rotations about single bonds are generally small, the energetic differences in the molecular conformations observed in polymorphic IMDA are also expected to be small. The system thus provides a fairly sensitive test of the applicability of our earlier computational approach to the relationship between crystal forces and molecular conformations (Bernstein & Hagler, 1978), and calculations on this system are currently under way.

The author is grateful to Professor I. C. Paul for providing encouragement and the facilities for this study. Financial assistance from NIH, Grant GM 19336-06, and partial support from the Israel Commission for Basic Research are also acknowledged.

References

ALBERTSSON, J. & OSKARSSON, Å. (1968). *Acta Chem. Scand.* **22**, 1700–1702.

BERNSTEIN, J. & HAGLER, A. T. (1978). *J. Am. Chem. Soc.* **100**, 673–681.

BOMAN, C.-E., HERBERTSSON, H. & OSKARSSON, Å. (1974). *Acta Cryst.* B**30**, 378–382.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

HAGLER, A. T. & BERNSTEIN, J. (1978). *J. Am. Chem. Soc.* **100**, 6349–6354.

International Tables for X-ray Crystallography (1968). Vol. III, pp. 202–206. Birmingham: Kynoch Press.

JOHNSON, C. K. (1965). *ORTEP* II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee.

LEISEROWITZ, L. (1976). *Acta Cryst.* B**32**, 775–802.

OSKARSSON, Å. (1973). *Acta Cryst.* B**29**, 1747–1751.

Syntex Inc. (1973). *EXTL Structure Determination Package*, Syntex Analytical Instruments, Cupertino, California, USA.

TOMITA, Y., ANDO, T. & UENO, K. (1965). *Bull. Chem. Soc. Jpn*, **38**, 138–139.

Acta Cryst. (1979). B**35**, 366–369

6β,17β-Dihydroxy-6α-pentyl-4-nor-3,5-secoandrostan-3-oic Acid. A Synthetic Prostaglandin Analog

BY D. A. LANGS AND G. T. DETITTA

Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, New York 14203, *USA*

(*Received* 8 *June* 1978; *accepted* 25 *September* 1978)

Abstract

The title compound ($C_{23}H_{40}O_4$, M_r = 380·57) is a prostaglandin analog synthetically prepared from a simple androstane derivative. Its crystals are orthorhombic, space group $P2_12_12_1$, with a = 12·0342 (7), b = 18·761 (1), c = 9·998 (1) Å, V = 2257·3 Å^3, Z = 4, D_{obs} = 1·10, D_{calc} = 1·121 Mg m^{-3}. Intensity measurements were made with Cu $K\alpha$ radiation on a κ-geometry diffractometer employing a crystal of dimensions 0·16 × 0·30 × 0·65 mm; of 2592 independent reflections measured, 1889 were considered observed ($I > 2\sigma_I$) and employed in the refinement. Final residuals are R = 0·045, R_w = 0·060; S, the goodness of fit parameter, is 1·45. Embedded within the compound are all the atoms normally present in the prostaglandin skeleton, with steroid-derived bridges between atoms C(5) and C(13), and C(4) and C(15) of the prostaglandin. Little conformational homology between the compound and any of the known prostaglandins can be found. A *gauche* twist at the end of the pentyl chain and a folding back of the carboxylic acid group over the remainder of the steroid *A* ring characterize the conformation.

Introduction

The configurational similarities of the prostaglandin (PG) and steroid (ST) skeletal structures (Fig. 1), coupled with the repeated observation of PG conformations characterized by the alignment of side chains (DeTitta, Langs, Edmonds & Duax, 1979), has led a number of groups working on steroid synthesis to modify steroids into prostaglandin analogs (Venton, Counsell, Sanner & Sierra, 1974; Baumgarth & Irmscher, 1975*a*,*b*). These hybrid steroid/prostaglandins (STPG's) have absolute configurations opposite to those found for PG's but in view of the biological potencies of various epimeric and enantiomeric PG analogs (Andersen & Ramwell, 1974) it is not obvious that STPG's would be inactive compounds on configurational grounds alone. Starting with the androstane skeleton a variety of PG analogs can be synthesized by specifying which of the *A*, *B*, or *C* rings of the ST nucleus will remain intact and which are opened up to form the α and ω chains of the PG. In the case of the title compound (STPG-1), synthesized by Baumgarth & Irmscher (1975*a*,*b*), the *A* ring has been cleaved, and a pentyl chain, corresponding to C(16)

