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Quinazolines and 1,4-Benzodiazepines. 74.[1] Phosphorylation[2] of Ambident Anions. Preparation of Some Di-4-morpholinylphosphinyloxy Imines via O-Phosphorylation of Anions of Lactams

Robert Y. Ning,* R. Ian Fryer, Pradeep B. Madan, and Barbara C. Sluboski

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

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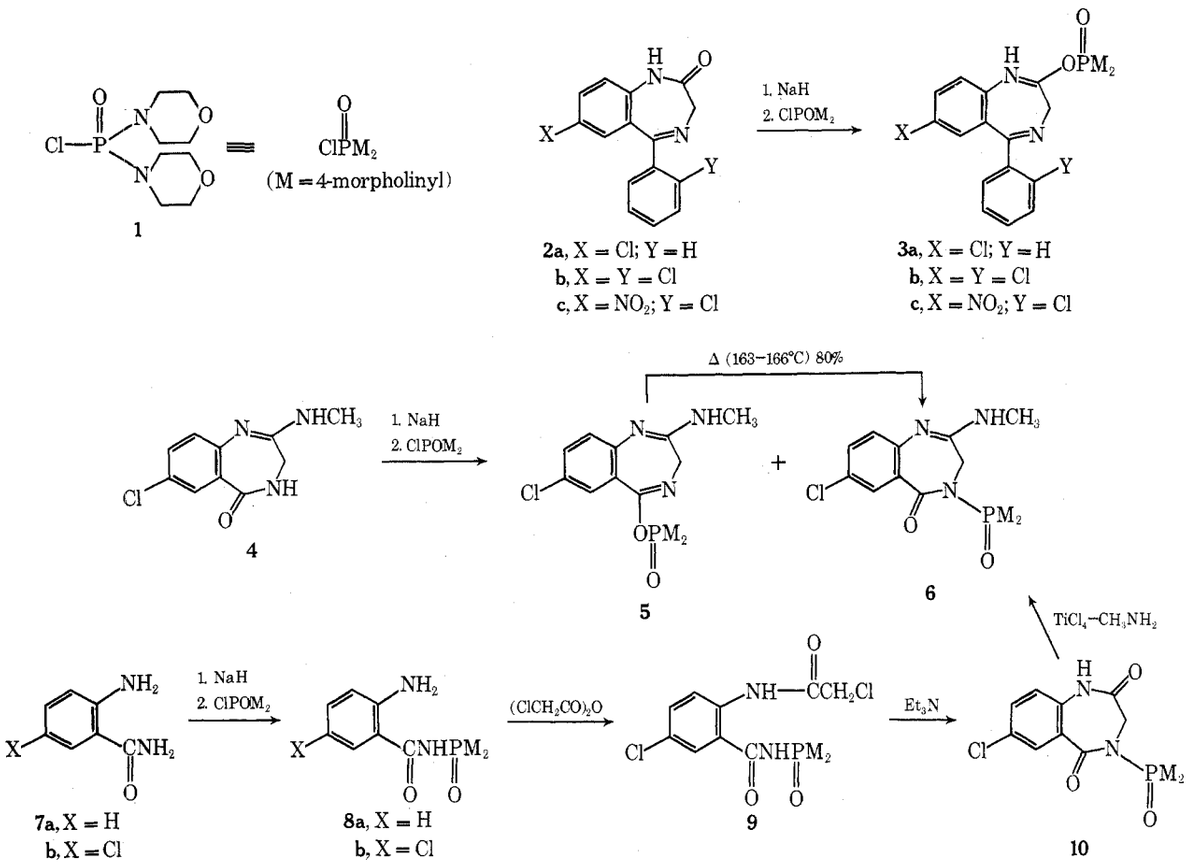
The reaction of ambident anions of amide type with di-4-morpholinylphosphinic chloride (1) has been investigated. O-Phosphorylations predominate in the cases of the lactams 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (**2**), 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one (**4**), and 2-phenyl-4-quinazolone. The novel dimorpholinylphosphinyloxy imines **3, 5,** and **11** formed are crystalline and readily isolable. In contrast, reaction of **1** with the anions of anthranilamides **7,** 8-chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one, 2-hydroxybenzimidazole, and 2-benzoxazolinone afforded good yields of the N-phosphorylated products **8, 13, 14,** and **15,** respectively. A thermal isomerization of the O-phosphorylated compound **5** to the N-phosphorylated isomer **6** is also observed. Compound **6** was prepared independently from the anthranilamide derivative **8.**

