The Synthesis of Pyrimido[4,5-*d*]Pyridazines

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The synthesis of pyrimido[4,5-*d*]pyridazin-2-one-4-thione (II), pyrimido[4,5-*d*]pyridazine-2,4-dithione (VI), 4-aminopyrimido[4,5-*d*]pyridazine-2-thione (III), 2-aminopyrimido[4,5-*d*]-pyridazin-4-one (X), 2-methylpyrimido[4,5-*d*]pyridazin-4-one (XII), and pyrimido[4,5-*d*]-pyridazin-4-one (XIII) are reported together with several new pyridazine intermediates.

Investigations in the pyrimido[4,5-*d*]pyridazine ring system has been limited to the synthesis of two compounds. Jones (3) reported the first compound, namely, 2-amino-pyrimido[4,5-*d*]pyridazine-5,8-dione. More recently, DiStefano and Castle (4) reported the synthesis of pyrimido[4,5-*d*]pyridazine-2,4-dione (V). In this paper is reported an extension of the synthetic chemistry of pyrimido[4,5-*d*]pyridazines utilizing pyrimido[4,5-*d*]-pyridazine-2,4-dione (V) as the key intermediate.

In order to provide pyrimido[4,5-*d*]pyridazines appropriately substituted for nucleophilic displacement reactions, satisfactory routes to 2,4-dichloropyrimido[4,5-*d*]-pyridazine were sought. Unfortunately the chlorination of pyrimido[4,5-*d*]pyridazine-2,4-dione (V) under a variety of chlorinating conditions was unsuccessful. Therefore, our attention was directed to the thiation of V in order to obtain pyrimido[4,5-*d*]pyridazine-2,4-dithione (VI) wherein it was expected that VI and its derivatives would provide good leaving groups in nucleophilic displacement reactions. Treatment of V with phosphorus pentasulfide in boiling pyridine solution for 1 hour gave pyrimido[4,5-*d*]pyridazin-2-one-4-thione (II) rather than the expected dithione (VI). The structural assignment of II as pyrimido[4,5-*d*]pyridazin-2-one-4-thione rather than the alternate pyrimido[4,5-*d*]pyridazin-4-one-2-thione was based upon analogy in the pyrimidine ring system (5) wherein the 4-position is more reactive to thiation than the 2-position. We cannot, however, rule out pyrimido-[4,5-*d*]pyridazin-4-one-2-thione as the structure for II. In order to prepare pyrimido[4,5-*d*]pyridazine-2,4-dithione, it was necessary to allow V to react with phosphorus pentasulfide in boiling pyridine for 19 hours. The yield of pyrimido[4,5-*d*]pyridazine-2,4-dithione (VI) was 78%.

The nucleophilic replacement of the mercapto group with an amino group in the pyrimidine series favors the replacement of the mercapto group in the 4-position over that in the 2-position, *e.g.*, Russell, *et al.*, (6) reported that the reaction of pyrimidine-2,4-dithione with aqueous ammonia gave 4-aminopyrimidine-2-thione exclusively. The reaction of pyrimido[4,5-*d*]pyridazine-2,4-dithione (VI) with ethanolic ammonia in a rocking autoclave gave 4-aminopyrimido[4,5-*d*]pyridazine-2-thione (III) in 20% yield. The structural assignment is based upon analogy with the pyrimidine series (6) however the structure of III is not unequivocal.

In order to prepare other pyrimido[4,5-*d*]pyridazines, the unknown 5-aminopyridazine-4-carboxylic acid (VII) appeared to be the most useful intermediate. 5-Amino-pyridazine-4-carboxylic acid (VII) was prepared by the hydrolytic ring-opening of V preferably with aqueous ammonia in a rocking autoclave. However, in other hydrolytic ring-opening experiments using aqueous sodium hydroxide on V, 5-hydroxypyridazine-4-carboxylic acid (IV) was obtained in 69% yield. Treatment of the acid (IV) with methanol and sulfuric acid gave methyl 5-hydroxypyridazine-4-carboxylate (I) in 82% yield.

5-Aminopyridazine-4-carboxylic acid (VII) was readily esterified with ethanol, *p*-toluenesulfonyl chloride and sulfuric acid. The product, ethyl 5-aminopyridazine-4-carboxylate (VIII) (59% yield) was acetylated with acetic anhydride in benzene solution. Ethyl 5-acetamidopyrida-zine-4-carboxylate (IX) was obtained in 72% yield. Treatment of the ester (IX) with ethanolic ammonia at room temperature for 4 days gave 2-methylpyrimido [4,5-*d*]pyridazin-4-one (XII) in 78% yield.

