Crystal and Molecular Structure of 3-Hydroxy-5-phenylisoxazole (α form)

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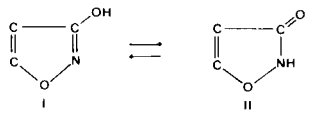
The crystal structure of the α form of 3-hydroxy-5-phenylisoxazole has been determined from three-dimensional X-ray data. The crystals are monoclinic, space group $P2_1/n$ with four molecules in the unit cell. The cell dimensions are: a = 10.41(2); b = 3.89(1); c = 19.14(4) Å; β = 96.1° (3). The structure was refined by the block-diagonal least-squares method to a final R value of 0.080 for 1111 observed reflections. The molecular dimensions are in good overall agreement with those in β form, while the packing is markedly different. Conjugation and planarity in the molecule are discussed.

Introduction.

Several investigations have been performed on the derivatives of 3-hydroxyisoxazole (I) which are tautomeric with isoxazolin-3-ones (II).



I II

3-Hydroxy-5-phenylisoxazole is the first 3-hydroxyisoxazole to be recognized as such and was assigned the hydroxy form on the basis of chemical properties and infrared and ultraviolet spectra (1-4).

The crystal structure determination was undertaken as part of a research project on isoxazole derivatives (5-10); the compound is dimorphic: it crystallizes from *n*-hexane solution as prismatic crystals (α form) which sublime at a temperature around 140° and form needle-shaped crystals (β form). The crystal structure of β form was published elsewhere (10); a preliminary report on the α form has already been presented (5) and here are given the results of a three-dimensional analysis.

EXPERIMENTAL

The unit cell dimensions were determined from hOl and Okl Weissenberg photographs calibrated with NaCl powder pattern.

Crystal data (11).

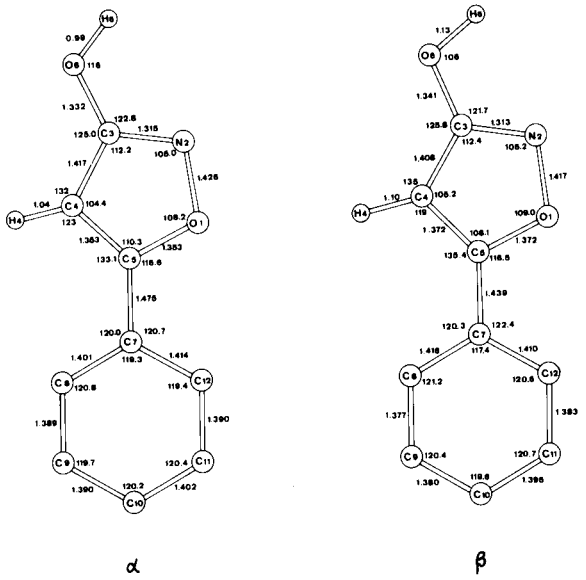
3-Hydroxy-5-phenylisoxazole ($C_9H_7NO_2$); MW 161.66; m.p. 163-164°.

a = 10.41(2) Å b = 3.89(1) Å c = 19.14(4) Å β = 96.1°(3)

V = 770.3Å^3 Dc (Z = 4) = 1.38 g.cm^{-3} Do = 1.37 g.cm^{-3}

Space group $P2_1/n$ λ = 1.5418 (Cu Kα)

A crystal with approximate cross section 0.30 x 0.30 mm was selected for data collection around **[010]**. Integrated equi-inclination Weissenberg photographs were taken on multiple films for the layers 0 to 3. The 1487 independent reflections were recorded and the intensities of 823 were determined photometrically with the aid of a microdensitometer; 330 weak reflections, estimated visually as strong, medium, weak, and very weak were given intensities equal to 0.75, 0.60, 0.45 and 0.30, the minimum photometrically determined intensity; a value of 0.15 I min. was assigned to unobserved reflections. Intensities were converted to observed structure factors in the usual way and were placed on



α β

Figure 1. Bond lengths (Å) and angles (°) in α (left) and β (right) modifications. Maximum standard deviations are 0.007 Å and 0.5° for bond lengths and angles involving heavy atoms. C-H bonds in benzene rings are in the range 0.90-1.15 Å and the angles in the range 115-125°. Standard deviations are 0.1 Å and 3° respectively.

