androstane, 69292-07-5; *N*-isopropyliden-17β-amino-5a-androstan-3a-ol, 69309-42-8; acetone, 67-64-1.

References and Notes

(1) Part 25: H. E. Smith, B. G. Padilla, J. R. Neergaard, and F.-M. Chen, *J. Am. Chem. Soc.*, **100**, 6035 (1978).
(2) Supported in part by National National Science Foundation Grant No. CHE77-24293.
(3) (a) Vanderbilt University; (b) Tennessee State University; supported by National Science Foundation Grant No. CHE77-04608.
(4) H. E. Smith, E. P. Burrows, E. H. Massey, and F.-M. Chen, *J. Org. Chem.*, **40**, 2897 (1975).
(5) P. W. Alexander and R. J. Sleet, *Aust. J. Chem.*, **23**, 1183 (1970).
(6) H. Ripperger, K. Schreiber, G. Snatzke, and K. Ponsold, *Tetrahedron*, **25**, 827 (1969).
(7) H. E. Smith, J. R. Neergaard, E. P. Burrows, and F.-M. Chen, *J. Am. Chem. Soc.*, **96**, 2908 (1974).
(8) H. E. Smith, E. P. Burrows, and F.-M. Chen, *J. Org. Chem.*, **40**, 1562 (1975).
(9) H. E. Smith, E. P. Burrows, and F.-M. Chen, *J. Org. Chem.*, **41**, 704 (1976).
(10) B. Ringdahl, H. E. Smith, and F.-M. Chen, *J. Org. Chem.*, **42**, 4184 (1977).
(11) H. E. Smith, E. P. Burrows, M. J. Marks, R. D. Lynch, and F.-M. Chen, *J. Am. Chem. Soc.*, **99**, 707 (1977).
(12) H. E. Smith, W. I. Cozart, T. de Paulis, and F.-M. Chen, *J. Am. Chem. Soc.*, submitted.
(13) M. El-Aasser, F. Abdel-Halim, and M. Ashraf El-Bayoumi, *J. Am. Chem. Soc.*, **93**, 590 (1971).
(14) V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and N. L. Ermolova, *Vestn. Mosk. Univ. Khim.*, **17**, 714 (1976); *Moscow Univ. Chem. Bull. (Engl. Transl.)*, **No. 6**, 55 (1976).
(15) H. E. Smith and R. Records, *Tetrahedron*, **22**, 813, 2400 (1966).
(16) H. E. Smith and T. C. Willis, *Tetrahedron*, **26**, 107, 2258 (1970).
(17) H. E. Smith, L. J. Schaad, R. B. Banks, C. J. Wiant, and C. F. Jordan, *J. Am. Chem. Soc.*, **95**, 811 (1973).
(18) R. Hakansson, B. Norden, and E. W. Thulstrup, *Chem. Phys. Lett.*, **50**, 305 (1977).
(19) C. Sandorfy, "Electronic Spectra and Quantum Chemistry", Prentice-Hall, Englewood Cliffs, N.J., 1964, pp 341 and 342.
(20) P. A. Snyder, P. M. Vipond, and W. C. Johnson, Jr., *Biopolymers*, **12**, 975 (1973).
(21) H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2265 (1964).
(22) J. Schmitt, J. J. Panouse, A. Hallot, H. Pluchet, P. Comoy, and P.-J. Cornu, *Bull. Soc. Chim. Fr.*, 771 (1964).
(23) L. Ruzicka and M. W. Goldberg, *Helv. Chim. Acta*, **19**, 107 (1936).

Neighboring Group Interaction in Ortho-Substituted Heterocycles. 2. 1,2,4-Oxadiazolylpyridines and Pyrido[2,3-*d*]pyrimidine 3-Oxides[1]

B. Verček, I. Leban, B. Stanovnik, and M. Tišler*

Department of Chemistry, University of Ljubljana, 61000 Lujbljana, Yugoslavia

Received November 2, 1978

Various synthetic methods have been elaborated to prepare pyrido[2,3-*d*]pyrimidines and their 3-oxides from *o*-aminocyanopyridine. Conversion of these 3-oxides into 1,2,4-oxadiazolylpyridines, *s*-triazolo[1,5-*a*]pyridines, and pyrazolo[3,4-*b*]pyridines as well as other transformations are described.