0567-7408/79/020366-04$01.00

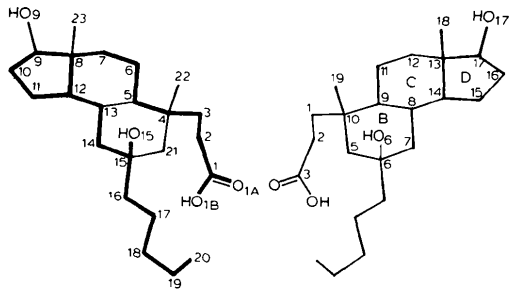

Fig. 1. The connectivity and nomenclature of STPG-1. On the left the molecule is seen as a prostaglandin chemist would normally view it; the nomenclature of the PG skeleton (in heavy line) is standard; the additional bonds and atoms introduced by the steroid skeleton are in light line. On the right, STPG-1 is seen as the steroid chemist would normally view it; the nomenclature (which is *not* in the text) of the parent androstane is indicated for reference.

through C(20), and a hydroxyl group, corresponding to O(15), of the PG skeleton have been added. Our initial curiosity was to see if there was any structural homology between STPG-1 and the PG's studied to date by diffraction techniques.

Experimental

Crystals were grown from a mixed benzene/cyclohexane solution. The structure was determined by multisolution tangent-refinement techniques (Germain, Main & Woolfson, 1971) coupled with a figure of merit based on four-phase cosine invariants estimated to be negative (DeTitta, Edmonds, Langs & Hauptman, 1975). The phase set consistently judged 'best' on the figures of merit ABSFOM (0·99), RESID (0·32), and NQEST (−0·23) yielded an E map in which the 27 nonhydrogen atom positions were located within the top 30 peaks of the map. Refinement was by standard full-matrix least-squares techniques. The positions and isotropic thermal parameters for the nonhydrogen atoms were varied in the first cycles of refinement until $R = 0{\cdot}12$. A difference Fourier map revealed the positions of 28 H atoms. Further refinement, permitting the thermal parameters of the nonhydrogen atoms to refine anisotropically, followed by a second difference map revealed the remaining 12 H atom locations. All H atom positions and isotropic thermal parameters were varied in the two final cycles of refinement. Throughout the refinement the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2$; σ is given by equation (H14) of Stout & Jensen (1968), except that the factor $0{\cdot}01N_{pk}$ has been replaced by $0{\cdot}06N_{pk}$. Final residuals are $R = 0{\cdot}045$ and $R_w = 0{\cdot}060$. S, the standard deviation of an observation of unit weight, is 1·45. Final positional parameters for nonhydrogen atoms and hydroxyl hydrogens are summarized in Table 1.* Bond distances and angles are shown in Fig. 2, and torsion angles are given in Table 2. The atomic nomenclature follows the prostaglandin scheme since the primary interest in this study is the relationship of STPG-1 to PG's. Scattering factors employed throughout the refinement are those given by Cromer & Waber (1974) for C and O, and those given by Stewart, Davidson & Simpson (1965) for H.

Discussion

The conformation of STPG-1 is shown in Fig. 3. The view is chosen to emphasize the PG skeletal structure which is usually viewed with the cyclopentane ring (the *D* ring of steroids) to the left. The crystal structure of STPG-1 is shown in Fig. 4.

