Acta Cryst. (1977). B33, 980–984

Crystal and Molecular Structures of α-(N)-Heterocyclic Carboxaldehyde Thiosemicarbazones. I. The Structure of 2-Formyl-4-phenylpyridine Thiosemicarbazone–Dimethylformamide

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(*Received* 4 *June* 1976; *accepted* 8 *September* 1976)

The crystal structure of 2-formyl-4-phenylpyridine thiosemicarbazone–dimethylformamide has been determined by single-crystal X-ray diffraction studies. The complex crystallizes in the space group $P2_1/c$ with $a = 17{\cdot}351\,(3)$, $b = 5{\cdot}836\,(1)$, $c = 17{\cdot}184\,(2)$ Å, and $\beta = 101{\cdot}66\,(1)°$. The structure was solved by multiple tangent refinement and refined by block-diagonal least squares to $R = 0{\cdot}07$ and $R_w = 0{\cdot}08$ for 2036 observed reflections measured on a Picker diffractometer. The entire thiosemicarbazone molecule is planar and must undergo two 180° rotations to change its conformation to one which will allow it to act as a tridentate ligand.

Introduction

Several studies, which have been reviewed recently (Agrawal & Sartorelli, 1975), have shown that α-(N)-heterocyclic carboxyaldehyde thiosemicarbazones possess significant antineoplastic activity against a wide variety of transplanted tumors. Current kinetic data indicate that either these compounds coordinate as tridentate ligands to an iron-charged ribonucleoside-diphosphate reductase, or a preformed iron chelate of these molecules interacts with this enzyme and therefore inhibits the biosynthesis of DNA by lowering the conversion rate of ribonucleotides to deoxyribonucleotides (Sartorelli, Agrawal & Moore, 1971). Among the initial molecules studied in man was 2-formyl-5-hydroxypyridine thiosemicarbazone (5-HP) (DeConti *et al.*, 1972; Krakoff, Etcubanas, Tan, Mayer, Bethune & Burchenal, 1974). However, this molecule was found to have little usefulness in man since it was rapidly metabolized and excreted as an *O*-glucuronide. In order to expand the utility of this class of molecules, one of us has synthesized (Agrawal, Booth, DeNuzzo & Sartorelli, 1975) a large number of derivatives to determine the bulk tolerance for the interaction between the enzyme, inhibitor, and the ferrous ion and to design an agent which was (*a*) not as susceptible to enzymatic degradation in man and (*b*) had a greater inhibitory activity towards the target enzyme.

To complement the synthetic approach to the structure–activity work already in progress and to determine more precisely the molecular conformations and electronic distributions necessary in these compounds for maximum inhibitory activity, we have begun a series of single-crystal X-ray diffraction studies on both active and inactive derivative molecules. Reported in this paper is the structure of 2-formyl-4-phenylpyridine thiosemicarbazone (4-PPT), an agent possessing borderline biological activity. We have selected this agent initially to gain information as to its loss of antineoplastic activity, since a structurally similar agent, 2-formyl-4-(*m*-aminophenyl)pyridine thiosemicarbazone, has been reported to be one of the most active agents of this class of compound.

Experimental section

A single crystal (0·30 × 0·30 × 0·18 mm) of the title compound (synthesis has previously been described; Agrawal, Booth, DeNuzzo & Sartorelli, 1975) was grown by slow evaporation from an ethanol–dimethylformamide solution. The reciprocal lattice showed $2/m$ symmetry with systematic extinctions $k = 2n + 1$ for $0k0$ and $l = 2n + 1$ for $h0l$ reflections, uniquely characterizing the space group as $P2_1/c$. Lattice constants were determined by carefully measuring the Cu $K\alpha_1$–$K\alpha_2$ doublet for 12 reflections with $2\theta > 60°$. The resultant parameters and their estimated standard deviations are $a = 17{\cdot}351\,(3)$, $b = 5{\cdot}836\,(1)$, $c = 17{\cdot}184\,(2)$ Å, and $\beta = 101{\cdot}66\,(1)°$. The calculated density, 1·28 g cm^{-3}, for $C_{13}H_{12}N_4S.C_3H_7NO$ and $Z = 4$ agrees with the measured density, 1·27 g cm^{-3} (flotation in $CH_3CN.CCl_4$ solution).

