

## Dehydromonocrotaline, C<sub>16</sub>H<sub>21</sub>NO<sub>6</sub>: Active Metabolite of the Pyrrolizidine Alkaloid Monocrotaline

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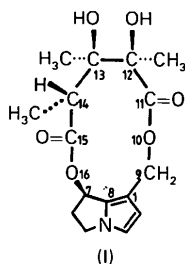
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**Abstract.**  $M_r = 323.3$ , orthorhombic,  $P2_12_12_1$ ,  $a = 7.409$  (1),  $b = 10.551$  (1),  $c = 20.175$  (1) Å,  $U = 1577.1$  (2) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.362$  Mg m<sup>-3</sup>,  $\lambda(\text{Cu } K\alpha) = 1.5418$  Å,  $\mu = 0.78$  mm<sup>-1</sup>,  $F(000) = 688$ ,  $T = 291$  K. Final  $R = 0.055$  for 1079 observed reflections. The molecular conformation of the 11-membered macroring is significantly different from that in the parent alkaloid monocrotaline as a result of the flattening of the pyrrolizidine ring. The perturbation of the macroring is revealed most notably in the conformation around the primary ester system.

**Introduction.** It is well established that the nucleotoxic properties of the hepatotoxic pyrrolizidine alkaloids are due to metabolic activation to the corresponding pyrrole derivatives or dehydroalkaloids (McLean, 1970; Huxtable, 1979, 1980). The conformation of the hepatotoxic alkaloid monocrotaline, C<sub>16</sub>H<sub>23</sub>NO<sub>6</sub>, has been defined by X-ray analyses (Stoekli-Evans, 1979; Wang, 1981). The present analysis of crystals of dehydromonocrotaline (I) was carried out for a comparative study between the conformation of the parent alkaloid and the corresponding pyrrole derivative.



**Experimental.** Title compound prepared by the method of Culvenor, Edgar, Smith & Tweeddale (1970) and crystallized from benzene/light petroleum (b.p. 333–353 K). As the crystals were unstable in air, a crystal of dimensions  $ca\ 0.50 \times 0.10 \times 0.25$  mm was sealed in a thin-walled Lindemann-glass tube for the data collection. 24 reflections used for measuring lattice

parameters. Intensities measured at 291 K, Cu  $K\alpha$  radiation (graphite-crystal monochromator), Rigaku-AFC four-circle diffractometer; of 1558 non-equivalent terms ( $2\theta_{\text{max}} = 130^\circ$ , range of  $hkl$ : 0–8, 0–12, 0–23) recorded by an  $\omega$ – $2\theta$  scan of  $8^\circ \text{ min}^{-1}$  and with 10s stationary background counts, 1079 with  $|F_o| > 2\sigma|F_o|$  used for structure refinement; three reference reflections monitored every 50 reflections showed no significant variation in intensity during data collection; intensities not corrected for absorption or extinction. Structure solved by direct methods with *SHELX76* (Sheldrick, 1976). Although a difference map, calculated subsequent to full-matrix least-squares refinement of O, N and C atoms with anisotropic temperature factors, had maxima at expected H-atom sites, not all were clearly resolved; non-hydroxyl H atoms therefore included at idealized positions. Coordinates and isotropic temperature factors of hydroxyl H atoms refined; overall isotropic temperature factors given to remaining non-methyl and methyl H atoms refined to  $B$  values 6.8 (6) and 8.7 (7) Å<sup>2</sup> respectively. Final refinement converged at  $R = 0.055$ ,  $R_w = 0.051$ ; function minimized  $\sum w(|F_o| - |F_c|)^2$  with terms weighted according to  $(\sigma^2|F_o| + 0.0005|F_o|^2)^{-1}$ . Largest peaks on final difference map  $+0.22$  and  $-0.25 \text{ e } \text{Å}^{-3}$ ; mean parameter shift-to-error ratios at convergence 0.09:1. Scattering factors for O, N and C from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965); anomalous-dispersion corrections made for non-H atoms with values of Cromer & Liberman (1970).