Fusion of ethyl 5-aminopyridazine-4-carboxylate (VIII) and guanidine carbonate gave 2-aminopyrimido[4,5-*d*]-pyridazin-4-one (X). The amino ester (VIII) upon treat-

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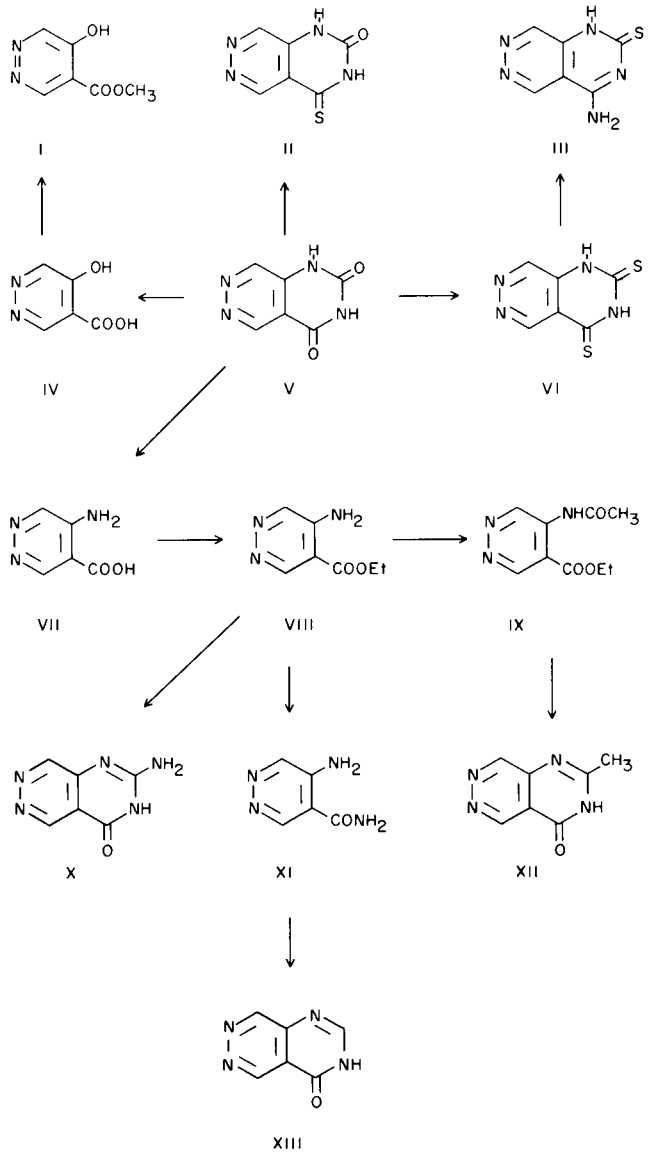

ment with ethanolic ammonia at 90-100° in a rocking autoclave for 48 hours gave 5-aminopyridazine-4-carboxamide (XI) in 52% yield. The reaction of XI with ethyl orthoformate in DMF gave pyrimido[4,5-*d*]pyridazin-4-one (XIII).

EXPERIMENTAL (7)

The Reaction of Phosphorus Pentasulfide with Pyrimido[4,5-*d*]-pyridazine-2,4-dione (V).

A. Pyrimido[4,5-*d*]pyridazin-2-one-4-thione (II).

Pyrimido[4,5-*d*]pyridazine-2,4-dione (V) (4) (0.5 g., 0.00305 mole) was suspended in 34 ml. of refluxing dry pyridine. To this refluxing mixture was added 1.35 g. (0.0061 mole) of phosphorus pentasulfide portionwise over a period of 5 minutes. At this point a solution was obtained which was heated under reflux for 1 hour at which time the excess pyridine was removed under reduced pressure. Ice water was added to the black viscous residue and the mixture was allowed to stand at room temperature for ~15 hours. The suspension was heated on the steam bath for 1 hour, filtered and the product was dried in air. There was obtained 0.35 g. (58%) of pyrimido[4,5-*d*]pyridazine-2-one-4-thione (II), m.p. ~310° dec. The product was recrystallized from hot water as long orange needles, m.p. 310° dec.; infrared cm^{-1}, 3480(m), 3350(w), 3235(w), 3130(w), 2920(m), broad band 2850-2650(m), 1751(s), 1698(w), 1602(s), 1502(w), 1449(m), 1398(w), 1293(s), 1257(s), 1210(w), 995(s), 900(m), 780(w), 768(w), 735(w), 715(w), 700(m), 500-490(m), 420(m); UV λ max (methanol), 214 (ε, 72,790), 285.5 (ε, 11,620), 350 mμ (ε, 9,160); NMR (deuterium oxide-sodium deuteroxide 10%), doublet 8.97 δ; doublet 9.69 δ; (J = 1 cps).