Complete three-dimensional X-ray diffraction data

were collected on a computer-controlled four-circle Picker FACS-1 diffractometer with Ni-filtered Cu $K\alpha$ radiation and a $\theta:2\theta$ scan with 10 s background measurements at both extremities of the scan. 2710 independent reflections were measured to a 2θ maximum of 125° (d = 0·87 Å). Intensities of three standard reflections, monitored after every block of 50 reflections, remained within 2% of their mean values throughout the entire data collection, indicating both crystal and electronic stability. Structure amplitudes and their estimated errors were calculated from the expressions $|F_o| = (QI_n)^{1/2}$ and $\sigma^2(F_o) = (Q/4I_n)[I_s + (t_s/t_b)^2 I_b + (0{\cdot}02I_n)^2]$, where Q contains corrections for Lorentz–polarization, absorption, and attenuation, I_s and I_b are the scan and background intensities, t_s and t_b are the scan and background times, and I_n is the net integrated intensity. Absorption was corrected as a function of φ (obtained from a φ scan at $\chi = 90°$) with a maximum deviation of 25% (linear μ = 17·4 cm^{-1} for Cu $K\alpha$ radiation). 2036 reflections (75%) had $|F_o| > 3\sigma(F_o)$ and were used in the structure determination.

Structure determination and refinement

The structure was determined by direct methods (Germain, Main & Woolfson, 1971), block-diagonal least squares with $1/\sigma^2$ weights [minimizing the quantity $\Sigma w(\Delta F)^2$] being alternated with electron density calculations. The scattering factors of all non-hydrogen atoms were from Cromer & Waber (1965), while that for H was from Stewart, Davidson & Simpson (1965). The coordinates of most of the H atoms were found in subsequent difference electron density map calculations. The refinement was terminated when the shifts for all parameters were less than one-tenth of their estimated standard deviations. The conventional R values ($\Sigma|\Delta F|/\Sigma|F_o|$) for 23 anisotropic non-hydrogen atoms and 11 isotropic H atoms (with β fixed at 4·0) are 0·07 for observed data and 0·09 for all data, and the weighted R values [$(\Sigma w|\Delta F|^2/\Sigma wF_o^2)^{1/2}$] are 0·08 both for observed data and for all data. The largest peak in a final difference electron density map is 0·3 e Å^{-3}.*

Results and discussion

The final fractional coordinates and anisotropic temperature factors for both the thiosemicarbazone and dimethylformamide are listed in Table 1 along with their estimated standard deviations. Fig. 1 is a schematic drawing of the molecule showing bond distances and bond angles among the non-hydrogen atoms. The maximum estimated standard deviations for nonhydrogen bond distances and angles are 0·008 Å and 0·6° respectively.

As can be seen from the *ORTEP* stereo drawing (Johnson, 1965), Fig. 2, the molecule is essentially planar with a r.m.s. deviation of ±0·032 Å from the best least-squares plane. Similar planarity was observed for 5-HP (Palenik, Rendle & Carter, 1974) but it is in contrast to the structure of 4-formylpyridine thiosemicarbazone (4-PT) (Restivo & Palenik, 1970) in which the side chain is twisted by 14° with respect to the plane of the pyridine ring. The formyl-thiosemicarbazone moiety [S, N(1), C(2), N(3), N(4), C(5), and C(6)] is structured from bonds with dihedral angles of alternating sign of approximately 2°, and is planar to ±0·013 Å. Even larger dihedral angles, 5°, have been reported in previous studies for the N(3)–C(2) bond. Since the thiosemicarbazone moiety is *trans* about the N(4)–C(5) double bond and in an extended configuration about N(3)–N(4), the molecule has overall an L-shaped appearance.

