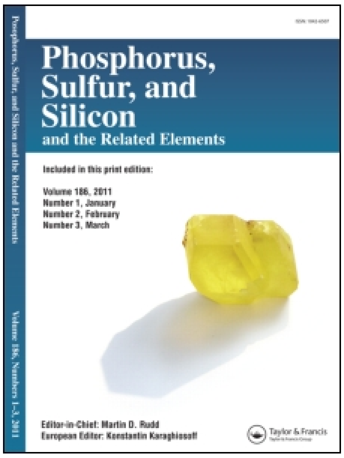


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

P-N COMPOUNDS 28. PHOSPHAMINIMIDES 3. 4-NITROBENZYLATION OF PHOSPHINYL-1, 1-DIMETHYL HYDRAZIDES AND FORMATION OF A UNIQUE HYDRAZINIUM INNER SALT[1]

L. A. Cates[a]; V. S. Li[a]
[a] Department of Medicinal Chemistry, College of Pharmacy, University of Houston, Houston, Texas

To cite this Article Cates, L. A. and Li, V. S.(1987) 'P-N COMPOUNDS 28. PHOSPHAMINIMIDES 3. 4-NITROBENZYLATION OF PHOSPHINYL-1, 1-DIMETHYL HYDRAZIDES AND FORMATION OF A UNIQUE HYDRAZINIUM INNER SALT[1]', Phosphorus, Sulfur, and Silicon and the Related Elements, 29: 2, 249 — 255
To link to this Article: DOI: 10.1080/03086648708080509
URL: http://dx.doi.org/10.1080/03086648708080509

Phosphorus and Sulfur, 1987, Vol. 29, pp. 249–255
Photocopying permitted by license only

P-N COMPOUNDS 28. PHOSPHAMINIMIDES 3. 4-NITROBENZYLATION OF PHOSPHINYL-1, 1-DIMETHYL HYDRAZIDES AND FORMATION OF A UNIQUE HYDRAZINIUM INNER SALT[1]

L. A. CATES and V.-S. LI

Department of Medicinal Chemistry, College of Pharmacy, University of Houston, University Park, Houston, Texas 77004

(Received May 12, 1986, in final form June 24, 1986)

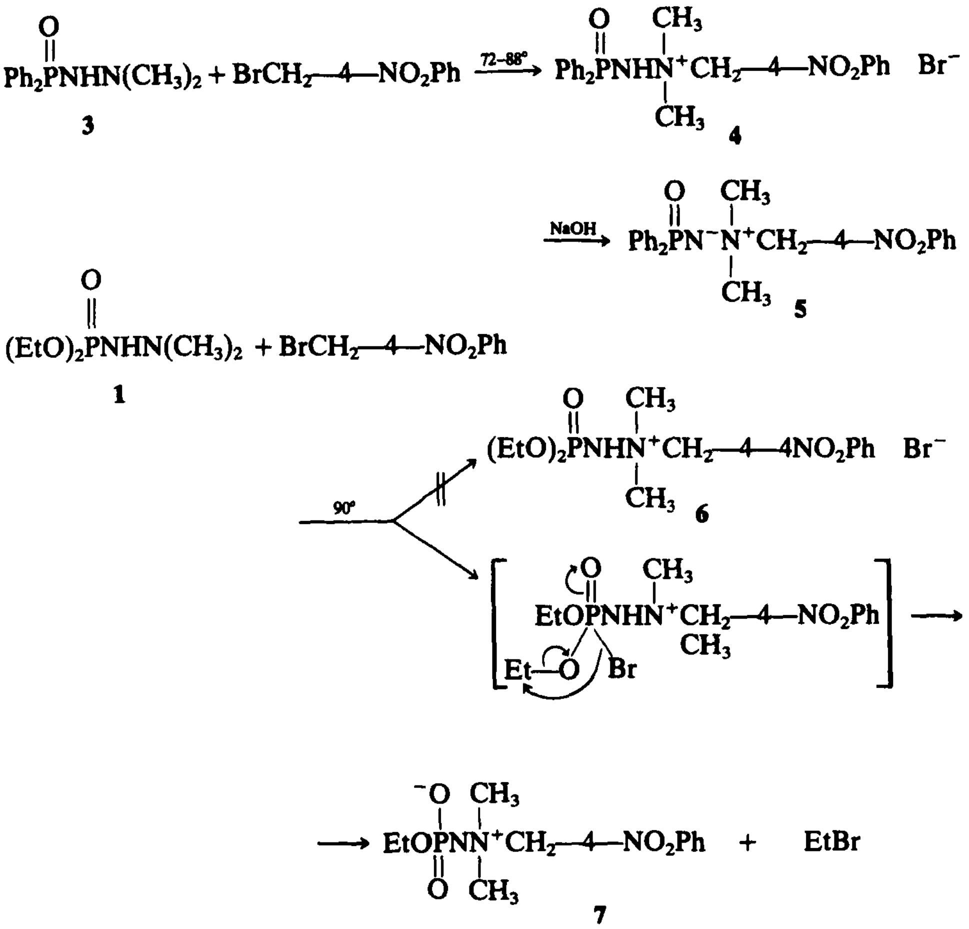
The treatment of diethoxyphosphinyl-1,1-dimethylhydrazide with 4-nitrobenzylbromide at 82–90°C resulted in the loss of EtBr and the formation of $EtO(^{-}O)P(O)\ NHN^{+}(CH_3)_2CH_2$-4-$NO_2Ph$, a novel type of phosphaminimide. At lower temperatures the diethoxyhydrazide gave the hydrazinium bromide which slowly underwent loss of EtBr to yield the same product. The diphenoxy compound similarly lost HBr at high, but not lower, temperature with production of the normal phosphaminimide. The diphenyl derivative yielded the expected hydrazinium bromide which was dehydrobrominated to the usual phosphaminide with NaOH. The reaction between all three hydrazides and iodomethane, followed by dehydroiodination, gave the usual phosphaminimides.

