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Steroids and Related Natural Products. 97.* The Structure of 3β,16β,23(*R*),26-Tetrahydroxy-5β-cholestane

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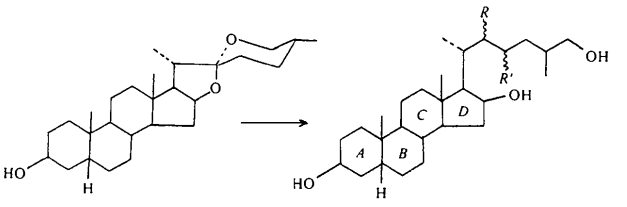
Abstract

Boron trifluoride catalyzed lithium aluminum hydride reduction of the steroidal sapogenin smilagenin was found to afford 3β,16β,23(*R*),26-tetrahydroxy-5β-cholestane and the crystal structure was determined by X-ray diffraction techniques. The crystals formed by this sterol correspond to the monoclinic space group $P2_1$ with lattice parameters a = 17·826 (5), b = 7·682 (2), c = 10·996 (4) A, β = 122·38 (2)° and Z = 2. Anisotropic least-squares refinement led to residual values of R = 0·058 and R_w = 0·048. The sterol crystals were shown to have two independent sets of hydrogen bonds that form spirals of molecules parallel to the screw axes. All three cyclohexane rings were found to exist in slightly flattened chair conformations while the cyclopentane ring resides in a distorted C(13) envelope conformation.

Introduction

Lithium aluminum hydride reduction of smilagenin (1) in the presence of boron trifluoride etherate leads to (1→2) four tetrahydroxy-5β-cholestanes (Pettit, Einck & Knight, 1978). Chemical degradation and mass-spectral evidence allowed two of the sterols to be characterized as the C(22) epimeric 3β,16β,22ξ,26-tetrahydroxy-5β-cholestanes (2*a*) and the other two tetrols as the C(23) epimeric 3β,16β,23ξ,26-tetrahydroxy-5β-cholestanes (2*b*). For the purpose of completing the structural and stereochemical assignments, one of the C(23) epimers was selected for X-ray analysis.



(–) Smilagenin

(2*a*) R = OH. R' = H
(2*b*) R = H. R' = OH

* Part 96: Pettit, Einck & Knight (1978).

Experimental

Crystals suitable for single-crystal X-ray analysis were obtained by cooling an acetone–methanol solution of (2*b*); the crystals melt at 469–475·5 K. Precession photographs revealed Laue symmetry and systematically extinct reflections, $0k0$ for $k = 2n + 1$, which correspond uniquely to the monoclinic space group $P2_1$. Cell constants obtained from a least-squares refinement of 15 strong general reflections ($5 < 2\theta < 24°$) centered on a Syntex $P\bar{1}$ autodiffractometer are summarized in Table 1. The crystal density was measured by flotation in carbon tetrachloride–toluene.

All X-ray diffraction intensity measurements were made with the same crystal by standard methods employing a Syntex $P\bar{1}$ four-circle autodiffractometer. Each reflection was scanned 0·7° in 2θ above and below the $K\alpha$ doublet values in a variable-speed 2θ–θ mode at a rate (from 1 to 12° min^{-1}) determined from a fast prescan. The time taken to collect each reflection was apportioned as follows: $\frac{1}{6}$ for initial background, $\frac{2}{3}$ for peak scan, and $\frac{1}{6}$ for final background. Standard deviations based on counting statistics were estimated from the formula $\sigma(I)_{\text{statistical}} = R[C + 1/k^2(B_1 + B_2)]^{1/2}$ where C is the total integrated counts at a rate R. The value k (0·5) is the background to scan time ratio, and B_1 and B_2 are background counts. Of 2849 reflections measured in one quadrant of reciprocal space, 2645 unique reflections with $|F_o| > 0$ were accepted. Corrections were made for Lorentz and