A comparison of the bond distances and bond angles for the side chain reveals no unusual features from previously reported thiosemicarbazone structures. All distances except N(1)–C(2) and all bond angles in this chain are within two estimated standard deviations of the 'averaged' 2-formylthiophene thiosemicarbazone (2-TT) (Mathew & Palenik, 1971). N(1)–C(2), 1·345 (6) Å, is approximately 0·02 Å greater than observed in 2-TT and 4-PT and 0·04 Å greater than the corresponding distance in 5-HP, 1·307(7) Å, but within one e.s.d. of the value observed in a Ni-thiosemicarbazone complex of 1-formylisoquinoline (Mathew & Palenik, 1969). The C–S bond distance, 1·675 (5) Å, is at the lower end of previously reported values, 1·678 to 1·707 Å. All values are in agreement with previously postulated canonical structures and the minor variances observed are probably attributable to differences in hydrogen-bonding patterns, as suggested by Palenik *et al.* (1974).

The pyridine ring is planar within experimental error and has a standard deviation of 0·014 Å. N(11)–C(6) and N(11)–C(10), 1·329 (6) Å, are within two e.s.d.'s of the same distance, 1·336 Å, observed in a recent pyridyl-containing compound (Brown, Jenevein, Stocker & Trefonas, 1972). The internal angles at N(11), 116·0°, C(10), 124·5°, and C(6), 123·2°, closely parallel those reported for a substituted pyridine (Seff & Trueblood, 1968) (CNC = 117·0 and NCC = 123·5°) as do the other internal ring angles. The large differences in the external angles C(5)–C(6)–N(11), 114·4°, and C(5)–C(6)–C(7), 122·4°, from 120° are in the same direction and magnitude as observed in other 2-substituted pyridines. The two aromatic rings are joined by a C–C bond, 1·499 Å, which is typical of biphenyls, and are slightly twisted, 2·5°, about this

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32144 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Final fractional coordinates and temperature factors*

Estimated standard deviations are in parentheses. Anisotropic thermal parameters are $\times 10^4$ and are of the form: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{13}hl + 2\beta_{12}hk + 2\beta_{23}kl)]$.
The H atoms are numbered according to the C or N atoms to which they are bonded. The B values for the H atoms are 4·0 Å².