In our previous report[2] neighboring group interactions in ortho-substituted aminopyridines were described. Among other reactions, the preparation of pyrido[2,3-*d*]pyrimidines via intermediate 1,3,4-oxadiazolypyridines was investigated. This paper deals mainly with a study of interconversions of pyrido[2,3-*d*]pyrimidine 3-oxides and 1,2,4-oxadiazolyl-3-pyridines.

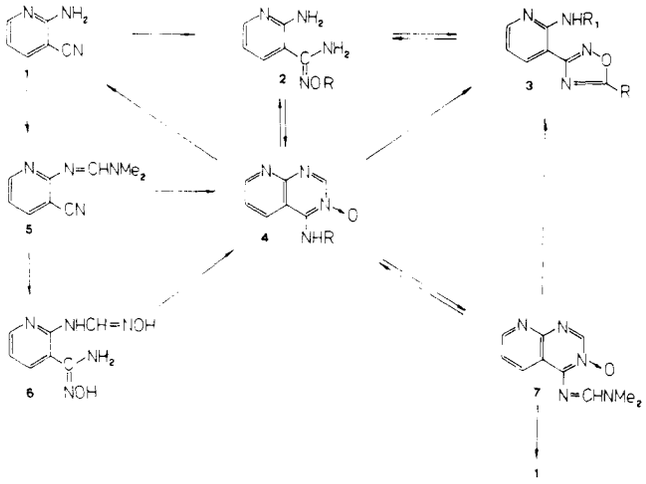
As staring material 2-amino-3-cyanopyridine (**1**) was used. With an ethanolic solution of hydroxylamine it was transformed into the amidoxime (**2**, R = H). Attempted cyclization of this compound in poly(phosphoric acid) failed and 2,3-diaminopyridine was formed. However, the amidoxime (**2**, R = H) could be acetylated and the product (**2**, R = COMe), when heated in water, was transformed into a compound analyzing for $C_8H_8N_4O$. Since from its IR spectrum the absence of a carbonyl group was evident, the compound could have either structure **3** (R = Me; R_1 = H) or structure **18**. On the basis of the NMR spectrum a differentiation between these structures is not possible. Based on further chemical transformations and in particular on the X-ray analysis[3] the structure of this compound as 2-amino-3-(5′-methyl-1′,2′,4′-oxadiazolyl-3′)pyridine (**3**, R = Me; R_1 = H) was unequivocally established. The compound is transformed back into the amidoxime **2** (R = H) in hot aqueous sodium hydroxide solution. It is known that the stability of 1,2,4-oxadiazoles varies with the number of substituents. Whereas disubstituted compounds are thermally stable and do not hydrolyze, the monosubstituted derivatives readily undergo hydrolysis by ring opening.[4-6]

The same oxadiazolylpyridine **3** (R = Me; R_1 = H) could be prepared also by hydrolysis of the formyl drivative **3** (R = Me; R_1 = CHO), obtained by treatment of 4-aminopyrido[2,3-*d*]pyrimidine 3-oxide (**4**, R = H) with acetic anhydride. This transformation parallels the ring opening of adenine 1-oxide which proceeds through the *O*-acetyl derivative which subsequently undergoes ring opening and recyclization into a oxadiazole derivative.[7] Finally, if the amidoxime **2** (R = H) was heated with triethyl orthoformate, compound **3** (R = R_1 = H) was obtained as byproduct (1%) together with **4** (R = H) as the main product (89%). Since one may postulate that the *N*-oxide (**4**, R = H) in this reaction may be formed from **3** (R = R_1 = H) in a thermal reaction, we have performed a separate experiment and established that this conversion does not occur under the conditions of the above reaction. Since other amidoximes react readily with triethyl orthoformate to give 1,2,4-oxadiazoles,[8] we anticipate that the *o*-amino group of **2** (R = H) must play an important role in this transformation. Evidently, this *o*-amino group participates more readily in ring closure than the amino group from the amidoxime function. The reverse transformation, i.e., **3** into **4**, was never observed during our experiments.

