Reissert-Type Reaction of *N*-Sulfonyl- or *N*-Acyl-phthalazinium Salts with Trimethyl Phosphite and Crystal Structure of Dimethyl 2-Mesyl-1,2-dihydro-1-phthalazinylphosphonate

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Dimethyl 2-sulfonyl- and 2-acyl-1,2-dihydro-1-phthalazinylphosphonates (1a—e) were synthesized by the reaction of phthalazine with sulfonyl chloride or acyl chloride and trimethyl phosphite. The crystal structure of 1a was determined by X-ray analysis.

Keywords phthalazine; X-ray analysis; phosphonate; phosphite; Reisset reaction; sulfonyl chloride; acyl chloride

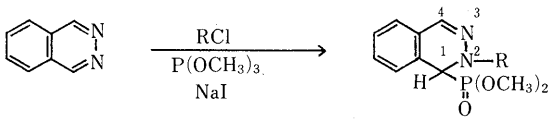
In a previous paper[1] we have reported that the Reissert reaction of 1,6-naphthyridine with sulfonyl chloride and potassium cyanide afforded 1,6-naphthyridine-5-carbonitrile in a high yield with release of the sulfonyl group. We have also investigated the Reissert-type reactions of several heterocyclic compounds with acid (or sulfonyl) chloride and trialkyl phosphite in place of potassium cyanide.[2] For example, benzo[*f*]quinoline[2a] and 1,7- or 4,7-phenanthroline [2b,c] gave the corresponding α- and γ-phosphonates, and 4,7-phenanthroline[2b,c] afforded the diphosphonate, which was separated into *cis* and *trans* isomers. As a part of our continuing studies on the reactivities of nitrogen-containing heterocyclic compound,[1-3] the Reissert-type reactions of phthalazine were examined in order to compare them with the Reissert reaction of 1,6-naphthyridine.

In this paper we describe the synthesis of the Reissert-type compounds (**1a—e**, see Chart 1 for the chemical structures) and the crystal structure of **1a**. We found that **1a** appears to have a weak muscle-relaxant activity. Some of the proton carbon-13, and phosphorus-31 nuclear magnetic resonance (^{1}H-, ^{13}C-, and ^{31}P-NMR) spectral data for **1a—e** have been reported previously.[3]

Results and Discussion

Reissert-Type Reactivities of Phthalazine The Reissert-type reaction of phthalazine with methanesulfonyl or benzenesulfonyl chloride (CH_3SO_2Cl or $PhSO_2Cl$) and trimethyl phosphite ($P(OCH_3)_3$) in acetonitrile gave the corresponding monophosphonate (**1a** or **1b**), bearing a sulfonyl group. Reissert reaction of phthalazine with $PhSO_2Cl$ and potassium cyanide (KCN) has been reported to afford the Reissert compound bearing a sulfonyl group.[4]

Although the Reissert reaction of 1,6-naphthyridine and phthalazine with *N*,*N*-diphenylcarbamoyl chloride (Ph_2NCOCl) and KCN afforded the corresponding Reissert compound,[1,4] the reaction of phthalazine with Ph_2NCOCl and $P(OCH_3)_3$ under the ordinary conditions for Reissert-type reactions (*i.e.*, 0 °C) did not proceed and the starting material was recovered. At an elevated temperature (80 °C), however, the expected phosphonate (**1c**) was obtained in low yield (38%). It has been demonstrated that for the Reissert-type reaction the phosphite is more reactive with *N*-heterocycles than KCN.[2-5] Nevertheless, under these reaction conditions *N*-acylation of phthalazine seems to be difficult to achieve in good yield. In fact, the Reissert-type reactions of phthalazine with acid chlorides and $P(OCH_3)_3$ afforded the corresponding compounds in very low yields (**1d**, only 5%; **1e**, 20%).



1a : R=SO_2CH_3
1b : R=SO_2Ph
1c : R=$CONPh_2$
1d : R=$COCH_3$
1e : R=COPh

Chart 1

X-Ray Crystallography of 1a Reissert-type reaction of phthalazine with $P(OCH_3)_3$ gave the phosphonate retaining the sulfonyl group, similar to the Reissert compound of phthalazine.[4] But 1,6-naphthyridine shows different reactivity, and the sulfonyl group is released from the Reissert compound.[1] The crystal structure of **1a** was determined to obtain some insight into the low Reissert reactivities of phthalazine and to obtain clues to the stereostructural requirements for muscle-relaxant activity. Since the vicinity of nitrogen (N_1) at the 2-position is not crowded sterically, as shown in Fig. 1,[6] the sulfonyl group is attached at the N_1 atom (desulfonylation from N_1 may be unnecessary). Knowledge of the crystal structure of **1a** may contribute to the development of new potent relaxants