Aminimides, also termed hydrazinium inner salts, are a type of compound in which a quaternary nitrogen is bonded to an anion derived from a carboxamide or related system.[2–4] The replacement of the carbonyl with a phosphinyl group results in a subclass of agent, which has been designated as phosphaminimides. Prior to the work begun in this laboratory in 1984 only some eight phosphaminimides, $PhP(O)N^{-}N^{+}Me_3$ (**3**)[5] and the surfactants of type $R^1{}_2P(O)N^{-}N^{+}R^2R^3CH_2CH(OH)R$,[4,6,7] had been cited in the literature. Since then we reported the synthesis of a cyclic phosphaminimide and of hydrazinium iodide-inner salts and their effect on ganglionic transmission.[8,9] This present study investigates reactions between 4-nitrobenzylbromide and iodomethane and three phosphinyl-1,1-dimethylhydrazides, the diethoxy (**1**), diphenoxy (**2**) and diphenyl (**3**), as potential routes to other phosphaminimides and describes the synthesis of a new type of these hydrazinium inner salts.

RESULTS AND DISCUSSION

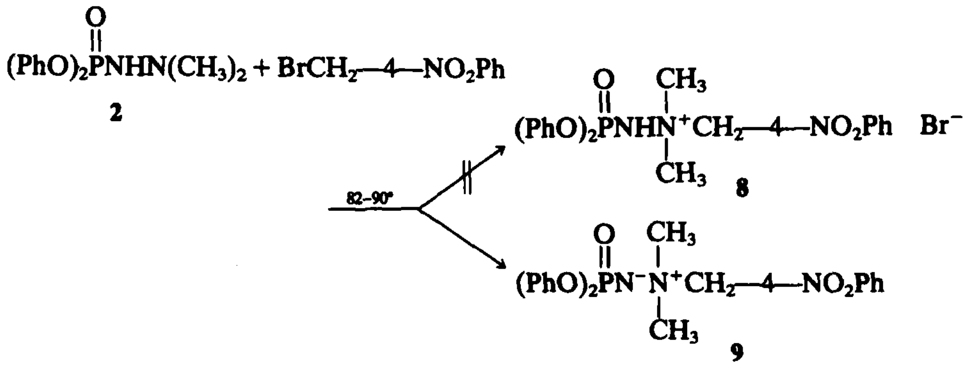
The 4-nitrobenzylation of **3** to the hydrazinium bromide **4** proceeded normally in 71% yield at 72–88°C as did the dehydrobromination of **4** to the corresponding phosphaminimide **5** (92% yield).

The reaction between 4-nitrobenzylbromide and **1** at 82–90°C did not, however, yield the expected hydrazinium bromide **6** but instead gave, in 47% yield, a product identified as **7**, a novel aminimide of type $R(^{-}O)P(O)NHN^{+}(Me)_2CH_2$-4-$NO_2Ph$ whose structure was confirmed by IR, NMR and MS spectrometry and elemental analyses.



