[Chem. Pharm. Bull. 25(5)1147—1150(1977)]

UDC 547.852.7.02 : 548.737

Reaction Products of 1-Hydrazinophthalazine with Mesityl Oxide; X-Ray Structural Characterization

KEN'ICHI YAMAZAKI, REIMEI MOROI, and MITSUJI SANO

Research Institute, Daiichi Seiyaku Co., Ltd.[1]

(Received August 21, 1976)

An X-ray structure determination of 1-(3,5,5-trimethyl-1-pyrazolinyl)phthalazine, synthesized from 1-hydrazino phthalazine with mesityl oxide, was performed. The structure was solved by the heavy atom method and refined by least-squares procedures to an R factor of 0.048.

Keywords——X-ray analysis; heavy atom method; pyrazoline derivative; 1-hydrazinophthalazine; mesityl oxide; ORTEP drawing

The reaction of 1-hydrazinophthalazine with mesityl oxide under reflux afforded five crystalline compounds[2] (Fig. 1). The structure of V(DC-2764), mp 82—83°, has been assumed as Vb, but the question has still remained whether the structure of V is Va or Vb. An X-ray diffraction study was therefore undertaken on the crystals. The structure analysis was achieved by the heavy atom method.

Experimental

DC-2764——a) DC-2764 was synthesized according to the method of K. Ueno, *et al.*[2] DC-2764 was also obtained by reaction of acetic acid with budralazine (DJ-1461, 1-[2-(1,3-dimethyl-2-butenylidene)-hydrazino]phthalazine).

b) A solution of budralazine (4.0 g) in acetic acid (100 ml) was refluxed for 1.5 hr and concentrated. The residue was poured into H_2O, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. After concentration of the $CHCl_3$ solution, the residue was chromatographed on silica gel and eluted with benzene. The eluate was crystallized from hexane to give DC-2764 (2.11 g), mp 82—83°. *Anal.* Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.99; H, 6.70; N, 23.46.

Hydrobromide of DC-2764——A mixture of conc. HBr (25 ml) and DC-2764 (2.0 g) in MeOH (100 ml) was heated at 50° for 10 min, and concentrated. The residue was crystallized from MeOH–ether to give the hydrobromide of DC-2764 (1.9 g), mp 268—271° (dec.). *Anal.* Calcd. for $C_{14}H_{17}N_4Br$: C, 52.34; H, 5.33; N, 17.44; Br, 24.88. Found: C, 52.22; H, 5.37; N, 17.54; Br. 25.16.

Data Collection——The lattice parameters and three dimensional intensity data were derived from the measurements using a Philips four-circle X-ray diffractometer with monochromated CuKα radiation (λ= 1.5418 Å). The crystal dimensions used for measurement were approximately $0.3\times0.2\times0.2$ mm. A total of 2676 independent reflexions of the crystal were obtained by θ—2θ scan method with the scan speed θ= 4°/min. The crystal data are as follows:

$C_{14}H_{17}N_4Br$, mol. wt.=321.22. Monoclinic,
$a=19.21_4$, $b=9.08_5$, $c=8.64_0$ Å, $\beta=96.29_2°$.
$U=1499.11$ Å^3, $Z=4$. Space group $P2_1/n$.

Determination of the Structure

Solution and Refinement

The position of the bromine atom was determined from a sharpened three-dimensional Patterson function. Repeated cycles of structure factors and Fourier calculations yielded the most probable locations of the remaining non-hydrogen atoms. Anisotropic tempera-

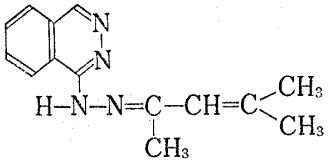
1) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
2) K. Ueno, R. Moroi, M. Kitagawa, K. Asano, and S. Miyazaki, *Chem. Pharm. Bull.* (Tokyo), **24**, 1068 (1976).