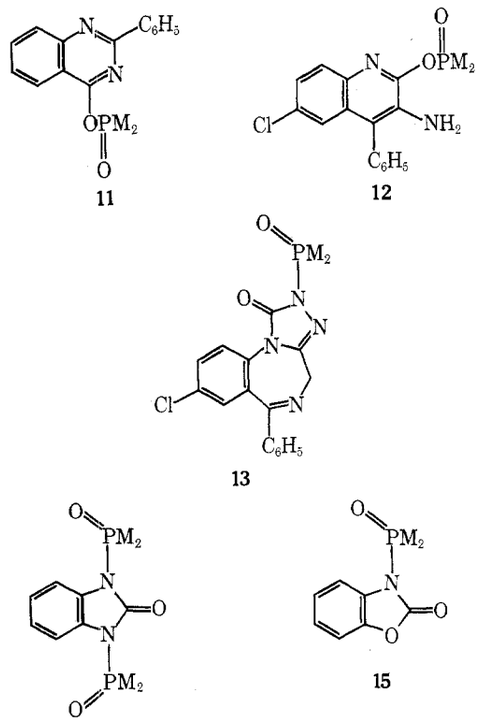
Although the reaction of phosphorylating agents[3-5] with enolate anions[6,7] has been studied extensively, there is a paucity of information on the reaction of these agents with ambident anions containing nitrogen and oxygen sites. Enolate anions phosphorylate almost exclusively on oxygen. In contrast, the site of phosphorylation of nitrogen-containing ambident anions seems less predictable. 2-Hydroxypyridine and 4-hydroxypyridine with phosphoryl chloride in aqueous alkali were reported to yield *O*-phosphoryl and *N*-phosphoryl derivatives, respectively.[8]

We now wish to report the results of some investigations carried out on the ambident anions of amides using di-4-morpholinylphosphinic chloride (**1**)[9,10] as the phosphorylating agent. Compound **1** is a crystalline (mp 80–82 °C) and readily available[14] reagent useful in the preparation of phosphate monoesters.[9a,15] Both O-phosphorylation and N-phosphorylation reactions were observed, with selectivity depending on the amide used. The preference for the oxygen site of the anions of cyclic secondary amides has permitted the isolation, in good yields, of the novel[11] and synthetically useful[13] dimorpholinylphosphinyloxy imines **3** and **5** in the 1,4-benzodiazepine series. When a slight excess of **1** was allowed to react with anions derived from 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (**2**) in tetrahydrofuran at room temperature, the predominant products formed, as evident by TLC, were the O-phosphorylated products **3,** which could be isolated in 43–66% yields. Although crystalline and readily isolable, these dimorpholinyloxy imines are quite reactive toward nucleophiles to give 2-substituted benzodiazepines.[13] The infrared spectra of **3** indicate the absence of lactam carbonyl signals (typically strong bands at about 1680 cm^{-1}). When 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one[16] compound **4** was treated with sodium hydride followed by **1,** the O-phosphorylated product **5** crystallized in 48% yield. The N-phosphorylated product **6** was eventually also isolated (9% yield) from the same reaction mixture. However, owing to the complexity of the mixture, this isolation was not achieved until a reference sample of **6** was synthesized from compound **8b** by an alternate process as described below. In contrast to the cyclic amides **2** and **5,** it was found that the anthranilamides **7,** under the same conditions, afforded the N-phosphorylated products **8** in yields of 58–62%. Chloroacetylation of 2-amino-5-chloro-*N*-(di-4-morpholinylphosphinyl)benzamide (**8b**) led to the chloroacetanilide **9** (95%) which was cyclized in the presence of triethylamine to 7-chloro-4-(di-4-morpholinyl)phosphinyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (**10,** 65%). The *N*-dimorpholinylphosphinylamide group in **10** survived a titanium tetrachloride–methylamine treatment[17] leading to the amidine **6** in 57% yield. While compound **6** was relatively thermally stable (as a melt at 220 °C for 2 min), the O-phosphorylated isomer compound **5** was not. In refluxing mesitylene (bp 163–166 °C), **5** isomerized in 80% yield, to the N isomer **6.** This observation suggests that the predominance of O-phosphorylation leading to **3** and **5** is kinetic in nature, and that N-phosphorylation is thermodynamically preferred.