4-Aminopyrido[2,3-*d*]pyrimidine 3-oxide (**4**, R = H) could be prepared by two additional methods. In one of them, compound **1** was treated with *N*,*N*-dimethylformamide dimethyl acetal to give **5**, which upon treatment with methanolic hydroxylamine hydrochloride at room temperature gives the bicyclic structure **4** (R = H) in reasonable yield. According to the second procedure, compound **5** was first transformed into **6** with free hydroxylamine in methanol at room temperature and cyclization to **4** (R = H) may then be accomplished either in the presence of poly(phosphoric acid) or thermally. In the last case, also a small amount of **8** (R = R_1 = H) could be isolated and identified. The bicyclic compound **4** (R = H) is decomposed in hot dilute hydrochloric acid into the amidoxime **2** (R = H) which was also obtained in admixture with **1** after treatment with hot aqueous sodium hydroxide solution.

0022-3263/79/1944-1695$01.00/0

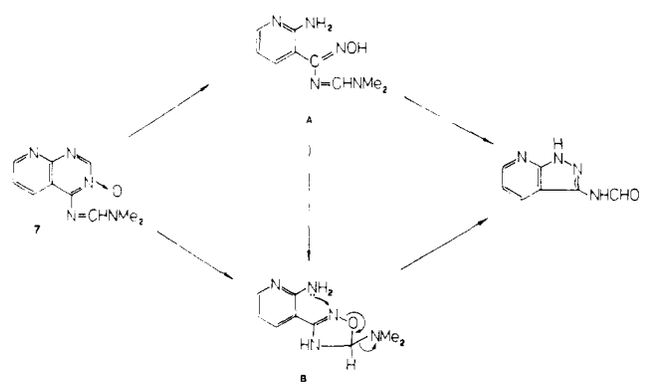
The N-oxide **4** (R = H) was easily transformed at room temperature into the corresponding N,N-dimethylaminomethyleneamino derivative **7** which proved to be a versatile

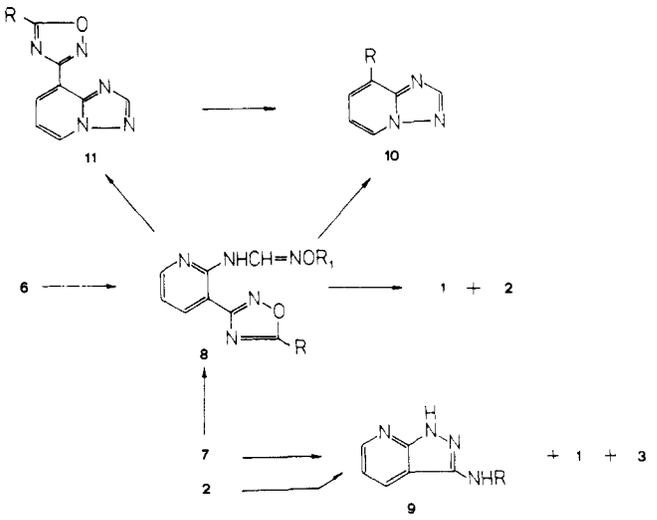


intermediate for various transformations. With ethanolic ammonia a mixture of the starting compound (**4**, R = H) and **1** was obtained, but in aqueous alkaline solution it is decomposed into compound **1**, 2-aminonicotinic acid, and traces of 2-aminonicotinamide. With methanolic hydroxylamine hydrochloride compound **7** is transformed at room temperature smoothly into **8** (R = R_1 = H). On the other hand, the formamidine **7** is hydrolyzed at room temperature to give a mixture of almost equal amounts of compound **1** and **3** (R = H, R_1 = CHO) together with a small amount of the pyrazolo[3,4-*b*]-pyridine derivatives (**9**, R = CHO). The formation of the first two products is easily understood, whereas the formation of the pyrazolo[3,4-*b*]pyridine system is somewhat surprising. By separate experiments we could establish that compound **9** (R = CHO) is not formed from either **3** (R = R_1 = H, or R = H; R_1 = CHO) or **4** (R = H). A possible mechanistic pathway is outlined in Scheme I. Neither A nor B could be detected in the reaction mixture. However, A is more likely to be an intermediate since we could establish that upon treatment of the amidoxime **2** (R = H) with N,N-dimethylformamide dimethyl acetal in boiling toluene for 1 h, a mixture of **9** (R = CHO) and **3** (R = R_1 = H) was formed in a ratio of about 2:1. Transformation of quinazoline with hydroxylamine-*O*-sulfonic acid and treatment of the resulting adduct with alkali has been reported recently to also give indazole among several reaction products.[9] Finally, the formamidine **7** is transformed in good yield into the oxadiazole **3** (R = R_1 = H) after treatment with dilute hydrochloric acid at room temperature.