Table 1. *Crystal data*

Molecular formula	$C_{27}H_{48}O_4$		
M_r	436·7		
Crystal system	Monoclinic		
Habit/form	Plates, elongated along *b*		
Crystal dimensions	0·43 × 0·25 × 0·05 mm		
Systematic absences	$0k0$, $k = 2n + 1$		
Space group	$P2_1$		
a	17·826 (5) Å	D_c	1·14 Mg m^{-3}
b	7·682 (2)	D_m	1·12
c	10·996 (4)	μ(Cu $K\alpha$)	0·54 mm^{-1}
β	122·38 (2)°	λ(Cu $K\alpha$)	1·5418 Å
V_c	1271·7 Å^3	φ axis	*b*
Z	2	$(\sin\theta/\lambda)_{\max}$	0·60 Å^{-1}

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polarization effects but not for absorption ($\mu = 0{\cdot}54$ mm^{-1}) or extinction. Exceptionally good crystal stability was noted as indicated by the 0·7 to 1·1% standard-deviation range using nine standards evaluated every 50 reflections. However, reflections were scaled according to any minor fluctuations present.

Structure solution and refinement

Initial attempts to solve the structure by direct methods using *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974) met with failure. However, when normalized structure factors were generated from reflections restricted to $0{\cdot}2 < (\sin\theta)/\lambda < 0{\cdot}5$ Å^{-1}, solution of the structure was achieved. The use of reflections with $E(hkl) > 1{\cdot}27$ and 2000 $\sum_2$ relationships (Sayre, 1952; Hauptman & Karle, 1953) generated 16 phase sets. When the set with the highest ψ_o figure of merit was used to synthesize an E map, geometrically acceptable positions for 17 of the 31 nonhydrogen atoms were produced. After an E map synthesized from structure factors calculated from the 17-atom fragment yielded only three additional atoms, the remaining 11 atoms were located by difference Fourier syntheses.

Due to the arbitrary positions of the atoms along the polar b axis, the y coordinate of C(13) was fixed throughout refinement. Each reflection was assigned a weight, $w = 1/\sigma^2(F)$, and real atomic scattering factors for C, O and H (*International Tables for X-ray Crystallography*, 1974). Isotropic refinement (Rollett & Carruthers, 1975) using full-matrix least-squares methods converged with a standard residual $R = 0{\cdot}135$ and a weighted residual $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ of 0·131. The quantity minimized throughout refinement was $\sum w(|F_o| - |F_c|)^2$. Estimated standard deviations for each reflection were determined by the relationship $\sigma(F_o) = \{[\sigma^2(I)_{\text{statistical}} + P^2I^2]/4I\text{Lp}\}^{1/2}$, where the instrument instability constant, $P = 0{\cdot}0052$, was determined by a smoothing-function modification of the method of McCandlish & Stout (1975). Anisotropic refinement was performed by a large-block least-squares treatment (the first block contained the atomic coordinates, the second consisted of the thermal parameters and a scale factor) until it converged with $R = 0{\cdot}113$ and $R_w = 0{\cdot}105$. All H atoms attached to C atoms were placed and verified in a difference Fourier electron density map at idealized positions 1·0 Å from the respective C atom. However, hydroxyl H atoms located from the same difference Fourier electron density map, assigned an isotropic thermal parameter $U = 0{\cdot}06$ Å^2, were refined.

Anisotropic refinement (in which the positional parameters of the hydroxyl H atoms were allowed to vary in addition to the anisotropic nonhydrogen atoms) converged to final residuals $R = 0{\cdot}058$ and $R_w = 0{\cdot}048$ for 2013 reflections. In the final cycle the largest shift of any parameter was 0·6 of the estimated standard deviation and the ratio of the number of observations to the number of parameters was 6·9:1. In the final cycles of refinement, reflections were restricted to $|F_o| > 1{\cdot}0\sigma_{F_o}$, $|F_o| < 87{\cdot}4$, and $(\sin\theta)/\lambda \leq 0{\cdot}57$ Å^{-1}. As an independent check, a difference Fourier map was found to be essentially flat with a maximum density differential of 0·18 e Å^{-3}. No unusual systematic variation of $(|F_o| - |F_c|)^2$ *versus* H, K, L, index parity, $|F_o|$, or $(\sin\theta)/\lambda$, was observed.