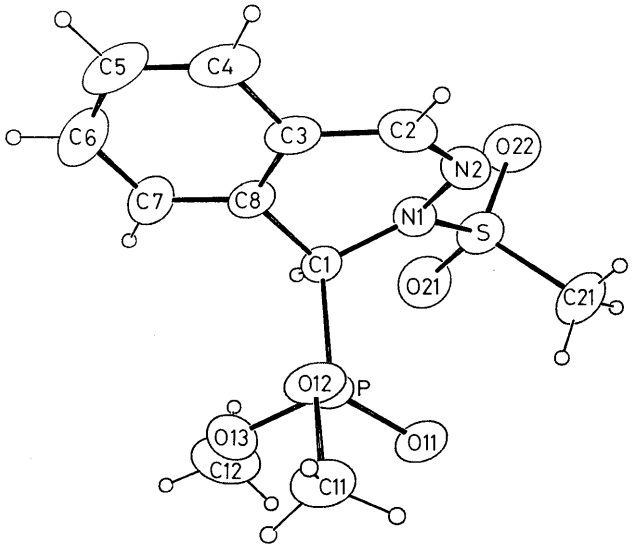


Fig. 1. Stereoscopic View of the Molecule (**1a**) and Atomic Nomenclature

TABLE I. Summary of Crystal Data of **1a** and Diffraction Data Collection

Formula	$C_{11}H_{15}N_2O_5PS$	Absorption	
M_r	318.29	Coefficient (cm^{-1})	3.5
Space group	$P\bar{1}$	$F(0, 0, 0)$	332
a (Å)	8.893 (1)	Temperature (°C)	22+1
b (Å)	9.132 (1)	Crystal size (mm^3)	$0.5 \times 0.6 \times 0.6$
c (Å)	9.530 (1)	Scan technique	ω–2θ scan
α (degree)	68.67 (1)	Scan range	$0.8+0.35 \tan\theta$
β (degree)	76.36 (1)	2θ limit (degree)	$2\theta < 50.0$
γ (degree)	80.31 (1)	No. of data measured	2623
V ($Å^3$)	697.68 (22)	No. of data with $F_O > 3\sigma(F_O)$	2226
Z	2	No. of variables	181
D_{calcd} ($g \cdot cm^{-3}$)	1.515	$R_F(R_{WF})$	0.046 (0.041)
Radiation	MoK_α		

based on various phosphites (alkyl and aryl) and sulfonyl (alkyl and aryl) chlorides.

Experimental

The ^{1}H-NMR spectra of **1a—e** were recorded using a JEOL JNM PS-100 spectrometer. Chemical shifts are given in ppm from tetramethylsilane (TMS) as an internal standard and coupling constants in Hz (s, singlet; d, doublet). Mass spectra (MS) were taken with a Hitachi GC-MS spectrometer.

General Procedure for Synthesis of Phosphonates (1a—e) Sulfonyl chloride of acyl chloride (0.01 mol) was added to a solution of phthalazine (0.01 mol) in acetonitrile (20 ml) at 0 °C, and the mixture was stirred for 10 min (in the case of Ph_2NCOCl, the mixture was stirred at 80 °C for 1 h). Then $P(OCH_3)_3$ (0.014 mol) and NaI (0.012 mol) were added to the reaction mixture at 0 °C, and the mixture was warmed to 50 °C with stirring for 10 min. The solvent was evaporated off under reduced pressure, and water (50 ml) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 and the extract was washed with water, and dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude phosphonate, which was purified by recrystallization (EtOAc) or chromatographed on silica gel with $CHCl_3$ to give **1a—e**.

Dimethyl 2-Mesyl-1,2-dihydro-1-phthalazinylphosphonate (**1a**): Colorless prisms, mp 138—140 °C, 67% yield. *Anal.* Calcd for $C_{11}H_{15}N_2O_5PS$: C, 41.51; H, 4.75; N, 8.80. Found: C, 41.51; H, 4.87; N, 8.66. ^{1}H-NMR ($CDCl_3$) δ: 3.32 (3H, s, SO_2CH_3), 3.62 (3H, d, OCH_3, J=10.4 Hz), 3.64 (3H, d, OCH_3, J=10.4 Hz), 5.83 (1H, d, C_1-H, J=12.8 Hz), 7.16—7.52 (4H, m, C_{5-8}-H), 7.72 (1H, s, C_4-H). MS m/z: 318 (M^+).

Dimethyl 2-Phenylsulfonyl-1,2-dihydro-1-phthalazinylphosphonate (**1b**): Colorless prisms, mp 140—142 °C, 75% yield. *Anal.* Calcd for $C_{16}H_{17}N_2O_5PS$: C, 50.52; H, 4.51; N, 7.37. Found: C, 50.54; H, 4.55; N, 7.18. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, d, OCH_3, J=10.4 Hz), 3.66 (3H, d, OCH_3, J=10.4 Hz), 5.95 (1H, d, C_1-H, J=15.6 Hz), 7.64 (1H, s, C_4-H), 7.52—7.85 (9H, Ph-H, C_{5-8}-H). MS m/z: 380 (M^+).

Dimethyl 2-*N*,*N*-Diphenylcarbamoyl-1,2-dihydro-1-phthalazinylphosphonate (**1c**): Colorless needles, mp 140—141 °C, 38% yield. *Anal.* Calcd for $C_{23}H_{22}N_3O_4P$: C, 63.45; H, 5.09; N, 9.65. Found: C, 63.24; H, 5.15; N, 9.37. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, d, OCH_3, J=10.8 Hz) 3.76 (3H, d, OCH_3, J=10.8 Hz), 6.20 (1H, d, C_1-H, J=15.6 Hz), 6.96—7.52 (14H, 2Ph-H, C_{5-8}-H), C_4-H (overlapped by other signals). MS m/z: 435 (M^+).