Anal. Calcd. for $C_6H_4N_4OS \cdot H_2O$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.35; H, 2.90; N, 28.10.

B. Pyrimido[4,5-*d*]pyridazine-2,4-dithione (VI).

A mixture of pyrimido[4,5-*d*]pyridazine-2,4-dione (V) (0.5 g., 0.00305 mole) and 34 ml. of dry pyridine was heated under reflux. During a period of 5 minutes 1.35 g. of freshly-opened phosphorus pentasulfide was added portionwise. The reaction mixture was heated under reflux for 19 hours. The dark brown mixture was evaporated *in vacuo*, and the residue added to crushed ice. The mixture was allowed to stand overnight at room temperature, then heated on the steambath for 1 hour and the product separated by filtration. The residue was purified by solution in 5% potassium hydroxide, the solution treated with charcoal, filtered and acidified with concentrated hydrochloric acid. The brown product, 0.47 g. (78%), had m.p. > 360° dec., infrared cm^{-1}, 3150(m), 3090(m), 2920(m), 1710(m), 1602(s), 1585(vs), 1550(vs), 1495(s), 1450(m), 1390(m), 1340(m), 1310(m), 1270(s), 1212(s), 1137(m), 1100(w), 1080(w), 1040(w), 965(w), 900(w), 940(w), 785(w), 760(w), 755(w), 685(w), 650(w), 535(w); NMR (2 *N* aqueous potassium hydroxide); doublet 9.02 δ; doublet 9.67 δ (J = 1.3-1.5 cps.).

Anal. Calcd. for $C_6H_4N_4S_2$: C, 36.72; H, 2.06; N, 28.54. Found: C, 36.56; H, 2.27; N, 28.63.

4-Aminopyrimido[4,5-*d*]pyridazine-2-thione (III).

A mixture containing 8 g. (0.0408 mole) of crude pyrimido-[4,5-*d*]pyridazine-2,4-dithione (VI) and 300 ml. of ethanolic ammonia (saturated in the cold) was heated at 100-110° for 3 hours in a stainless steel rocking autoclave. The reaction mixture was cooled and filtered. The solid was shown to be largely starting material (VI) by infrared analysis. The filtrate was evaporated to dryness and the residue (4.5 g.) was treated with ~50 ml. of 10% hydrochloric acid solution. A portion (~0.75 g.) remained undissolved. The suspension was filtered and the acid-insoluble material was shown by infrared analysis to be starting material (VI). The acidic filtrate was neutralized with solid sodium bicarbonate. A yellow crystalline mass separated. The solid was separated by filtration and dried in air (2.4 g.). The solid product was dissolved in 5% sodium hydroxide solution, the solution was filtered and neutralized with acetic acid. The precipitate was collected, washed with water and dried in air, yield 1.5 g. (20%). Finely divided yellow crystals were obtained by recrystallization from water, m.p. > 360°; infrared cm^{-1}, 3400 (m), 3325(m), 3180(m), 1640(s), 1575(s), 1535(s), 1485(m).

1450(m.sh.), 1350(m), 1310(m), 1258(m), 1208(m), 1130(m), 1050(w), 990(w), 902(w), 875(w), 847(w), 804(w), 788(w), 746(m), 698(w), 630(w), 585(w), 528(m); UV λ max (95% ethanol) 225(sh) (ε, 21,370), 294 (ε, 8,340), 350 (sh) (ε, 6,490), 393 mμ (ε, 5,170).

Anal. Calcd. for $C_6H_5N_5S \cdot H_2O$: C, 36.55; H, 3.58; N, 35.52. Found: C, 36.36; H, 3.42; N, 35.43.

5-Hydroxypyridazine-4-carboxylic Acid (IV).