Also with compound **8** (R = R_1 = H) some interesting transformations could be observed. When treated either with hot aqueous acid or alkali it is transformed into a mixture of

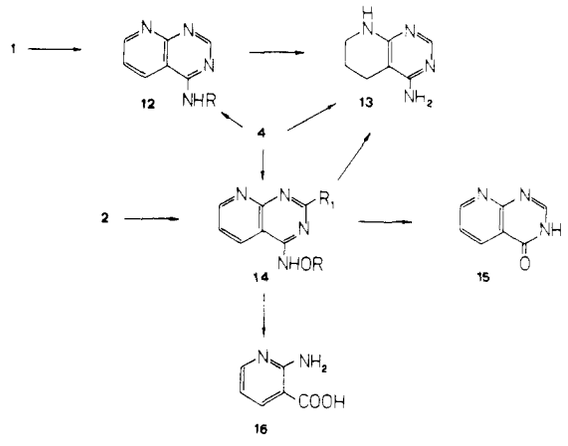
Scheme I





compound **1** and **2** (R = H). However, in hot poly(phosphoric acid) compound **8** (R = R_1 = H) is transformed into the *s*-triazolo[1,5-*a*]pyridine derivative **11** (R = H). This, when heated to about 200 °C, is transformed by the decomposition of the oxadiazolyl part of the molecule into the cyano derivative **10** (R = CN). This could be prepared in a similar manner directly from **8** (R = R_1 = H). The formation of a fused triazolo ring in these reactions is well established since we have studied it recently on several heterocyclic systems.[10-12] In an extension of these transformations the methyl analogue **11** (R = Me) could be prepared from **6** after treatment with acetic anhydride at room temperature and upon heating the isolated intermediate **8** (R = Me; R_1 = COMe) in water. With aqueous sodium hydroxide at room temperature compound **11** (R = H) gives the corresponding carboxamide **10** (R = $CONH_2$).

4-Aminopyrido[2,3,-*d*]pyrimidine (**12**, R = H) was prepared

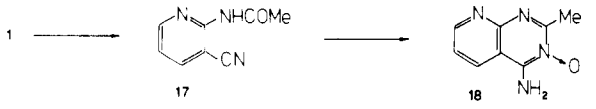


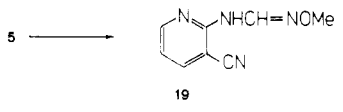
either by the usual way of deoxygenation of the 3-oxide (**4**, R = H) with titanium trichloride or from **1** after treatment with triethyl orthoformate and subsequent cyclization of the ethoxymethyleneamino derivative in the presence of ammonia at room temperature. Isomerization similar to the conversion of **4** to **3** has not been observed. The bicycle is reduced in the presence of palladized charcoal at the pyridine part of the molecule to give **13**. The same product is obtained also from either the N-oxide (**4**, R = H) or the hydroxylamino compound **14** (R = R_1 = H). The latter could be prepared from the N-oxide (**4**, R = H), by heating it in water for 7 h, together with compound **1** as minor product. The hydroxylamino compound is transformed in the presence of sodium hydroxide at room temperature into 2-aminonicotinic acid, whereas in hot hydrochloric acid (1:1) the pyridopyrimidinone **15** is formed.

The acetoxy derivative of the 2-methyl analogue (**14**, R = MeCO; R_1 = Me) could be obtained either from the amidox-

ime **2** (R = H) or its acetoxy derivative (**2**, R = MeCO) and acetic anhydride. On the other hand, the 2-methyl analogue of the *N*-oxide (**18**) could be synthesized from **1** via **17** upon treatment with hydroxylamine hydrochloride in toluene and in the presence of some pyridine.

Finally, it should be mentioned that the *O*-methyl derivative of the formamidoxime **19** was prepared with the intention





to attempt a study of some transformations which were not successful. Nevertheless, many of the described reactions show the versatility of the above amidoximes in neighboring group participation for the synthesis of heterocyclic systems.