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	1·0841 (1)	1·3467 (3)	0·4304 (1)	36 (1)	324 (5)	57 (1)	−21 (3)	20 (1)	−27 (4)
N(1)	0·9406 (2)	1·2220 (7)	0·4477 (2)	34 (2)	349 (17)	46 (2)	9 (9)	15 (3)	−3 (10)
C(2)	1·0029 (3)	1·1838 (8)	0·4139 (3)	31 (2)	300 (18)	34 (2)	6 (10)	10 (3)	8 (11)
N(3)	0·9996 (2)	0·9995 (7)	0·3670 (2)	32 (2)	301 (15)	39 (2)	−7 (8)	14 (3)	−5 (9)
N(4)	0·9329 (2)	0·8672 (7)	0·3513 (2)	25 (1)	304 (14)	38 (2)	−18 (8)	8 (3)	−3 (9)
C(5)	0·9346 (3)	0·7008 (9)	0·3035 (3)	27 (2)	322 (19)	41 (2)	4 (10)	13 (3)	2 (11)
C(6)	0·8697 (3)	0·5396 (8)	0·2827 (3)	28 (2)	294 (18)	32 (2)	1 (10)	6 (3)	−4 (10)
C(7)	0·8005 (3)	0·5583 (9)	0·3128 (3)	29 (2)	297 (18)	36 (2)	9 (10)	9 (3)	−5 (10)
C(8)	0·7417 (2)	0·3969 (8)	0·2918 (3)	25 (2)	243 (17)	36 (2)	0 (9)	6 (3)	15 (10)
C(9)	0·7567 (3)	0·2197 (9)	0·2446 (3)	32 (2)	308 (19)	48 (3)	−11 (10)	10 (4)	−20 (12)
C(10)	0·8257 (3)	0·2156 (9)	0·2171 (3)	40 (2)	318 (20)	47 (3)	10 (11)	12 (4)	−30 (12)
N(11)	0·8819 (2)	0·3730 (7)	0·2339 (2)	29 (1)	297 (15)	39 (2)	8 (8)	9 (3)	−16 (9)
C(12)	0·6661 (3)	0·4146 (8)	0·3207 (3)	29 (2)	292 (19)	39 (2)	6 (10)	7 (3)	0 (11)
C(13)	0·6060 (3)	0·2585 (11)	0·2993 (4)	42 (2)	486 (26)	71 (3)	−54 (13)	23 (5)	−65 (16)
C(14)	0·5377 (3)	0·2762 (11)	0·3250 (4)	43 (2)	559 (29)	65 (3)	−61 (15)	18 (5)	−25 (16)
C(15)	0·5233 (3)	0·4460 (10)	0·3732 (3)	32 (2)	469 (26)	68 (3)	0 (12)	17 (4)	27 (15)
C(16)	0·5812 (3)	0·5992 (11)	0·3961 (4)	57 (3)	498 (20)	105 (5)	−9 (16)	45 (6)	−80 (19)
C(17)	0·6511 (3)	0·5873 (11)	0·3689 (4)	38 (2)	439 (28)	117 (5)	−34 (14)	31 (6)	−78 (19)
O(18)	0·3365 (2)	0·2926 (8)	0·3653 (3)	55 (2)	504 (19)	98 (3)	−12 (10)	13 (4)	62 (12)
C(19)	0·2950 (3)	0·1835 (12)	0·3998 (4)	33 (2)	554 (30)	90 (4)	17 (15)	7 (5)	−2 (19)
N(20)	0·3121 (3)	−0·0099 (8)	0·4407 (3)	56 (2)	323 (17)	56 (2)	19 (11)	−2 (4)	13 (11)
C(21)	0·3888 (4)	−0·1160 (12)	0·4400 (4)	60 (3)	554 (32)	97 (5)	101 (18)	0 (6)	−15 (21)
C(22)	0·2557 (4)	−0·1207 (12)	0·4812 (4)	83 (4)	579 (35)	81 (4)	−40 (20)	18 (7)	84 (20)

	x	y	z		x	y	z
H(3)	1·0416 (22)	0·9577 (71)	0·3436 (22)	H(14)	0·4979 (22)	0·1850 (70)	0·3074 (23)
H(5)	0·9806 (21)	0·6720 (67)	0·2837 (22)	H(15)	0·4705 (22)	0·4561 (70)	0·3898 (22)
H(7)	0·7957 (21)	0·6868 (72)	0·3471 (23)	H(16)	0·5815 (21)	0·7183 (70)	0·4373 (23)
H(9)	0·7252 (21)	0·1162 (68)	0·2278 (22)	H(17)	0·6910 (21)	0·6701 (70)	0·4031 (23)
H(10)	0·8371 (22)	0·1089 (67)	0·1835 (23)	H(19)	0·2585 (23)	0·2169 (69)	0·4004 (23)
H(13)	0·6172 (22)	0·1312 (69)	0·2661 (22)				