Although other resonance forms for **7** are possible, such as those containing $^{-}O{-}P(OH){=}N$ and $O{=}P(OH){-}N^{-}$ moieties, that shown appears to be one definite structure since it displays an absorbance at 3050 cm^{-1}, a frequency assigned to an NH group.

A similar reaction at 82–90° involving **2** also did not proceed as anticipated with the formation of the corresponding hydrazinium bromide **8** and only the phosphaminimide **9** (15% yield) was isolated.



A further investigation of these two latter reactions indicated that the nature of major products is dependent upon reaction temperatures. At 75–85°C the yield of **8** increased to 29%, along with 2.3% of **9**, and at 70°C a 91–94% yield was realized. Treatment of the hydrazinium bromides from both sources with NaOH gave the phosphaminimide **9** (84% yield) which was identical to the product previously obtained through the reaction of only **2** and 4-nitrobenzylbromide. The reaction between the latter reactant and **1**, when heated briefly at 82°C, yields a gummy mass (82%) which was identified by its IR and NMR spectra as consisting of the corresponding hydrazinium bromide **6** and **7** (5.6%). Compound **6** slowly decomposes when stored at 10°C and yields 25% of **7** over a period of four months. The elimination of EtBr occurring during the formation of **7** from **1** may proceed via a mechanism related to the second step in the Michaelis–Arbusov reaction. This process, involving nucleophilic displacement of an alkyl group by a displaced halide, proceeds with P-alkoxy but not P-aryloxy group except at high temperatures (ca. 200°).[10] Thus, following the 4-nitrobenzylation of **2** HBr is lost to yield the aminimide **9** but no PhBr elimination with formation of the new type of aminimide occurred.

We have demonstrated that ethoxy (**1**), phenoxy (**2**) and phenyl (**3**) phosphinyl-1,1-dimethylhydrazides can each undergo a different type of reaction with 4-nitrobenzylbromide. This is not true with methylation using MeI whereby **2** and **3** yield the corresponding phenoxy **10** and phenyl hydrazinium iodides[5] which were subsequently dehydroiodinated to the phenoxy **11** and phenyl[5] phosphaminimides. Compound **1**, similarly treated, gave a gummy mass which, on the basis of its TLC and IR characteristics, also appears to be a hydrazinium iodide. These differences in reactions involving alkylation with 4-nitrobenzylbromide and iodomethane may relate to the electronegativity of the iodide and bromide ions with the latter more capable of achieving nucleophilic displacement of the ethyl group. This may also partially account for the spontaneous loss of HBr from **2** to form **9** with the bromide ion having greater affinity for the NH proton. Another contributing factor may be the presence of electron attacting groups which would tend to labilize this proton. The phenoxy and 4-nitrobenzyl groups have σ^* values of 2.43 and ca. 0.45,[11] respectively, in **9** compared to 0.75 and 0.0 for the phenyl and methyl moieties, respectively, in **4** and **5**.

EXPERIMENTAL

The ^{1}H-NMR spectra were measured on a Varian Associates FT-80A or Nicolet NT-300 spectrometer using tetramethylsilane as the internal standard and deuterated chloroform (**1**, **2**, **5**, **6** and **9**–**11**), deuterated dimethylsulfoxide (**4** and **8**) or deuterium oxide (**7**) as the solvent. Chemical shifts are reported in δ units and coupling constants in Hz. The IR (KBr) spectra were obtained with a Perkin–Elmer 283 spectrophotometer and absorbances are reported in cm^{-1}. The mass spectrum (**7**) was determined at 70 eV on a Finnigan 1020 GC/MS spectrometer equipped with a solid sample probe. The elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Melting points were taken on a Thomas–Hoover apparatus and readings were corrected to reference standards. A 25 × 500 mm column and silica gel 60 (70–230 mesh) were used for chromatography. Evaporation and drying were carried out under reduced pressure.