To extend our observations to ambident anions of aromatic cyclic amide, cyclic urea, and cyclic carbamate types, we chose the following compounds purely on the basis of their potential usefulness as intermediates leading to new derivatives of potential medicinal utility: 2-phenyl-4-quinazolone,[18] 3-amino-6-chloro-4-phenylcarbostyril,[19] 8-chloro-2,4-dihy-



dro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one,[20] 2-hydroxybenzimidazole, and 2-benzoxazoline. The anions, which were generated with sodium hydride, were treated with di-4-morpholinylphosphinic chloride (1) as before. In each case, only one crystalline product was isolated: compounds **11** (77%), **12** (33%), **13** (72%), **14** (42%), and **15** (42%), respectively. The structures were assigned on the basis of the presence or the absence of the carbonyl absorption band in the infrared spectra, and were further corroborated by NMR, uv, and mass spectral data. Owing to the complexity of the reaction product mixtures, no other products were isolated. In the cases where only the products of N-phosphorylation were isolated (**13, 14,** and **15**), we did not expend any great effort in an attempt to isolate the corresponding O-phosphorylated products. Since there is no reason to doubt that these compounds are formed we suspect that they are too unstable to survive the reaction conditions and isolation procedures. The relatively good yields of **13, 14,** and **15** may reflect not only their formation in the primary step, but also their formation in secondary reactions involving the more reactive O-phosphorylated intermediates. Both O to N isomerizations, as observed in the conversion of **5** to **6,** and intermolecular phosphoryl transfer[12] involving unreacted starting anions are possible.



An extension of these observations to other ambident anions as well as the synthetic utility of both the O- and N-phosphorylated products is currently being investigated.

Experimental Section

All melting points were taken in capillaries heated in oil baths, and are corrected. Infrared spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrometer, mass spectra on a Jeolco O1SG or a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Varian A-60 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard, and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. Petroleum ether used boils at 30–60 °C. Tetrahydrofuran and dimethylformamide were dried by passage over activity 1 alumina or molecular sieves. Unless otherwise specified, all solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure using a water bath set at 40–70 °C.

The progress of reactions was routinely followed by thin layer chromatography (TLC). The TLC was performed on glass plates

coated with Mallinckrodt Silica 7GF5 (with fluorescent indicator) in the case of analytical TLC and Merck silica gel PF254 in the case of preparative TLC. All plates were activated by heating to 100 °C for 1 h, then stored at 20–50 °C. The chromatograms were developed over a distance of 10 cm, then viewed or photographed under uv light.

Di-4-morpholinylphosphinic Chloride (1).[9,10] A solution of 95 ml (1.03 mol) of phosphorus oxychloride in 1000 ml of benzene in a dry 3-l., three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel mounted on an adaptor with a small vent for escaping HCl was chilled in an ice bath to 5 °C. To the chilled mixture was added, dropwise over 1.5 h, 355 g (4.075 mol) of morpholine keeping the temperature between 10 and 20 °C by regulating the rate of addition. After addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. Insoluble, colorless salts which formed were collected in a sintered glass funnel and washed thoroughly three times with 800-ml portions of benzene. The combined filtrate and washings were evaporated to dryness. The residue was dissolved by heating (steam bath) in 300 ml of benzene. The hot benzene solution was filtered to remove an insoluble gum (about 5 g) and diluted with 200 ml of cyclohexane. If dilution at this point causes a small amount of precipitation, this should be removed by filtration before further dilution. The mixture should be kept warm throughout this process. The mixture was further diluted with 700 ml of cyclohexane and the product allowed to crystallize at room temperature. The colorless prisms were collected with minimal exposure to moist air, and washed with two 500-ml portions of petroleum ether. It weighed 205.5 g, mp 79–81 °C. Concentration of the mother liquors yielded a second crop of colorless prisms, 26.5 g, mp 77–79 °C. The total yield was 232 g (91%). This material was dried under high vacuum (avoid water aspirators) at 40–50 °C and was used without recrystallization. Recrystallizations did not appreciably raise the melting point. An analytical sample melted at 80–82 °C (lit.[9] mp 81 and 76–80 °C); ir (KBr) 1238 cm^{-1} (P=O).

