Crystal Structure of Syringaresinol

By **Robert F. Bryan** and **Lawrence Fallon, tert.**, Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, U.S.A.

A crystal structure analysis has been carried out on a sample of the lignan (−)-syringaresinol, $C_{22}H_{26}O_8$, isolated from *Tripterygium wilfordii*. Crystals conform to space group $P2_12_12_1$ with a = 13.051(2), b = 18.106(4), c = 8.565(1) Å, and Z = 4. Intensities of 1 073 independent reflections were measured by counter diffractometry. The structure was solved by direct methods and least-squares refinement of the parameters gave R 0.064. All hydrogen atoms were located but no assignment of absolute configuration was possible.

The chemical assignment of the structure as 2,6-bis-(4-hydroxy-3,5-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane is confirmed as is the *cis*-configuration of the bridgehead hydrogens which have the same relative orientation as the aryl groups. The dioxabicyclo-octane nucleus has an effective diad axis bisecting the 1,5-bond of the lignan but there is a significant difference in the 1,2- [(5,6-)] and 4,5- [(8,9-)] bond lengths. Each oxolan ring adopts an envelope conformation with the flap at the site of attachment of the aryl substituent. The molecules are held together in the crystal in layers by hydrogen bonds between the phenolic hydroxy-groups and the furan oxygens.

SYRINGARESINOL (I) is a member of the substantial group of lignans having a 2,6-diaryl-*cis*-3,7-dioxabicyclo[3.3.0]-octane structure.[1] These lignans differ from one another principally in the pattern of oxygenation and relative orientation of the aryl groups. Although considerable confusion has attended the naming and identification of the syringaresinols and their dimethyl ethers,[2] well-

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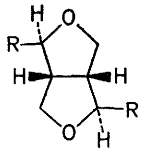
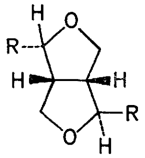
[1] For reviews see W. M. Hearon and W. S. MacGregor, *Chem. Rev.*, 1955, **55**, 957; M. S. Adjangba, *Bull. Soc. chim. France*, 1963, 2344.

[2] W. Stöcklin, L. B. de Silva, and T. A. Geissman, *Phytochemistry*, 1969, **8**, 1565.

characterized (+)-, (−)-, and (±)-forms of the lignan have been isolated from plant sources and the optically inactive material has been synthesized.[3] Episyringaresinol (II) is also known in (+)- and (−)-forms [3d,f] as is the compound (III) which has a *quasi*-diaxial conformation.[4] The assignment of structure and absolute configuration of (+)-syringaresinol deduced chemically and by comparison of its molecular rotation with those of lignans of known absolute configuration seems secure.[5]


(I)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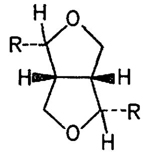
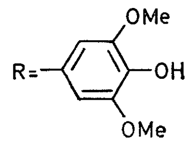

(III)



However, although a partial *X*-ray study of a dibromo-derivative of (+)-syringaresinol dimethyl ether (lirioresinol-B dimethyl ether) was used [6] to confirm the *cis* disposition of the bridgehead hydrogen atoms in the bicyclo-octane nucleus, by establishing crystallographic two-fold axial symmetry in the molecule, no other *X*-ray analysis seems to have been carried out for this family of lignans. The isolation, by Kupchan and Baxter, of (−)-syringaresinol in the course of a continuing phytochemical examination of *Tripterygium wilfordii* (Celastraceae) which earlier yielded the antileukaemic diterpenoid triepoxides triptolide and tripdiolide,[7] afforded an opportunity to study the stereochemistry of this lignan.