Dimethyl 2-Acetyl-1,2-dihydro-1-phthalazinylphosphonate (**1d**): Colorless oil, 5% yield. *Anal.* Calcd for $C_{12}H_{15}N_2O_4P$: C, 51.07; H, 5.36; N, 9.93. Found: C, 50.96; H, 5.30; N, 9.82. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $COCH_3$), 3.53 (3H, d, OCH_3, J=10.8 Hz), 3.71 (3H, d, OCH_3, J=10.8 Hz), 6.32 (1H, d, C_1-H, J=16.0 Hz), 7.16—7.48 (4H, C_{5-8}-H), 7.56 (1H, s, C_4-H). MS m/z: 282 (M^+).

Dimethyl 2-Benzoyl-1,2-dihydro-1-phthalazinylphosphonate (**1e**): Colorless oil, 20% yield *Anal.* Calcd for $C_{17}H_{17}N_2O_4P$: C, 59.30; H, 4.98; N, 8.14. Found: C, 59.58; H, 4.85; N, 8.06. ^{1}H-NMR ($CDCl_3$) δ: 3.51 (3H, d, OCH_3, J=10.8 Hz), 3.74 (3H, d, OCH_3, J=10.8 H), 6.46 (1H, d, C_1-H, J=16.0 Hz), 7.12—7.16 (9H, Ph-H, C_{5-8}-H), 7.54 (1H, s, C_4-H). MS m/z: 344 (M^+).

X-Ray Crystallography of 1a Colorless prism crystals with dimensions of about $0.5 \times 0.6 \times 0.6$ mm^3 were suitable for X-ray examination. An Enraf-Nonius CAD-4 diffractometer was used with graphite-monochromated Mo $K\alpha$ radiation (λ=0.7093 Å). The crystal data of **1a** and the diffraction data collection are summarized in Table I. Intensity data were corrected for Lorentz and polarization effects but not for absorption.

TABLE II. Final Atomic Parameters and Equivalent Thermal Parameters with Estimated Standard Deviations in Parentheses

Atom	x	y	z	B(Å^2)
S	−0.1232 (1)	0.1139 (1)	0.2860 (1)	3.27 (2)
P	0.2821 (1)	0.2166 (1)	0.1037 (1)	2.55 (2)
O11	0.2201 (3)	0.1510 (3)	0.0120 (2)	3.81 (5)
O12	0.3270 (3)	0.3900 (2)	0.0238 (2)	3.25 (5)
O13	0.4362 (3)	0.1260 (3)	0.1585 (3)	3.64 (5)
O21	−0.0311 (3)	−0.0319 (3)	0.3405 (3)	4.36 (6)
O22	−0.2717 (3)	0.1399 (3)	0.3766 (3)	4.94 (6)
N1	−0.0145 (3)	0.2523 (3)	0.2682 (3)	2.64 (5)
N2	−0.0813 (3)	0.4048 (3)	0.2033 (3)	3.05 (6)
C1	0.1482 (3)	0.2201 (3)	0.2831 (3)	2.28 (6)
C2	−0.0178 (4)	0.5144 (4)	0.2158 (3)	3.15 (7)
C3	0.1073 (4)	0.4885 (3)	0.2990 (3)	2.82 (6)
C5	0.2530 (4)	0.5692 (4)	0.4372 (4)	4.44 (8)
C8	0.1860 (3)	0.3388 (3)	0.3429 (3)	2.50 (6)
C6	0.3297 (4)	0.4196 (4)	0.4805 (4)	4.30 (8)
C4	0.1421 (4)	0.6051 (4)	0.3468 (4)	3.86 (8)
C7	0.2973 (4)	0.3032 (4)	0.4331 (3)	3.35 (7)
C11	0.4268 (4)	0.4371 (4)	−0.1270 (4)	3.88 (8)
C21	−0.1515 (4)	0.1470 (4)	0.0995 (4)	4.49 (8)
C12	0.4472 (5)	−0.0449 (5)	0.2278 (5)	5.5 (1)

The structure was solved by the direct method and refined by full-matrix least-squares techniques.[7] Least-squares refinement was eventually carried to convergence with anisotropic thermal parameters for all non-hydrogen atoms and with idealized isotropic thermal parameters for fixed hydrogen atoms. The final difference Fourier was judged to be essentially featureless. The final positional coordinates with the estimated standard deviations and the isotropic equivalent temperature factors for the non-hydrogen atoms are given in Table II.[6]

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6) Final tables of the individual bond lengths and angles, hydrogen atomic positions, anisotropic thermal parameters for nonhydrogen atoms, and structure amplitude (F_O and F_C) are available on request.
7) Programs of Enraf–Nonius's SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerg, and Woolfson's MULTAN, Johnson's ORTEP II, and LSFM for full-matrix least-squares refinement.