2-Ethoxy- and 2-phenoxyphosphinyl-1,1-dimethylhydrazide (**1** *and* **2**). To a solution of 1,1-dimethylhydrazine (15.0 g, 0.25 moles) in CH_2Cl_2 (100 mL) was added diethyl chlorphosphate (17.25 g, 0.1 mole) or diphenyl chlorophosphate (26.86 g, 0.1 mole) in CH_2Cl_2 (50 mL) at 0–5°C with stirring. The mixture was stirred for 18 h at 25°C, refluxed for 1 h, cooled and filtered. The filtrate was evaporated and the residue chromatographed using, in sequence, $CHCl_3$ (100 mL) for **1** and **2**, 1 (for **2**) or 2 (for **1**)% MeOH in $CHCl_3$ and 2 (for **2**) or 5 (for **1**)% MeOH in $CHCl_3$ to yield 17.5 g (89%) of **1** and 26.5 g (91%) of **2**. For **1**: bp 89°C/0.1 mm; IR 3170 (NH), 1230 (P=O), 1030–1060 (POEt), 743 (PN); NMR 1.35 (t,6H,2CH_3), 2.55 (s,6H,CH_3NCH_3), 4.13 (q,4H,2CH_2O), 4.76, 5.17 (bd,1H,J_{N-H} = 32.35,NH). Anal. Calc. for $C_6H_{17}N_2O_3P$: C, 36.71; H, 8.74; N, 14.27. Found C, 36.60; H, 8.75; N, 14.21. For **2**: mp 74–75° C; IR 3180 (NH), 1585 (C=C), 1200, 1220, 1250 (P=O), 940, 960 (POPh). Anal. Calc. for $C_{14}H_{17}N_2O_3P$: C, 57.51; H, 5.86; N, 9.58. Found C, 57.63; H, 5.88; N, 9.55.

2-Diphenylphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium bromide (**4**). To 4-nitrobenzylbromide (2.16 g, 10 mmole) in CH_3CN (25 mL) was added **3**[5] (2.6 g, 10 mmole) and the mixture was heated at 72°C in an oil bath for 18 h and then at 88°C for 2 h. The mixture was evaporated under reduced pressure to yield a gummy residue which, when triturated with acetone, washed with acetone and Et_2O and dried, gave 3.4 g (71%) of **4** ($C_{21}H_{23}BrN_3O_3P \cdot H_2O$): mp 142–143°C; IR 3470 (OH), 3060 (NH), 1590, 1610 (C=C), 1350, 1525 (CNO_2), 1200 (P=O); NMR 3.48 (s,6H,2CH_3), 5.13 (s,2H,CH_2N), 7.51–7.70 (m, 10H,2Ph), 7.98 (d,2H,$J_{CH=CH}$ = 8.28, arom), 8.46 (d,2H,$J_{CH=CH}$ = 8.24, arom), 9.28 (d,1H,J_{N-H} = 7.60, NH). Anal. Calc.: C, 51.00; H, 5.10; N, 8.50; Br, 16.17. Found C 51.17; H, 5.09; N, 8.50; Br, 15.71.

2-Diphenylphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium inner salt (**5**). To a suspension of **4** (3.4 g, 7.14 mmole) in H_2O (35 mL) was added 10% NaOH (5.7 mL). The resulting paste was extracted three times with CH_2Cl_2 and this solution was washed with portions of H_2O until the aqueous layer gave a negative bromide ion test with $AgNO_3$. Evaporation of the CH_2Cl_2 layer produced a white solid which, when dried, washed with Et_2O and redried, gave 2.6 g (92%) of **5** ($C_{21}H_{22}N_3O_3P$): mp 134–135°C dec; IR 1600 (C=C), 1345, 1515 (CNO_2), 1120, 1150 (P=O); NMR 3.26 (s,6H,2CH_3), 4.78 (s,2H,CH_2N), 7.29 (m,6H,arom), 7.78 (m,4H,arom), 7.88 (d,2H,$J_{CH=CH}$ = 8.62, arom), 8.26 (d,2H,$J_{CH=CH}$ = 8.56, arom). Anal. Calc.: C, 63.77; H, 5.61; N, 10.63. Found C, 63.84; H, 5.65; N, 10.55.

2-Ethoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium inner salt (**7**). To 4-nitrobenzylbromide (4.9 g, 25 mmole) was added **1** (5.4 g, 25 mmole) and the mixture was heated under N_2 at 82–90°C for 4 h. After cooling to 25°C the resulting white precipitate was collected on a filter, washed with CH_2Cl_2 and Et_2O and dried to yield **7** as a white solid (3.6 g, 47%) which was recrystallized from methanol ($C_{11}H_{18}N_3O_5P$): mp 219–221°C dec; IR 3150 (NH), 1605 (C═C), 1350, 1525 (CNO_2), 1230, 1245, 1255 (P═O), 1075, 1090 (POEt), 740 (PN); NMR 1.16 (t,3H,CH_3), 3.54 (s,6H,CH_3NCH_3), 3.83 (q,2H,CH_2O), 4.99 (s,2H,CH_2N), 7.86, 7.97 (d,2H,$J_{CH═CH}$ = 8.84, arom), 8.32, 8.43 (d,2H, $J_{CH═CH}$ = 8.73, arom). GC/MS m/e(RI) 59 (100), 195 (50), 231 (28), 303 (M^+,14), 304 (M^{+1},5). Anal. Calc.: C, 43.54; H, 5.98; N, 13.85; Br, 0.00. Found C, 43.48; H, 5.88; N, 13.77; Br, 0.00.