Stability and Handling of 1. Although **1** has been used conveniently and successfully without dryboxes, its instability is obvious. Crystals kept in open dishes on dry days turned to puddles within 2 days. Several batches of this reagent, kept without special precautions in brown glass screw-cap bottles, developed elevated melting points and wider melting ranges even though there was little change in the fluidity of the solids. Although the pure reagent is entirely soluble in warm benzene in the concentration of 2 g per 5 ml of benzene, partly degenerated samples contained considerable amounts of benzene-insoluble materials, which could be due to the salts of morpholine which results from the hydrolysis of the reagent. On this basis, we recommend that the reagent be handled and stored as much as possible under argon. The purity of the material could be tested by determination of melting point (both elevation and depression of melting point from 79–81 °C indicate impurity) and solubility in benzene (2 g per 5 ml of hot benzene). Partially decomposed materials may be recrystallized by the following procedure. The solid was dissolved by gentle heating in benzene (5 ml per 2 g). The insoluble material was removed by filtration. To the warm benzene filtrate was added 1.5 volumes of cyclohexane. The mixture was allowed to crystallize in a stoppered flask. The crystals (colorless prisms) were collected with minimum exposure to air, washed with cyclohexane and then petroleum ether, and dried under high vacuum.

General Procedure for Phosphorylations with Di-4-morpholinylphosphinic Chloride in the Preparations of 3a–c, 5, 6, 8a,b, 11, 12, 13, and 15. To a stirred solution (suspension in the case of **5**) of the amide in dry tetrahydrofuran (2–15 ml/mmol; dimethylformamide was used in the case of **12**) was added a 50% dispersion of sodium hydride in mineral oil (1.1–2.0 equiv of hydride). The mixture was stirred at room temperature under nitrogen until hydrogen evolution ceased (0.5–1 h). Di-4-morpholinylphosphinic chloride (**1**, 1.2–2.0 equiv relative to the amide) was added in one portion (at 0–25 °C). The mixture was stirred at room temperature for 2–4 h. Insoluble salts were removed by filtration. Solvent was evaporated. Crystallization of the residue from an appropriate solvent afforded the products.

7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3*H*-1,4-benzodiazepine (3a). From 5.4 g (20 mmol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[21] (**2a**), following the general phosphorylation procedure, the product (4.2 g, 43%, mp 189–191 °C) was obtained by crystallization from ethyl acetate. Recrystallization from methylene chloride–ether–petroleum ether afforded colorless prisms: mp 184–186 °C; ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (2-PrOH) 217 nm (ϵ 34 700), 255 (sh 14 300), and 317 (2060); mass spectrum *m/e* 488 (M^+).

Anal. Calcd for $C_{23}H_{26}ClN_4O_4P$: C, 56.50; H, 5.36; N, 11.46. Found: C, 56.30; H, 5.30; N, 11.40.

7-Chloro-5-(2-chlorophenyl)-2-(di-4-morpholinylphosphinyloxy)-3*H*-1,4-benzodiazepine (3b).[22] From 122 g (0.40 mol) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[21] (**2b**), following the general procedure, the product (140 g, 66%, mp 180–183 °C) was obtained by crystallization from ethyl acetate. Recrystallization from methylene chloride–ether afforded colorless needles: mp 185–187 °C; ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (CH_3CN) 216 nm (δ 41 500), 270 (sh, 8000), and 315 (2100); mass spectrum *m/e* 522 (M^+).

Anal. Calcd for $C_{23}H_{25}Cl_2N_4O_4P$: C, 52.78; H, 4.81; N, 10.71. Found: C, 52.95; H, 4.99; N, 10.81.

5-(2-Chlorophenyl)-2-(di-4-morpholinylphosphinyloxy)-7-nitro-3*H*-1,4-benzodiazepine (3c). From 4.74 g (15 mmol) of 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one[21] (**2c**), following the general procedure, the product (3.75 g, 47%, mp 214–216 °C) was obtained as colorless needles by crystallization from methylene chloride–ether: ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (CH_3CN) 215 nm (sh, ϵ 30 800), 245 (sh 17 300), and 313 (11 250); mass spectrum *m/e* 533 (M^+).

Anal. Calcd for $C_{23}H_{25}ClN_5O_6P$: C, 51.74; H, 4.72; N, 13.12. Found: C, 51.90; H, 4.70; N, 13.11.

7-Chloro-5-(di-4-morpholinyl)phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (5). From 22 g (0.10 mol) of 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one (**4**),[16] following the general procedure above, **5** crystallized from ethyl acetate as 20.8 g (47%) of colorless prisms, mp 195–196 °C.

An analytical sample was prepared by recrystallizations from ethyl acetate to yield colorless prisms: mp 210–212 °C; ir (KBr) 1190 and 1240 cm^{-1} (P=O); mass spectrum *m/e* 441 (M^+), 206 (M − dimorpholinylphosphinyloxy).

