Steroids Derived from Fusidic Acid. Part 3.[1] Formation of a 9β-Steroid from a $\Delta^{9,11}$-Steroid Precursor. *X*-Ray Crystal Structure of 3α-Acetoxy-4α,8α,14β-trimethyl-18-nor-5α,9β,13β-androstan-17-one

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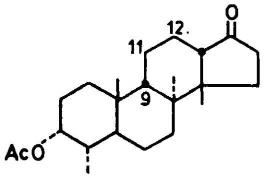
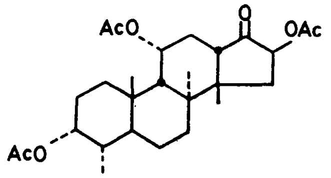
The crystal and molecular structure of the title compound (1) has been determined by *X*-ray crystallography. Crystals are orthorhombic, space group $P2_12_12_1$ with $Z = 4$, in a unit cell of dimensions $a = 7.274(1)$, $b = 10.041(1)$, $c = 28.263(4)$ Å. The structure was solved by direct methods and refined by full-matrix least-squares calculations to R 0.043 for 1 761 observed reflections. The C(9) β-configuration for the steroid is established unequivocally; rings A and C have chair conformations, ring B a twisted boat, and ring D a half-chair conformation. It is concluded that compound (1) is, unexpectedly, more stable than its C(9) α-epimer.

ANDROSTANONE (1) was required by us for synthetic purposes, and by adapting the method of Diassi and his co-workers,[2] we synthesised[1] it from fusidic acid[3] *via* the triacetate (2). However, we found strong evidence[1] to suggest that the chemical basis used by these previous workers[2] for assigning a β-configuration to C-9 in (1) was incorrect. Although estimation[2] by c.d. of the equilibrium position between (1) and its 13α-epimer indicated a C-9 β-configuration, the structure of (1) remained uncertain. There is additional interest in (1) since protosterol (3), synthesised by Huber and Immer[4] from (1) (which in turn was synthesised[4] from fusidic acid by the method of Diassi[2]), did not rearrange to lanosterol when incubated with rat-liver homogenase but was recovered unchanged.[4] The possibility presents itself that (3) may have had a 9α-configuration. Since the configuration of C-9 in (1) could not be determined by the usual spectroscopic techniques, nor chemically without major chemical modification, an *X*-ray crystallographic study of androstanone (1) was undertaken.



(1)



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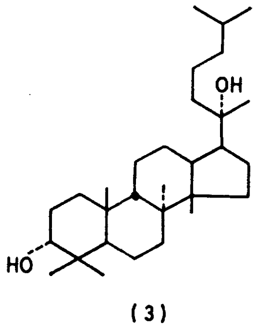

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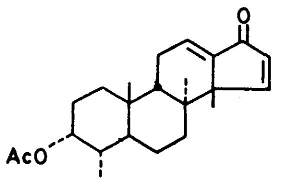

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RESULTS

The crystal structure (Figure 1) contains discrete, well separated molecules separated by normal van der Waals distances and the *X*-ray analysis establishes the relative configuration of the molecule as shown in Figure 2. The absolute configuration of (1), shown in formula (1) and also in Figure 2, is derived from that of fusidic acid; the absolute configuration of the latter has been deduced from c.d. measurements[5] and confirmed[6] by a single-crystal *X*-ray analysis of the 3-*p*-bromobenzoate of its methyl ester. The C(9) β-configuration for (1) is thus established beyond doubt. Torsion-angle data (Table 1), and Figure 1, show that rings A and C have chair conformations, ring B has a twisted boat, and ring D a half-chair conformation.