RESULTS AND DISCUSSION

The *X*-ray analysis has confirmed the chemically assigned structure for syringaresinol, but we have been unable to make an independent determination of the absolute configuration by use of anomalous dispersion. Atomic parameters and their standard deviations [8] are given in Table 1. A perspective view of the molecule is shown in Figure 1, and bond lengths and angles and the numbering scheme adopted in Figure 2. Torsion angles defining the conformation of the dioxabicyclo-octane ring and the orientations of the aryl groups and their substituents are given in Table 2. A projection of the ring system viewed down the bridgehead axis is shown in Figure 3. Co-ordinates and representations are given to conform to the assignment of absolute configuration to (+)-syringaresinol by Freudenberg and Weinges.[5]

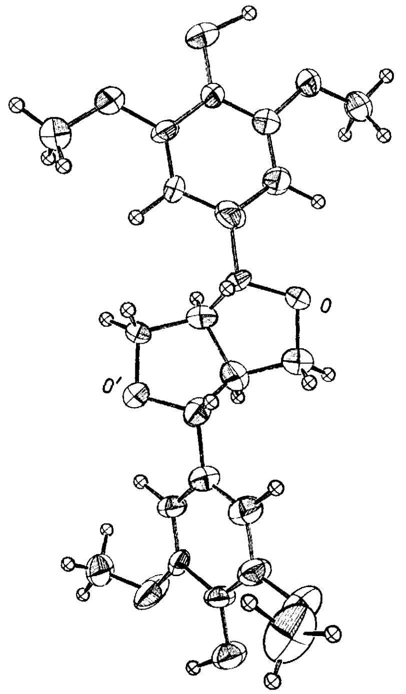


FIGURE 1 Perspective view of the molecule as found in the crystal. Thermal ellipsoids for oxygen and carbon are drawn with the 50% probability level as boundary surface

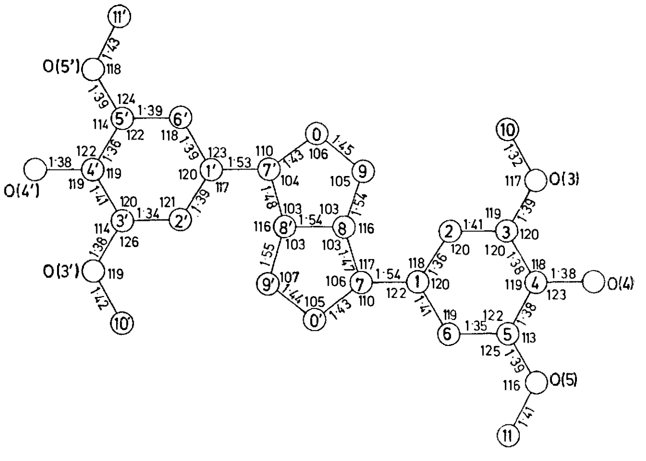


FIGURE 2 Bond lengths and angles and numbering scheme for syringaresinol. σ for bond lengths 0.012—0.016 Å, and for bond angles 0.75—1.06°

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[3] (*a*) K. Freudenberg, R. Kraft, and W. Heimberger, *Chem. Ber.*, 1951, **84**, 472; (*b*) K. Freudenberg and H. Dietrich, *ibid.*, 1953, **86**, 4; (*c*) K. Freudenberg and H. Schraube, *ibid.*, 1955, **88**, 16; (*d*) E. E. Dickey, *J. Org. Chem.*, 1958, **23**, 179; (*e*) H. Nimz and H. Gaber, *Chem. Ber.*, 1965, **98**, 538; (*f*) L. A. Eljakova, A. K. Dzizenko, and G. B. Elyakov, *Doklady Akad. Nauk S.S.S.R.*, 1965, **165**, 562; (*g*) R. R. Arndt, S. H. Brown, N. C. Ling, P. Roller, C. Djerassi, J. M. Ferreira, F. B. Gilbert, E. C. Miranda, S. E. Flores, A. P. Duarte, and E. P. Carrazzoni, *Phytochemistry*, 1967, **6**, 1653; see also ref. 2.

[4] L. H. Briggs, R. C. Cambie, and R. A. F. Couch, *J. Chem. Soc.* (*C*), 1968, 3042.

[5] P. R. Jeffries, J. R. Knox, and D. E. White, *Austral. J. Chem.*, 1961, **14**, 175; K. Freudenberg and G. S. Sidhu, *Chem. Ber.*, 1961, **94**, 851; K. Freudenberg and K. Weinges, *Tetrahedron*, 1961, **15**, 115 give the systematic nomenclature and numbering scheme adopted in describing the *X*-ray results.