The fixed portion of the PG backbone, from C(4) to C(15), contains a number of conformational features not found in natural PG's. For example, ring closure by bond C(5)–C(12) closes the C(7)–C(8)–C(12)–C(13)

* Lists of structure factors, anisotropic thermal parameters and covalent H positional and isotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33977 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional parameters for STPG-1*

	x	*y*	*z*
O(1*A*)	0·1657 (3)	0·4512 (1)	0·2688 (3)
O(1*B*)	0·1493 (2)	0·3366 (1)	0·3055 (3)
O(9)	−0·1826 (2)	0·1566 (1)	−0·4657 (2)
O(15)	0·3058 (2)	0·4032 (1)	−0·2883 (2)
C(1)	0·1216 (3)	0·3957 (2)	0·2445 (2)
C(2)	0·0281 (3)	0·3864 (2)	0·1460 (4)
C(3)	0·0351 (3)	0·4350 (2)	0·0244 (3)
C(4)	0·0965 (3)	0·4071 (2)	−0·1017 (3)
C(5)	0·0475 (3)	0·3355 (2)	−0·1515 (2)
C(6)	−0·0765 (3)	0·3406 (2)	−0·1870 (4)
C(7)	−0·1259 (3)	0·2703 (2)	−0·2407 (4)
C(8)	−0·0561 (3)	0·2417 (2)	−0·3567 (3)
C(9)	−0·0803 (3)	0·1651 (1)	−0·3974 (3)
C(10)	0·0236 (3)	0·1410 (2)	−0·4738 (4)
C(11)	0·1192 (3)	0·1888 (2)	−0·4198 (4)
C(12)	0·0647 (3)	0·2327 (2)	−0·3092 (3)
C(13)	0·1182 (2)	0·3025 (2)	−0·2649 (3)
C(14)	0·2372 (3)	0·2911 (2)	−0·2176 (4)
C(15)	0·2934 (3)	0·3600 (2)	−0·1704 (3)
C(16)	0·4106 (3)	0·3419 (2)	−0·1164 (3)
C(17)	0·4801 (3)	0·4035 (2)	−0·0661 (5)
C(18)	0·6012 (3)	0·3838 (3)	−0·0444 (5)
C(19)	0·6691 (4)	0·4384 (4)	0·0300 (8)
C(20)	0·6821 (7)	0·5031 (4)	−0·0303 (16)
C(21)	0·2213 (3)	0·3962 (2)	−0·0666 (3)
C(22)	0·0837 (3)	0·4661 (2)	−0·2087 (4)
C(23)	−0·0658 (3)	0·2906 (2)	−0·4795 (3)
H(1*B*)	0·216 (5)	0·345 (3)	0·364 (6)
H(9)	−0·181 (3)	0·137 (2)	−0·526 (4)
H(15)	0·325 (3)	0·443 (2)	−0·266 (4)