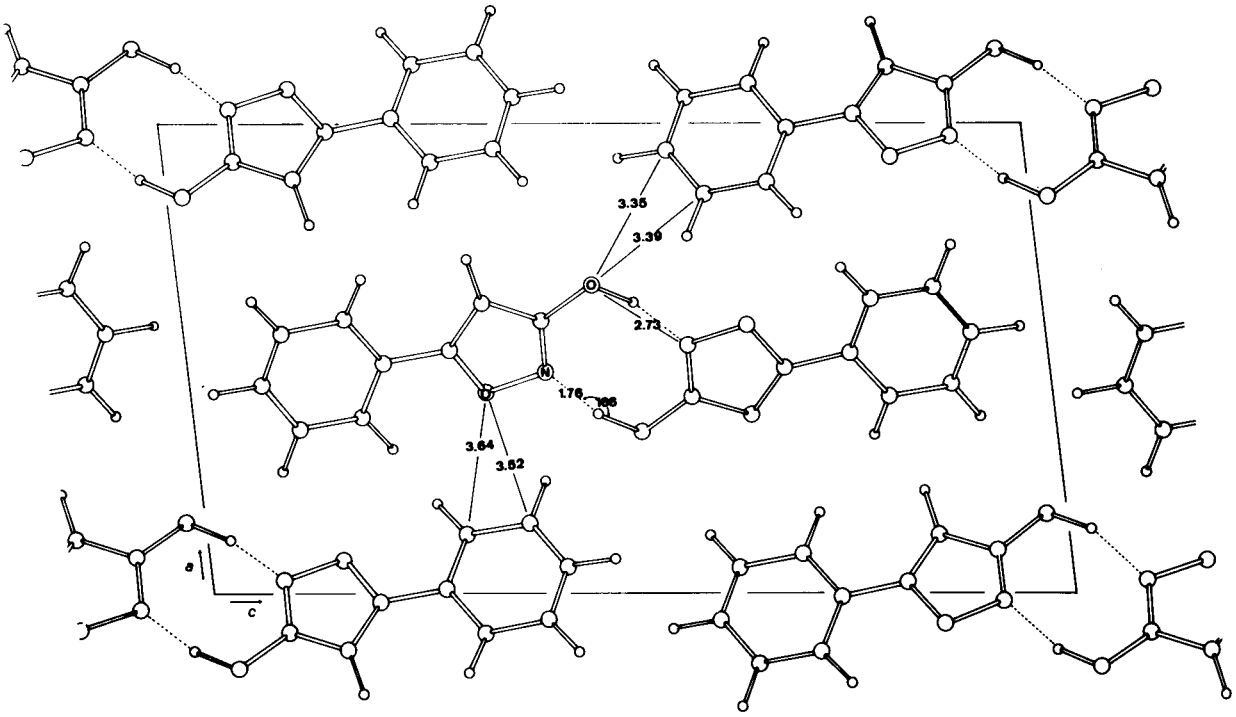


Figure 2. Projection of the structure along b axis. Dotted lines are intermolecular hydrogen bonds.