Experimental Section

Melting points were determined on a Kofler hot-plate melting point apparatus. The NMR spectral measurements were performed on a JEOL JNM C-60 HL spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L spectrometer.

2-Aminopyridine-3-carboxamidoxime (2, R = H). A solution of 2-amino-3-cyanopyridine (0.6 g) in ethanolic hydroxylamine (prepared from 2.1 g of hydroxylamine hydrochloride and an ethanolic solution of sodium ethoxide; from 0.7 g of sodium and 50 mL of ethanol and filtered from NaCl) was heated under reflux for 7 h. The reaction mixture was concentrated under reduced pressure and the residue was crystallized from ethanol and hexane to give 0.5 g (65%) of **2** (R = H): mp 128–130 °C. This compound gave: M^+ 152; ^1H NMR (CD_3SOCD_3) δ 7.70 (dd, H_4), 6.51 (dd, H_5), 7.88 (dd, H_6), 5.83 and 6.90 (broad s, NH_2 groups), 9.75 (s, OH) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz).

Anal. Calcd for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.31; H, 5.35; N, 36.59.

The compound upon acetylation with acetic anhydride afforded the acetoxy derivative **2** (R = $COCH_3$): mp 147–160 °C with cyclization into **3** (R = Me); M^+ 194; ^1H NMR (CD_3SOCD_3) δ 7.68 (dd, H_4), 6.52 (dd, H_5), 7.93 (dd, H_6), 2.14 (s, Me), 6.70 and 6.84 (broad s, NH_2 groups) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz).

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.59; H, 5.39; N, 28.61.

The above compound **2** (R = H) when heated in poly(phosphoric acid) at 80 °C for 3 h was transformed in 28% yield into 2,3-diaminopyridine, identified by comparison with an authentic sample.

2-Amino-3-(5′-methyl-1′,2′,4′-oxadiazolyl-3′)pyridine (3, R = Me, R_1 = H). Method A. The acetylated amidoxime (**2**, R = COMe) (0.5 g) when heated in water (10 mL) for 2.5 h was transformed into **3** (R = Me) in 48% yield. It was found to be identical with the compound prepared as described under method B.

Method B. The formylamino compound **3** (R = Me, R_1 = CHO) (0.2 g), obtained from **4** (R = H) and acetic anhydride, was dissolved in water (10 mL), solid $NaHCO_3$ was added until the solution reached pH 8, and the reaction mixture was heated under reflux for 0.5 h. Upon cooling, the crystals which separated were collected and recrystallized from H_2O (0.11 g, 64%), mp 145 °C: M^+ 176; ^1H NMR (CD_3SOCD_3) δ 8.16 (m, H_4, H_6), 6.71 (dd, H_5), 2.69 (s, Me), 6.80 (broad s, NH_2) ($J_{4,5}$ = $J_{5,6}$ = 7.0 Hz).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.70; H, 4.57; N, 31.88.

If the compound was heated in 10% aqueous NaOH for 7 h, it was transformed into compound **2** (R = H).

Reaction of 2-Aminopyridine-3-carboxamidoxime with Triethyl Orthoformate. A mixture of the amidoxime (**2**, R = H) (0.51 g) and triethyl orthoformate (5 mL) was heated under reflux for 2 h. Upon cooling the product was collected and identified at **4** (R = H) (0.485 g, 89%), mp 250–255 °C. The filtrate was evaporated to dryness and the oily residue sublimed at 100–110 °C/0.1 mm to give compound **3** (R = R_1 = H) (7 mg, 1%).

2-[(Dimethylamino)methyleneamino]-3-cyanopyridine (5). Compound **1** (2.4 g) was suspended in *N,N*-dimethylformamide dimethyl acetal (3 mL) and the mixture was heated under reflux for 2 h. Excess of the reagent was removed in vacuo and the oily residue (3.5 g) was distilled in vacuo (150 °C/2 mm) and thereafter crystallized from cyclohexane: mp 66–69 °C; M^+ 174; ^1H NMR (CD_3SOCD_3) δ 7.85 (dd, H_4), 6.84 (dd, H_5), 8.25 (dd, H_6), 8.50 (s, CH), 3.03, and 3.10 (s, NMe_2) ($J_{4,5}$ = 8,0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.5 Hz).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17. Found: C, 61.64; H, 5.67; N, 32.30.