Table 2. *Torsion angles* (°) *about the bonds in STPG-1*

O(1*A*)C(1)C(2)C(3)	34·7	C(23)C(8)C(12)C(11)	−69·4
O(1*B*)C(1)C(2)C(3)	−147·1	C(23)C(8)C(12)C(13)	61·8
C(1)C(2)C(3)C(4)	91·3	O(9)C(9)C(10)C(11)	151·1
C(2)C(3)C(4)C(5)	55·8	C(8)C(9)C(10)C(11)	25·1
C(2)C(3)C(4)C(21)	−64·6	C(9)C(10)C(11)C(12)	4·1
C(2)C(3)C(4)C(22)	176·9	C(10)C(11)C(12)C(8)	−31·6
C(3)C(4)C(5)C(6)	59·0	C(10)C(11)C(12)C(13)	−159·0
C(3)C(4)C(5)C(13)	−172·2	C(8)C(12)C(13)C(5)	57·6
C(21)C(4)C(5)C(6)	180·0	C(8)C(12)C(13)C(14)	180·0
C(21)C(4)C(5)C(13)	−52·0	C(11)C(12)C(13)C(5)	−180·0
C(22)C(4)C(5)C(6)	−59·0	C(11)C(12)C(13)C(14)	−57·5
C(22)C(4)C(5)C(13)	69·7	C(5)C(13)C(14)C(15)	−58·1
C(3)C(4)C(21)C(15)	172·1	C(12)C(13)C(14)C(15)	−180·0
C(5)C(4)C(21)C(15)	50·0	C(13)C(14)C(15)O(15)	−67·3
C(22)C(4)C(21)C(15)	−72·3	C(13)C(14)C(15)C(16)	176·5
C(4)C(5)C(6)C(7)	178·3	C(13)C(14)C(15)C(21)	53·1
C(13)C(5)C(6)C(7)	50·1	O(15)C(15)C(16)C(17)	64·9
C(4)C(5)C(13)C(12)	−180·0	C(14)C(15)C(16)C(17)	180·0
C(4)C(5)C(13)C(14)	57·7	C(21)C(15)C(16)C(17)	−58·8
C(6)C(5)C(13)C(12)	−50·8	O(15)C(15)C(21)C(4)	66·8
C(6)C(5)C(13)C(14)	−173·5	C(14)C(15)C(21)C(4)	−50·0
C(5)C(6)C(7)C(8)	−52·6	C(16)C(15)C(21)C(4)	−171·4
C(6)C(7)C(8)C(9)	166·8	C(15)C(16)C(17)C(18)	−167·2
C(6)C(7)C(8)C(12)	56·3	C(16)C(17)C(18)C(19)	−168·8
C(6)C(7)C(8)C(23)	−68·0	C(17)C(18)C(19)C(20)	−63·4
C(7)C(8)C(9)O(9)	72·0	H(1*B*)O(1*B*)C(1)O(1*A*)	−6·4
C(7)C(8)C(9)C(10)	−159·8	H(1*B*)O(1*B*)C(1)C(2)	175·3
C(12)C(8)C(9)O(9)	−171·1	H(9)O(9)C(9)C(8)	130·5
C(12)C(8)C(9)C(10)	−43·7	H(9)O(9)C(9)C(10)	9·0
C(23)C(8)C(9)O(9)	−53·0	H(15)O(15)C(15)C(14)	170·2
C(23)C(8)C(9)C(10)	74·4	H(15)O(15)C(15)C(16)	−73·2
C(7)C(8)C(12)C(11)	167·5	H(15)O(15)C(15)C(21)	51·0
C(7)C(8)C(12)C(13)	−61·3		
C(9)C(8)C(12)C(11)	46·5		
C(9)C(8)C(12)C(13)	177·7		

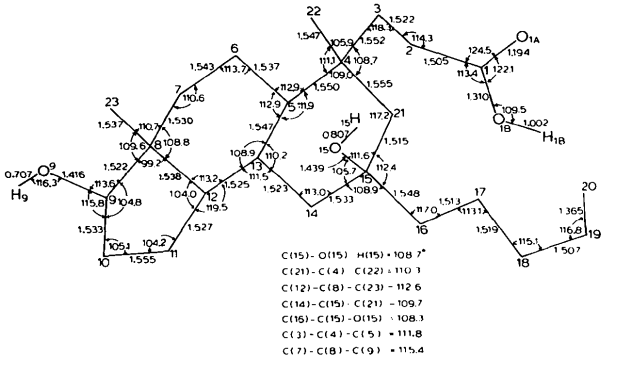

Fig. 2. Bond distances (Å) and bond angles (°) for STPG-1. The estimated standard deviations in bond distances are 0·006 Å and in bond angles 0·3°.

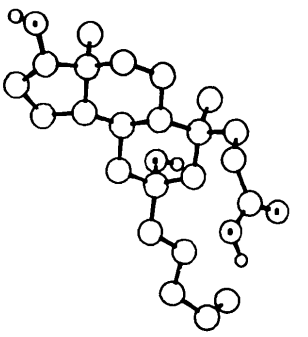

Fig. 3. The observed conformation of STPG-1. Note the *gauche* twist at the end of the pentyl chain and the folding of the carboxyl chain.