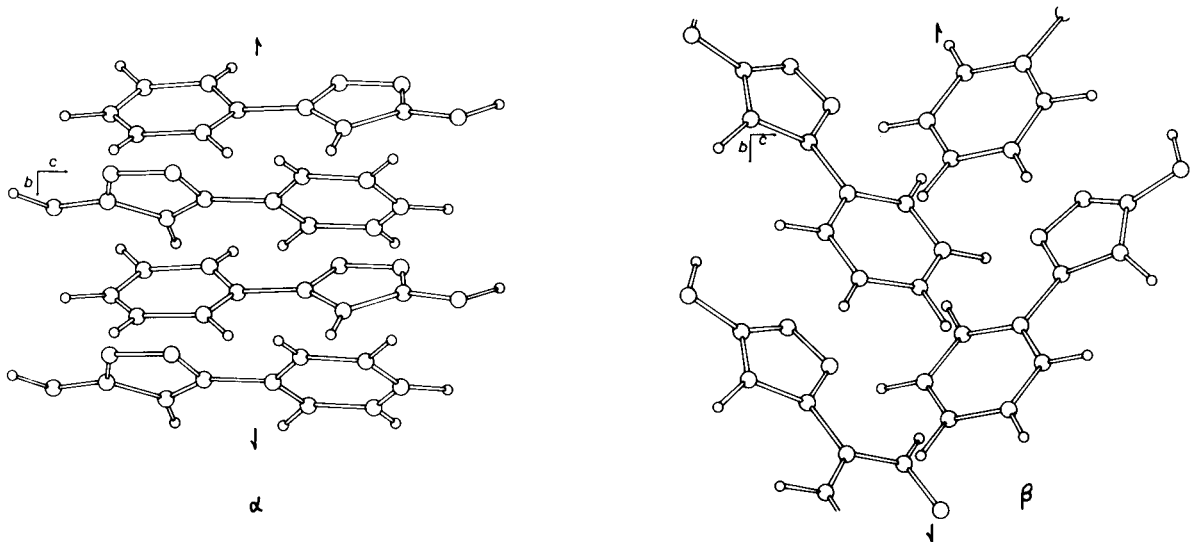


Figure 3. A view of the packing of α (left) and β (right) modifications; molecules related by the two-fold screw axis are shown.

TABLE 1

Final Positional and Thermal Parameters.
The estimated standard deviations given in parentheses refer to the last decimal position.

	X	Y	Z	B_1	B_2	B_3
O(6)	-0.1568(3)	0.2406(6)	0.0210(1)	3.99	9.85	3.19
O(1)	0.0726(3)	0.0037(6)	0.1571(1)	3.64	6.55	2.61
N(2)	0.0283(3)	0.0221(6)	0.0841(1)	3.32	6.63	2.88
C(3)	-0.0844(4)	0.1769(6)	0.0812(2)	3.53	5.06	2.93
C(4)	-0.1183(4)	0.2633(7)	0.1488(2)	3.69	4.98	3.38
C(5)	-0.0176(3)	0.1507(7)	0.1934(1)	3.21	4.11	2.32
C(7)	0.0097(4)	0.1543(7)	0.2706(1)	3.22	4.05	2.37
C(8)	-0.0811(4)	0.2916(7)	0.3119(2)	3.84	4.44	3.62
C(9)	-0.0563(4)	0.3026(8)	0.3846(2)	4.17	5.90	3.17
C(10)	0.0601(5)	0.1762(9)	0.4169(2)	4.31	6.79	2.96
C(11)	0.1518(4)	0.0364(8)	0.3764(2)	3.79	5.06	3.45
C(12)	0.1281(4)	0.0269(7)	0.3036(1)	3.77	4.30	2.71
H(6)	-0.120	0.168	-0.022			
H(4)	-0.195	0.405	0.165			
H(8)	-0.174	0.348	0.287			
H(9)	-0.117	0.370	0.414			
H(10)	0.075	0.200	0.472			
H(11)	0.238	-0.040	0.402			
H(12)	0.190	-0.095	0.275			

	β11	β22	β33	β12	β13	β23
O(6)	0.01115(42)	0.14766(279)	0.00224(7)	0.02626(168)	0.00017(29)	-0.00105(53)
O(1)	0.00893(29)	0.10417(199)	0.00185(5)	0.00911(120)	0.00097(23)	-0.00263(48)
N(2)	0.00838(38)	0.10391(241)	0.00207(7)	0.01278(159)	0.00147(29)	0.00121(63)
C(3)	0.00830(42)	0.08277(229)	0.00206(7)	0.00301(167)	0.00125(32)	0.00129(65)
C(4)	0.00941(42)	0.07433(243)	0.00245(8)	0.00839(154)	0.00131(34)	-0.00054(61)
C(5)	0.00631(36)	0.06389(195)	0.00219(7)	-0.00469(148)	0.00202(29)	-0.00169(61)
C(7)	0.00722(39)	0.06185(190)	0.00202(7)	-0.00504(146)	0.00222(29)	-0.00116(54)
C(8)	0.00917(43)	0.07070(236)	0.00257(9)	-0.00242(161)	0.00137(35)	-0.00154(65)
C(9)	0.01041(47)	0.08647(269)	0.00254(9)	-0.00718(174)	0.00262(38)	-0.00543(67)
C(10)	0.01188(52)	0.09537(260)	0.00216(8)	-0.01641(195)	0.00017(38)	-0.00261(71)
C(11)	0.00835(43)	0.08124(252)	0.00261(9)	-0.00518(170)	0.00072(34)	0.00080(69)
C(12)	0.00679(41)	0.06963(223)	0.00257(8)	-0.00433(151)	0.00161(33)	0.00008(65)

the same relative scale by the least-squares procedure of A. D. Rae (12), using common reflections collected with a second crystal mounted around [110]. Layers 0 to 3 were recorded but only observed reflections were considered and were estimated photometrically; 32 reflections which were not present in the first data were also included for structure refinement. The standard deviations of each intensity was estimated assuming a constant fractional error (σ = 0.1 I). The scattering factors were interpolated from the values given by Cromer and Waber (13) for O, N and C and by Stewart, Davidson and Simpson (14) for hydrogen.