2-[(Hydroxyimino)methyleneamino]pyridine-3-carboxamidoxime (6). A solution of free hydroxylamine was prepared (from 0.46 g of sodium and 30 mL of methanol a solution of sodium methoxide was prepared and to this 1.4 g of hydroxylamine hydrochloride was added) and treated with the formamidine **5** (0.87 g). Upon standing overnight at room temperature the solvent was evaporated, the residue treated with some water, and the product collected (0.7 g, 72%), mp 190–205 °C with cyclization into **4** (R = H) which melted at 270–275 °C: M^+ 195; ^1H NMR (CD_3SOCD_3) δ 7.87 (dd, H_4), 6.83 (dd, H_5), 8.05 (dd, H_6), 7.89 (d, CH), 6.0 (broad s, NH_2), 9.95 and 10.0 (s, OH groups), 10.73 (d, NH) ($J_{4,5}$ = 7.5, $J_{5,6}$ = 5.0, $J_{4,6}$ = 1.5, $J_{NH,CH}$ = 10.0 Hz).

Anal. Calcd for $C_7H_9N_5O_2$: C, 43.07; H, 4.65; N, 35.89. Found: C, 43.30; H, 4.71; N, 35.66.

4-Aminopyrido[2,3-*d*]pyrimidine 3-Oxide (4, R = H). Method A. A solution of the formamidine (**5**) (3.5 g) in methanol (50 mL) was treated with hydroxylamine hydrochloride (1.4 g) at room temperature. The separated product was collected and crystallized from water and for analysis also from ethanol (2.2 g, 68%): mp 270–275 °C; M^+ 162; ^1H NMR (D_2O, 98 °C) δ 8.95 (s, H_2), 8.55 (dd, H_5), 7.70 (dd, H_6), 9.03 (dd, H_7) ($J_{5,6}$ = 8.4, $J_{6,7}$ = 4.6, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 52.10; H, 3.85; N, 34.64.

Method B. A mixture of the oxime **6** (0.4 g) and poly(phosphoric acid) (10 g) was heated at 70 °C for 2 h. Upon dilution with water and neutralization with solid $NaHCO_3$ the separated product was collected and crystallized from ethanol (0.22 g, 66%). The compound was identical with the product of method A.

Method C. A suspension of the oxime **6** (0.3 g) in triethyl orthoformate (3 mL) was heated under reflux for 2 h. Upon cooling, the separated product (40 mg) was collected and identified as compound **4** (R = H). The residue was evaporated in vacuo and the oily residue was treated with water (2 mL). After 2 days the oil crystallized and upon crystallization from H_2O compound **8** (R = R_1 = H) (11 mg) was obtained and identified by comparison with an authentic sample; mp 180–190 °C dec.

Compound **4** (R = H) is decomposed in hot dilute hydrochloric acid (1:1) into compound **2** (R = H), whereas in hot aqueous NaOH (10%) a mixture of compounds **2** (R = H) and **1** was obtained.

2-(Formylamino)-3-(5′-methyl-1′,2′,4′-oxadiazolyl-3′)pyridine (3, R = Me, R_1 = CHO). Compound **4** (R = H) (0.55 g) was treated with acetic anhydride (5 mL) and the mixture was gently warmed until a solution was obtained. Excess of the reagent was distilled off in vacuo and the residue was treated with ethanol (2 mL). The obtained product (0.6 g, 87%) was crystallized from ethanol: mp 140–142 °C; M^+ 204; ^1H NMR (CD_3SOCD_3) δ 8.48 (dd, H_4), 7.40 (dd, H_5), 8.59 (dd, H_6), 2.76 (s, Me), 9.55 (d, CHO), 10.15 (d, NH) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0, J_{CHNH} = 10.0 Hz).

Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.04; H, 4.02; N, 27.30.