Results and discussion

Refined positional parameters of the atoms in the 23(R) sterol (2b) are listed in Tables 2 and 3.* Thermal

* Lists of structure factors, anisotropic thermal parameters, intermolecular distances and details of the least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34944 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional coordinates* ($\times 10^4$) *for nonhydrogen atoms*

E.s.d.'s are given in parentheses.

	x	y	z
C(1)	6203 (3)	1200 (8)	2836 (6)
C(2)	6672 (3)	1102 (9)	4443 (6)
C(3)	6578 (3)	2749 (10)	5101 (5)
O(3)	5696 (2)	2826 (8)	4798 (3)
C(4)	6790 (3)	4328 (9)	4530 (6)
C(5)	6326 (3)	4416 (8)	2897 (5)
C(6)	6603 (3)	6038 (8)	2437 (6)
C(7)	7558 (3)	5953 (8)	2786 (6)
C(8)	7732 (3)	4284 (8)	2215 (5)
C(9)	7474 (2)	2673 (8)	2754 (4)
C(10)	6483 (3)	2732 (8)	2287 (4)
C(11)	7759 (3)	980 (8)	2381 (5)
C(12)	8730 (3)	956 (8)	2788 (5)
C(13)	8941 (2)	2500*	2179 (4)
C(14)	8706 (3)	4141 (8)	2718 (5)
C(15)	9124 (3)	5660 (8)	2382 (5)
C(16)	9946 (3)	4895 (8)	2488 (5)
O(16)	9898 (2)	5284 (7)	1171 (3)
C(17)	9946 (3)	2912 (8)	2784 (4)
C(18)	8428 (3)	2383 (8)	525 (4)
C(19)	5851 (3)	2733 (10)	622 (5)
C(20)	10450 (3)	1800 (8)	2291 (4)
C(21)	10489 (3)	−114 (9)	2656 (5)
C(22)	11401 (2)	2507 (8)	2907 (4)
C(23)	11728 (3)	2281 (8)	1903 (4)
O(23)	11118 (2)	3136 (7)	549 (3)
C(24)	12628 (3)	3147 (8)	2489 (4)
C(25)	13089 (3)	2715 (11)	1697 (4)
C(26)	13557 (3)	967 (11)	2133 (6)
O(26)	14204 (2)	788 (7)	3629 (4)
C(27)	13730 (3)	4155 (11)	1912 (7)

* C(13) was fixed arbitrarily along the polar y axis throughout the least-squares refinement.

parameters are shown graphically in the form of their 50% probability ellipsoids in Fig. 1, which also displays configurational and conformational aspects of the molecule. Bond lengths, bond angles and torsion angles are given in Fig. 2. Since sterol (*2b*) (23*R*) was obtained by reduction of the steroidal sapogenin smilagenin, the absolute configuration is shown in the correct enantiomorphic form. Therefore, the twelve chiral centers are assigned: C(3)–*S*, C(5)–*R*, C(8)–*R*, C(9)–*S*, C(10)–*S*, C(13)–*S*, C(14)–*S*, C(16)–*S*, C(17)–*R*, C(20)–*R*, C(23)–*R*, and C(25)–*R*.

