 0·16. A difference map calculated at this stage showed the positions of relatively few hydrogen atoms. Accordingly, the coordinates for most of the 40 hydrogen atoms were calculated on the basis of ideal C–H bond lengths and angles and inserted into the least-squares refinement as constant parameters. Several more cycles of refinement with anisotropic thermal parameters resulted in a conventional R of 11·4% for all the data with $2\theta<100°$ and a weighted R of 4·2%.*

Coordinates and thermal parameters are listed in Table 1 while the bond lengths, bond angles and torsional angles are shown in Fig. 2. The numbering scheme for the atoms and the labeling of the rings are indicated in Fig. 2(*c*).

Results and discussion

The rapid decrease of intensity as a function of scattering angle for values of 2θ greater than 90°, as well as the relatively high R value, indicates a fair amount

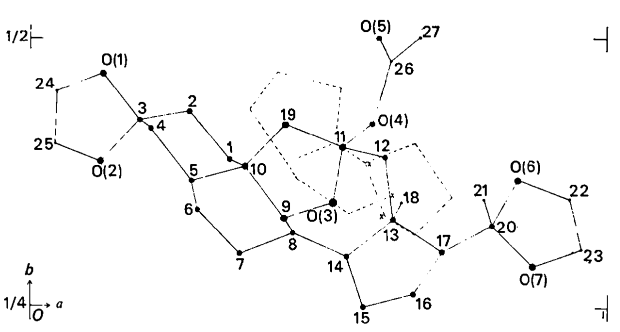


Fig. 1. The 13-atom fragment from the initial phase determination and the complete structure as derived from the 13-atom fragment when shifted by $y-0{\cdot}045$. Note that three atoms marked with an X in the original fragment are spurious. The size of the circles is proportional to the weight of the peaks in the E map.

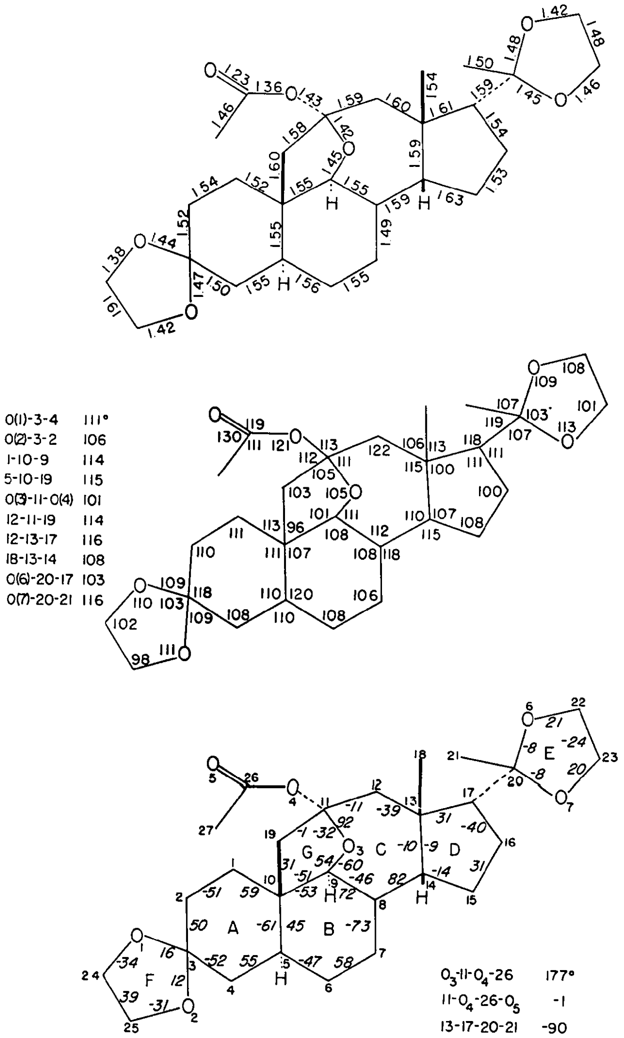


Fig. 2. Bond lengths, bond angles and torsional angles. The numbering of the atoms and the labeling of the rings are indicated in the lowest diagram.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30869 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

of positional disorder. The thermal ellipsoids in the stereo diagram of the molecule, Fig. 3, as well as the B_{ij} values in Table 1, show that the disorder occurs chiefly in the outermost atoms in the five-membered rings at either end of the molecule. The high R is correlated with high standard deviations for the bond lengths and angles, *i.e.* ~0·017 Å for bonds in rings A, B, C, D, and G and up to ~0·025 Å for bonds in rings

Table 1. *Fractional coordinates and thermal parameters with standard deviations*