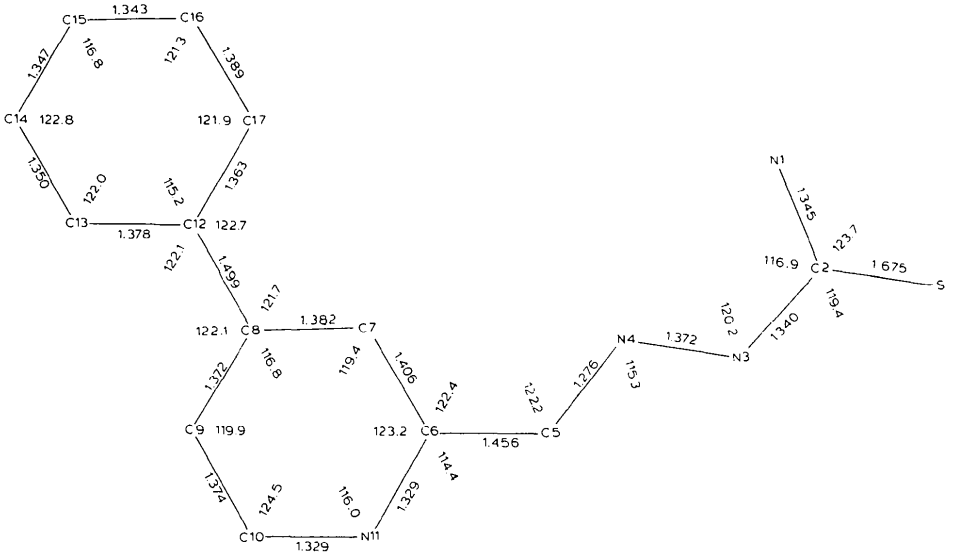

Fig. 1. Schematic drawing of 2-formyl-4-phenylpyridine thiosemicarbazone with bond distances and bond angles indicated.

bond. Like the pyridine ring, the phenyl ring is also planar within experimental error, 0·008 Å. However, unlike the pyridine ring, the phenyl ring has bond angles ranging from 115·2 to 122·8° about an average value of 120·0°, which are not in agreement with the accepted values. A slightly constricted internal angle at C(12) was observed in the two structure determinations of biphenyl (118·9 and 118·8°) (Hargreaves & Rizvi, 1962; Trotter, 1961) but not to the extent observed here. Since the distances within this ring are nearly identical with those for biphenyl, the remainder of the structure is in such excellent agreement with previous results, and the thermal motions of the atoms within this ring are similar to the remainder of the structure, it is difficult to explain the C(13)–C(16)–C(7) angle of 115·2 °.

A schematic drawing of the dimethylformamide (DMF) molecule with bond distances and angles is given in Fig. 3. The two CH_3–N distances, 1·469 (8) and 1·462 (8) Å, are slightly longer than those observed in a DMF–substituted-azaheptane molecular complex (Cobbledick & Small, 1973), 1·432 (7) and 1·439 (6) Å. This may be a result of the methyl H atoms being omitted from the structure refinement. The angle N(20)–C(19)–O(18), 128·2°, is larger by almost 3° than that previously observed, 125·4 (4)°.

Table 2 lists the intermolecular contact distances between non-hydrogen atoms that are less than 3·5 Å. The hydrogen bond S···N(1), 3·35 Å, is in the middle of the range of distances, 3·2 to 3·5 Å, previously observed. This distance is 0·15 Å less than that observed for an identical bond in 4-PT and 5-HP. Conversely, the N(3)–H(3)···N(11) hydrogen bond [N(3)–H(3) = 1·05, H(3)···N(11) = 2·02, N(3)···N(11) = 3·05 Å, and N(3)–H(3)···N(11) = 166°] is longer than that observed in 4-PT, 2·96 Å, but falls at the average value of $-NH_2\cdots$N(ring) distances reported by Fuller (1959), 3·06 ± 0·08 Å. It is interesting to note that with the exception of the C(9)–O(18) contact of 3·34 Å, there are no contacts between DMF and other atoms less than 3·5 Å although the DMF carbonyl is capable of being an acceptor in a hydrogen bond.

The overall conformation of the molecule is such that for it to act as a tridentate ligand, two major changes, as illustrated in Fig. 4, must occur before the side chain will be in the proper orientation: (1) there must be a 180° rotation about the C(5)–C(6) bond to bring N(4) into position with N(11) to form a five-membered chelate ring with a ferrous ion and (2) there must then be a 180° rotation about N(3)–C(2) to switch the positions of N(1) and S so that the S will participate in a second five-membered chelate ring with the metal and N(4). Since the C(5)–C(6) and C(2)–N(3) bond distances are shorter than normal single bonds, the delocalization may increase the barrier to free rotation and the hindrance to achieve the preferred conformation for iron chelation may play an important role for reduced biological activity of 4-PPT, although the pharmacokinetic parameters are not ruled out. It is apparent, however, that an insight into the conformational structures of these agents would be of immense value for future design and structure–activity correlations.