Rings *A*, *B*, and *C* all exist in chair conformations and are slightly flattened by torsion angles of less than 60°. Deviations of eight bond lengths, C(1)–C(2), C(2)–C(3), C(3)–C(4), C(9)–C(10), C(12)–C(13), C(13)–C(17), C(16)–C(17), and C(22)–C(23), from an expected value of 1·533 ± 0·033 Å for C–C bond lengths in *n*-hydrocarbons (Bartell, 1959) by more than 2·6 standard deviations ($p < 0{\cdot}01$) are considered significant (Cruickshank & Robertson, 1953). Similar deviations from normal bond lengths within the *A* and *B* rings were also noted for digitoxigenin (Karle & Karle, 1969), the only other 3β-hydroxy-5β-androstane

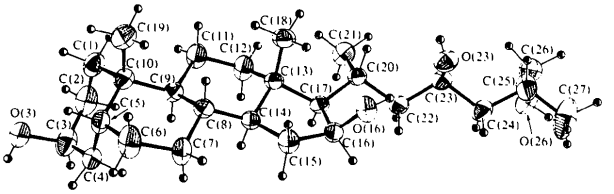

Fig. 1. Perspective view of the crystalline structure of 3β,16β,23(*R*),26-tetrahydroxy-5β-cholestane (*2b*); thermal ellipsoids for C and O are shown to include the 50% probability boundary surface. H atoms are represented as spheres with arbitrary radii (Johnson, 1976).

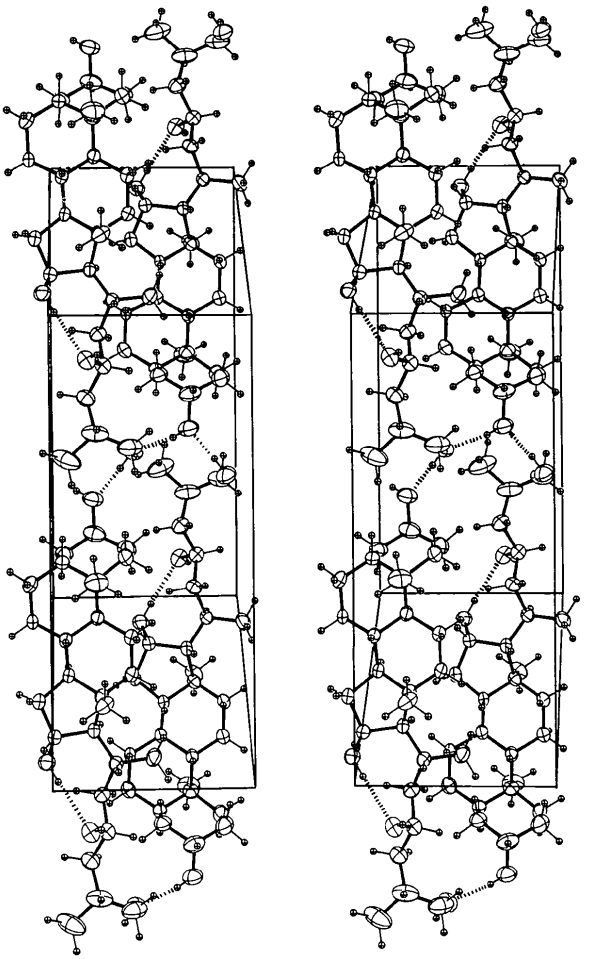

Fig. 3. Stereoscopic view of the molecular packing in the unit cell viewed down the *c* axis. Hydrogen bonds are represented by dotted lines. The O(23)–H···O(16) hydrogen bond is not shown in the diagram; however, it can be visualized by translating a molecule one cell length along *c*.

