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; Reissert reaction; sulfonyl chloride; acyl chloride

In a previous paper 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. For example, benzo[j]quinoline and 1,7- or 4,7-phenanthroline gave the corresponding α- and γ-phosphonates, and 4,7-phenanthroline afforded the diphenophosphate, which was separated into cis and trans isomers. As a part of our continuing studies on the reactivities of nitrogen-containing heterocyclic compounds, 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 (1H-, 13C-, and 31P-NMR) spectral data for 1a—e have been reported previously.

Results and Discussion

Reissert-Type Reactivities of Phthalazine The Reissert-type reaction of phthalazine with methanesulfonyl or benzenesulfonyl chloride (CH3SO2Cl or PhSO2Cl) and trimethyl phosphite (POCH3)3 in acetonitrile gave the corresponding monophosphonate (1a or 1b), bearing a sulfonyl group. Reissert reaction of phthalazine with PhSO2Cl and potassium cyanide (KCN) has been reported to afford the Reissert compound bearing a sulfonyl group.

Although the Reissert reaction of 1,6-naphthyridine and phthalazine with N,N-diphenylcarbamoyl chloride (Ph2NCOCl) and KCN afforded the corresponding Reissert compound, the reaction of phthalazine with Ph2NCOCl and P(OCH3)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 (1e) was obtained in low yield (38%). It has been demonstrated that for the Reissert-type reaction the phoshphite is more reactive with N-heterocycles than KCN. 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(OCH3)3 afforded the corresponding compounds in very low yields (1d, only 5%; 1e, 20%).

X-Ray Crystallography of 1a Reissert-type reaction of phthalazine with P(OCH3)3 gave the phosphonate retaining the sulfonyl group, similar to the Reissert compound of phthalazine. But 1,6-naphthyridine shows different reactivity, and the sulfonyl group is released from the Reissert compound. 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 (N1) at the 2-position is not crowded sterically, as shown in Fig. 1, the sulfonyl group is attached at the N1 atom (desulfonylation from N1 may be unnecessary). Knowledge of the crystal structure of 1a may contribute to the development of new potent relaxants.

![Chart 1](image)

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based on various phosphites (alkyl and aroyl) and sulfonyl (alkyl and aroyl) 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 acrylonitrile (0.01 mol) was added to a solution of phosphazene (0.01 mol) in acetonitrile (20 ml) at 0 ºC, and the mixture was stirred for 10 min (in the case of Ph$_2$NCOCI, the mixture was stirred at 80 ºC for 1 h). Then P(OCH$_2$)$_3$H (0.014 mol) and NaI (0.012 mol) were added to the reaction mixture at 0 ºC, and the mixture was warmed to 50 ºC 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$_2$Cl$_2$, and the extract was washed with water, and dried over anhydrous Na$_2$SO$_4$. 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-Metys-1,2-dihydro-1-phthalazinylphosphonate (1a): Colorless prisms, mp 138–140 ºC, 67% yield. Anal. Calc. for C$_3$H$_7$N$_2$O$_4$PS: C, 41.51%; H, 7.45%; N, 8.80%. Found: C, 41.51%; H, 4.87%; N, 8.66. $^1$H-NMR (CDCl$_3$): $\delta$: 3.32 (3H, s, SO$_2$CH$_3$), 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$_2$HJ = 12.8 Hz), 7.16–7.52 (4H, m, C$_2$H$_2$H$_2$), 7.72 (1H, s, C$_2$H$_2$). MS m/z: 238 (M$^+$).

Dimethyl 2-Phenylosulfonyl-1,2-dihydro-1-phthalazinylphosphonate (1b): Colorless prisms, mp 140–142 ºC, 75% yield. Anal. Calc. for C$_3$H$_7$N$_2$O$_4$PS: C, 50.52%; H, 4.51%; N, 7.37. Found: C, 50.54%; H, 4.55%; N, 7.18. $^1$H-NMR (CDCl$_3$): $\delta$: 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$_2$HJ = 15.6 Hz), 7.64 (1H, s, C$_2$H$_2$), 7.52–7.85 (9H, Ph-H, C$_2$H$_2$-H). MS m/z: 340 (M$^+$).

Dimethyl 2-N,N-Diphenycarbamoyl-1,2-dihydro-1-phthalazinylphosphonate (1c): Colorless needles, mp 140–141 ºC, 38% yield. Anal. Calc. for C$_3$H$_7$N$_2$O$_4$PS: C, 63.45; H, 5.09; N, 9.65. Found: C, 63.42; H, 5.13; N, 9.37. $^1$H-NMR (CDCl$_3$): $\delta$: 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$_2$HJ = 15.6 Hz), 6.96–7.52 (14H, 2Ph-H, C$_2$H$_2$-H), 7.46 (overlapped by other signals). MS m/z: 455 (M$^+$).

Dimethyl 2-Acetyl-1,2-dihydro-1-phthalazinylphosphonate (1d): Colorless oil, 5% yield. Anal. Calc. for C$_3$H$_7$N$_2$O$_4$PS: C, 51.07; H, 5.36; N, 9.93. Found: C, 50.96; H, 5.30; N, 9.82. $^1$H-NMR (CDCl$_3$): $\delta$: 2.36 (3H, s, CO$_2$H), 3.33 (3H, d, OCH$_3$J = 10.8 Hz), 3.71 (3H, d, OCH$_3$J = 10.8 Hz), 6.32 (1H, d, C$_2$HJ = 16.0 Hz), 7.16–7.48 (4H, C$_2$-H). MS m/z: 282 (M$^+$).

Dimethyl 2-Benzoyl-1,2-dihydro-1-phthalazinylphosphonate (1e): Colorless oil, 20% yield. Anal. Calc. for C$_3$H$_7$N$_2$O$_4$PS: C, 59.30; H, 4.98; N, 8.14. Found: C, 59.58; H, 4.85; N, 8.06. $^1$H-NMR (CDCl$_3$): $\delta$: 3.51 (3H, d, OCH$_3$J = 10.8 Hz), 3.74 (3H, d, OCH$_3$J = 10.8 Hz), 6.46 (1H, d, C$_2$HJ = 16.0 Hz), 7.12–7.16 (9H, Ph-H, C$_2$H$_2$-H), 7.54 (1H, s, C$_2$H$_2$). MS m/z: 344 (M$^+$).

X-Ray Crystallography of 1a: Colorless prism crystals with dimensions of about 0.5 x 0.6 x 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 (\lambda = 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.

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**References and Notes**


6) Final tables of the individual bond lengths and angles, hydrogen atomic positions, anisotropic thermal parameters for nonhydrogen atoms, and structure amplitude ($F_0$ and $F_{c}$) are available on request.

7) Programs of Enraf-Nonius SDF package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerq, and Woolfson’s MULTAN, Johnson’s ORTEP II, and LSFM for full-matrix least-squares refinement.