[6] E. N. Maslen, C. Nockolds, and M. Paton, *Austral. J. Chem.*, 1962, **15**, 161.

[7] S. M. Kupchan, W. A. Court, R. G. Dailey, jun., C. J. Gilmore, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1972, **94**, 7194.

[8] L. I. Hodgson and J. S. Rollett, *Acta Cryst.*, 1963, **17**, 329.

The dioxabicyclo-octane nucleus has near C_2 symmetry about an axis bisecting the C(8)–C(8′) bond and shows some curious geometrical features. There is a significant difference in the bond lengths of the C(7)–C(8) and C(8)–C(9) pairs, the former being significantly shorter than the standard sp^3–sp^3 bond length of 1.54 Å. This shortening is accompanied by a significant lengthening of the C(7)–C(1) bonds from the ring to the syringyl residues. These anomalies may be associated with transmission of a σ-inductive effect from the aryl residues.

TABLE 1

Atomic parameters defining the crystal structure of syringaresinol

(*a*) Positional parameters (C and O × 10^4, H × 10^3)

Atom	*x*/*a*	*y*/*b*	*z*/*c*
O	2 261(5)	7 281(3)	7 835(10)
O(3)	−1 735(5)	5 124(5)	4 921(10)
O(4)	−1 672(5)	3 711(4)	6 026(10)
O(5)	30(5)	3 163(4)	7 308(13)
O′	2 788(5)	5 109(4)	6 132(9)
O(3′)	6 798(6)	7 408(4)	6 266(10)
O(4′)	6 744(5)	8 652(4)	7 864(10)
O(5′)	5 051(5)	9 126(3)	9 270(10)
C(1)	933(8)	5 025(6)	6 213(13)
C(2)	59(8)	5 287(6)	5 545(14)
C(3)	−828(7)	4 840(6)	5 520(14)
C(4)	−797(7)	4 133(5)	6 118(12)
C(5)	110(7)	3 879(5)	6 752(13)
C(6)	953(7)	4 306(5)	6 847(14)
C(7)	1 871(8)	5 537(6)	6 279(15)
C(8)	1 993(9)	5 983(6)	7 706(16)
C(9)	1 444(8)	6 738(6)	7 712(16)
C(10)	−1 857(12)	5 106(10)	3 392(15)
C(11)	956(9)	2 765(6)	7 451(16)
C(1′)	4 091(8)	7 411(5)	7 446(14)
C(2′)	4 997(7)	7 187(5)	6 744(15)
C(3′)	5 857(7)	7 586(5)	6 896(14)
C(4′)	5 851(7)	8 246(5)	7 766(13)
C(5′)	4 971(8)	8 456(5)	8 483(13)
C(6′)	4 069(8)	8 048(6)	8 360(13)
C(7′)	3 129(8)	6 960(5)	7 085(16)
C(8′)	3 138(8)	6 191(6)	7 671(16)
C(9′)	3 606(8)	5 603(5)	6 568(19)
C(10′)	6 920(9)	6 713(6)	5 543(19)
C(11′)	4 259(9)	9 315(6)	10 349(15)
H(2)	2	586	510
H(4)	−146	313	635
H(6)	168	409	738
H(7)	179	593	532
H(8)	173	566	872
H(9a)	95	678	874
H(9b)	100	681	669
H(10a)	−106	510	287
H(10b)	−224	462	306
H(10c)	−224	559	297
H(11a)	83	221	786
H(11b)	139	275	637
H(11c)	147	303	829
H(2′)	501	668	606
H(4′)	654	924	841
H(6′)	336	819	900
H(7′)	304	696	586
H(8′)	356	613	881
H(9′a)	389	589	553
H(9′b)	423	531	710
H(10′a)	759	670	489
H(10′b)	690	629	643
H(10′c)	626	665	467
H(11′a)	437	982	1 090
H(11′b)	415	887	1 122
H(11′c)	350	934	970

(*b*) Thermal parameters (× 10^4) for the exponent in the form $[h^2\beta_{11} + \ldots 2hk\beta_{12} + \ldots]$