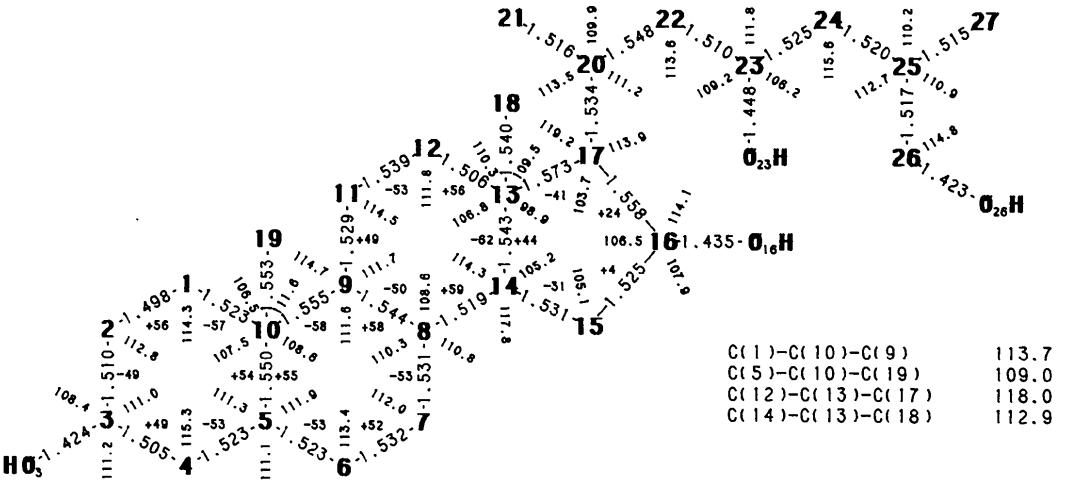

Fig. 2. Bond lengths (Å), bond angles (°), and torsion angles (°) in 3β,16β,23(*R*),26-tetrahydroxy-5β-cholestane (*2b*). E.s.d.'s for bond lengths are in the range 0·005–0·008 Å and average 0·006 Å. Bond angles have e.s.d.'s between 0·6 and 1·2° and average 0·8°. E.s.d.'s for the torsion angles range from 1·0 to 2·3° and average 1·8°.

structure reported. Digitoxigenin has short bond distances for C(1)–C(2) (1·521 ± 0·012 Å), C(2)–C(3) (1·520 ± 0·012 Å), and C(3)–C(4) (1·516 ± 0·012 Å) and a long C(9)–C(10) bond (1·550 ± 0·012 Å). Steroids with a free 3β-hydroxyl substituent generally have C(2)–C(3) and C(3)–C(4) bond distances significantly shorter than 1·533 Å (Karle & Karle, 1969; Weeks, Cooper, Norton, Hauptman & Fisher, 1971; Precigoux, Busetta, Courseille & Hospital, 1972; Gilardi & Karle, 1970; Hall, Maslen & Cooper, 1974), as is the case for sterol (2*b*) (23*R*).

Table 3. *Atomic positional parameters* (×10³) *of the hydrogen atoms*

Hydrogen atom bonded to	*x*	*y*	*z*
O(3)	567 (3)	361 (6)	523 (4)
O(16)	1027 (3)	473 (6)	106 (4)
O(23)	1083 (3)	262 (7)	35 (4)
O(26)	1467 (3)	141 (6)	389 (4)
C(1)	632	7	244
	553	123	237
C(2)	731	84	484
	641	10	470
C(3)	703	267	616
C(4)	745	447	497
	658	542	484
C(5)	568	439	253
C(6)	652	706	291
	617	615	136
C(7)	768	699	233
	800	601	385
C(8)	732	427	111
C(9)	786	270	385
C(11)	737	76	129
	765	−6	284
C(12)	914	108	392
	891	−12	254
C(14)	898	416	379
C(15)	926	664	307
	868	610	137
C(16)	1055	545	322
C(17)	1026	259	383
C(18)	857	346	11
	860	133	19
	777	238	8
C(19)	600	379	18
	593	167	19
	522	288	30
C(20)	1014	171	119
C(21)	989	−59	223
	1082	−80	231
	1083	−21	374
C(22)	1182	196	386
	1138	381	308
C(23)	1178	99	176
C(24)	1304	276	355
	1255	444	251
C(25)	1260	266	61
C(26)	1385	75	154
	1309	1	179
C(27)	1404	390	132
	1424	428	293
	1345	533	154