Five g. of pyrimido[4,5-*d*]pyridazine-2,4-dione (V) was dissolved in 125 ml. of 10% sodium hydroxide solution. The reaction mixture was heated at 155-165° for 7.5 hours in a stainless steel rocking autoclave. The clear, light brown solution was acidified with concentrated hydrochloric acid to ~*p*H 4-6. Near the neutral point a white solid separated which dissolved in the weakly acidic medium. Upon chilling a solid separated, yield 2.95 g. (69%), m.p. 260-261° dec. The filtrate was neutralized with solid sodium bicarbonate and allowed to stand at room temperature whereupon a white solid separated. This was shown by NMR analysis to be the sodium salt of IV, m.p. > 360° dec. An analytical sample was prepared by recrystallization from hot water (charcoal), m.p. 260-261° dec.; infrared cm^{-1}, 3185(m), 3145(s), 3070(s), 2940(m), 2570(w), 1720(vs), 1604(s), 1570(s), 1540(m), 1510(s), 1485(s), 1349(w), 1295(m), 1245(m), 1200(s), 1118(w), 1098(w), 1015(m), 980(w), 960(w), 917(w), 887(w), 800(m), 770(w), 725(w), 670(m), 662(m), 610(m), 590(m), 557(w), 450(w), 430(w); NMR (deuterium oxide-sodium deuteroxide) doublet, 850 δ, (J = 1 cps) (ring H6), doublet 8.76 δ, (J = 1 cps) (ring H3).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.81; H, 2.95; N, 20.14.

Methyl 5-Hydroxypyridazine-4-carboxylate (I).

A mixture containing 0.5 g. (0.0036 mole) of 5-hydroxypyridazine-4-carboxylic acid (IV), 0.1 ml. of concentrated sulfuric acid and 15 ml. of dry methanol was heated under reflux for 3 hours. After 1 hour the suspended material dissolved, then a crystalline solid began to separate after heating an additional 30 minutes. After cooling the crystalline solid was collected by filtration, m.p. 248-249° dec., yield 0.45 g. (82%). The product was recrystallized from methanol as a white powder, m.p. 248-249° dec.; infrared cm^{-1}, 3160-2850 (broad s), 1715(s), 1602(s), 1545(m), 1485(s), 1445(m), 1380(s), 1330(m), 1300(s), 1255(m), 1205(s), 1097(s), 1010(w), 965(w), 920(m), 812(w), 800(s), 732(w), 668(s), 590(s), 538(w), 436(w), 415(w); NMR spectrum (deuterium oxide-sodium deuteroxide) singlet 3.32 δ (OCH_3), doublet 8.37 δ (J = 1 cps) (ring proton H6), doublet 8.62 δ (J = 1 cps) (ring proton H3).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.79; H, 3.91; N, 18.42.

5-Aminopyridazine-4-carboxylic Acid (VII).

A mixture containing 2.0 g. (0.0122 mole) of pyrimido[4,5-*d*]-pyridazine-2,4-dione (V) and 50 ml. of concentrated ammonium hydroxide was heated at 170-180° for 7 hours in a stainless steel rocking autoclave. The reaction mixture was evaporated to dryness under reduced pressure. The residue, 1.7 g. (98% yield), m.p. 316° dec., required no further purification; infrared cm^{-1}, 3335(m), 3175(m), 2945(m), 2660-2590(w), 2045(w), 1960(w), 1628(vs), 1530(m), 1463(m), 1440(m), 1365(s), 1320(m), 1295(m), 1230(m), 1137(w), 1058(w), 1005(w), 945(w), 918(w), 910(w), 888(w), 812(m), 712(w), 693(s), 580(s), 535(w), 430(w), 405(w); NMR spectra (deuterium oxide-sodium deuteroxide) doublet 8.73 δ (J = 1 cps) (ring proton H6), doublet 8.93 δ (J = 1 cps) (ring proton H3).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 42.99; H, 3.58; N, 30.45.

Ethyl 5-Aminopyridazine-4-carboxylate (VIII).