Atom						
O	41(4)	17(2)	294(18)	−4(3)	16(8)	−21(6)
O(3)	52(5)	54(3)	228(17)	5(4)	−10(8)	37(7)
O(4)	43(5)	28(2)	269(18)	−6(3)	−14(8)	12(6)
O(5)	37(5)	37(3)	399(24)	5(3)	−2(9)	45(7)
O′	33(4)	25(2)	216(16)	−1(3)	10(7)	−14(5)
O(3′)	54(5)	33(3)	297(20)	−12(3)	59(9)	−36(6)
O(4′)	41(5)	36(3)	269(18)	−12(3)	20(9)	−16(6)
O(5′)	44(5)	27(2)	208(15)	−1(3)	12(8)	36(6)
C(1)	40(7)	31(4)	155(21)	−5(5)	−7(11)	−11(8)
C(2)	44(7)	33(4)	168(21)	−7(5)	6(11)	1(9)
C(3)	39(7)	33(4)	160(21)	−2(5)	−25(11)	3(8)
C(4)	36(6)	23(3)	139(21)	−10(4)	−7(10)	4(7)
C(5)	25(6)	21(3)	193(23)	6(4)	1(10)	3(8)
C(6)	35(6)	22(3)	175(22)	−7(4)	−3(11)	0(8)
C(7)	37(7)	40(4)	224(27)	3(5)	−3(12)	−41(9)
C(8)	65(9)	31(4)	260(29)	−5(5)	30(14)	38(10)
C(9)	53(8)	29(4)	244(27)	−8(5)	10(13)	−16(9)
C(10)	110(12)	107(9)	113(22)	26(10)	−20(15)	31(14)
C(11)	60(8)	24(4)	254(29)	10(5)	−6(14)	8(9)
C(1′)	55(8)	19(3)	203(24)	1(4)	−22(12)	6(8)
C(2′)	32(6)	25(4)	224(25)	3(4)	28(12)	23(8)
C(3′)	24(6)	22(3)	220(24)	−2(4)	10(11)	9(8)
C(4′)	31(6)	22(3)	162(21)	−1(4)	3(10)	−18(8)
C(5′)	44(7)	23(3)	140(20)	−3(4)	0(10)	−8(8)
C(6′)	40(7)	33(4)	142(21)	−1(5)	−14(11)	−26(8)
C(7′)	27(6)	24(3)	269(27)	−8(4)	39(12)	−12(8)
C(8′)	42(7)	29(3)	259(27)	−8(5)	−9(13)	−23(9)
C(9′)	45(7)	15(3)	390(37)	−9(4)	43(14)	−27(10)
C(10′)	70(9)	31(4)	344(34)	−4(5)	54(16)	−26(11)
C(11′)	65(8)	28(4)	204(26)	−2(5)	20(13)	−33(9)

The individual oxa-rings have distorted-envelope conformations with Δ values of −21 and −26°.[9] In each case the flap of the envelope is the atom to which the

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[9] H. J. Geise, C. Altona, and C. Rombers, *Tetrahedron*, 1967, **23**, 439.

aryl residue is attached equatorially. C(7) is 0.55 and C(7′) 0.59 Å above the respective least-squares mean plane through the remaining four atoms of the ring, and these two mean planes are inclined at 146°. The endocyclic torsion angles at the C(8)–C(8′) bridgehead are each –20° leading to an H(8) · · · H(8′) separation of 2.54 Å. The conformations adopted by the oxa-rings serve to minimize steric obstruction between the aryl residues and the central nucleus. In the overall molecular conformation found in the crystal H(2′) is 2.09 from H(9′a), and H(2) 2.55 Å from H(9b). Clearly, the particular orientation of the aryl residues observed in the crystal is dictated solely by packing requirements.

