1-Aralkyl-2(1*H*)pyridinimines and their Derivatives

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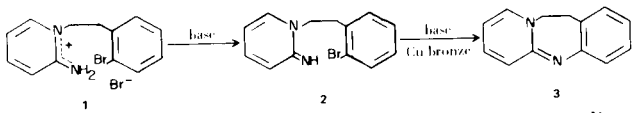
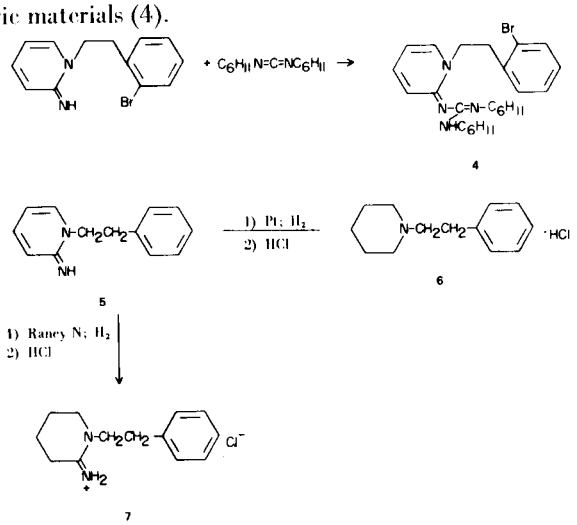
In a recent paper (3), we described the synthesis of several novel bridgehead nitrogen heterocycles; for example, **3** could be prepared by treatment of the quaternary derivative, **1**, with two equivalents of base and a catalytic amount of copper bronze. In the absence of the catalyst, under precisely the same conditions, no cyclization occurred, and the product was the pyridinimine, **2**. When **2** was treated with one equivalent of base and a trace of copper



1 2 3

bronze, **3** was obtained. In general, in these earlier studies, no attempt was made to isolate the other intermediate derivatives related to **2**, since the immediate goal of the program was the preparation of the tricyclic bridgehead nitrogen derivatives. Subsequently, when it was found that **2** possessed an interesting pharmacological profile, the program was broadened to include the isolation of a number of pyridinimines in order to develop a structure-pharmacological activity relationship. These derivatives were obtained as pale yellow crystalline solids; when pure, they could be stored unchanged for months in brown capped bottles; however, when exposed to laboratory light and air, they were rapidly converted to orange-colored polymeric materials (4).



In this preliminary Note, we are reporting a general procedure for the preparation of the pyridinimines, as well as a procedure for their reaction with carbodiimides to give compounds like **4**. In addition, there is described a hitherto unreported hydrogenolysis involving loss of the 2-imino group from 2-pyridinimines as ammonia during a platinum catalyzed hydrogenation of **5** to give **6**; under the same conditions a pyrophoric Raney nickel catalyst led to the isolation of several novel piperidinimines, *e.g.*, **7**. The structure of **7** was confirmed by elemental analyses and its pmr and mass spectrum.

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected. The ir spectra were obtained on mineral oil mulls employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on deuteriochloroform or DMSO-d_6 solutions with a Perkin-Elmer R12B or a Varian Associates XL-100-15 spectrophotometer. The authors are indebted to Mrs. B. Toeplitz and Dr. M. Puar of this Institute for these spectra. The microanalyses were carried out by Mr. J. F. Alicino and his associates of this Institute.

2-Amino-1-(phenylmethyl)pyridinium Bromide, **8**.

To 82.0 g. (0.87 mole) of 2-aminopyridine in 800 ml. of anhydrous xylene was added 100.0 g. (0.58 mole) of benzyl bromide in 200 ml. of anhydrous xylene, and the solution heated under reflux for 7 hours. The solid that separated during this time was collected by filtration, triturated with 200 ml. of warm 2-propanol, and dried to give 99.1 g. of **8**. An analytical sample was obtained from 2-propanol, m.p. 187-190°; ir: ν 3250 (s), 1655 (s), 1625 (m), 1590 (s), 1575 (s), 1520 (s), 1490 (m), 1455 (s), 1445 (s) cm^{-1}; pmr (DMSO-d_6): δ 5.50 (s, 2H, CH_2-Ar), 6.70-8.80 (m, 11H, 4 Py-*H* + 5 Ar-*H* + NH_2).