2-Diethoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium bromide (**6**). 4-Nitrobenzylbromide and **1** were reacted in the same manner and amounts as for **7** but at 82°C for 45 min. A small amount of white solid was collected and identified as **7** (0.34 g, 5.6%). The filtrate was evaporated and the residue chromatographed sequentially using $CHCl_3$ (100 mL), 2% MeOH in $CHCl_3$ (100 mL), 5% MeOH in $CHCl_3$ (300 mL) and 10% MeOH in $CHCl_3$ (600 mL) to yield 6.36 g (82%) of **6** as an intractable mass that was unsuitable for elemental analysis but its IR and NMR spectra were consistent with the assigned structure for **6** ($C_{13}H_{23}BrN_3O_5P$): IR 3060 (NH), 1605 (C═C), 1350, 1525 (CNO_2), 1260 (P═O), 1025 (POEt); NMR 1.26 (t,6H,2CH_3), 3.76 (s,6H,$(CH_3)_2N$), 4.12 (q,4H,2CH_2O), 5.59 (s,2H,CH_2N), 8.11 (d,2H,$J_{CH═CH}$ = 8.48, arom), 8.24 (d,2H,$J_{CH═CH}$ = 8.45, arom). A 4.7 g sample of **6** was stored at 10°C for 4 months then triturated with acetone, filtered and the residue washed acetone, CH_2Cl_2 and Et_2O and dried under reduced pressure. The resulting 1.2 g (25% yield) of white solid gave a negative bromide ion test and identical mp and IR and NMR spectra to **7**.

2-Diphenoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium bromide (**8**). To 4-nitrobenzylbromide (2.2 g, 10 mmole) in CH_3CN (20 mL) was added **2** (2.9 g, 10 mmole) and the mixture was heated at 70°C for 18 h. The resulting white solid was collected by filtration, washed with CH_2Cl_2 and dried to give 2.3 g of **8**. The filtrate was evaporated, dried and the residue washed with CH_2Cl_2 to yield an additional 2.3 g of **8** for a total of 4.6 g (91%). The same reaction conducted a second time gave a 94% yield. ($C_{21}H_{23}BrN_3O_5P$): mp 152–153°C; ir 3030 (NH), 1590, 1600 (C═C), 1340, 1510 (CNO_2), 1170, 1200, 1210 (P═O), 940 (POPh); NMR 3.66 (s,6H,2CH_3), 5.15 (s,2H,CH_2N), 7.35 (m,10H,2Ph), 7.73 (d,2H,$J_{CH═CH}$ = 8.25, arom), 8.13 (d,2H,$J_{CH═CH}$ = 8.08, arom), 10.42 (bs,1H,NH). Anal. Calc.: C, 49.60; H, 4.56; N, 8.27; Br, 15.73. Found C, 49.55; H, 4.57; N, 8.26; Br, 15.66. Chromatography, using the same eluant system as for **1**, of the residue obtained by evaporation of the filtrate gave, after recrystallization from acetone/H_2O, 0.1 g (2.3%) of only **9**. The reaction was repeated with heating to 72°C for 18 h and worked up as above with CH_2Cl_2 washing to yield 2.3 g of **8**. Evaporation of the filtrate and treatment of the residue with CH_2Cl_2 gave an additional 1.5 g of **8** for a total of 3.8 g (75%).

2-Diphenoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium inner salt (**9**). From **2**: To 4-nitrobenzylbromide (2.2 g, 10 mmole) in CH_3CN (20 mL) was added **2** (2.9 g, 10 mmole) and the mixture heated at 82–90°C for 18 h. The residue obtained from evaporation of the mixture was chromatographed, using the eluant system for **1**, to yield 0.63 g (15%) of **9** ($C_{21}H_{22}N_3O_5P$): mp 154–156°C; IR 1590 (C=C), 1350, 1510 (CNO_2), 1200, 1230 (P=O), 880, 910 (POPh); NMR 3.45 (s,6H,2CH_3), 4.76 (s,2H,CH_2N), 7.37 (d,10H,$J_{P-CH} = 4.36$,2Ph), 7.74 (d,2H,$J_{CH=CH} = 8.7$, arom), 8.18 (d,2H,$J_{CH=CH} = 8.7$, arom). Anal. Calc.: C, 58.99; H, 5.19; N, 9.83; Br, 0.00. Found C, 58.73; H, 5.20; N, 9.80; Br, 0.00. From **8**: To a suspension of **8** (3.1 g, 6.1 mmole) in H_2O (25 mL) was added 10% NaOH (4.9 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the extract washed with H_2O. The organis layer was evaporated and washed with EtOH and acetone to yield 2.2 g (84%) of **9** with identical mp and spectra as obtained in the reaction using **2**.