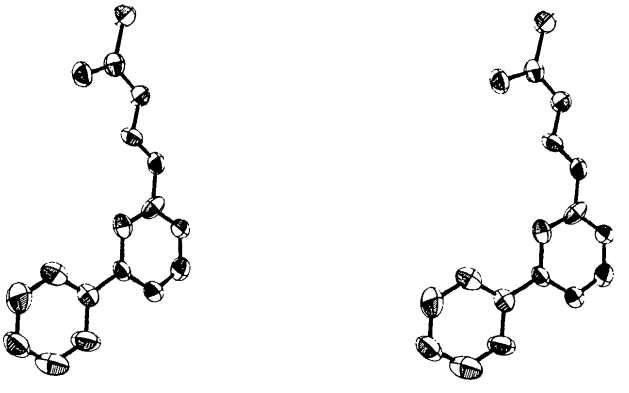

Fig. 2. *ORTEP* stereo drawing of the thiosemicarbazone molecule.

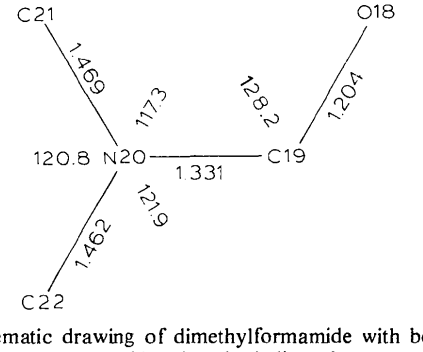

Fig. 3. Schematic drawing of dimethylformamide with bond distances and bond angles indicated.

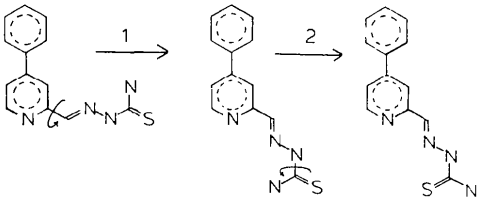

Fig. 4. Rotations necessary for the thiosemicarbazone to act as a tridentate ligand.

Table 2. *Non-hydrogen intermolecular contacts less than* 3·5 Å

S···N(1)	$2-x, 3-y, 1-z$	3·35 Å
N(1)···C(2)	$2-x, 2-y, 1-z$	3·37
N(1)···N(3)	$2-x, 2-y, 1-z$	3·40
N(1)···C(6)	$x, 1+y, z$	3·40
N(3)···N(11)	$2-x, \frac{1}{2}+y, \frac{1}{2}-z$	3·05
N(4)···C(10)	$x, 1+y, z$	3·35
C(9)···O(18)	$1-x, y-\frac{1}{2}, \frac{1}{2}-z$	3·34

This work was supported in part by grants from the Research Corporation and from NIH-CA-17594 for JNB.

References

AGRAWAL, K. C., BOOTH, B. A., DENUZZO, S. M. & SARTORELLI, A. C. (1975). *J. Med. Chem.* **18**, 368–371. This paper is the twelfth in a series of papers concerning the synthesis and activity of α-(N)-heterocyclic carboxaldehyde thiosemicarbazones.

AGRAWAL, K. C. & SARTORELLI, A. C. (1975). *Handbook of Experimental Pharmacology*, Vol. 38, Part II, edited by A. C. SARTORELLI & D. G. JOHNS, pp. 793–807. Berlin: Springer.

BROWN, J. N., JENEVEIN, R. M., STOCKER, J. H. & TREFONAS, L. M. (1972). *Org. Chem.* **37**, 3712–3718.