Structure Refinement.

The structure was solved by trial and error methods in the projections along the a and b axes, assuming a planar molecular model which forms centrosymmetric dimers through OH. . . .N hydrogen bonds; because of the short b axis (3.89 Å) the dimers were assumed to lie approximately on (010), with the center of symmetry coincident with the cell origin. That orientation of the molecule which gave the best agreement between observed and calculated structure factors for a number of intense low-order reflections was selected for the starting point of a two-dimensional Fourier refinement.

Parameters were then refined by the block-diagonal least-squares method using the programs I.C.R. N° 4 (15) and I.C.R. N° 7 (16). The minimized quantity is $\Sigma\, w(KFo-Fc)^2$. The weights were given values equal to $1/\sigma^2$. The initial R value was 0.23 which was reduced to 0.15 with 4 cycles of isotropic refinement based on heavy atoms. Only the 855 photometrically measured reflections were considered at this stage. Two more cycles were performed assigning to the heavy atoms anisotropic temperature factors of the form:

$$\exp -[\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl]$$

A difference map was computed at this stage and all the hydrogen atom positions were readily found; no attempt has been made to refine their parameters, though their contribution to the structure factors were herewith always incorporated.

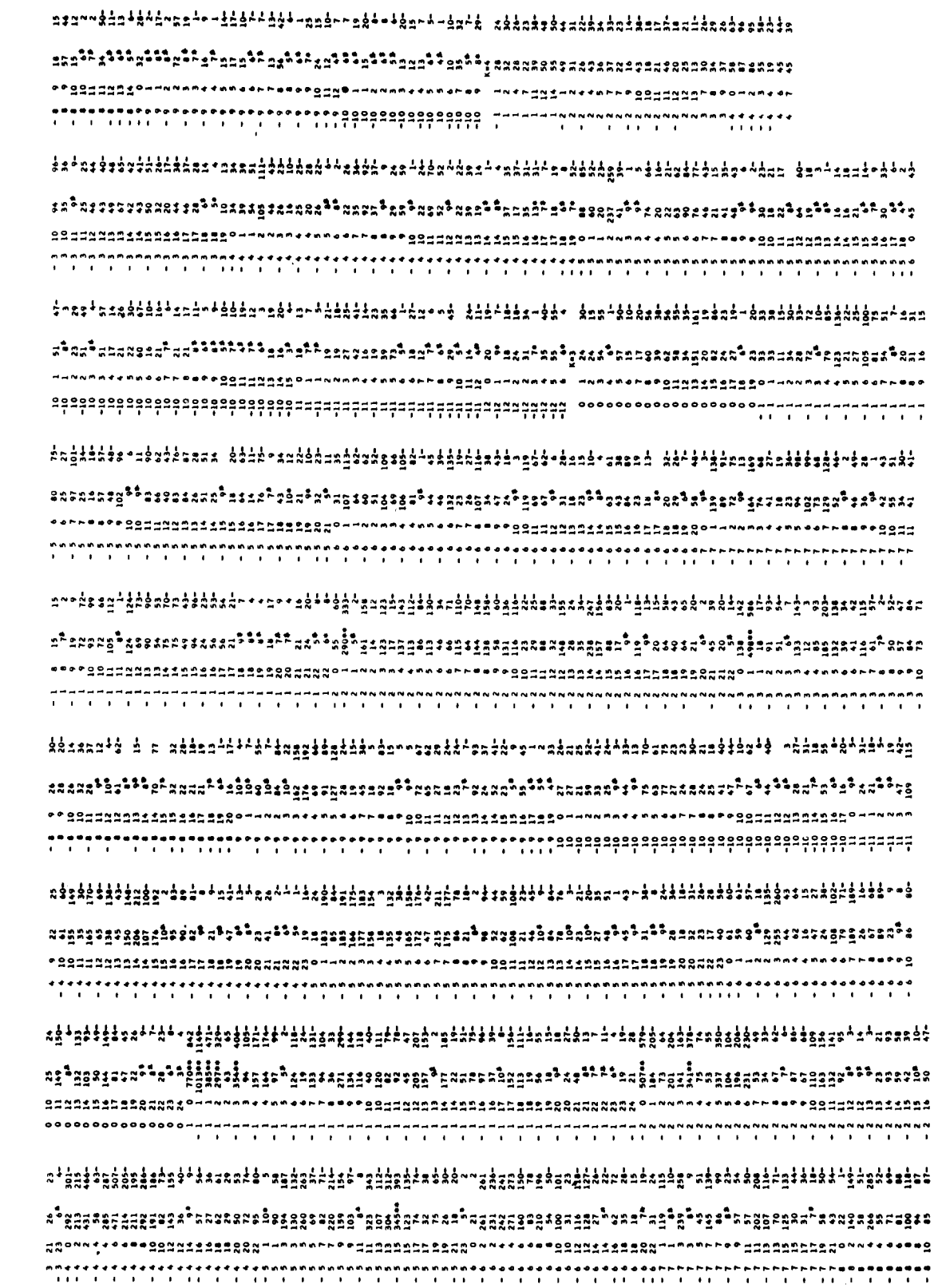
Final refinement was carried out introducing all the observed reflections but those where Fo $<$ 1.6; twenty-three of the strongest reflections, which were suspected of suffering from secondary extinction or from a particularly bad measurement were also given zero weight.