4-[(*N,N*-Dimethylamino)methyleneamino]pyrido[2,3-*d*]pyrimidine 3-Oxide (7). The amino compound **4** (R = H) (0.81 g) was suspended in *N,N*-dimethylformamide dimethyl acetal (1.2 mL) and the mixture was left at room temperature for 2 h. Excess of the reagent was evaporated in vacuo, the residue was treated with ethyl acetate (2 mL) and cooled, and the product was collected. It was crystallized from benzene and petroleum ether (0.84 g, 77%): mp 205–210 °C; M^+ 217; ^1H NMR ($CDCl_3$) δ 8.99 (s, H_2), 8.78 (dd, H_5), 7.45 (dd, H_6), 8.99 (dd, H_7), 10.73 (s, CH) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 4.0, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.01; H, 4.60; N, 32.13.

Compound **7** is transformed in a solution of ammonia in ethanol at room temperature into a mixture of compound **4** (R = H) and **1**. With an aqueous alkaline solution, however, compound **1** was obtained together with 2-aminonicotinic acid and traces of 2-aminonicotinamide.

2-[(Hydroxyimino)methyleneamino]-3-(1′,2′,4′-oxadiazolyl-3′)-pyridine (8), R = R_1 = H). A solution of compound **7** (0.217 g)

in methanol (2 mL) was treated with hydroxylamine hydrochloride (0.1 g). The product which separated after a few minutes was collected and crystallized from methanol (0.17 g, 83%): mp 184–186 °C; M^+ 205; ^1H NMR ($CDCl_3$) δ 7.08 (dd, H_5), 8.40 (m, H_4 and H_6), 9.79 (s, $H_{5'}$), 8.10 (d, CHO), 10.03 (d, NH), 10.50 (s, OH) ($J_{5,6}$ = 5.5, $J_{4,5}$ = 6.5, J_{NHCH} = 9.0 Hz.

Anal. Calcd for $C_8H_7N_5O_2$: C, 46.83; H, 3.44. Found, C, 47.07; H, 3.59.

The above compound when heated under reflux in dilute (1:1) hydrochloric acid is transformed after 1.5 h into a mixture of compound **1** and **2** (R = H) in a ratio of about 2:1. The same mixture of compounds was also obtained after treatment with hot 10% aqueous NaOH (2 h under reflux), but here compound **2** (R = H) was the major product and only traces of compound **1** were present.

Hydrolytic Decomposition of Compound 7. A solution of formamidine **7** (0.217 g) in water (5 mL) was stirred at 15–20 °C for 6 h and then left to stand at room temperature for 15 h. The separated product was collected (90 mg, 47%) and identified as compound **3** (R = H, R_1 = CHO), mp 156–159 °C (from $CHCl_3$ and petroleum ether). This compound gave: M^+ 190; ^1H NMR ($CDCl_3$) δ 8.55 (dd, H_4), 7.19 (dd, H_5), 8.45 (dd, H_6), 8.93 (s, $H_{5'}$), 9.75 (d, CHO), 10.20 (d, NH) ($J_{5,6}$ = 8.0, $J_{5,7}$ = 2.0, $J_{6,7}$ = 4.5, J_{NHCH} = 10.0 Hz).

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N 29.47. Found: C, 50.84; H, 3.29; N, 29.41.

The above filtrate was extracted with $CHCl_3$ to give compound **1** (51 mg, 43%), identified with the aid of an authentic specimen. The aqueous solution was evaporated to dryness and the residue was crystallized from water to give 3-(formylamino)pyrazolo[3,4-*b*]pyridine (**9**, R = CHO) (2 mg, 1%), identified on the basis of spectroscopic data and comparison with an authentic specimen.

3-(Formylamino)pyrazolo[3,4-*b*]pyridine (9, R = CHO) was synthesized from 3-aminopyrazolo[3,4-*b*]pyridine[13] (67 mg) and formic acid (2 mL of 100%) after 100 min under reflux. The mixture was evaporated to dryness, the residue was treated with ethanol (1 mL), and the product was filtered (37 mg, 46%), mp 228–230 °C. The compound was found to be identical with the above mentioned product and with a hot aqueous $NaHCO_3$ solution was converted back into the starting amino compound. A reaction took place between compound **2** (R = H) and *N*,*N*-dimethylformamide dimethyl acetal. A mixture of the amidoxime **2** (R = H) (0.152 g), *N*,*N*-dimethylformamide dimethyl acetal (0.134 g), and toluene (5 mL) was heated under reflux for 1 h. Upon cooling a few drops of ethanol were added to dissolve the oily layer at the bottom of the flask and the remaining crystals were collected. The product (40 mg, 25%) was identified as 3-(formylamino)pyrazol[3,4-*b*]pyridine (**9**, R = CHO): mp 230–232 °C; M^+ 162; ^1H NMR (CF_3COOD) δ 9.55 (dd, H_4), 7.77 (dd, H_5), 8.90 (dd, H_6), 8.74 (s, CHO) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.8, $J_{4,6}$ = 1.2 Hz).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.70; H, 3.66; N, 34.85.