Table I. Atomic Parameters and Their Standard Deviations

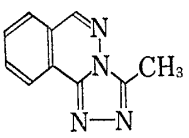
	X	*Y*	*Z*	B11	B22	B33	B12	B13	B23
BR	0.3759(0)	0.6070(1)	0.4125(1)	0.0027(0)	0.0182(1)	0.0089(1)	0.0000(0)	−0.0002(0)	−0.0013(1)
C(1)	0.0602(2)	0.3099(5)	0.5203(5)	0.0020(1)	0.0102(5)	0.0102(6)	0.0002(2)	0.0001(2)	0.0013(5)
C(2)	−0.0058(2)	0.2386(4)	0.4631(4)	0.0020(1)	0.0093(5)	0.0099(6)	0.0005(2)	0.0001(2)	0.0012(4)
C(3)	−0.0335(2)	0.2276(5)	0.3061(5)	0.0026(1)	0.0116(6)	0.0109(6)	0.0001(2)	−0.0001(2)	−0.0005(5)
C(4)	−0.0948(2)	0.1492(5)	0.2663(5)	0.0029(1)	0.0114(6)	0.0132(7)	0.0000(2)	−0.0006(2)	0.0003(5)
C(5)	−0.1303(2)	0.0807(5)	0.3800(5)	0.0028(1)	0.0112(6)	0.0150(7)	−0.0007(2)	−0.0007(3)	0.0012(5)
C(6)	−0.1035(2)	0.0869(5)	0.5323(5)	0.0026(1)	0.0118(6)	0.0149(7)	−0.0005(2)	0.0003(2)	0.0025(6)
C(7)	−0.0404(2)	0.1637(5)	0.5754(5)	0.0024(1)	0.0094(5)	0.0114(6)	0.0003(2)	0.0002(2)	0.0012(5)
C(8)	−0.0072(2)	0.1554(5)	0.7298(5)	0.0027(1)	0.0114(6)	0.0105(6)	0.0002(2)	0.0004(2)	0.0023(5)
C(9)	0.1162(2)	0.5083(6)	0.2185(5)	0.0029(1)	0.0148(7)	010148(7)	−0.0008(3)	0.0002(2)	0.0025(6)
C(10)	0.1883(3)	0.4773(7)	0.2939(6)	0.0026(1)	0.0226(10)	0.0157(8)	−0.0018(3)	0.0008(3)	0.0041(7)
C(11)	0.1763(2)	0.4208(5)	0.4558(5)	0.0018(1)	0.0129(7)	0.0133(7)	−0.0004(2)	−0.0001(2)	0.0005(5)
C(12)	0.1002(3)	0.5846(7)	0.0657(6)	0.0043(2)	0.0226(11)	0.0160(9)	−0.0023(4)	0.0004(3)	0.0084(8)
C(13)	0.1896(3)	0.5395(6)	0.5808(7)	0.0032(2)	0.0123(7)	0.0218(10)	−0.0005(3)	0.0001(3)	−0.0034(7)
C(14)	0.2190(2)	0.2838(6)	0.4974(6)	0.0024(1)	0.0136(7)	0.0214(9)	−0.0005(3)	0.0002(3)	−0.0022(7)
N(1)	0.0538(2)	0.2156(4)	0.7630(4)	0.0028(1)	0.0121(5)	0.0096(5)	0.0004(2)	0.0001(2)	0.0018(4)
N(2)	0.0900(2)	0.2959(4)	0.6656(4)	0.0024(1)	0.0131(5)	0.0102(5)	−0.0003(2)	−0.0002(2)	0.0015(4)
N(3)	0.0995(2)	0.3862(4)	0.4271(4)	0.0019(1)	0.0146(6)	0.0116(5)	−0.0001(2)	−0.0001(2)	0.0039(5)
N(4)	0.0673(2)	0.4542(4)	0.2900(4)	0.0024(1)	0.0132(5)	0.0113(5)	−0.0003(2)	0.0000(2)	0.0037(4)
H(1)	−0.0099(27)	0.2779(60)	0.2075(58)	6.10(1.33)					
H(2)	−0.1111(22)	0.1320(49)	0.1381(49)	4.47(1.01)					
H(3)	−0.1792(26)	0.0093(58)	0.3389(56)	6.47(1.27)					
H(4)	−0.1285(29)	0.0365(67)	0.6262(64)	8.22(1.56)					
H(5)	−0.0295(23)	0.1080(53)	0.8113(52)	4.96(1.11)					
H(6)	0.2090(34)	0.4266(76)	0.2126(75)	10.58(1.94)					
H(7)	0.2131(28)	0.5744(62)	0.3218(61)	7.63(1.45)					
H(8)	0.1144(33)	0.6721(74)	0.0255(73)	11.63(1.87)					
H(9)	0.0475(27)	0.5915(60)	0.0282(60)	7.13(1.36)					
H(10)	0.1224(29)	0.5110(65)	−0.0233(63)	8.35(1.50)					
H(11)	0.1649(29)	0.6102(64)	0.5460(63)	7.77(1.48)					
H(12)	0.1913(30)	0.5096(68)	0.7147(66)	8.02(1.58)					
H(13)	0.2465(27)	0.5721(61)	0.5990(61)	7.20(1.40)					
H(14)	0.2117(29)	0.1983(64)	0.4360(64)	7.47(1.51)					
H(15)	0.2692(25)	0.3123(55)	0.4865(54)	5.63(1.21)					
H(16)	0.2194(28)	0.2560(65)	0.6182(62)	7.65(1.49)					
H(17)	0.0853(25)	0.2018(56)	0.8868(55)	5.53(1.23)					