The thermal parameters are of the form $T=\exp\,[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	0·3468	0·3837	−0·1345	5·57	3·38	4·22	−0·02	−2·10	0·74
C(2)	0·2787	0·4313	−0·1585	3·53	5·60	8·99	−0·37	−0·05	1·26
C(3)	0·1935	0·4273	−0·0270	5·88	3·19	11·46	−0·03	−1·88	−0·45
C(4)	0·2144	0·4164	0·1711	4·81	4·88	6·49	0·22	0·60	1·04
C(5)	0·2811	0·3674	0·1828	3·82	4·48	7·20	−0·18	0·07	0·51
C(6)	0·2910	0·3497	0·3863	4·18	4·75	7·94	−0·13	1·00	1·37
C(7)	0·3634	0·3034	0·3928	6·08	5·95	9·25	0·28	0·27	3·22
C(8)	0·4551	0·3237	0·3117	3·25	4·44	5·66	−0·49	0·24	1·04
C(9)	0·4411	0·3287	0·1013	3·94	2·97	7·43	−1·57	0·16	0·51
C(10)	0·3730	0·3760	0·0654	3·45	2·88	7·86	−0·71	1·57	0·41
C(11)	0·5487	0·3963	0·0948	4·18	2·36	5·81	0·63	0·23	−0·36
C(12)	0·6173	0·3902	0·2679	3·16	4·18	7·44	−0·73	−1·43	−0·13
C(13)	0·6410	0·3341	0·3560	4·43	3·56	11·06	1·19	2·00	1·57
C(14)	0·5525	0·2941	0·3639	4·35	4·86	9·36	−0·56	0·89	1·60
C(15)	0·5798	0·2447	0·2307	5·11	4·64	12·73	1·11	−0·88	−0·21
C(16)	0·6660	0·2609	0·1120	5·11	3·24	12·95	0·89	−0·57	−3·89
C(17)	0·7177	0·2985	0·2459	5·16	4·14	6·59	−0·41	0·43	0·84
C(18)	0·6731	0·3457	0·5549	7·80	9·21	2·45	1·12	−1·93	−1·23
C(19)	0·4458	0·4202	0·1393	2·96	3·06	7·24	0·67	−0·19	0·32
C(20)	0·8049	0·3274	0·1452	3·55	4·56	14·80	0·74	0·69	−4·91
C(21)	0·7916	0·3449	−0·0493	6·38	11·05	5·12	0·47	−0·65	3·87
C(22)	0·9628	0·3066	0·2428	5·41	6·74	12·52	−0·26	−0·29	1·78
C(23)	0·9292	0·3494	0·3655	6·90	11·05	15·26	0·99	−4·16	−1·96
C(24)	0·0387	0·4595	−0·0738	2·80	12·41	20·37	1·13	−0·23	7·81
C(25)	0·0507	0·4063	−0·1927	8·69	8·26	22·68	−3·47	−10·27	5·09
C(26)	0·6215	0·4744	−0·0380	2·86	4·62	11·54	1·79	1·47	0·33
C(27)	0·6708	0·4924	−0·2033	7·70	4·95	12·20	−0·30	3·59	3·81
O(1)	0·1341	0·4738	−0·0458	4·47	5·40	13·32	0·52	−1·01	1·55
O(2)	0·1318	0·3850	−0·1003	5·55	6·30	10·14	−0·68	−2·51	0·87
O(3)	0·5291	0·3465	0·0136	4·01	2·69	5·68	0·31	−0·34	−0·23
O(4)	0·5939	0·4231	−0·0548	3·50	3·62	6·91	−0·12	0·74	0·82
O(5)	0·6063	0·4978	0·1066	4·72	3·51	12·74	−0·68	1·36	−0·93
O(6)	0·8821	0·2869	0·1445	4·72	6·38	12·29	1·43	−0·93	−2·48
O(7)	0·8418	0·3665	0·2713	4·90	5·81	10·78	0·70	−1·59	−2·04

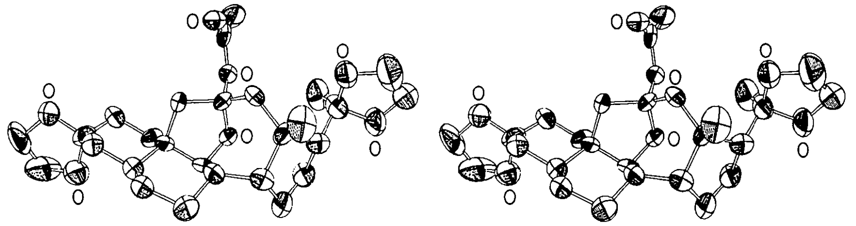

Fig. 3. Stereodiagram of the molecule. Thermal ellipsoids are at the 50% probability level (Johnson, 1965).