COBBLEDICK, R. E. & SMALL, R. W. (1973). *Acta Cryst.* B**29**, 1659–1666.

CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.

DECONTI, R. C., TOFTNESS, B. R., AGRAWAL, K. C., TOMCHICK, R., MEAD, J. A. R., BERTINO, J. R., SARTORELLI, A. C. & CREASEY, W. A. (1972). *Cancer Res.* **32**, 1455–1462.

FULLER, W. (1959). *J. Phys. Chem.* **63**, 1705–1717.

GABE, E. J., TAYLOR, M. R., GLUSKER, J. P., MINKIN, J. A. & PATTERSON, A. L. (1969). *Acta Cryst.* B**25**, 1620–1631.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

HARGREAVES, A. & RIZVI, S. H. (1962). *Acta Cryst.* **15**, 365–373.

JOHNSON, C. K. (1965). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.

KRAKOFF, I. H., ETCUBANAS, E., TAN, C., MAYER, K., BETHUNE, V. & BURCHENAL, J. H. (1974). *Cancer Chemother. Rep.* **58**, (1), 207.

MATHEW, M. & PALENIK, G. J. (1969). *J. Amer. Chem. Soc.* **91**, 6310–6314.

MATHEW, M. & PALENIK, G. J. (1971). *Acta Cryst.* B**27**, 59–66.

PALENIK, G. J., RENDLE, D. F. & CARTER, W. S. (1974). *Acta Cryst.* B**30**, 2390–2395.

RESTIVO, R. & PALENIK, G. J. (1970). *Acta Cryst.* B**26**, 1397–1402.

SARTORELLI, A. C., AGRAWAL, K. C. & MOORE, E. C. (1971). *Biochem. Pharmacol.* **20**, 3119–3123.

SEFF, K. & TRUEBLOOD, K. N. (1968). *Acta Cryst.* B**24**, 1406–1415.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

TROTTER, J. (1961). *Acta Cryst.* **14**, 1135–1140.

Acta Cryst. (1977). B**33**, 984–990

The Crystal and Molecular Structure of 5α,8α-Dimethyl-4aβ,5,8,8aβ-tetrahydro-1,4-naphthoquinone and its Solid-State Photodimer

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(*Received* 22 *July* 1976; *accepted* 12 *September* 1976)

Crystals of 5α,8α-dimethyl-4aβ,5,8,8aβ-tetrahydro-1,4-naphthoquinone are monoclinic, space group $P2_1/c$, with $a = 7{\cdot}189\,(1)$, $b = 22{\cdot}241\,(4)$, $c = 6{\cdot}843\,(1)$ Å, $\beta = 106{\cdot}51\,(1)°$ and $Z = 4$. The molecules occur in pairs related by centres of symmetry, and irradiation of the crystals with ultraviolet light causes linking of the pairs to form dimers. Crystals of the product also have space group $P2_1/c$, with $a = 11{\cdot}393\,(1)$, $b = 8{\cdot}029\,(1)$, $c = 10{\cdot}771\,(5)$ Å, $\beta = 91{\cdot}04\,(1)°$ and $Z = 2$. The dimer molecule has a crystallographic centre of symmetry and a planar four-membered ring. In both molecules the fused six-membered rings have the 'twist' conformation observed for other *cis*-4a,5,8,8a-tetrahydro-1,4-naphthoquinones.

Introduction

A study of the photochemistry of various substituted *cis*-4a,5,8,8a-tetrahydro-1,4-naphthoquinone derivatives in solution (Scheffer, Jennings & Louwerens, 1976) has revealed unusual reaction pathways. Irradiation of the same derivatives in the crystalline state produces, in some cases, differing product ratios and even entirely different products (Dzakpasu, Phillips, Scheffer & Trotter, 1976). Photolysis of 5α,8α-dimethyl-4aβ,5,8,8aβ-tetrahydro-1,4-naphthoquinone (I) in solution results in abstraction of a methyl H by