Anal. Calcd for $C_{18}H_{25}ClN_5O_4P$: C, 48.93; H, 5.70; N, 15.84. Found: C, 49.17; H, 5.77; N, 15.87.

7-Chloro-3,4-dihydro-4-(di-4-morpholinylphosphinyl)-2-methylamino-5*H*-1,4-benzodiazepin-5-one (6). A. From Phosphorylation of Amide. The experiment described for the preparation of **5** was conducted on 1.0-mmol scale (223 mg, **4**). The O-phosphorylated product **5** (R_f 0.40, silica gel, 1:1 EtOH–EtOAc; mp 209–211 °C) was obtained as before by crystallization from ethyl acetate in 48% yield (210 mg). The product mixture in the mother liquor was separated by preparative TLC (silica gel, 1:1 EtOH–EtOAc). The N-phosphorylated product **6** (R_f 0.30) was isolated, using ethanol for desorption from silica gel. Crystallization from acetonitrile afforded 40 mg (9%) of **6**, mp 236–238 °C, identical (TLC, mixture melting point) with reference **6** prepared by method B.

B. From 10. To a stirred solution of 429 mg (1.00 mmol) of **10** in 10 ml of a 3.8 M solution of methylamine in tetrahydrofuran at room temperature was added a solution of 0.18 ml (1.5 mmol) of titanium tetrachloride in 3 ml of benzene. The resulting mixture was kept at room temperature for 2 days. About 2 ml of water was added and the insoluble salts were removed by filtration. Tetrahydrofuran was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from ethyl acetate–hexane gave 258 mg (57%) of the desired product. An analysis sample was prepared by recrystallization from acetonitrile. Colorless prisms were obtained: mp 233–235 °C; ir (KBr) 3265 and 3110 (NH), 1650 (C=O), and 1260 and 1220 cm^{-1} (P=O); uv max (CH_3CN) 227 nm (ϵ 22 190), 274 (15 800), and 333 (4250); mass spectrum *m/e* 441 (M^+); NMR ($CDCl_3$) δ 2.93 (d, 3, CH_3), 3.18 (broad, 8, NCH_2 of morpholines), 3.61 (broad, 8, OCH_2 of morpholines), 3.9 and 4.4 (broad, 2, CH_2), 5.70 (broad, 1, NH), 7.06 (d, J_o = 9 Hz, 1, H-9), 7.35 (dd, J_o = 9, J_m = 2.5 Hz, 1, H-8), and 7.75 ppm (d, 1, H-6).

Anal. Calcd for $C_{18}H_{25}ClN_5O_4P$: C, 48.93; H, 5.70; N, 15.85. Found: C, 49.16; H. 5.70; N, 16.12.

C. By Thermal Isomerization of 5. A suspension of 442 mg (1.0 mmol) of **5** in 5 ml of mesitylene (bp 163–166 °C) was heated to reflux for 2 h. The solids dissolved before precipitation of the isomerized product: 345 mg (80%), mp 228–230 °C; identical with **6** obtained from B by TLC and comparison of infrared spectra.

The N-phosphorylated product **6** is relatively stable thermally. It remained essentially unchanged (TLC) after heating as a melt at 220 °C for 2 min or in refluxing solution in dimethylformamide.

2-Amino-*N*-(di-4-morpholinylphosphinyl)benzamide (8a). Following the general phosphorylation procedure described above, 81.6 g (0.60 mol) of anthranilamide (Aldrich) afforded a dry product mixture which was shaken with aqueous sodium bicarbonate and methylene chloride. The colorless product crystallized from the two-phase mixture and was collected and washed with water followed

by a mixture of methylene chloride and petroleum ether. It weighed 131 g (62%), mp 216–218 °C. On recrystallization from methylene chloride–ether, colorless needles were obtained: mp 215–217 °C; ir (KBr) 3460 and 3340 (NH_2), 3160 (NH), 1670 (C=O), and 1260 and 1190 cm^{-1} (P=O); uv max (CH_3CN) 219 nm (ϵ 26 500), 250 (7850), and 338 (5190); (1.0 N HCl) 230 nm (ϵ 11 750) and 270 (shoulder, 1740); NMR ($CDCl_3$) δ 5.84 (s, 2, NH_2) and 7.91 ppm (d, 1, NH).