$(T=\exp-(B11h^2+B22k^2+B33l^2+2B12hk+2B13hl+2B23kl)$

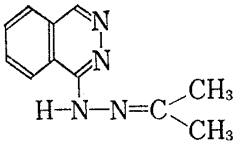
ture factors for the non-hydrogen atoms were adopted. Difference-Fourier syntheses revealed all the hydrogen atoms at the expected positions. Refinement was carried out by the block-diagonal least-squares method using anisotropic temperature factors for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The final R value was 0.048. Atomic parameters and their estimated standard deviations are listed in Table I.



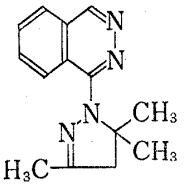
I(*anti*), II(*syn*)



III

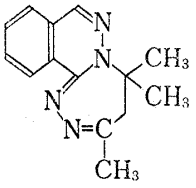


IV



Va

or



Vb

V(DC-2764)

Fig. 1

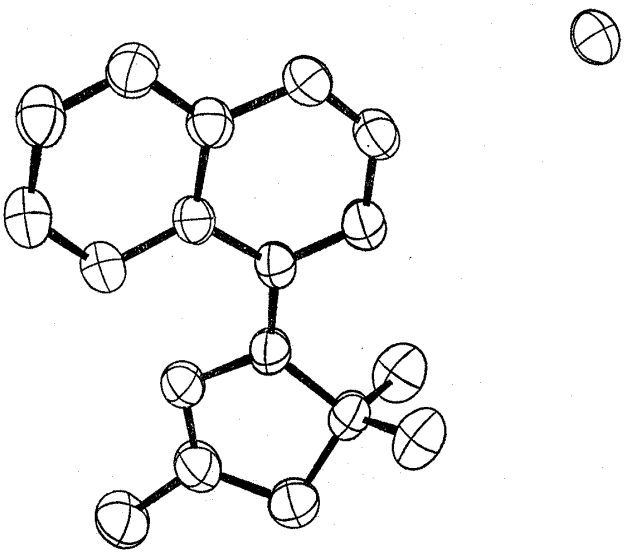


Fig. 2. Molecular Structure

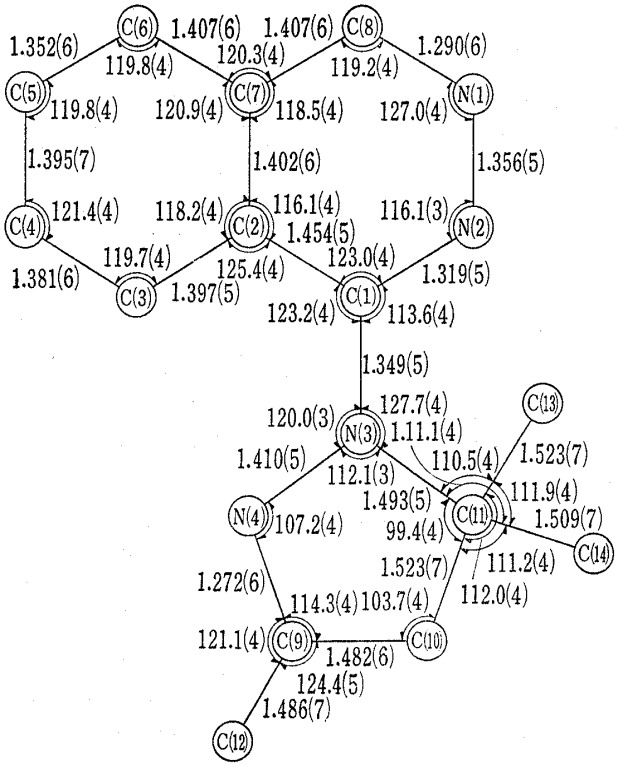


Fig. 3. Bond Lengths and Angles

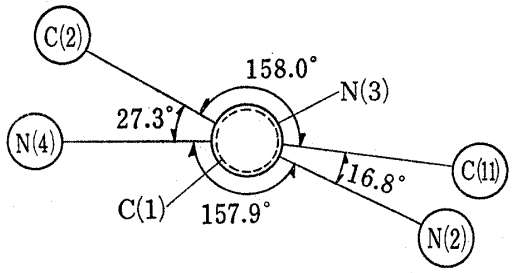


Fig. 4. Newman Projection along Bond C(1)–N(3)