The final R value for the 1111 reflections which contributed

TABLE II

Observed and Calculated Structure Factors.

Columns are: h, l, 10Fobs, 10Fcalc. Unobserved reflections are marked with an asterisk. Reflections marked with two asterisks are affected by extinction or from a particularly bad measurement.



to the least-squares sums is 0.080 (R = 0.087 for all observed reflections). The final positional and thermal parameters and their standard deviations are listed in Table I. The observed and calculated structure factors are shown in Table II.

Discussion.

As shown in Figure 1 bond lengths and angles are in good overall agreement with the values obtained for the β modification, the largest difference being five standard deviations for the C(5)-C(7) bond length. We can offer no explanation of this fact but we feel that it is unlikely that this difference in bond length is real.

It was the aim of our studies on biisoxazoles and phenylisoxazoles to investigate the extent of conjugation between the rings, also as a function of the position of the interring bond. As a matter of fact infrared and ultraviolet spectra (17), values of dipole moments (18) and theoretical calculations (19) support that interaction energy between the π-systems in biisoxazoles and phenylisoxazoles changes with the carbon atom which is involved in the interring bond: it seems to be highest for derivatives in C(5) and smallest for derivatives in C(4).

As a result of our X-ray investigations no conclusions can be drawn about this problem. In fact the trend of values for interring bond, which should shorten as conjugation increases, does not point out any quantitative indication for this effect. The range of the values (1.44-1.47 Å), always under 1.497 Å as found in bisphenyl (20), typical $C(sp^2)$-$C(sp^2)$ bond, suggests that conjugation takes place, but the difference expected in the investigated compounds seem not to be detectable by X-ray diffraction methods. The results, on the other hand, unequivocally show that conjugation within the isoxazole ring stops through N-O bond, whose value does not in any case differ significantly from 1.41 Å, which is that accepted for a single bond.

The least-squares planes through the entire molecule and the two rings separately were calculated according to Schomaker *et al.* (21); the results are given in Table III. It can be seen that atoms fit better in two separate planes through the individual rings, although the value of the twisting angle is hardly significant; however, since a slight deviation from planarity is found to be always present in the other asymmetrical molecules (8-10), we think that a small twisting of the two rings might be really present.

A view of the structure along the b axis is shown in Figure 2, where the closest intermolecular approaches are quoted. Molecules form planar dimers across a centre of symmetry through OH. . . .N hydrogen bonds, as found in β form.