2-Amino-5-chloro-*N*-(di-4-morpholinylphosphinyl)benzamide (8b). Starting with 0.5 mol of 2-amino-5-chlorobenzamide[23] (mp 169–171 °C, needles from ethanol, prepared from commercial 5-chloroisatoic anhydride by heating in 1 M aqueous ammonia), and following the same procedure described above for the dechloro analogue **8a**, the colorless product **8b** was isolated in the same manner in 58% yield, mp 223–225 °C. Recrystallization from ethanol afforded prisms: mp 218–220 °C; ir (KBr) 3460 and 3320 (NH_2), 3180 (NH), 1670 (C=O), and 1255 and 1180 cm^{-1} (P=O); uv max ($CHCl_3$) 239 nm (ϵ 7290), 249 (8820), and 354 (4920); NMR ($CDCl_3$) δ 3.27 (m, 8, NCH_2 of morpholines), 3.65 (m, 8, OCH_2 of morpholines), 5.80 (s, 2, NH_2) 6.60 (d, J = 9 Hz, 1 aromatic H-3), 7.18 (dd, J = 9 and 2.5 Hz, 1, aromatic H-4), 7.95 (d, J = 2.5 Hz, 1 aromatic H-6), and 8.85 ppm (d, 1, NH).

Anal. Calcd for $C_{15}H_{22}ClN_4O_4P$: C, 46.34; H, 5.70; N, 14.41. Found: C, 46.46; H, 5.71; N, 14.28.

5-Chloro-2-(2-chloroacetylamino)-*N*-(di-4-morpholinylphosphinyl)benzamide (9). A mixture of 54.5 g (140 mmol) of **8b** and 72 g (420 mmol) of chloroacetic anhydride was stirred in 250 ml of benzene at room temperature overnight. Approximately 1200 ml of aqueous sodium bicarbonate (0.8 M) was added and the two-phase mixture was stirred vigorously until all bubbling stopped. The solids which precipitated were collected and washed with water to give 61.5 g (95%) of the desired product, mp 212–214 °C dec. An analysis sample was prepared by recrystallization from methylene chloride–hexane to give colorless prisms: mp 215–216 °C dec; ir (KBr) 1690 and 1665 (two C=O) and 1260 and 1200 cm^{-1} (P=O); uv max (2-PrOH) 223 nm (ϵ 24 000), 257 (14 600), and 312 (3800); NMR (DMF-d_7) 3.26 (m, 8, NCH_2 of morpholines) 3.65 (m, 8, OCH_2 of morpholines), 4.47 (s, 2, CH_2), 7.67 (dd, J = 2.5 and 9.0 Hz, 1, aromatic H-4), 8.08 (d, 1, J = 2.5 Hz, aromatic H-6), 8.40 (d, J = 9.0 Hz, 1, aromatic H-3), 9.82 (broad, 1, NH), and 11.31 ppm (broad, 1, NH).

Anal. Calcd for $C_{17}H_{23}Cl_2N_4O_5P$: C, 43.89; H, 4.98; N, 12.04; Cl, 15.24. Found: C, 43.85; H. 4.97; N, 12.17; Cl, 15.28.

7-Chloro-4-(di-4-morpholinyl)phosphinyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (10). A mixture of 2.3 g (5.0 mmol) of **9** in 40 ml of methanol containing 5 ml of triethylamine was heated to reflux for 3 h. Methanol was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from ethanol yielded 1.4 g (65%) of the desired product, mp 213–215 °C. An analysis sample was prepared by recrystallization from ethanol to give colorless prisms: mp 216–218 °C; ir (KBr) 1700 and 1658 (two C=O) and 1260 and 1210 cm^{-1} (P=O); uv max (EtOH) 220 nm (ϵ 35 500), 250 (13 800), and 310 (2800); NMR ($CDCl_3$) δ 3.23 (m, 8, NCH_2 of morpholines), 3.65 (m, 8, OCH_2 of morpholines), 4.35 (d, J_{H-P} = 9.0 Hz, 2, CH_2), 7.13 (d, J = 9.0 Hz, 1, H-9), 7.48 (dd, J = 2.5 and 9.0 Hz, 1, H-8), 7.86 (d, J = 2.5 Hz, 1, H-6), and 9.57 ppm (s, 1, NH).

Anal. Calcd for $C_{17}H_{22}ClN_4O_5P$: C, 47.62; H, 5.17; N, 13.07. Found: C, 47.57; H, 5.09; N, 13.36.