Anal. Calcd. for $C_{12}H_{13}BrN_2$: C, 54.38; H, 4.94; N, 10.57; Br, 30.16. Found: C, 54.50; H, 4.83; N, 10.36; Br, 30.30.

1-(Phenylmethyl)-2(1*H*)pyridinimine, **9**.

To 94.5 g. (0.35 mole) of **8** in 700 ml. of methanol was added, portionwise, a total of 38.5 g. of solid sodium methoxide, and the solution heated under reflux for 2.5 hours. The solution was concentrated *in vacuo* and the residual oil partitioned between 150 ml. of water and 200 ml. of chloroform. The chloroform layer was separated, the water was reextracted with 100 ml. of chloroform, the combined chloroform extracts were washed with saturated aqueous sodium chloride, dried, and concentrated to give 62.1 g.

of a crystalline residue. Recrystallization from 2.3 liters of petroleum ether gave 37.4 g. (58% yield) of **9**, m.p. 52.0-54.5°; ir: ν 3320 (s), 1635 (s), 1560 (s), 1525 (s), 1485 (s), 1445 (s), 1415 (s), 1390 (m), 1365 (s), 1350 (s), 1320 (s), 1305 (m) cm^{-1}; pmr (deuteriochloroform): δ 5.05 (s, 2H, CH_2-Ar), 5.20-7.00 (m, 5H, 4 Py-*H*, N*H*), 7.28 (s, 5H, 5 Ar-*H*).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.33; H, 6.57; N, 15.20. Found: C, 78.16; H, 6.63; N, 15.10.

2-Amino-1-(phenylethyl)pyridinium Bromide, **10**.

The procedure described for **8** was utilized for the reaction between 94.0 g. (1.0 mole) of 2-aminopyridine, 138.0 g. (0.75 mole) of 2-phenethyl bromide in 800 ml. of anhydrous xylene. The yield of **10** was 141.5 g. (67%), m.p. 195-198°, after recrystallization from 2-propanol; ir: ν 3280 (s), 1660 (s), 1630 (w), 1580 (s), 1530 (s), 1500 (m), 1480 (m), 1460 (m), 1450 (m), 1440 (w) cm^{-1}; pmr (DMSO-d_6): δ 3.07 [t (J = 5 Hz), 2H, CH_2Ar], 6.65-8.05 (m, 9H, 4 Py-*H* + 5 Ar-*H*), 8.65 (s, 2H, NH_2).

Anal. Calcd. for $C_{13}H_{15}BrN_2$: C, 55.96; H, 5.42; N, 10.04; Br, 28.64. Found: C, 55.95; H, 5.37; N, 9.77; Br, 28.55.

1-(2-Phenylethyl)-2(1*H*)pyridinimine, **11**.

The procedure employed with **9** was used with 136.3 g. (0.49 mole) of **10** and 52.5 g. (0.97 mole) of sodium methoxide, in 1 liter of methanol. The yield of **11**, m.p. 59.0-61.5° (sinters at 56°), was 75.4 g. (78%) after recrystallization from hexane; ir: ν 3320 (s), 3070 (w), 3035 (w), 1640 (s), 1560 (s), 1530 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.06 [t (J = 5 Hz), 2H, CH_2-Ar], 4.03 [t (J = 5 Hz), 2H, CH_2-Py], 5.25-7.40 (m, 10H, 4-Py-*H* + 5 Ar-*H* + N*H*).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 78.85; H, 7.13; N, 14.15. Found: C, 79.04; H, 7.33; N, 14.17.

1-(2-Phenylethyl)piperidine Hydrochloride, **6**.

A suspension of 5.94 g. (0.03 mole) of **11**, 0.5 g. of platinum oxide catalyst, and 100 ml. of methanol was hydrogenated at 50 psi and ambient temperature. Reaction ceased after 4 hours when 0.12 mole of hydrogen had been absorbed. The reaction mixture smelled strongly of ammonia. The filtered solution, concentrated *in vacuo*, gave 5.03 g. of a colorless oil; this, in 100 ml. of anhydrous ether, treated with an excess of 2-propanolic hydrogen chloride gave 6.83 g. of crude hydrochloride, m.p. 222-227°. Recrystallization from 105 ml. of acetonitrile gave 4.17 g. (62% yield) of **6**, m.p. 226-229° (6); ir: ν 2640 (s), 2550 (s), 1600 (w), 1495 (m), 1485 (w), 1455 (s), 1450 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.50-3.90 [m, 10H, $(CH_2)_5N$], 7.27 (s, 5H, 5 Ar-*H*), 12.20 (broad s, 1H, H^+).