Flexibility of the five-membered *D* ring and the relative strain of the *C*/*D* ring junction can be an important consideration in steroid chemistry. Of all the torsion angles within rings *A*, *B* and *C*, only C(12)–C(13)–C(14)–C(8) is greater than 60° (−62°). The strain inherent in the *C*/*D* ring junction is responsible for the valency angles C(12)–C(13)–C(17) (118·0 ± 0·6°) and C(8)–C(14)–C(15) (117·8 ± 0·7°) being greater than those normally observed for quaternary (109·5°) and tertiary (110·5°) substituted C atoms (Geise, Altona & Romers, 1967). The sum of the torsion angles C(12)–C(13)–C(14)–C(8) and C(17)–C(13)–C(14)–C(15) (106°) conforms to an empirical value of 109 ± 3° for *C*/*D* junctions with an axial methyl at C(13) and a β substituent at C(17) (Geise, Altona & Romers, 1967).

The three-dimensional conformation of a cyclopentane ring may be described most concisely by the parameters Δ and φ_m (Altona, Geise & Romers, 1968; Duax & Norton, 1975). The overall ring conformation is defined by the phase-angle parameter, Δ [$\Delta = +36°$, C(13) envelope; $\Delta = 0°$, half-chair; $\Delta = -36°$, C(14) envelope], while φ_m is the maximum torsion angle attainable for the conformation described by Δ. The *D* ring of sterol (2*b*) (23*R*) can be described as a distorted C(13) envelope conformation with $\Delta = 25°$ and $\varphi_m = 45°$. The distances of C(13) and C(14) from the C(15)–C(16)–C(17) plane are 0·617 and −0·095 Å respectively.

Examination of the three-dimensional packing of molecules within the crystalline lattice, Fig. 3, reveals that all available hydroxyl substituents are involved in hydrogen bonding (*cf.* Table 4) with each serving in a proton-donor and a proton-acceptor capacity. Two distinct types of hydrogen-bonding sequences create a rigid three-dimensional network of molecules. The first type connects the 'ends' of the molecules as spirals consisting of two alternating strong hydrogen bonds (Brown, 1976) in the sequence $\cdots$[O(3)–H$\cdots$O(26)–H$\cdots$]$_x$O(3)–, which run along a screw axis through the center of the unit cell (at $\frac{1}{2},y,\frac{1}{2}$). Another spiral

Table 4. *Hydrogen bonds*

Donor	Acceptor	Coordinates of acceptor	O···O	O···H	O···H	∠O–H···O
O(3)	O(26)	$2-x, \frac{1}{2}+y, 1-z$	2·805 (5) Å	0·81 (4) Å	2·01 (4) Å	171 (4)°
O(26)	O(3)	$1+x, y, z$	2·741 (4)	0·86 (4)	1·90 (4)	167 (4)
O(16)	O(23)	x,y,z	3·084 (4)	0·85 (4)	2·24 (4)	174 (3)
O(23)	O(16)	$2-x, -\frac{1}{2}+y, -z$	2·826 (4)	0·66 (4)	2·19 (4)	162 (5)

running parallel to b along the screw axes located at the edges of the unit cell (through $0,\frac{1}{2},0$; $1,\frac{1}{2},0$; *etc.*) consists of alternating weak and strong hydrogen bonds, $\cdots[O(16)-H\cdots O(23)-H\cdots]_x O(16)-$.