TABLE 1

Selected torsion angles (°)

C(10)–C(1)–C(2)–C(3)	−50.7(5)
C(1)–C(2)–C(3)–C(4)	47.4(5)
C(2)–C(3)–C(4)–C(5)	−51.2(5)
C(3)–C(4)–C(5)–C(10)	60.8(5)
C(4)–C(5)–C(10)–C(1)	−64.0(5)
C(5)–C(10)–C(1)–C(2)	57.2(5)
C(10)–C(5)–C(6)–C(7)	−72.5(5)
C(5)–C(6)–C(7)–C(8)	44.4(5)
C(6)–C(7)–C(8)–C(9)	12.6(5)
C(7)–C(8)–C(9)–C(10)	−47.1(5)
C(8)–C(9)–C(10)–C(5)	20.9(5)
C(6)–C(5)–C(10)–C(9)	38.0(5)
C(14)–C(8)–C(9)–C(11)	61.4(5)
C(8)–C(9)–C(11)–C(12)	−60.2(5)
C(9)–C(11)–C(12)–C(13)	49.9(5)
C(11)–C(12)–C(13)–C(14)	−45.0(5)
C(12)–C(13)–C(14)–C(8)	47.4(5)
C(13)–C(14)–C(8)–C(9)	−53.9(5)
C(15)–C(14)–C(13)–C(17)	34.8(5)
C(14)–C(13)–C(17)–C(16)	−29.4(5)
C(13)–C(17)–C(16)–C(15)	11.0(5)
C(17)–C(16)–C(15)–C(14)	11.6(5)
C(16)–C(15)–C(14)–C(13)	−28.3(5)

Mean bond lengths (Table 2) are close to the values normally expected[7-9] with C(sp^3)–C(sp^3) 1.539, C(sp^2)–C(sp^3) 1.495 Å, C(sp^2)–O 1.191, and C(sp^3)–O 1.469 Å. The bonds C(8)–C(14) [1.591(5) Å] and C(9)–C(10) [1.573(5) Å] are significantly longer than the mean value for bonds of their type (1.539 Å). Both these distances involve atoms which are overcrowded. Atoms C(8), C(10), and C(14) are fully substituted by carbon atoms and atom C(9) is bonded to

TABLE 2

Interatomic distances (Å) and angles (°), with standard deviations in parentheses

(*a*) Bonds

C(1)–C(2)	1.536(5)	C(13)–C(14)	1.552(5)
C(1)–C(10)	1.538(5)	C(14)–C(15)	1.556(5)
C(2)–C(3)	1.512(6)	C(15)–C(16)	1.528(6)
C(3)–C(4)	1.530(5)	C(16)–C(17)	1.503(7)
C(4)–C(5)	1.541(5)	C(17)–C(13)	1.495(6)
C(5)–C(10)	1.551(5)	C(14)–C(20)	1.527(6)
C(5)–C(6)	1.527(5)	C(8)–C(21)	1.535(5)
C(6)–C(7)	1.524(5)	C(10)–C(19)	1.547(5)
C(7)–C(8)	1.566(5)	C(4)–C(22)	1.523(6)
C(8)–C(9)	1.554(5)	C(17)–O(3)	1.196(5)
C(9)–C(10)	1.573(5)	C(3)–O(1)	1.469(5)
C(8)–C(14)	1.591(5)	C(23)–O(2)	1.186(5)
C(9)–C(11)	1.528(5)	C(23)–C(24)	1.486(6)
C(11)–C(12)	1.515(6)	C(23)–O(1)	1.333(5)
C(12)–C(13)	1.523(6)		