Anal. Calcd. for $C_{13}H_{19}N$·HCl: C, 69.39; H, 8.96; N, 6.23; Cl, 15.76. Found: C, 69.37; H, 8.87; N, 6.36; Cl, 15.78.

1-(2-Phenylethyl)-2-piperidinimine Hydrochloride, **13**.

When the above hydrogenation was carried out with *ca.* 0.5 g. of pyrophoric Raney nickel replacing the platinum oxide as catalyst, reduction ceased after 4 hours when 0.06 mole of hydrogen had been absorbed. The yield of crude hydrochloride was 5.22 g.; recrystallization from 20 ml. of acetonitrile gave 3.78 g. (53%) of **13**, m.p. 156-158°; ir: ν 3370 (s), 3320 (w), 1670 (s), 1625 (s), 1595 (m), 1490 (m), 1460 (s), 1445 (s), 1435 (s), 1410 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.20-2.05 (m, 4H, C_4-H_2 + C_5-H_2), 2.50-3.40 (m, 6H, C_3-H_2, C_6-H_2, CH_2-Ar), 4.02 [t (J = 5 Hz), 2H, CH_2-N), 7.03-7.48 (m, 5H, 5 Ar-*H*), 9.60, 9.94 (two broad s, 2H, NH_2^+; both equilibrate with deuterium oxide).

Anal. Calcd. for $C_{13}H_{18}N_2$·HCl: C, 65.60; H, 8.05; N, 11.77; Cl, 14.90. Found: C, 65.32; H, 7.90; N, 11.51; Cl, 14.97.

1-[2-(2-Bromophenyl)ethyl]-2-piperidinimine Hydrochloride, **7**.

A solution of 2.77 g. (0.01 mole) of **2**(3) in 100 ml. of methanol and *ca.* 0.5 g. of pyrophoric Raney nickel was hydrogenated as with **13**. The product was obtained as an oil which gave 2.20 g. of crude hydrochloride, m.p. 191-197° (sinters at 183°). This was recrystallized from 45 ml. of acetonitrile to give 1.62 g. of **14**, m.p. 203-205° (sinters at 199°); ir: ν 3440 (w), 3380 (w), 1680 (s), 1625 (s), 1560 (m), 1515 (m), 1485 (m), 1470 (s), 1455 (s), 1440 (s), 1430 (s), 1415 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.50-1.95 (m, 4H, C_4-H_2+C_2-H_2), 2.60-3.55 (m, 6H, C_3-H_2, CH_2Ar), 4.03 [t (J = 5 Hz), 2H, CH_2-Py], 6.95-7.82 (m, 4H, 4-Ar-*H*), 9.75, 10.04 [two broad s, 2H, NH_2^+; both equilibrate with deuterium oxide].

Anal. Calcd. for $C_{13}H_{17}BrN_2$·HCl: C, 49.25; H, 5.72; N, 8.84; Cl⁻, 11.19; M^+, 280. Found: C, 49.08; H, 5.72; N, 8.92; Cl⁻, 11.22; M^+, 280.

2-Amino-1-[2-(Chlorophenoxy)methyl]pyridinium Chloride, **14**.

To a solution of 5.65 g. (0.06 mole) of 2-aminopyridine in 50 ml. of sulfolane was added 10.6 g. (0.06 mole) of *o*-chloro-α-chloroanisole (3) in 5 ml. of sulfolane. During 4 days at room temperature, a colorless solid separated. Subsequently, the mixture was heated at 85° for 16 hours, cooled, and diluted with 200 ml. of anhydrous ether. The yield of crude product, m.p. 160-163°, was 13.1 g. Recrystallization from 140 ml. of 2-propanol gave 9.0 g. (55% yield) of **14**, m.p. 167-169°; ir: ν 3370 (w), 3330 (w), 1670 (s), 1640 (m), 1580 (s), 1530 (m), 1480 (s), 1460 (s), 1445 (s) cm^{-1}; pmr (DMSO-d_6): δ 6.31 (CH_2O), 6.61-8.28 (m, 8H, 4 Py-*H* + 4 Ar-*H*), 9.41 (broad s, NH_2, both equilibrate with deuterium oxide).