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References

ALTONA, C., GEISE, H. J. & ROMERS, C. (1968). *Tetrahedron*, **24**, 13–32.
BARTELL, L. S. (1959). *J. Am. Chem. Soc.* **81**, 3497–3498.
BROWN, I. D. (1976). *Acta Cryst.* A**32**, 24–31.
CRUICKSHANK, D. W. J. & ROBERTSON, A. P. (1953). *Acta Cryst.* **6**, 698–705.
DUAX, W. L. & NORTON, D. A. (1975). *Atlas of Steroid Structure*, p. 17. New York: Plenum.
GEISE, H. J., ALTONA, C. & ROMERS, C. (1967). *Tetrahedron*, **23**, 439–463.
GILARDI, R. D. & KARLE, I. L. (1970). *Acta Cryst.* B**26**, 207–218.
HALL, S. R., MASLEN, E. N. & COOPER, A. (1974). *Acta Cryst.* B**30**, 1441–1447.
HAUPTMAN, H. & KARLE, J. (1953). *Solution to the Phase Problem. I. The Centrosymmetric Crystal.* Am. Crystallogr. Assoc. Monograph No. 3. Pittsburgh: Polycrystal Book Service.
International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99–101. Birmingham: Kynoch Press.
JOHNSON, C. K. (1976). *ORTEP* II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee.
KARLE, I. L. & KARLE, J. (1969). *Acta Cryst.* B**25**, 434–442.
MCCANDLISH, L. E. & STOUT, G. H. (1975). *Acta Cryst.* A**31**, 245–249.
MAIN, P., WOOLFSON, M. M., LESSINGER, L., GERMAIN, G. & DECLERCQ, J. P. (1974). *MULTAN* 74. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.
PETTIT, G. R., EINCK, J. J. & KNIGHT, J. C. (1978). *J. Am. Chem. Soc.* **100**, 7781–7782.
PRECIGOUX, C., BUSETTA, B., COURSEILLE, C. & HOSPITAL, M. (1972). *Cryst. Struct. Commun.* **1**, 265–270.
ROLLETT, R. S. & CARRUTHERS, J. R. (1975). *CRYSTALS.* Personal communication. All calculations other than data reduction and direct methods were made using an expanded *CRYSTALS* X-ray crystallographic computing programs package.
SAYRE, D. (1952). *Acta Cryst.* **5**, 60–65.
WEEKS, C. M., COOPER, A., NORTON, D. A., HAUPTMAN, H. & FISHER, J. (1971). *Acta Cryst.* B**27**, 1562–1572.

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Structures of Polyfluoroaromatic Compounds. VII.* The Structure of 2,2′-Dibromooctafluorobiphenyl

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Abstract

$C_{12}Br_2F_8$ is monoclinic, space group $P2_1/c$, with a = 12·29 (1), b = 8·20 (1), c = 12·905 (10) Å, β = 102·64 (5)°, Z = 4. The structure was refined to R = 4·26% for 1658 observed counter amplitudes. The inter-ring bond length is 1·489 (7) Å (uncorrected for thermal libration), and the inter-ring dihedral angle is 75·9 (5)°.

Introduction

The biphenyl system has been extensively studied by X-ray crystallography (*e.g.* Robertson, 1961; Charbonneau & Delugeard, 1976, 1977; Hamor & Hamor, 1978*a*,*b*), gas-phase electron diffraction (*e.g.* Rømming, Seip & Aanesen Øymo, 1974), spectroscopy (*e.g.* Schmid & Brosa, 1972), and theoretical calculations (*e.g.* Almlöf, 1974). Of particular interest in relation to bonding theory is the length of the central inter-ring bond and its variation (if any) with inter-ring dihedral angle. However, most crystal structures of biphenyls in the literature have inter-ring angles in the rather limited range 30–60°, and in only four structures, 2,2′-dichlorobiphenyl (Rømming, Seip & Aanesen Øymo, 1974), 2,2′-dibromo-4,4′-bis(*p*-methoxybenzylideneamino)biphenyl (Lesser, de Vries, Reed & Brown, 1975), 2-nitrononafluorobiphenyl (Hamor & Hamor, 1978*b*) and decachlorobiphenyl

* Part VI: Goodhand & Hamor (1979).

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