**Discussion.** Final atomic coordinates of the non-H atoms are given in Table 1.\* The molecular conformation and numbering scheme are illustrated in the

\* Lists of structure amplitudes, anisotropic temperature factors, H-atom coordinates and intermolecular contacts have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38976 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

ORTEP plot (Johnson, 1965) given in Fig. 1. Bond lengths and angles are given in Table 2 and torsional angles in Table 3.

The pyrrolizidine ring undergoes a higher degree of flattening in dehydromonocrotaline than it did in

Table 1. Final atomic coordinates ( $\times 10^4$ ) and equivalent isotropic temperature factors with *e.s.d.*'s in parentheses

$$B_{eq} = 8\pi^2 U_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	$B_{eq} (\text{\AA}^2)$
C(1)	4480 (8)	-348 (6)	5776 (3)	3.6 (3)
C(2)	4041 (9)	-1198 (6)	6301 (3)	4.2 (3)
C(3)	5448 (9)	-2002 (6)	6401 (3)	4.3 (3)
N(4)	6729 (6)	-1707 (5)	5948 (2)	3.7 (2)
C(5)	8544 (9)	-2186 (6)	5796 (3)	4.8 (4)
C(6)	9037 (8)	-1444 (6)	5169 (3)	4.5 (4)
C(7)	7573 (8)	-407 (5)	5064 (3)	3.2 (3)
C(8)	6201 (8)	-706 (6)	5572 (3)	3.2 (3)
C(9)	3383 (8)	719 (6)	5514 (3)	4.0 (3)
O(10)	3119 (5)	595 (4)	4793 (2)	3.6 (2)
C(11)	4148 (8)	1328 (6)	4413 (3)	3.3 (3)
C(12)	3570 (8)	1232 (6)	3684 (3)	3.7 (3)
C(13)	5180 (8)	1174 (6)	3171 (3)	3.8 (3)
C(14)	6379 (8)	-13 (6)	3274 (3)	3.6 (3)
C(15)	7498 (9)	36 (6)	3907 (3)	3.5 (3)
O(16)	6706 (5)	-561 (4)	4414 (2)	3.2 (2)
C(17)	2310 (9)	2376 (6)	3567 (3)	4.8 (4)
C(18)	6251 (9)	2387 (6)	3122 (3)	4.5 (4)
C(19)	7692 (10)	-196 (8)	2691 (3)	5.2 (4)
O(20)	5276 (6)	2050 (4)	4608 (2)	4.6 (2)
O(21)	2588 (6)	93 (5)	3556 (2)	4.1 (3)
O(22)	4308 (6)	1016 (5)	2537 (2)	4.8 (3)
O(23)	8956 (6)	549 (5)	3961 (2)	4.5 (3)

Table 2. Bond lengths ( $\text{\AA}$ ) and angles ( $^\circ$ ) with *e.s.d.*'s in parentheses