Anal. Calcd. for $C_{12}H_{12}N_2Cl_2O$: C, 53.18; H, 4.46; N, 10.34; Cl⁻, 16.17. Found: C, 53.33; H, 4.72; N, 10.43; Cl⁻, 26.31.

1-[(2-Chlorophenoxy)methyl]-2-(1*H*)pyridinimine, **15**.

The procedure described for **9** was employed with 2.30 g. (0.0085 mole) of **14**, 75 ml. of methanol, and 0.92 g. (0.017 mole) of sodium methoxide. The yield of **15**, m.p. 70-72°, was 0.83 g. (42%), after recrystallization from hexane; ir: ν 3320 (w), 1645 (s), 1565 (s), 1550 (s), 1530 (w), 1480 (s), 1455 (s), 1440 (m) cm^{-1}; pmr (deuteriochloroform): δ 5.20-5.50 (m, 1H, N*H*; equilibrates with deuterium oxide), 5.86 (s, 2H, CH_2O), 6.15-7.55 (m, 8H, 4 Py-*H*, 4 Ar-*H*).

Anal. Calcd. for $C_{12}H_{11}ClN_2O$: C, 61.59; H, 4.74; N, 11.97; Cl, 15.15. Found: C, 61.89; H, 4.45; N, 12.15; Cl, 15.19.

1-[(2-Bromophenoxy)methyl]-2-(1*H*)pyridinimine, **16**.

The procedure described for **9** was employed with 68.0 g. (0.22 mole) of the quaternary derivative (2), 500 ml. of methanol and 23.2 g. (0.43 mole) of sodium methoxide to give 26.7 g. (45% yield) of **16**, m.p. 60.5-62.0°; ir: ν 3320 (w), 1645 (s), 1565 (s), 1530 (s), 1475 (s), 1455 (s), 1440 (m) cm^{-1}; pmr (deuteriochloroform): δ 5.54-5.83 (m, 1H, N*H*; equilibrates with deuterium oxide), 5.85 (s, 2H, CH_2-O), 6.02-8.00 (m, 8H, 4-Py-*H*, 4 Ar-*H*).

Anal. Calcd. for $C_{12}H_{11}BrN_2O$: C, 51.66; H, 3.97; N, 10.04; Br, 28.64. Found: C, 51.43; H, 4.01; N, 9.88; Br, 28.84.

2-Amino-1-[2-(2-bromophenyl)ethyl]-3-methylpyridinium Bromide, **17**.

The procedure for **8** was followed, with the single substitution of 16.2 g. of 2-amino-3-methylpyridine for the 2-aminopyridine. The product was obtained in 41% yield, m.p. 185-187° after recrystallization from 2-propanol; ir: ν 3270 (s), 3100 (s), 1640 (s), 1625 (s), 1580 (s), 1515 (s), 1455 (s) cm^{-1}; pmr (DMSO-d_6):

δ 2.29 (s, 3H, CH_3), 3.22 [t (J = 5 Hz), 2H, CH_2Ar], 4.62 [t (J = 5 Hz), 2H, $PyCH_2$], 6.69 [t (J = 5 Hz), 1H, Py-H_5], 7.00-8.00 (m, 6H, 2 Py-H + 4-Ar-H), 8.34 (s, 2H, NH_2; both equilibrate with deuterium oxide); uv λ (methanol, 1%): 306 (ε, 7,100).

Anal. Calcd. for $C_{14}H_{16}Br_2N_2$: C, 45.20; H, 4.34; N, 7.53; Br, 42.97. Found: C, 45.23; H, 4.59; N, 7.52; Br, 43.18.

1-[2-(2-Bromophenyl)ethyl]-3-methyl-2(1*H*)pyridinimine, **18**.

The procedure described for **9** was used with 11.2 g. (0.03 mole) of **17** to give 6.8 g. (78% yield) of **18**, m.p. 64-66°; ir: ν 3350 (w), 1635 (s), 1565 (s), 1545 (s), 1465 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.07 (s, 3H, CH_3), 3.27 [t (J = 5 Hz), 2H, CH_2-Ar], 4.18 [t (J = 5 Hz), 2H, CH_2-Py], 5.53 [t (J = 5 Hz), 1H, Py-H_5], 5.75 (broad s, 1H, N*H*; equilibrates with deuterium oxide), 6.50-7.75 (m, 7H, 3 Py-H + 4 Ar-H); uv λ (methanol, 1%): 225 (sh), 233 (sh), 306 nm (ε, 9,380, 7,900, 6,950).