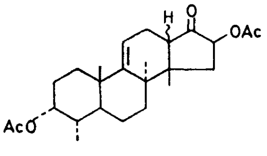
(*b*) Angles

C(2)–C(1)–C(10)	112.2(3)	C(4)–C(3)–O(1)	106.4(3)
C(1)–C(2)–C(3)	113.7(3)	C(3)–O(1)–C(23)	118.3(3)
C(2)–C(3)–C(4)	114.3(3)	C(8)–C(14)–C(15)	112.3(3)
C(3)–C(4)–C(5)	108.2(3)	C(14)–C(15)–C(16)	107.6(3)
C(4)–C(5)–C(10)	111.7(3)	C(15)–C(16)–C(17)	105.8(4)
C(5)–C(10)–C(1)	106.3(3)	C(16)–C(17)–C(13)	108.0(4)
C(4)–C(5)–C(6)	117.8(3)	C(17)–C(13)–C(14)	105.5(3)
C(6)–C(5)–C(10)	109.5(3)	C(17)–C(13)–C(12)	117.2(4)
C(5)–C(6)–C(7)	108.4(3)	C(13)–C(14)–C(20)	109.3(3)
C(6)–C(7)–C(8)	115.1(3)	C(15)–C(14)–C(20)	110.4(3)
C(7)–C(8)–C(9)	110.8(3)	C(8)–C(14)–C(20)	112.5(3)
C(8)–C(9)–C(10)	117.5(3)	C(14)–C(8)–C(21)	111.9(3)
C(9)–C(10)–C(5)	110.6(3)	C(9)–C(8)–C(21)	110.0(3)
C(9)–C(10)–C(1)	115.2(3)	C(7)–C(8)–C(21)	107.3(3)
C(9)–C(8)–C(14)	107.8(3)	C(1)–C(10)–C(19)	108.2(3)
C(7)–C(8)–C(14)	109.1(3)	C(5)–C(10)–C(19)	112.3(3)
C(8)–C(9)–C(11)	111.2(3)	C(9)–C(10)–C(19)	104.4(3)
C(9)–C(11)–C(12)	111.9(3)	C(3)–C(4)–C(22)	110.9(3)
C(10)–C(9)–C(11)	112.9(3)	C(5)–C(4)–C(22)	114.4(3)
C(11)–C(12)–C(13)	113.0(4)	C(13)–C(17)–O(3)	126.3(5)
C(12)–C(13)–C(14)	116.2(3)	C(16)–C(17)–O(3)	125.7(5)
C(13)–C(14)–C(8)	110.8(3)	O(1)–C(23)–C(24)	111.7(4)
C(13)–C(14)–C(15)	100.9(3)	O(1)–C(23)–O(3)	123.7(4)
C(2)–C(3)–O(1)	108.3(3)	O(2)–C(23)–C(24)	124.6(4)

three carbons and one hydrogen. Bond-length extension under these conditions has been observed previously, and our data are consistent with these observations.[8-10]

DISCUSSION

The synthesis of (1) involved [1] catalytic hydrogenation of dienone (4) which was obtained from triacetate (2) by reaction with zinc in refluxing acetic acid. We have shown [1] by means of deuteriation experiments with n.m.r. and m.s. analysis that elimination of the 11α-



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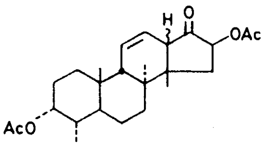

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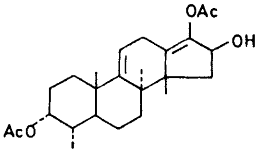

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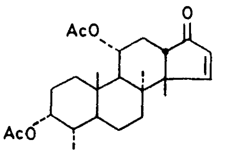

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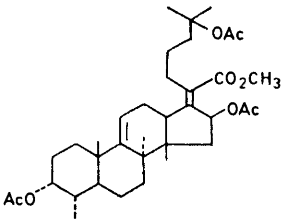

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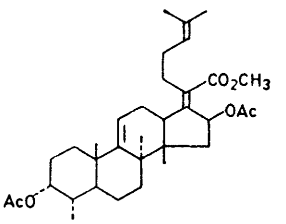