2-Diphenoxyphosphinyl-1,1,1-trimethylhydrazinium iodide (**10**). To iodomethane (14.2 g, 100 mmole) in CH_3CN (40 mL) was added **2** (2.9 g, 10 mmole) and the mixture was heated at 60°C for 18 h. The mixture was filtered and the filtrate evaporated to yield a residue which, when washed with Et_2O, gave 4.2 g (97%) of **10** ($C_{15}H_{20}IN_2O_3P$): mp 134–136°C dec; IR 3040 (NH), 1580 (C=C), 1160, 1175, 1205 (P=O), 950 (POPh). Anal. Calc.: C, 41.47; H, 4.64; N, 6.45; I, 29.23. Found C, 41.38; H, 4.66; N, 6.40; I, 29.17.

2-Diphenoxyphosphinyl-1,1,1-trimethylhydrazinium inner salt (**11**). To a suspension of **10** (2.9 g, 6.7 mmole) in H_2O (12 mL) was added 10% NaOH (3.2 mL). The resulting solution was evaporated and the residue treated with CH_2Cl_2 and filtered. The filtrate was washed with H_2O (6 × 100 mL) and the organic layer evaporated to yield 1.9 g of crude product which was recrystallized from CH_2Cl_2—Et_2O to give 1.53 g (76%) of **11** ($C_{15}H_{19}N_2O_3P$): mp 122–123°C; IR 1590 (C=C), 1205, 1230 (P=O), 890, 920 (POPh); NMR 3.37 (s,9H,3CH_3), 7.27 (m,10H,2Ph). Anal. Calc.: C, 58.79; H, 6.25; N, 9.14. Found C, 58.69; H, 6.26; N, 9.08.

ACKNOWLEDGMENT

This work was supported by the Robert A. Welch Foundation, Houston, Tx, Grant E-920.

REFERENCES AND NOTES

1. For part 27 see: L. A. Cates and V.-S. Li *J. Heterocycl. Chem.*, **22**, 1559 (1985).
2. H. J. Timpe, *Z. Chem.*, **12**, 250 (1972).
3. W. J. McKillip, E. A. Sedor, B. M. Culbertson and W. Wawzonek, *Chem. Rev.*, **73**, 255 (1973).
4. S. Wawzonek, *Ind. Eng. Chem. Prod. Res. Dev.*, **19**, 338 (1980).
5. E. Kameyana, S. Inokuma and T. Kuwamura *Bull. Chem. Soc. Jpn*, **49**, 1439 (1976).
6. T. Kuwamura, E. Kameyama, S. Inokuma and H. Goto, Japan Kokai 75126620, 1974; *Chem. Abstr.*, **84**, 58631 (1974).
7. T. Kuwamura, E. Kameyama, S. Inokuma and Y. Sato, Japan Kokai 77125125, 1977; *Chem. Abstr.*, **88**, 91406 (1977).
8. L. A. Cates, V.-S. Li, J. P. Basrur, B. H. Saddawi and K. A. Alkadhi, *J. Heterocycl. Chem.*, **22**, 183 (1985).
9. L. A. Cates, V.-S. Li, B. H. Saddawi and K. A. Alkadhi, *J. Med. Chem.*, **28**, 595 (1985).
10. J. Emsley and D. Hall, *The Chemistry of Phosphorus* (Harper & Row Ltd, London, 1976), pp. 117–119.

11. The σ^* value of the 4-nitrobenzyl group is not recorded, however, that of 4-cyanobenzyl is given as 0.45 [D. D. Perrin, B. Dempsey and E. P. Serjeant, *pKa Prediction for Organic Acids and Bases* (Chapman and Hall, New York, 1981), p. 123]. Since the σ_{para} values for the NO_2 and CN group are 0.78 and 0.70, respectively, it is assumed that the σ^* values for the two substituted benzyl moieties are close.