5-Aminopyridazine-4-carboxylic acid (VII) (2 g., 0.0144 mole) was dissolved in 200 ml. of absolute ethanol containing 2 ml. of concentrated sulfuric acid and 0.1 g. of *p*-toluenesulfonyl chloride. The solution was heated under reflux for 4.5 days, then the reaction mixture was evaporated to dryness under reduced pressure. The residue was suspended in ice water and neutralized with solid sodium bicarbonate followed by extraction of the mixture with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate, the drying agent was removed by filtration and the chloroform filtrate evaporated to dryness. The residue was recrystallized from ethanol-ethyl acetate or acetone, yield 1.4 g. (59%), m.p. 162-163°; infrared cm^{-1}, 3400(s), 3300(s), 3220(m), 3175(s), 3040(m), 2995(m), 2900(w), 1700(s), 1636(s), 1570(m), 1470(m), 1450(w), 1415(w), 1390(w), 1370(s), 1310(s), 1295(s), 1249(s), 1180(s), 1130(s), 1073(w), 1025(m), 968(s), 928(w), 910(w), 868(w), 827(w), 800(m), 730(w), 705(m), 595(m), 546(w), 507(w), 430(w); Nmr (deuteriochloroform), triplet 1.43 δ (J = 7.5 cps) (OCH_2CH_3); quartet 4.43 δ (J = 7.5 cps) (OCH_2CH_3); broad diffuse band at *ca.* 6.8 δ (NH_2); doublet 8.85 δ (J = 1 cps) (ring proton at H6); doublet 9.15 δ (J = 1 cps) (ring proton at H3); UV δ max (ethanol), 249 (ε, 12,540); 308 mμ (ε, 5,630).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.54; H, 5.38; N, 25.27.

Ethyl 5-Acetamidopyridazine-4-carboxylate (IX).

A mixture containing 0.5 g. (0.003 mole) of ethyl 5-aminopyridazine-4-carboxylate (VIII), 1 ml. of acetic anhydride and 20 ml. of dry benzene was heated under reflux for 4 hours. The reaction mixture was evaporated to dryness, ethanol added again and evaporated to dryness under reduced pressure. The residue was dissolved in ether (Norite), filtered and evaporated to dryness, yield, 0.45 g. (72%), m.p. 90°. The product was recrystallized from ether, m.p. 90°; infrared cm^{-1}, 3280(m), 3100(w), 3070(w), 3000(w), 2985(w), 2945(w), 1720(s), 1695(s), 1595(s), 1555(s), 1480(m), 1450(s), 1390(m), 1375(m), 1350(m), 1305(s), 1280(s), 1225(s), 1185(s), 1132(w), 1115(m), 1015(m), 990(w), 963(w), 926(w), 995(w), 885(w), 865(w), 809(m), 747(w), 731(w), 704(w), 690(w), 599(w), 569(w), 544(w), 506(w), 410(w); UV λ max (ethanol), 213 (ε, 17,730), 250 (ε, 11,540); 286 mμ (ε, 8,160).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.44; H, 5.46; N, 19.86.

5-Aminopyridazine-4-carboxamide (XI).

Ethyl 5-aminopyridazine-4-carboxylate (VIII) (2 g., 0.012 mole) was suspended in 300 ml. of ethanolic ammonia (saturated in the cold). The suspension was heated at 90-100° in a pressure bottle for 48 hours. The pressure bottle was cooled, opened and the mixture was evaporated to dryness under reduced pressure. The residue was extracted with hot chloroform. This extract gave only starting material. The chloroform-insoluble residue (0.85 g.) was recrystallized from methanol colorless needles, m.p. 293° dec. (blackens at ~290° yield 0.5 g. (30%); infrared cm^{-1}, 3530(w), 3420(s), 3300(s), 3210-3100(s), 2780(w), 1680(s), 1620(s), 1520(w), 1460(w), 1400(s), 1320(w), 1285(w), 1247(m), 1117(w), 992(m), 952(w), 915(w), 890(w), 798(w), 760(w), 710(w), 662(m), 550(m), 518(m); UV λ max (95% ethanol), 205 (ε, 25,620), 251 (ε, 12,680), 312 mμ (ε, 5,935).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.48; H, 4.38; N, 40.56.

Found: C, 43.84; H, 4.32; N, 40.56.

2-Aminopyrimido[4,5-*d*]pyridazin-4-one (X).