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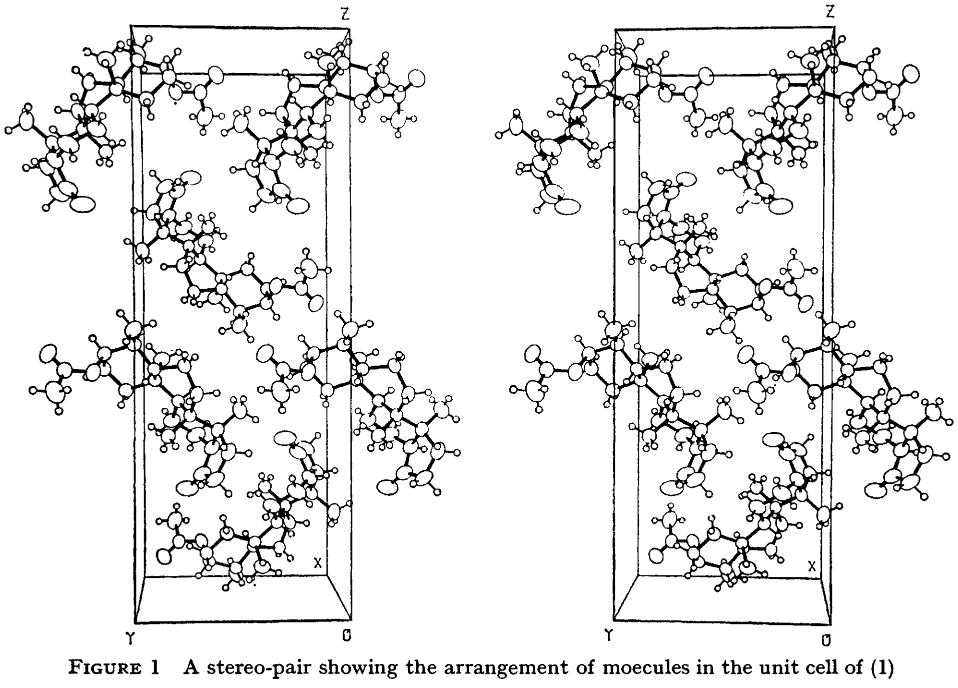

FIGURE 1 A stereo-pair showing the arrangement of moecules in the unit cell of (1)

acetoxy-group from (2) involved the loss of the C-9 proton. We therefore suggested that an initially formed $\Delta^{9,11}$-product such as (5) rearranged by prototropic rearrangement to dienone (4) after elimination of acetic acid. However, this theory presents the difficulty that the $\Delta^{9,11}$-transient product (5) must initially rearrange to a less stable $\Delta^{11,12}$-enone (6). Alternatively, we now suggest * that enone (5) rearranges to the enol acetate (7). There is then a driving force for the double-bond migration $\Delta^{9,10}\rightarrow\Delta^{11,12}$. Some evidence for this hypothesis is provided by our observation [1] that the enone (8) is not converted into the dienone (4) under the same conditions in which the triacetate (2) is converted into dienone (4). Further evidence for the involvement of enol acetate (7) is provided by the results of acid-catalysed acetylation of methyl fusidate. The diacetates (9) and (10) were isolated,[1] among other products. This indicates that unless a $\Delta^{13,17}$-intermediate such as (7) is involved, the C-9 to C-11 double bond does not migrate. There remains the question of why a 9β-configuration results from this prototropic rearrangement. Inspection of Dreiding models leads to the following conclusions: (*a*) 9α-attack on (7) by a proton is less hindered than 9β-attack, and (*b*) the 9β-epimer of (4) is more stable than the 9α-epimer. It appears therefore that protonation of (7) is reversible and that the initially formed 9α-epimer rearranges when heated under reflux in acetic acid to the more stable 9β-product.

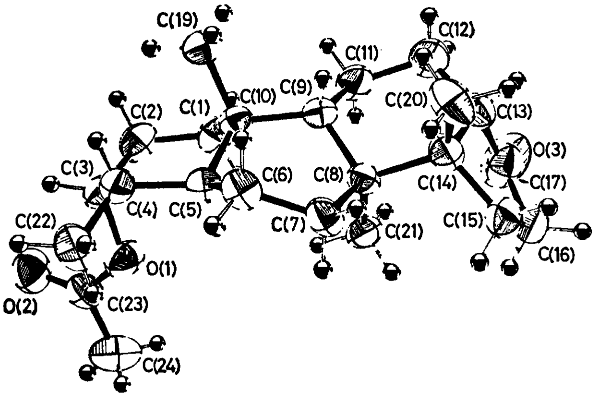

FIGURE 2 A perspective view of (1) showing the crystallographic numbering system used in the *X*-ray analysis

This result means that the structural assignment and conclusions of Huber and Immer [5] appear correct. Protosterol (3) appears not to be a biosynthetic precursor of lanosterol. Now that the first total synthesis of 11-deoxyfusidic acid is nearing completion,[11] androstanone (1) can now be employed as a relay.[12] Finally, androstanone (1), suitably modified in ring A, can be used for n.m.r. correlations with the stictanes [13] and related terpenoids.

EXPERIMENTAL

Suitable needle crystals of (1) were obtained from ethanol–water.