C(1)–C(2)	1.425 (9)	C(11)–C(12)	1.535 (9)
C(1)–C(8)	1.391 (8)	C(11)–O(20)	1.197 (7)
C(1)–C(9)	1.487 (9)	C(12)–C(13)	1.580 (8)
C(2)–C(3)	1.360 (10)	C(12)–C(17)	1.544 (9)
C(3)–N(4)	1.354 (8)	C(12)–O(21)	1.428 (8)
N(4)–C(5)	1.469 (8)	C(13)–C(14)	1.550 (9)
N(4)–C(8)	1.357 (8)	C(13)–C(18)	1.509 (9)
C(5)–C(6)	1.532 (9)	C(13)–O(22)	1.443 (7)
C(6)–C(7)	1.555 (8)	C(14)–C(15)	1.524 (9)
C(7)–C(8)	1.479 (8)	C(14)–C(19)	1.538 (9)
C(7)–O(16)	1.469 (7)	C(15)–O(16)	1.337 (7)
C(9)–C(10)	1.474 (7)	C(15)–O(23)	1.213 (8)
O(10)–C(11)	1.329 (7)		
C(2)–C(1)–C(8)	104.9 (5)	C(12)–C(11)–O(20)	123.5 (6)
C(2)–C(1)–C(9)	128.0 (6)	C(11)–C(12)–C(13)	114.8 (5)
C(8)–C(1)–C(9)	127.0 (6)	C(11)–C(12)–C(17)	105.3 (5)
C(1)–C(2)–C(3)	109.2 (6)	C(11)–C(12)–O(21)	111.8 (5)
C(2)–C(3)–N(4)	107.1 (6)	C(13)–C(12)–C(17)	112.7 (5)
C(3)–N(4)–C(5)	134.7 (5)	C(13)–C(12)–O(21)	103.5 (5)
C(3)–N(4)–C(8)	110.7 (5)	C(17)–C(12)–O(21)	108.8 (5)
C(5)–N(4)–C(8)	114.5 (5)	C(12)–C(13)–C(14)	112.1 (5)
N(4)–C(5)–C(6)	102.4 (5)	C(12)–C(13)–C(18)	114.0 (5)
C(5)–C(6)–C(7)	107.8 (5)	C(12)–C(13)–O(22)	104.3 (5)
C(6)–C(7)–C(8)	103.6 (5)	C(14)–C(13)–C(18)	113.2 (5)
C(6)–C(7)–O(16)	110.4 (5)	C(14)–C(13)–O(22)	106.4 (5)
C(8)–C(7)–O(16)	107.2 (5)	C(18)–C(13)–O(22)	106.0 (5)
C(1)–C(8)–N(4)	108.1 (5)	C(13)–C(14)–C(15)	113.3 (5)
C(1)–C(8)–C(7)	141.0 (6)	C(13)–C(14)–C(19)	111.2 (5)
N(4)–C(8)–C(7)	110.8 (5)	C(15)–C(14)–C(19)	107.5 (5)
C(1)–C(9)–O(10)	110.9 (5)	C(14)–C(15)–C(16)	112.7 (5)
O(10)–C(9)–C(10)	110.7 (5)	C(14)–C(15)–O(23)	125.1 (6)
O(10)–C(9)–C(11)	125.5 (6)	C(16)–C(15)–O(23)	122.2 (6)

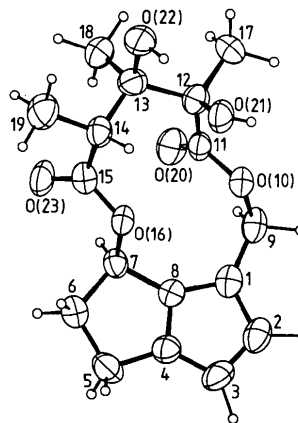


Fig. 1. Perspective view of the molecule with thermal ellipsoids scaled to 50% probability. The C atoms are denoted by numerals only.

dehydrosenecionine (Mackay, Sadek, Culvenor & Smith, 1983). Thus the angle between the mean planes defined by the atoms C(1), C(2), N(4), C(8) and N(4), C(5), C(7), C(8) is  $178.6 (6)^\circ$  compared with the value  $176.3 (4)^\circ$  in dehydrosenecionine. The saturated ring is *exo*-buckled but with only a small puckering angle  $11.1 (6)^\circ$  compared with the value  $39.5 (7)^\circ$  in monocrotaline.\* The atoms in the unsaturated ring are coplanar within  $\pm 0.01 (1) \text{\AA}$  with C(9) lying  $0.04 (1) \text{\AA}$  from the plane.