Ethyl 5-aminopyridazine-4-carboxylate (VIII) (2 g., 0.012 mole) and guanidine carbonate (2.8 g.) were ground together and heated at 160-180° for 1 hour then at 180-190° for 45 minutes. The residue was dissolved in water and a small amount of insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was washed with acetone, then with chloroform. The residue was then extracted with cold ethanol. The insoluble residue was recrystallized from methanol-ethyl acetate followed by recrystallization from isopropyl alcohol, yield 1.4 g., m.p. > 350° dec.; infrared cm^{-1}, 3350(s), 3170(m), 2800(w), 1870(vw), 1685(s), 1670(s), 1603(s), 1575(m), 1535(m), 1502(s), 1430(m), 1405(m), 1325(m), 1290(w), 1264(w), 1165(w), 1110(w), 1030(w), 955(w), 920(w), 815(w), 800(w), 785(w), 736(w), 712(m), 630(w), 500(w); UV λ max (95% ethanol) 220(sh) (ε, 25,310), 276 (ε,16,560), 330 mμ (sh) (ε, 4,630).

Anal. Calcd. for $C_6H_5N_5O \cdot H_2O$: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.62; H, 4.19; N, 38.53.

Pyrimido[4,5-*d*]pyridazine-4-one (XIII).

5-Aminopyridazine-4-carboxamide (XI) (0.35 g., 0.00253 mole) and ethyl orthoformate (3.5 ml.) were heated in DMF (7 ml.) under reflux for 1 hour. After cooling the precipitate was removed by filtration. An additional crop of product (same m.p.) was optained by evaporation to dryness. The combined solid product was recrystallized from hot water. Light yellow needles (0.3 g.) were obtained, m.p. 330° dec.; infrared cm^{-1}, 3200-2900(s), 2030(w), 2010(w), 1700(s), 1630(m), 1600(s), 1550(s), 1470(m), 1440(m), 1430(m), 1400(s), 1345(s), 1296(w), 1270(w), 1250(s), 1230(m), 1197(w), 1168(w), 1150(s), 1095(m), 1023(w), 952(s), 928(s), 862(s), 843(s), 914(s), 760(w), 720(w), 622(s), 610(m), 534(s), 503(m), 448(m), 413(s); UV λ max (95% ethanol) 227 (ε, 12,540), 273 (ε, 8,710), 298 mμ (sh) (ε, 6,660).

Anal. Calcd. for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.82. Found: C, 48.92; H, 2.82; N, 37.67.

2-Methylpyrimido[4,5-*d*]pyridazin-4-one (XII).

Ethyl 5-acetamidopyridazine-4-carboxylate (IX) (1 g., 0.0048 mole) was dissolved in 100 ml. of ethanolic ammonia (saturated in the cold) and the solution was allowed to stand at room temperature for 4 days. The reaction mixture was evaporated under reduced pressure and the solid separated by filtration. The product was recrystallized from hot water, 0.6 g., of colorless plates (78% yield), m.p. 235° dec.; infrared cm^{-1}, 3410(m), 3210(s), 3125(s), 3060(s), 3025(s), 2970(s), 2940(s), 2795(m), 2740(m), 2605(w), 2490(w), 2440(w), 2260(w), 1960(w), 1925(w), 1880(w), 1840(w), 1810(w), 1760(w), 1690(vs), 1630(m), 1600(s), 1560(s), 1480(m), 1435(s), 1425(s), 1365(s), 1316(m), 1260(s), 1242(w), 1220(w), 1183(w), 1144(s), 1036(w), 1020(m), 948(s), 901(m), 814(s), 785(m), 700(m), 690(m), 646(w), 595(s), 575(w), 538(w), 502(m), 459(w), 411(w); UV λ max (ethanol), 225 (ε, 9,140), 273 mμ (ε,9,390).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.66; H, 3.88; N, 34.70.

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REFERENCES

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(2) Inquiries concerning this paper should be directed to Professor Raymond N. Castle.

(3) R. G. Jones, *J. Am. Chem. Soc.*, 78, 159 (1956).

(4) L. DiStefano and R. N. Castle, *J. Heterocyclic Chem.*, 5, 53 (1968).

(5) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).

(6) P. B. Russell, G. B. Elion, E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, 71, 2279 (1949).

(7) All melting points were determined in a Thomas-Hoover capillary melting point apparatus or in a copper block and are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 spectrophotometer in potassium bromide discs. The ultraviolet spectra were taken in the solvent indicated with a Cary 15 spectrophotometer. The NMR spectra were taken with the standard and the solvent indicated with a Varian A60 A spectrophotometer, chemical shifts (δ) are reported in ppm downfield from TMS in organic solvents and from TPS in aqueous solvents.

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