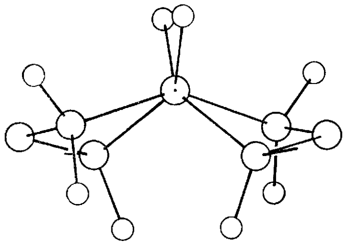

FIGURE 3. The dioxabicyclo-octane ring viewed in projection along C(8′)–C(8), and showing the near C_2 symmetry of the nucleus

TABLE 2

Torsion angles (°)

C(7)–C(8)–C(8′)–C(9′)	–20	3(7′)–C(8′)–C(8)–C(9)	–20
C(8)–C(8′)–C(9′)–O′	–3	C(8′)–C(8)–C(9)–O	–5
C(8′)–C(9′)–O′–C(7)	26	C(8)–C(9)–O–C(7′)	30
C(9′)–O′–C(7)–C(8)	–40	C(9)–O–C(7′)–C(8′)	–44
O′–C(7)–C(8)–C(8′)	38	O–C(7′)–C(8′)–C(8)	39
O–C(7′)–C(1′)–C(6′)	–1	O′–C(7)–C(1)–C(6)	35
C(2′)–C(1′)–C(7′)–C(8′)	66	C(2)–C(1)–C(7)–C(8)	93
C(6′)–C(5′)–O(5′)–C(11′)	17	C(6)–C(5)–O(5)–C(11)	–24
C(2′)–C(3′)–O(3′)–C(10′)	–8	C(2)–C(3)–O(3)–C(10)	83

Each phenyl ring of the syringyl systems is planar. Three of the four methoxy-groups are oriented only slightly out of the planes of the rings and the familiar distortion of the exocyclic C–C–O valence angles is noted.[10] For the fourth methoxy-group, which is oriented nearly perpendicular to the phenyl plane, these angles are as expected. The anomalously short O(3)–C(10) bond length is presumably attributable to the neglect of any correction for the pronounced thermal motion of the C(10) methyl group. Application of a riding-model correction increases the bond length to 1.37 Å.

TABLE 3

Shorter intermolecular contact distances (Å)

H(3b) · · · H(3′b^{I})	2.20	O(10) · · · H(4^{III})	1.98
H(4′) · · · H(9′b)	2.22	O(10) · · · O(4^{III})	2.87
H(7′) · · · H(3c^{I})	2.29	O(10′) · · · H(4^{IV})	1.85
H(5a) · · · H(5′b^{I})	2.41	O(10′) · · · O(4^{IV})	2.84
O(4) · · · H(3c^{V})	2.53	H(4′) · · · C(9′^{II})	2.48
O(10′) · · · H(8^{I})	2.57	C(6) · · · H(8′^{I})	2.79

Superior Roman numerals refer to the following equivalent positions, relative to the reference molecule at x, y, z:

I $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$
II $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$
III $-x, \frac{1}{2} + y, \frac{1}{2} - z$
IV $1 - x, y - \frac{1}{2}, \frac{1}{2} - z$
V $-x - \frac{1}{2}, 1 - y, z - \frac{1}{2}$

Within the crystal, molecules are linked in layers by a system of hydrogen bonds involving the hydroxy-groups as donors and the oxygen atoms of the dioxabicyclo-octane nucleus as acceptors. The arrangement, within a given layer, is shown in Figure 4 and shorter intermolecular contact distances are given in Table 3.

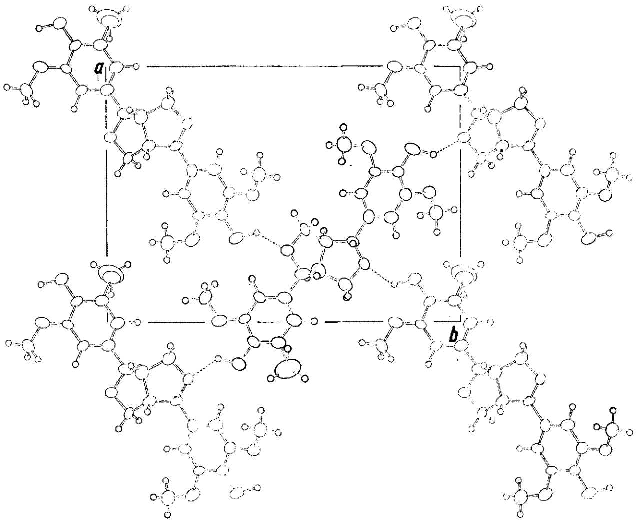

FIGURE 4 Arrangement of molecules within a single layer in the crystal. Hydrogen bonds are indicated by broken lines