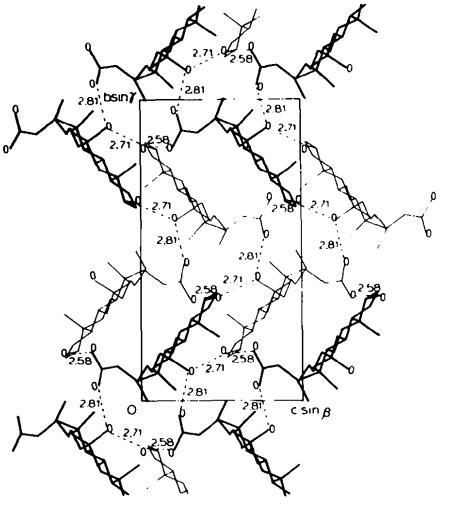

Fig. 4. The crystal and molecular structure of STPG-1 as viewed in projection down the crystallographic *a* axis. Hydrogen bonds are indicated by broken lines.

torsion angle to −61·3°. In natural PG's this angle is in the +70 to +90° range; in *ent*-PG's the range would be −70 to −90°. Although the C(8)-junction geometry, which is antiperiplanar to C(9) and synclinal to C(12), is similar to that found for PGA_1 (Edmonds & Duax, 1975; DeTitta, Langs & Edmonds, 1979) and PGE_1 (Spek, 1977), the C(12)-junction geometry, which is antiperiplanar to C(8) and (−)-synclinal to C(11), is completely different from the (±)-anticlinal C(12) junction geometry of most PG's. The cyclopentane ring geometry of STPG-1 is best described as a C(8) envelope, $\Delta C_s = 3·5°$ (Duax, Weeks & Rohrer, 1976); this is somewhat similar to the geometry found in monoclinic PGA_1, except that in STPG-1 internal ring torsion angles range in magnitude from 4·1° about the C(10)–C(11) bond to 46·5° about the C(8)–C(12) bond while in PGA_1 the largest torsion angle is only 17·4°, about C(8)–C(9). Bridging *via* C(21) between C(4) and C(15) positions the O(15) hydroxyl group below the plane of the fused-ring system as opposed to out and away from the centroid of the molecule as found for PG's (DeTitta, 1976).

The flexible portions of the STPG-1 skeleton [C(1) to C(3), and C(16) to C(20)] also display conformational characteristics not normally found in PG's. For instance, the carboxylic acid chain starting at O(1*B*) and extending to C(5) is usually all-*trans* planar in PG's. In STPG-1 the side chain twists away from the planar arrangement at every possible bond between O(1*B*) and C(6) to form a highly kinked chain. Similarly C(16) through C(20) is usually, but not always (Langs, Erman & DeTitta, 1977), fully exten-

ded. In STPG-1 the chain undergoes a *gauche* twist at its very end.

Upon visual examination, the conformation of STPG-1 seems to resemble only faintly the hairpin conformations of prostaglandins we have previously studied. In particular the bending down of the C(13) side chain and attendant distortion of the C(12)-junction geometry seemed to suggest that STPG-1 would be a very poor PG mimic. On the other hand, the arrangement C(8)–C(12)–C(13)–C(14) $\simeq$ 180° has also been observed for L-shaped PGB_1 and so a more precise search for structural homology between STPG-1 and PGB_1 was undertaken. Employing a fitting algorithm similar to that described by Nyburg (1974) the structural moiety C(7) through C(15) of STPG-1 was fit to the corresponding moiety of *ent*-PGB_1. The results of the fitting are shown in Fig. 5. The individual conformations of the two molecules which constitute the best fit (average separation 0·19 Å, e.s.d. of the average 0·09 Å) are shown below the composite drawing. The point of worst fit occurred at C(8) (separation of 0·38 Å). Below the individual molecules is the composite seen edgewise. Note that the angular methyls and O(15) hydroxyl of STPG-1 extend out from the fused rings, while the O(15) hydroxyl of PGB_1 is approximately within the plane of the fused rings. Also note that while the pentyl chains remain within 2·3 $\pm$ 0·7 Å of one another (the distance between corresponding atoms in the composite), the carboxyl chains range in separation from 2·22 Å for C(6) to 7·94 Å for C(1). We conclude that STPG-1 is also a poor mimic of PGB_1.