4-(Di-4-morpholinylphosphinyloxy)-2-phenylquinazoline (11). Phosphorylation of 33.4 g (150 mmol) of 2-phenyl-4-quinazolone[18] using the general procedure described above afforded a mixture which crystallized from ethyl acetate to give 50.8 g (77%) of the desired product, mp 153–155 °C. Recrystallization from ethyl acetate–ether afforded colorless prisms: mp 152–154 °C; ir (KBr) no carbonyl band (1600–1800 cm^{-1}); 1250 cm^{-1} (P=O); uv max (2-PrOH) 207 nm (ϵ 40 500), 255 (sh, 33 800), 259 (35 000), 285 (16 500), and 330 (sh, 2550); mass spectrum m/e 440 (M^+).

Anal. Calcd for $C_{22}H_{25}N_4O_4P$: C, 60.00; H, 5.73; N, 12.72. Found: C, 59.93; H, 5.71; N, 12.62.

3-Amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (12). A solution of 2.7 g (10 mmol) of 3-amino-6-chloro-4-phenylcarbostyril[19] in 40 ml of dry dimethylformamide was treated in the manner described in the general procedure. The residue from the evaporation of dimethylformamide, on trituration with ether, gave 1.6 g (33%) of a light brown amorphous solid, mp 185–187 °C.

An analytical sample was prepared by recrystallization from ethyl acetate to yield buff prisms: mp 188–190 °C; ir (KBr) 1220 and 1250 cm^{-1} (P=O), no carbonyl band; uv max (2-PrOH) 249 nm (ϵ 42 100) and 344 (8600).

Anal. Calcd for $C_{23}H_{26}ClN_4O_4P$: C, 56.50; H, 5.36; N, 11.45. Found: C, 56.43; H, 5.21; N, 11.40.

8-Chloro-2,4-dihydro-2-(di-4-morpholinyl)phosphinyl-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (13). From 621 mg (2 mmol) of 8-chloro-2,3-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one[20] (mp 251–253 °C with correct C, H, N elemental analyses) following the general phosphorylation procedure and crystallization from ether, 770 mg (72%) of **13** was obtained, mp 172–175 °C. Recrystallizations from ethyl acetate–ether afforded colorless, amorphous solids: mp 179–181 °C; ir (KBr) 1720 (C=O) and 1240 cm^{-1} (P=O); uv max (CH_3CN) 208 nm (ϵ 41 200), 245 (20 000), and 306 (700), almost identical with that of starting material.

Anal. Calcd for $C_{24}H_{26}ClN_6O_4P$: C, 54.50; H, 4.95; N, 15.89. Found: C, 54.37; H, 4.73; N, 16.08.

1,3-Bis[(di-4-morpholinyl)phosphinyl]benzimidazol-2-one (14). To a stirred solution of 10.7 g (80 mmol) of 2-hydroxybenzimidazole (Aldrich Chemical Co.) in 150 ml of dry dimethylformamide at room temperature was added 7.7 g of a 50% dispersion of sodium hydride in oil (160 mmol of hydride). The thick mixture was stirred at room temperature for 1.5 h until hydrogen evolution stopped. The mixture was then chilled in a dry ice–acetone bath and 44.8 g (176 mmol) of di-4-morpholinylphosphinic chloride was added in portions. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Dimethylformamide was evaporated and the residue was slurried with methylene chloride. Insoluble salts were removed by filtration and methylene chloride was evaporated. Crystallizations of the residue from ethanol gave 19.1 g (42%) of colorless flakes: mp 214–217 °C; ir (KBr) 1710 cm^{-1} (C=O); NMR indicated a symmetrical molecule; mass spectrum m/e 570 (M^+).

Anal. Calcd for $C_{23}H_{36}N_6O_7P_2$: C, 48.42; H, 6.36; N, 14.73. Found: C, 48.70; H, 6.14; N, 14.60.

3-(Di-4-morpholinylphosphinyl)benzoxazolin-2-one (15). Phosphorylation of 1.00 g (7.4 mmol) of 2-benzoxazolinone (Aldrich Chemical Co.) following the general procedure, then crystallization from ether afforded 1.5 g of **15** as a colorless, amorphous solid, mp 143–145 °C. Recrystallization from ethanol afforded 1.1 g (42%) of colorless prisms, mp 148–150 °C (repeated recrystallizations raised the melting point to 152–153 °C); ir (KBr) 1785 cm^{-1} (C=O); mass spectrum m/e 353 (M^+).

Anal. Calcd for $C_{15}H_{20}N_3O_5P$: C, 50.99; H, 5.71; N, 11.89. Found: C, 50.98; H, 5.67; N, 11.80.