Results and Discussion

Molecular Structure

The hydrobromide of DC-2764 was determined to be 1-(3,5,5-trimethyl-1-pyrazolinyl) phthalazine hydrobromide (Fig. 1. Va), contrary to the structure assumed as 3,5,5-trimethyl-4,5-dihydro-1, 2, 4-triazepino- [3, 4-*a*] phthalazine (Fig. 1. Vb). Fig. 2 shows an ORTEP[3] drawing of the molecule.

3) C.K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A.

Distances and Angles

Intramolecular bond lengths and angles not involving hydrogen atoms are listed in Fig. 3. The standard labelling of atoms is in the same figure. The H atom of the hydrobromide combines with N^3 of the phthalazine ring. Distances between N(1)-H(17), H(17)-Br and N(1)-Br are 1.17, 2.00 and 3.12 Å, respectively. The N(1)-H(17)----Br bond is a hydrogen bond, but no intermolecular hydrogen bonds are observed. The C(1)-N(3) bond length is shorter than the normal length (1.47 Å) by 0.12 Å. This fact indicates that the nitrogen atom (N(3)) would resonate with the phthalazine ring. The dihedral angle between the phthalazine ring and pyrazoline ring is 27.3°. The torsion angle C(2)-C(1)-N(3)-N(4), C(2)-C(1)-N(3)-C(11),N(2)-C(1)-N(3)-N(4) and N(2)-C(1)-N(3)-C(11) are 27.3°,—158.0°,—157.9° and 16.8°, respectively (Fig. 4).

Acknowledgement The authors wish to express their deep gratitude to Prof. Y. Iitaka, Tokyo University, for his valuable advice.

[Chem. Pharm. Bull. 25(5)1150—1154(1977)]

UDC 547.814.5.04 : 547.821.04

Synthetic Studies of Azaflavonoids. I. Studies on the Synthesis of 5-Azaflavone[1)]

TAKAO YAMAZAKI, KATSUHIDE MATOBA, YUKO MATSUZAWA, and MASAHISA KITAGAWA

Faculty of Pharmaceutical Sciences, University of Toyama[2)]

(Received August 23, 1976)

Azachalcones (IV) were synthesized from 2-cyano-3-hydroxy-pyridine (I) *via* three steps. Based on the ultraviolet spectroscopic data, the cyclization of IV to 5-azaflavanones (V) was assumed, but V could not be isolated. On the other hand, a 5-azaflavone (VIII) was prepared from I *via* five steps in a moderate yield.

Keywords——azaflavone; azaflavanone; azachalcone; pyridine derivative; Grignard reaction; acid catalyzed cyclization

In our laboratory, the synthetic studies of the heterocyclic compounds containing nitrogen atoms in the skeleton are in progress,[3)] and the several pyridoflavanones have already been synthesized.[4)]

Many years since the flavonoids as plant pigments have widely been studied. Rutin, hesperidin and myricitrin among them have some pharmacological activities against increased capillary fragility. The appropriate solubilizing and suspending agents were used in order to apply them to medicinal use because of their insolubility in water. Now azaflavonoids may be expected to have more activity than that of the flavonoids, because the solubility of azaflavonoids may be enhanced by salt formation. From the above point of view, the

1) A part of this work was presented at the 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, June 1975 (Kanazawa), and at the 96th Annual Meeting of Pharmaceutical Society of Japan, April 1976 (Nagoya).
2) Location: *Gofuku, Toyama.*
3) T. Yamazaki, K. Matoba, M. Yajima, M. Nagata, and R.N. Castle, *J. Heterocyclic Chem.*, **12**, 973 (1975), and references therein.
4) H. Matsumoto, M. Nagata, J. Kawahira, and T. Yamazaki, *Yakugaku Zasshi*, **88**, 1412 (1968).