Atoms in the primary ester group, C(9), O(10), C(11), C(12), O(20), are coplanar within  $\pm 0.05 (1) \text{\AA}$ . The carbonyl bonds of the ester functions are *syn*-parallel as observed in monocrotaline and the related 11-membered macrocyclic alkaloids fulvine (Sussman & Wodak, 1973) and crispatine (Mackay, Sadek & Culvenor, 1984). The angle between the bonds is  $20.8 (5)^\circ$  compared with the value  $15.2 (5)^\circ$  in monocrotaline,  $12.0 (3)^\circ$  in fulvine and  $18.9 (5)^\circ$  in crispatine. It is interesting to note that in 1,2-didehydrocrotalanine (Stoekli-Evans & Robins, 1983), a synthetic pyrrolizidine alkaloid in which the 11-membered macrocycle is unsubstituted, the carbonyl bonds are *anti*-parallel. This so far has been found in only one other alkaloid with the 11-membered macrocycle, trichodesmine (Tashkhodzhaev, Yagudaev & Yunusov, 1979). The intramolecular O(16)···O(10) distance  $3.023 (7) \text{\AA}$  is similar to that in monocrotaline [ $3.040 (8) \text{\AA}$ ] but longer than that in fulvine, crispatine and didehydrocrotalanine in which the respective values are  $2.957 (5)$ ,  $2.921 (6)$  and  $2.954 (7) \text{\AA}$ . In dehydromonocrotaline, the transannular distance C(11)···O(16),  $2.750 (8) \text{\AA}$  is the shorter [cf.  $2.964 (10) \text{\AA}$  in 1,2-didehydrocrotalanine] while it is the O(10)···C(15)

\* All numerical values refer to the more recent analysis by Wang (1981).

Table 3. Selected torsional angles ( $^{\circ}$ )

E.s.d.'s are about  $0.6^{\circ}$ . Atoms are represented by their identification number. Corresponding values for monocrotaline (Wang, 1981) are included.

	Dehydromono- crotaline	Monocrot- aline		Dehydromono- crotaline	Monocrot- aline
1-9-10-11	-102.1	-157.4	1-2-3-4	-1.4	0.8
9-10-11-12	-172.7	175.1	2-1-9-10	-125.6	-66.4
10-11-12-13	-138.9	-84.6	2-3-4-5	178.9	-121.5
11-12-13-14	62.2	53.5	3-4-5-6	174.6	144.8
12-13-14-15	-70.2	-73.9	4-5-6-7	9.2	-38.9
13-14-15-16	95.4	155.4	4-8-7-6	2.2	-25.0
14-15-16-7	-171.8	-177.7	4-8-7-16	119.0	88.0
15-16-7-8	159.4	113.2	5-6-7-8	-7.3	39.1
16-7-8-1	-55.9	-27.8	5-6-7-16	-121.8	-75.5
7-8-1-9	-6.4	-61.0	6-7-16-15	-88.4	-137.2
8-1-9-10	56.9	111.8			

distance which is the shorter in monocrotaline [2.741 (9) Å], fulvine [2.765 (7) Å] and crispatine [2.647 (7) Å].

The conformation of the macroring in dehydromonocrotaline is significantly different from that of the parent alkaloid (see Table 3), unlike the case of senecionine (Mackay & Culvenor, 1982) and dehydro-senecionine in which there is a fairly close resemblance between the two conformations. The flattening of the pyrrolizidine ring has caused appreciable perturbation of the 11-membered ring whereas it did not do so in the larger 12-membered ring. The perturbation shows up in several torsional angles which are compared in Table 3, and notably in the conformation around the primary ester system. The torsional angle C(2)-C(1)-C(9)-O(10) is  $-125.6 (5)^{\circ}$  in dehydromonocrotaline and  $-66.4 (5)^{\circ}$  in monocrotaline. This change is largely reversed by the difference in the torsional angle C(1)-C(9)-O(10)-C(11),  $-102.1 (5)^{\circ}$  in dehydromonocrotaline and  $-157.4 (5)^{\circ}$  in monocrotaline. As a result, one of the H atoms at C(9) is close to the primary ester group in dehydromonocrotaline, whereas the methylene H atoms at C(9) are fairly symmetrically placed about this plane in monocrotaline [torsional angle H(9A)-C(9)-O(10)-C(11)  $74 (5)^{\circ}$ ]. The significance of this in relation to the differences in chemical shift of the H atoms at C(9) in the nuclear magnetic spectra of the two compounds (Culvenor & Woods, 1965; Culvenor *et al.*, 1970), will be discussed elsewhere.