TABLE 3

Atom positional parameters for (1)

(*a*) Non-hydrogen atoms ($\times 10^4$)

Atom	*x*/*a*	*y*/*b*	*z*/*c*
C(1)	9 177(5)	4 368(3)	6 145(1)
C(2)	8 966(5)	3 320(3)	5 573(1)
C(3)	7 220(5)	3 466(3)	5 467(1)
C(4)	6 827(5)	4 887(3)	5 301(1)
C(5)	6 952(4)	5 822(3)	5 732(1)
C(6)	6 334(5)	7 264(3)	5 668(1)
C(7)	5 869(4)	7 836(3)	6 153(1)
C(8)	7 288(4)	7 507(3)	6 553(1)
C(9)	9 087(4)	6 925(3)	6 340(1)
C(10)	8 894(4)	5 793(3)	5 959(1)
C(11)	10 473(5)	6 584(4)	6 728(1)
C(12)	11 006(5)	7 797(4)	7 016(1)
C(13)	9 354(5)	8 586(4)	7 192(1)
C(14)	7 803(5)	8 842(3)	6 826(1)
C(15)	6 226(5)	9 327(3)	7 155(1)
C(16)	6 513(6)	8 686(5)	7 639(1)
C(17)	8 405(6)	8 087(4)	7 627(1)
C(19)	10 429(5)	6 096(4)	5 596(1)
C(20)	8 391(6)	9 956(4)	6 491(1)
C(21)	6 385(5)	6 480(3)	6 882(1)
C(22)	5 008(6)	4 958(4)	5 035(1)
C(23)	4 991(5)	1 848(3)	5 723(1)
C(24)	3 458(6)	1 601(4)	6 060(2)
O(1)	5 662(4)	3 077(2)	5 768(1)
O(2)	5 566(5)	1 054(3)	5 450(1)
O(3)	9 045(6)	7 359(4)	7 918(1)

(*b*) Calculated positions for hydrogen atoms † ($\times 10^3$)

Atom	*x*/*a*	*y*/*b*	*z*/*c*
H(11)	829	420	638
H(12)	1 038	430	628
H(21)	897	246	590
H(22)	998	340	554
H(31)	737	292	520
H(41)	772	518	508
H(51)	606	545	594
H(61)	528	729	547
H(62)	730	777	553
H(71)	580	878	612
H(72)	471	749	625
H(91)	956	764	616
H(111)	1 155	623	659
H(112)	995	594	693
H(121)	1 170	751	728
H(122)	1 174	836	683
H(131)	999	939	726
H(151)	507	907	703
H(152)	627	1 027	718
H(161)	562	801	769
H(162)	644	934	788
H(191)	1 040	545	535
H(192)	1 159	607	575
H(193)	1 024	696	546
H(201)	744	1 011	627
H(202)	948	970	633
H(203)	861	1 075	667
H(211)	721	626	713
H(212)	609	570	671
H(213)	529	685	701
H(221)	479	585	494
H(222)	404	468	524
H(223)	506	439	477
H(241)	301	72	602
H(242)	250	222	600
H(243)	389	171	638

† Hydrogen atoms are numbered to correspond with the carbon atom to which they are bonded, *e.g.* H(191) is bonded to C(19).

Crystal Data.—$C_{23}H_{36}O_3$, $M = 360.1$, Orthorhombic, $a = 7.274(1)$, $b = 10.041(1)$, $c = 28\,263(4)$ Å, $U = 2\,064.3$ Å^3, $D_m = 1.16$ g cm^{-3}, $F(000) = 792$. λ(Mo-K_α) = 0.710 69 Å, μ(Mo-K_α) = 0.41 cm^{-1}. Space group $P2_12_12_1$ (D_2^4, No. 19)

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determined uniquely from systematic absences (*h*00 if $h = 2n + 1$; 0*k*0 if $k = 2n + 1$; 00*l* if $l = 2n + 1$).