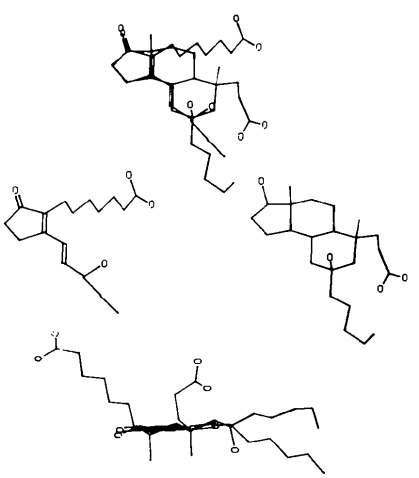

Fig. 5. A composite view, calculated by a least-squares fitting routine, of STPG-1 and PGB_1. Below the composite are the individual molecules PGB_1 (left) and STPG-1 (right) in the conformations which form the composite. At the bottom the composite is seen edgewise (rotated 90° from the top drawing). As can be seen, although there is some structural homology in the C(7) through C(15) region, there is very little homology in the pentyl or carboxylic acid chains or in the O(15) position.

We thank Drs K. Irmscher and M. Baumgarth, Merck Geschaftsbereich Pharm, Darmstadt, for crystals of STPG-1, Drs D. C. Rohrer and G. D. Smith for making *FITMOL*, the least-squares fitting procedure, available to us, Dr D. C. Rohrer for the supervision of the data collection and J. P. Hazel for his assistance in performing the computations. Figs. 1, 3, and 5 were composed on *PROPHET*, a computing system dedicated to biomedical computing and supported by the Division of Research Resources, NIH. This work was generously supported by Grant No. HL-15378 awarded by the National Heart, Lung, and Blood Institute, DHEW.

References

ANDERSEN, N. H. & RAMWELL, P. W. (1974). *Arch. Intern. Med.* **133**, 30–50.

BAUMGARTH, M. & IRMSCHER, K. (1975*a*). *Tetrahedron*, **31**, 3109–3118.

BAUMGARTH, M. & IRMSCHER, K. (1975*b*). *Tetrahedron*, **31**, 3119–3130.

CROMER, D. T. & WABER, J. T. (1974). *International Tables for X-ray Crystallography*. Vol. IV, p. 71. Birmingham: Kynoch Press.

DETITTA, G. T. (1976). *Science*, **191**, 1271–1272.

DETITTA, G. T., EDMONDS, J. W., LANGS, D. A. & HAUPTMAN, H. (1975). *Acta Cryst.* A**31**, 472–479.

DETITTA, G. T., LANGS, D. A. & EDMONDS, J. W. (1979). In preparation.

DETITTA, G. T., LANGS, D. A., EDMONDS, J. W. & DUAX, W. L. (1979). In preparation.

DUAX, W. L., WEEKS, C. M. & ROHRER, D. C. (1976). *Stereochemistry*. Vol. 9, edited by N. L. ALLINGER & F. L. ELIEL, pp. 271–383. New York: John Wiley.

EDMONDS, J. W. & DUAX, W. L. (1975). *J. Am. Chem. Soc.* **97**, 413–417.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

LANGS, D. A., ERMAN, M. & DETITTA, G. T. (1977). *Science*, **197**, 1003–1005.

NYBURG, S. (1974). *Acta Cryst.* B**30**, 251–253.

SPEK, A. L. (1977). *Acta Cryst.* B**33**, 816–824.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

STOUT, G. H. & JENSEN, L. H. (1968). *X-ray Structure Determination. A Practical Guide*, p. 457. London: Macmillan.

VENTON, D. L., COUNSELL, R. E., SANNER, J. H. & SIERRA, K. (1974). *J. Med. Chem.* **18**, 9–16.