The bond lengths and angles are similar to those reported for comparable structures. The bond lengths in the unsaturated ring are indicative of extensive electron delocalization around the ring as observed in other pyrrole systems (English, McGillivray & Smal, 1980; Acheson, Ferris, Critchley & Watkin, 1980); the C-C bond lengths range from 1.360 (10) Å for C(2)-C(3) to 1.425 (9) Å for C(1)-C(2) and the C-N bonds have a mean length 1.356 (8) Å [comparable values in dehydro-senecionine are 1.369 (5), 1.419 (5) and 1.370 (5) Å]. As in dehydro-senecionine a similar distortion of the exocyclic angles, C(3)-N(4)-C(5)

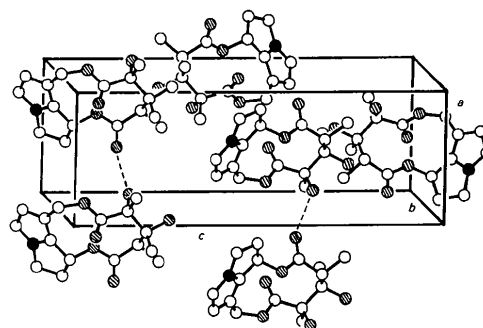


Fig. 2. The crystal packing.

134.7 (5) $^{\circ}$  and C(1)-C(8)-C(7) 141.0 (6) $^{\circ}$ , from standard trigonal values is noted. There is one intramolecular hydrogen-bonding interaction; this involves the hydroxyl substituent at C(13) and O(21), the O(22)...O(21), H(O22)...O(21) and O(22)-H(O22) distances being 2.606 (7), 2.12 (7) and 0.99 (9) Å respectively with the O(22)-H(O22)...O(21) angle 108 (6) $^{\circ}$ . There are no intramolecular hydrogen bonds in monocrotaline.

The molecular packing illustrated in Fig. 2 differs from that observed in the parent alkaloid in which the hydroxyl substituent at C(13) forms an intermolecular hydrogen bond with the N of an adjacent molecule. In the dehydromonocrotaline crystal, the hydroxyl substituent at C(12) forms an intermolecular hydrogen-bonding interaction with the carbonyl O of the secondary ester system, O(23), of a molecule related by a unit-cell translation along *a*. The O(21)...O(23), H(21)...O(23) and O(21)-H(21) distances have the respective values 2.853 (7), 2.17 (6) and 0.74 (6) Å and the angle O(21)-H(21)...O(23) is 154 (5) $^{\circ}$ . All other intermolecular contacts are of normal length.

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## References

- ACHESON, R. M., FERRIS, M. J., CRITCHLEY, S. R. & WATKIN, D. J. (1980). *J. Chem. Soc. Perkin Trans. 2*, pp. 326–329.
- CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.
- CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* **A24**, 321–324.
- CULVENOR, C. C. J., EDGAR, J. A., SMITH, L. W. & TWEEDDALE, H. J. (1970). *Aust. J. Chem.* **23**, 1853–1867.
- CULVENOR, C. C. J. & WOODS, W. G. (1965). *Aust. J. Chem.* **18**, 1625–1637.
- ENGLISH, R. B., MCGILLIVRAY, G. & SMAL, E. (1980). *Acta Cryst.* **B36**, 1136–1141.
- HUXTABLE, R. J. (1979). *Gen. Pharmacol.* **10**, 159–167.
- HUXTABLE, R. J. (1980). *Trends Pharmacol. Sci.* **1**, 299–303.
- JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.
- MACKAY, M. F. & CULVENOR, C. C. J. (1982). *Acta Cryst.* **B38**, 2754–2758.
- MACKAY, M. F., SADEK, M. & CULVENOR, C. C. J. (1984). *Acta Cryst.* **C40**, 470–472.
- MACKAY, M. F., SADEK, M., CULVENOR, C. C. J. & SMITH, L. W. (1983). *Acta Cryst.* **C39**, 1230–1233.
- MCLEAN, E. K. (1970). *Pharmacol. Rev.* **22**, 429–483.
- SHELDRIK, G. M. (1976). *SHELX76*. A program for crystal structure determination. Univ. of Cambridge, England.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
- STOECKLI-EVANS, H. (1979). *Acta Cryst.* **B35**, 231–234.
- STOECKLI-EVANS, H. & ROBINS, D. T. (1983). *Helv. Chim. Acta*, **66**, 1376–1380.
- SUSSMAN, J. L. & WODAK, S. J. (1973). *Acta Cryst.* **B29**, 2918–2926.
- TASHKHODZHAEV, B., YAGUDAEV, M. R. & YUNUSOV, S. YU. (1979). *Khim. Priir. Soedin.* **3**, 368–373.
- WANG, S. (1981). *Sci. Sin.* **24**, 497–507.