Anal. Calcd. for $C_{14}H_{15}BrN_2$: C, 57.78; H, 5.20; N, 9.63; Br, 27.46. Found: C, 58.05; H, 5.28; N, 9.36; Br, 27.27.

2-Amino-1-[2-(2-bromophenyl)ethyl]-5-methylpyridinium Bromide, **19**.

To 16.20 g. (0.15 mole) of 2-amino-5-methylpyridine in 100 ml. of anhydrous xylene was added 26.40 g. (0.10 mole) of *o*-bromophenethyl bromide. The mixture was heated under reflux, under nitrogen, for a total of 20 hours. A solid product began to separate within 0.5 hours. The reaction mixture was cooled, the solid filtered, and air-dried; the crude product weighed 29.90 g. Recrystallization from 135 ml. of absolute ethanol gave 16.42 g. (44% yield) of **19**, m.p. 237-239°; ir: ν 3245 (s), 3050 (s), 1660 (s), 1625 (s), 1585 (s), 1525 (s), 1480 (m), 1465 (m), 1455 (m), 1435 (m) cm^{-1}; pmr (DMSO-d_6): δ 2.04 (s, 3H, CH_3), 3.20 [t (J = 5 Hz), 2H, CH_2Ar], 4.47 [t (J = 5 Hz), 2H, CH_2Py], 7.00-8.00 (m, 7H, 3-Py-H + 4 Ar-H), 8.55 [2H, NH_2; both equilibrate with deuterium oxide]; uv λ (methanol, 1%): 236, 315 nm (ε, 12,500, 7,430).

Anal. Calcd. for $C_{14}H_{16}Br_2N_2$: C, 45.20; H, 4.34; N, 7.53; Br, 42.97. Found: C, 45.10; H, 4.37; N, 7.53; Br, 42.89.

1-[2-(2-Bromophenyl)ethyl]-5-methyl-2(1*H*)pyridinimine, **20**.

A 0.03 molar run as with **19** gave a 58% yield of **20**, m.p. 100-102°; ir: ν 3310 (w), 3270 (w), 1655 (s), 1560 (s), 1530 (s), 1470 (m), 1445 (m), 1425 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.80 (s, 3H, CH_3), 3.20 [t (J = 5 Hz), 2H, CH_2Ar], 4.05 [t (J = 5 Hz), 2H, CH_2Py], 5.15 (broad s, 1H, N*H*; equilibrates with deuterium oxide), 6.15-7.80 (m, 7H, 3 Py-H + 4 Ar-H); uv λ (methanol, 1%): 236, 315 nm (ε, 10,100, 6,050).

Anal. Calcd. for $C_{14}H_{15}BrN_2$: C, 57.78; H, 5.20; N, 9.63; Br, 27.46. Found: C, 57.64; H, 5.02; N, 9.41; Br, 27.32.

N-[1-[2-(2-Bromophenyl)ethyl]-2(1*H*)pyridinylidene[-*N'*,*N''*-bis-(1-methylethyl)guanidine, **4**.

A solution of 2.77 g. (0.010 mole) of 2-[(2-bromophenyl)-ethyl]-2(1*H*)pyridinimine (3), 1.50 g. (0.012 mole) of diisopropylcarbodiimide in 30 ml. of anhydrous *t*-butanol was heated under reflux under nitrogen for 24 hours and then concentrated *in vacuo*. The residual solid was recrystallized once from 50 ml. of hexane, and the solid obtained recrystallized again from 70 ml. of hexane to give 1.83 g. (45% yield), m.p. 125-128° (sinters at 119°); ir: ν 3270 (s), 1640 (s), 1605 (s), 1510 (s), 1450 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.03-1.70 [(m, 12H, 2(CH(CH_3)$_2$)], 2.85-3.45 (m, 3H, N*H* + CH_2Ar), 3.54-3.66 [m, 2H, 2(C*H*)CH_3)$_2$)], 4.32 [t (J = 5 Hz), 2H, CH_2-Py], 5.96-7.75 (m, 8H, 4 Py-H + 4 Ar-H); uv λ (methanol, 1%): 272, 330 nm (ε, 10,600, 9,350).