The two-fold screw axis operation makes clear the packing differences in the two structures, as shown in Figure 3. In the α form, due to the almost perpendicularity of the longest molecular dimension to the two-fold axis, molecules are packed almost parallel one to the other. In the β form, where the direction of the interring bond makes an angle of about 45° with the two-fold axis, molecules pack close to perpendicular to each other. The different molecular arrangements give a closer packing in the α-modification, where there is a larger number of intermolecular contacts: those less than 4 Å are almost twice as many. Other remarkable facts are the differences in the thermal motion, the overall isotropic temperature factor being 4.05 and 5.14 $Å^2$ in α and β forms respectively; besides in the α modification there is a more pronounced anisotropy, the higher vibration amplitudes being perpendicular to the molecular plane.

TABLE III

Least-Squares Planes

Description of planes.

I Complete 3-hydroxy-5-phenylisoxazolemolecule
II Isoxazole ring
III Phenyl ring

I 4.558 x + 3.488 y - 1.947 z = 0.066
II 4.778 x + 3.446 y - 2.037 z = 0.040
III 4.393 x + 3.516 y - 2.013 z = 0.042

The equations of the planes are referred to the direct cell. The angle between II and III is 2.36°.

Distances From Planes

O(6)	0.0177	-0.0030*	0.0730*
O(1)	-0.0281	-0.0006	-0.0262*
N(2)	-0.0236	-0.0001	-0.0091*
C(3)	0.0083	0.0008	0.0459*
C(4)	0.0235	-0.0011	0.0646*
C(5)	0.0029	0.0011	0.0213*
C(7)	-0.0104	-0.0133*	-0.0015
C(8)	-0.0258	-0.0581*	-0.0008
C(9)	-0.0159	-0.0498*	0.0004
C(10)	0.0108	0.0049*	0.0024
C(11)	0.0200	0.0438*	-0.0047
C(12)	0.0206	0.0461*	0.0043

* Atoms not included in least-squares plane calculation.

REFERENCES

(1) P. Bravo, G. Gaudiano, A. Quilico and A. Ricca, *Gazz. Chim. Ital.*, 91, 47 (1961).

(2) S. Cabiddu, G. Gaudiano and A. Quilico, *ibid.*, 92, 501 (1962).

(3) H. D. Stachel, *Chem. Ber.*, 96, 1088 (1963).

(4) A. J. Boulton, A. R. Katritzky, A. Majid Hamed and S. Øksne, *Tetrahedron*, **20**, 2835 (1964).

(5) M. Cannas and G. Mocci, *Ric. Sci.*, **35**, (II-A) 467 (1965).

(6) M. Cannas and G. Marongiu, *Z. Krist.*, **124**, 143 (1967).

(7) M. Cannas and G. Marongiu, *ibid.*, **127**, 388 (1968).

(8) S. Biagini, M. Cannas and G. Marongiu, *Acta Cryst.*, **B25**, 730 (1969).

(9) M. Cannas, S. Biagini and G. Marongiu, *ibid.*, **B25**, 1050 (1969).

(10) S. Biagini, M. Cannas and G. Marongiu, *ibid.*, **B25**, 2108 (1969).

(11) The cell reported in (5) has been changed in order to reduce β from 113.3° to 96.1°. This was done primarily to reduce the correlation coefficient between the X and Z parameters in the least-squares refinement. The modified cell is also more nearly the same shape as that of the β form.

(12) A. D. Rae, *Acta Cryst.*, **19**, 683 (1965).

(13) D. T. Cromer and J. T. Waber, *ibid.*, **18**, 104 (1965).

(14) R. F. Stewart, E. R. Davidson and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

(15) D. van der Helm, I.C.R. No. 4, Structure Factor Program and Least-Squares Sum Maker, The Institute for Cancer Research, Philadelphia, Pa. (1961).

(16) C. K. Johnson and J. P. Glusker, I.C.R. No. 7, Least-Squares Sums Solver Program (Part 1) and Parameter Shifter Program (Part 2), The Institute for Cancer Research, Philadelphia, Pa. (1966).

(17) G. Speroni in "The Chemistry of Heterocyclic Compounds," Vol. 17, R. H. Wiley, Ed., Interscience Publishers, New York (1962) pp. 190-194.

(18) P. Pino and G. Speroni, *Rend. Ist. Lombardo Sci.*, **88**, 331 (1955).

(19) G. Del Re, *J. Chem. Soc.*, 3324 (1962).

(20) G. B. Robertson, *Nature*, **191**, 593 (1961); *ibid.*, **192**, 1026 (1961).

(21) V. Schomaker, J. Waser, R. E. Marsh and G. Bergmann, *Acta Cryst.*, **12**, 600 (1959).

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