Space-group and unit-cell information were obtained from Weissenberg (Cu-K_α, $\lambda = 1.541\,8$ Å) and precession (Mo-K_α, $\lambda = 0.710\,69$ Å) photographs. Unit-cell dimensions and crystal orientation were determined by a least-squares treatment of the diffractometer co-ordinates of 12 reflections (θ_{hkl} 10—20°). Three-dimensional intensity data for a unique octant with $\theta(\text{Mo-}K_\alpha) \leqslant 25°$ were collected on a Hilger and Watts Y 290 computer-controlled four-circle diffractometer in our usual way[14] for a small needle crystal. A total of 1 761 independent reflections having $I \geqslant 2\sigma(I)$ were used in all subsequent calculations. Data were corrected for Lorentz and polarization factors but not for absorption, which was negligible.

Structure Solution and Refinement.—The structure was solved by direct methods using the program SHELX.[15] A suitable starting set of phases were found after a few trials and the resulting E map revealed all the oxygen and carbon atoms, except for two methyl carbons which were located in a subsequent difference-Fourier synthesis.

Two cycles of full-matrix least-squares refinement with anisotropic thermal parameters for carbon and oxygen atoms resulted in R 0.107, and a difference-Fourier synthesis revealed electron-density maxima in plausible locations for the hydrogen atoms. These were then allowed for (in the idealised positions with C–H 0.95 Å) in subsequent least-squares cycles; an overall isotropic thermal parameter was refined for each type (C–H, CH_2, or CH_3) of hydrogen atom. Three further cycles of full-matrix calculations converged with R 0.043 and R' ($= \Sigma w\Delta^2/\Sigma wF_o^2$) 0.053. In these calculations weights derived from counting statistics were applied; the scattering factor curves for carbon and oxygen atoms were obtained from ref. 16 and for hydrogen atoms from ref. 17. In the final cycle of refinement no shifts were $> 0.7\sigma$, and a final difference map was featureless.

A list of calculated and observed structure factors, thermal parameters, an analysis of variance calculated after the final refinement cycle, and details of intermolecular distances have been deposited as Supplementary Publication No. SUP 22428 (16 pp.).* Final co-ordinates for the atoms are given in Table 3.

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REFERENCES

[1] Part 2, W. S. Murphy and D. A. Cocker, *J.C.S. Perkin I*, 1977, 2565.

[2] P. A. Diassi, I. Bacso, G. W. Krakower, and H. A. Van Dine, *Tetrahedron*, 1966, 3459.

[3] W. O. Godtfredsen, 'Fusidic Acid and Some Related Antibiotics,' Copenhagen, 1967.

[4] V. H. Immer and K. Hüber, *Helv. Chim. Acta*, 1971, **54**, 1346.

[5] W. O. Godtfredsen, W. von Daehne, S. Vangedal, D. Arigoni, A. Marquet, and A. Melera, *Tetrahedron*, 1965, **21**, 3505.

[6] A. Cooper, *Tetrahedron*, 1966, **22**, 1379.

[7] *Special Publ. No.* 18, The Chemical Society, London, 1965.

[8] D. F. Rendle and J. Trotter, *J.C.S. Perkin II*, 1975, 1361.

[9] P. J. Roberts, J. C. Coppola, N. W. Isaacs, and O. Kennard, *J.C.S. Perkin II*, 1973, 774.

[10] C. M. Weeks, W. L. Duax, and M. E. Wolff, *Acta Cryst.*, 1976, **B32**, 261.

[11] R. E. Ireland, R. Giger, and S. Kamatu, *J. Org. Chem.*, 1977, **42**, 1276.

[12] M. Tanabe, D. M. Yasuda, and R. H. Peters, *Tetrahedron Letters*, 1977, **17**, 1481.

[13] R. E. Corbett and A. L. Wilkins, *J.C.S. Perkin I*, 1976, 1316.

[14] W. B. Whalley, G. Ferguson, W. C. Marsh, and R. J. Restivo, *J.C.S. Perkin I*, 1976, 1366.

[15] All calculations were performed using the programme system SHELX written by G. M. Sheldrick, University Chemical Laboratory, Cambridge, England.

[16] D. T. Cromer and J. B. Mann, *Acta Cryst.*, 1968, **A24**, 321.

[17] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

* For details see Notice to Authors, No. 7, *J.C.S. Perkin I*, 1978, Index issue.