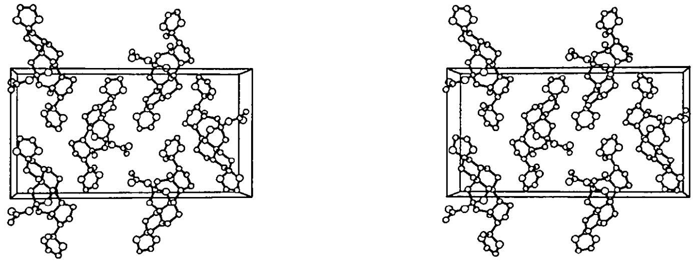

Fig. 4. Stereodiagram of the packing scheme. The axial directions are **a** ↓, **b** → and **c** directed up from the page.

E and *F*. Standard deviations for angles are of the order of 1·0°. These values for the standard deviations are derived from the least-squares refinement. Comparison of the bond lengths in this determination with those of other steroids with better scattering characteristics indicates that the values of the standard deviations are actually higher. Nevertheless, the conformational features of the molecule are established and the areas of accommodation for the strain caused by the oxygen bridge between C(9) and C(11) and the ring closure by the C(11)–C(19) bond are quite apparent. For example, angles C(2)C(3)C(4) = 118°, C(10)C(5)-C(6) = 120°, and C(11)C(12)C(13) = 122° (in rings *A*, *B* and *C*, respectively) are considerably larger than the values usually encountered for tetrahedral carbon atoms.

Rings *A* and *B* are in the chair conformation while the seven-membered ring *C* has a boat conformation. The five-membered rings *D*, *E* and *F* are close to the half-chair form with Δ values of $+4{\cdot}6°$, $+1{\cdot}5°$ and $-3{\cdot}3°$, respectively, where

$$\tan\frac{\Delta}{2}=\frac{(\varphi_2+\varphi_4)-(\varphi_1+\varphi_3)}{3{\cdot}0777\varphi_0}$$

(Altona, Giese & Romers, 1967). Ring *G*, on the other hand, has $\Delta = 34{\cdot}0°$, corresponding to an envelope form with C(9) out of the plane formed by the other four atoms. The acetoxy group is nearly coplanar with atoms C(11) and O(3) with the O(3)C(11)O(4)C(26) dihedral angle equal to 177°. Atom O(5) in the acetoxy group is equidistant at 2·98 Å from C(12) and C(19).

The *cis* junction between rings *C* and *D* folds the molecule at the C(13)–C(14) bond. As a consequence of the fold, atom C(16) in ring *D* is within 2·97 Å of the bridge oxygen O(3). Rotation is possible about the C(17)–C(20) bond and an equilibrium position appears to be at a torsional angle value of −90° for the C(13)C(17)C(20)C(21) angle. This orientation brings the methyl carbon atom C(21) to within 3·38 Å of atom O(4) and an intramolecular C(12)···O(6) separation of 3·16 Å. There are five intervening atoms between C(21) and O(4) and three between C(12) and O(6).

The packing scheme is illustrated in the stereodiagram in Fig. 4. The molecules are held together by van der Waals forces with one of the closest approaches, 3·32 Å, being between methyl groups C(18) and C(21) in molecules separated by one translational unit in the **c** direction. Other near approaches are O(5)···C(24) = 3·26 Å, O(5)···C(25) = 3·57 Å, and O(5)···C(27) = 3·39 Å.

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Structure Cristalline du Chlorhydrate de Pronéthanol, (+)-Isopropylamino-1 (β-Naphtyl)-2 Ethanol-2 Chlorhydrate

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(*Reçu le* 10 *décembre* 1974, *accepté le* 16 *janvier* 1975)

The crystal structure of pronethanol hydrochloride ($C_{15}H_{20}NOCl$) has been solved by direct methods with program *MULTAN*. Crystal data are: space group $P2_1$, $Z=2$, $a=12{\cdot}55$ (0), $b=9{\cdot}96$ (9), $c=5{\cdot}96$ (1) Å, $\beta=96{\cdot}00°$. The final R value is 0·041. The Cl^- anion is responsible for crystalline cohesion.

Introduction

Nous poursuivons l'étude de la structure tridimensionnelle de dérivés adrénolytiques β bloquants. Dans cette optique nous rapportons ici la structure cristalline du chlorhydrate de pronéthanol (Fig. 1).

Partie expérimentale

Le chlorhydrate de pronéthanol cristallise à partir d'une solution saturée d'éthanol sous forme de petits prismes monocliniques incolores.

Les diagrammes de Bragg et de Weissenberg nous