*Acta Cryst.* (1984). **C40**, 476–479

## Chiral and Hexacoordinated Chloro(methyl)bis(8-quinolinolato)silicon(IV), Si(CH<sub>3</sub>)(C<sub>9</sub>H<sub>6</sub>NO)<sub>2</sub>Cl\*

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**Abstract.**  $M_r = 366.89$ , triclinic,  $P\bar{1}$ ,  $a = 8.085$  (2),  $b = 8.195$  (1),  $c = 15.040$  (5) Å,  $\alpha = 76.14$  (2),  $\beta = 74.59$  (5),  $\gamma = 60.41$  (2)°,  $V = 828.3$  (3) Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.465$  Mg m<sup>-3</sup>, Mo  $K\alpha$  (graphite monochromator),  $\lambda = 0.71069$  Å,  $\mu = 0.320$  mm<sup>-1</sup>,  $F(000) = 380$ ,  $T = 295$  K,  $R_w(F) = 0.049$  using 2922 independent reflections. Hexacoordinated silicon is found in a distorted octahedral geometry. Hexacoordination is achieved by intramolecular Lewis acid–base interaction. The coordinative Si–N distance is 2.015 (4) Å, the Si–O bond length 1.765 (2) Å. The bidentate ligands are arranged in *cis* configuration along two edges of the octahedral polyhedron and methyl and chlorine are found at the remaining sites in equipopulation. Si represents a center of chirality and two isomeric forms are present in the crystal, which correspond to the left- and right-hand arrangements.

**Introduction.** Although silicon and carbon have the same number of valence electrons, there are pronounced differences in the chemical behavior of the two

elements. Many of these dissimilarities are attributed to an expansion of the valence shell of silicon, which leads to compounds and suggested reaction intermediates with coordination number higher than four. Penta- and hexavalency have been detected in neutral and charged complexes when the central atom is bonded to electronegative elements like O, N or F, e.g. Si(C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>)Cl<sub>3</sub> (Klebe, Bats & Hensen, 1983a), SiF<sub>4</sub>(pyridine)<sub>2</sub> (Bain, Killeen & Webster, 1969), SiF<sub>6</sub><sup>2-</sup> (Frlec, Gantar, Golič & Leban, 1980).

**Experimental.** The compound was prepared from lithium quinolinolate, (C<sub>9</sub>H<sub>6</sub>NO)Li, and CH<sub>3</sub>SiCl<sub>3</sub> as described by Hensen & Klebe (1981): pale yellow crystals from slow evaporation of a saturated solution in CH<sub>2</sub>Cl<sub>2</sub>; pronounced sensitivity to moisture, so crystals selected under dried argon and sealed in thin glass tubes; crystal 0.3 × 0.2 × 0.2 mm; space group determined by film methods to be  $P1$  or  $P\bar{1}$ ; lattice parameters refined from 25 reflections on a Nonius CAD-4 diffractometer.  $\sin\theta/\lambda \leq 0.594$  Å<sup>-1</sup>,  $\omega$ -scan mode, scan width: (1.4 + 0.35 tan $\theta$ )°, 5380 reflections,  $h - 9-5$ ,  $k - 9-9$ ,  $l - 17-17$ , three standard reflections, no significant fluctuations, no correction for absorption; background correction and averaging, 2922 unique reflections [ $R_{\text{int}} = 0.044$ , 641 unobserved,  $I < \sigma(I)$ ] for

\* Coordinative Interactions in Chelated Complexes of Silicon. Part X. Part IX: Klebe, Nix & Hensen (1983).

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