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Quinazolines and 1,4-Benzodiazepines. 76[1]. Reactions of Some Di-4-morpholinylphosphinyloxy Imines

Robert Y. Ning,* R. Ian Fryer, Pradeep B. Madan, and Barbara C. Sluboski

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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The reaction of 7-chloro-2-(di-4-morpholinyl)phosphinyloxy-5-phenyl-3*H*-1,4-benzodiazepine (**6**), 7-chloro-5-(di-4-morpholinyl)phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**), and 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**) with a variety of nucleophiles illustrates the imidoyl character of the dimorpholinylphosphinyloxy imines. Of particular interest is the facile reaction of **6** with amines, alcohols, hydrogen sulfide, and carbanions to give the corresponding 2-substituted benzodiazepines. Pyrolysis of **6** in refluxing trichlorobenzene afforded a mixture of 7-chloro-2-(4-morpholinyl)-5-phenyl-3*H*-1,4-benzodiazepine (**3**) and 3-amino-6-chloro-2-(4-morpholinyl)-4-phenylquinoline (**4**). Compound **3** under the same conditions was shown to isomerize to **4**.

The chemical activation of secondary amides via transformations to imidates,[2] imidoyl halides,[2] thioamides,[3] amidines,[2c,4] and *N*-nitrosoamidines,[5] among others, have imparted great synthetic utility to these amides as intermediates. We have recently reported that medicinally interesting cyclic secondary amides in the 1,4-benzodiazepine[6] series can be derivatized by O-phosphorylation under *mild, basic* conditions.[7] Phosphorylation of the ambident amide anions with dimorpholinylphosphinic chloride (**16**) afforded the novel dimorpholinylphosphinyloxy imines such as **6** and **13** which were isolated in good yields. In this paper, we describe reactions of some of these dimorpholinylphosphinyloxy imines which point to their versatility as intermediates.[8] These intermediates offer a valuable alternate to other imidoyl compounds which are often difficult to generate in sensitive molecules.

7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3*H*-1,4-benzodiazepine (**6**)[7] reacts with a variety of nucleophiles to give various 2-substituted benzodiazepines through displacement of the dimorpholinylphosphinyloxy group. Exposure of **6** to methanol containing sodium methoxide and to ethylene glycol containing triethylamine afforded the corresponding 2-alkoxy derivatives **5a** and **5b** in 87 and 82% yields, respectively. The displacement reaction is nearly instantaneous at room temperature with hydrogen sulfide–triethylamine, methylamine, and methyl hydrazinocarboxylate, giving **7** (78%), **9a** (96%), and **9b** (84%), respectively. Of particular interest is the carbon–carbon bond formation through the displacement of the dimorpholinylphosphinyloxy group with carbanions. We have found (conditions not optimized) that the reaction of **6** with the anions of nitromethane and dimethyl malonate afforded 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine (**10,** 27%)[9] and 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (**11,** 13%),[5] respectively. The utility of **6** as an intermediate has been further demonstrated by its facile conversion (80%) to 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**2**),[3c,10] a benzodiazepine of clinical interest.[6] We have also found that compound **2** can be prepared in a simple procedure by reacting 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**) with sodium hydride, di-4-morpholinylphosphinic chloride,[7] and acetylhydrazide, in that order, in the same reaction vessel. Compound **2** was readily isolable in 62% yield.

Hydrolysis of **6** (aqueous tetrahydrofuran, room temperature, 7 days) led to lactam **1** (52%) and, interestingly, the 2-morpholinyl derivative **3** as a by-product in 8% yield. When the hydrolysis was conducted in refluxing aqueous tetrahydrofuran, compound **3** was obtained in 21% yield. Higher yield of **3** was obtained when **6** was treated with morpholine (74%). Pyrolysis of **6** in refluxing 1,2,4-trichlorobenzene (214 °C) afforded **3** in 26% yield along with an isomeric product **4** obtained in 17% yield. The assignment of the 3-amino-2-morpholinylquinoline structure **4** was correlated with a synthesis from 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**)[7] and morpholine. The fact that **4** is a secondary pyrolysis product derived from **3** was demonstrated by the conversion of **3** to **4** under similar conditions. The pyrolytic conversion of the di-4-morpholinylphosphinyloxy imine **6** to morpholinylimine **3** is an exemplification of the process proposed in the literature[11] to explain the conversion of secondary amides to their corresponding amidines by heating with amides of phosphoric acid. Although phosphorodiamidates of type **6** have been proposed as intermediates in these reactions, it appears that in no case have they been isolated.