Anal. Calcd. for $C_{20}H_{27}BrN_4$: C, 59.60; H, 6.75; N, 13.90; Br, 19.83. Found: C, 59.66; H, 7.01; N, 13.80; Br, 19.93.

In a similar fashion were prepared the following compounds:

N-[1-[2-(2-Bromophenyl)ethyl]-2(1*H*)pyridinylidene]-*N'*,*N''*-dicyclohexylguanidine, **21**.

This compound had m.p. 127.0-129.5°, in 28% yield, after recrystallization from 1:1 cyclohexane-hexane; ir: ν 3310 (m), 1640 (s), 1605 (s), 1550 (s), 1500 (s), 1460 (m), 1445 (m) cm^{-1}; pmr (deuteriochloroform): δ 0.5-2.5 [m, 22H, 2(C_6H_{11})], 3.25 [t (J = 5 Hz), 2H, CH_2Ar].

Anal. Calcd. for $C_{26}H_{35}BrN_4$: C, 64.65; H, 7.30; N, 11.60; Br, 16.60. Found: C, 64.35; H, 7.78; N, 11.36; Br, 16.46.

N',*N''*-Dicyclohexyl-*N*-[1-(2-phenylethyl)-2(1*H*)pyridinylidene]-guanidine, **22**.

This compound had m.p. 142.5-145.0° (sinters at 132°) in 45% yield, after recrystallization from hexane; ir: ν 3290 (m), 3070 (w), 1635 (s), 1600 (s), 1545 (s), 1505 (s), 1455 (s), 1445 (s) cm^{-1}; pmr (deuteriochloroform): δ 0.50-2.30 [m, 22H, 2(C_6H_{11})], 2.97-3.50 (m, 3H, N*H* + CH_2-Ar), 4.25 [t (J = 5 Hz), 2H, CH_2N], 5.90-7.70 (m, 9H, 4Py-H + 5 Ar-H).

Anal. Calcd. for $C_{26}H_{34}N_4$: C, 77.24; H, 8.98; N, 13.87. Found: C, 76.94; H, 9.10; N, 13.59.

N',*N''*-Dicyclohexyl-*N*-[1-(phenylmethyl)-2(1*H*)pyridinylidene]-guanidine, **23**.

This compound had m.p. 111-115° (sinters at 88°) in 31% yield, after recrystallization from hexane; ir: ν 3310 (m), 1635 (s), 1610 (s), 1555 (s), 1505 (s), 1460 (s), 1450 (s), 1445 (s), 1425 (m) cm^{-1}; pmr (deuteriochloroform): δ 0.50-2.15 [m, 22H, 2(C_6H_{11})], 2.70-3.30 (broad s, 1H, N*H*), 5.25 (s, 2H, CH_2-Ar), 6.00-7.70 (m, 9H, 4 Py-H + 5 Ar-H).

Anal. Calcd. for $C_{25}H_{34}N_4$: C, 76.99; H, 8.79; N, 14.37. Found: C, 76.82; H, 8.55; N, 14.35.

REFERENCES

(1) To whom all correspondence should be addressed.

(2) Present address: Schering Corp., Bloomfield, New Jersey.

(3) R. B. Petigara and H. L. Yale, *J. Heterocyclic Chem.*, **11**, 331 (1974).

(4) Less than 24 hours of exposure to light and air gave the polymeric material. Preliminary examination revealed markedly altered m.p., ir, and pmr spectra.

(5) Comparatively little can be found in the literature on the chemistry of pyridinimines; what has been reported is limited to the chemical behavior of 1-methyl-2(1*H*)pyridinimines; *cf.*, A. S. Tomcufcik and L. N. Starker, "Aminopyridines," in "Pyridine and its Derivatives," Interscience Publishers, N.Y., N.Y., Part Three, 1962, pp. 57-58; C. S. Giam, "Aminopyridines," in "Pyridine and its Derivatives," Interscience Publishers, N.Y., N.Y., Part Three, 1974, p. 90.

(6) T. C. Sommers and G. J. Handley, *J. Med. Chem.*, 7, 784 (1964) have described this compound and report a m.p. of 220-226°.