EXPERIMENTAL

Crystal Data.—$C_{22}H_{26}O_8$, $M = 418.4$, m.p. 182—185 °C, $[\alpha]_D^{25}$ $-36°$ ($CHCl_3$). Orthorhombic, $a = 13.051(2)$, $b = 18.106(4)$, $c = 8.565(1)$ Å, $D_m = 1.36$, $Z = 4$, $D_c = 1.37$, $F(000) = 888$. Space group $P2_12_12_1$. Cu-K_α radiation, $\lambda = 1.5418$ Å; μ(Cu-K_α) = 8.8 cm^{-1}.

Unit-cell dimensions were determined from a least-squares fit to the values of $\pm 2\theta$ measured by diffractometry for 18 strong general reflections.

Intensity Measurements.—These were made from a single crystal 0.4 × 0.2 × 0.3 mm^3 mounted with c^* parallel to the ϕ-axis of a Picker four-circle diffractometer controlled by an XDS σ2 computer. Graphite-monochromated Cu-K_α radiation was used with scintillation counting and pulse-height analysis, and a single octant surveyed to 2θ 0.497. The θ—2θ scan method was used with a scan range of 3° in 2θ and a scan speed of 2° min^{-1}. Scattered intensity significantly above background [$I > 3\sigma(I)$] was measured at 1073 reciprocal lattice points. Background intensities were calculated from a carefully predetermined curve of scattered intensity *vs.* diffractometer angle. Two reference reflections monitored every 50 measurements showed no significant variation in intensity during data collection. No absorption correction was applied and structure amplitudes and normalized structure amplitudes were derived in the usual way.

Structure Determination and Refinement.—Four origin- and enantiomorph-defining reflections were assigned phases and combined with 19 phases predicted with high probability

[10] R. F. Bryan, *J. Chem. Soc.* (*B*), 1967, 1311.

by the Σ_1 formula,[11] the squared-tangent formula,[12] and pairs relationships,[13] as a starting set for the program MULTAN.[14] For the 180 $E(hkl) > 1.25$, 128 phase sets were generated and E-maps calculated for all with $FOM > 0.8$. No correct solution emerged, but images of phenyl rings in consistent orientations were present in several of the incorrect maps. The correct positions of these rings were sought by application of a translation function.[15] Structure factors were calculated for an appropriately translated fragment and phases for 50 $E(hkl)$ accepted where $F_c > 0.75F_o$. These phases were expanded by use of the tangent formula and an E map based on the resulting set gave correct locations for all C and O atoms.

Refinement was by block-diagonal least-squares methods with 3 × 3 and 6 × 6 blocks for the positional and anisotropic thermal parameters. The function minimized was $\Sigma w(\Delta F)^2$, a Hughes-type weighting scheme being used.[16] Hydrogen atoms were located from a difference-Fourier map and fixed contributions for these atoms (B 3.5 Å^2) included in the least-squares calculations. Atomic scattering factors for the neutral atoms [17] were modified to take account of the real component of the anomalous dispersion terms for carbon and oxygen.[18] In the final cycle of the least-squares process the average and maximum calculated shift-to-error ratios were 0.02 and 0.11. For the 1073 observed reflections R was 0.066 and R' 0.082. No discrimination of absolute configuration emerged when separate structure-factor calculations were made for the two enantiomers and account was taken of the $\Delta f''$ terms for oxygen and carbon. Observed and calculated structure amplitudes are listed in Supplementary Publication No. SUP 21566 (9 pp., 1 microfiche).*

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* See note about Supplementary Publications in Notice to Authors, No. 7, *J.C.S. Perkin II*, 1975, Index issue.

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[12] H. Hauptman, *Acta Cryst.*, 1970, **B26**, 531.

[13] H. Hauptman, *Acta Cryst.*, 1972, **B28**, 2337.

[14] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[15] J. Karle, *Acta Cryst.*, 1972, **B28**, 820.

[16] E. W. Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.

[17] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040; R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

[18] D. T. Cromer and D. Liberman, *J. Chem. Phys.*, 1970, **53**, 1891.