The above filtrate was evaporated to dryness, the residue was dissolved in $CHCl_3$, and the product precipitated after addition of petroleum ether. The product (17 mg, 11%) was identified as compound **3** (R = R_1 = H) on the basis of comparison with an authentic specimen.

2-Amino-3-(1′,2′,4′-oxadiazolyl-3′)pyridine (3, R = R_1 = H). The formamidine **7** (0.108 g) was treated with dilute hydrochloric acid (1:1) and the mixture was left at room temperature for 17 h. Upon neutralization with solid $NaHCO_3$ the separated product was filtered (38 mg, 47%). The aqueous solution was evaporated and the residue was extracted with hot $CHCl_3$ to give another 29 mg (36%) of the same compound. Upon crystallization from H_2O the product had mp 147–148 °C: M^+ 162; ^1H NMR ($CDCl_3$) δ 8.37 (dd, H_4), 6.75 (dd, H_5), 8.26 (dd, H_6), 8.80 (s, $H_{5'}$), 6.20 (broad s, NH_2) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.76; H, 3.67; N, 34.68.

If compound **3** (R = R_1 = H) was heated in water for 8 h it was transformed into compound **1**.

8-Cyano-*s*-triazolo[1,5-*a*]pyridine (10 R = CN). Method A. Compound **8** (R = R_1 = H) was heated in a tube at 195–205 °C until a melt was obtained and thereafter the tube was connected to the vacuum. The collected sublimate (26 mg, 37%) was identified as compound **10** (R = CN), mp 193–195 °C, and gave: M^+ 144; ^1H NMR (CD_3SOCD_3) δ 8.70 (s, H_2), 9.30 (dd, H_5), 7.36 (dd, H_6), 8.36 (dd, H_7) ($J_{5,6}$ = $J_{6,7}$ = 7.4, $J_{5,7}$ = 1.2 Hz).

Anal. Calcd for $C_7H_4N_4$: C, 55.33; H, 2.80; N, 38.87. Found: C, 56.05; H, 2.90; N, 38.57.

Method B. Compound **11** (R = H) (0.1 g) was heated in vacuo at 200–215 °C and the sublimate was collected to give compound **10** (R = CN) (57 mg, 74%), mp 193–195 °C, identical with the product as obtained in method A. The residue in the tube was identified as cyanuric acid (4 mg).

8-(1′,2′,4′-Oxadiazolyl-3′)-*s*-triazolo[1,5-*a*]pyridine (11, R = H). Compound **8** (R = R_1 = H) (0.6 g) was suspended in poly(phosphoric acid) (7 g) and the reaction mixture was heated 1 h at 90 °C and then 2 h at 110 °C. The cooled reaction mixture was poured on ice and neutralized with $NaHCO_3$. Upon extraction with $CHCl_3$ and removal of the solvent the residue was crystallized from H_2O (0.135 g, 25%), mp 180–185 °C, with conversion into compound **10** (R = CH): M^+ 187; ^1H NMR ($CDCl_3$) δ 8.60 (s, H_2), 8.87 (dd, H_5), 7.26 (dd, H_6), 8.50 (dd, H_7), 9.02 (s, $H_{5'}$) ($J_{5,6}$ = 6.6, $J_{6,7}$ = 5.8, $J_{5,7}$ = 1.2 Hz).

Anal. Calcd for $C_8H_5N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.21; H, 2.87; N, 37.64.

8-(5′-Methyl-1′,2′,4′-oxadiazolyl-3′)-*s*-triazolo[1,5-*a*]pyridine (11, R = Me). Compound **6** (0.345 g) was suspended in acetic anhydride (4 mL) and the mixture was left at room temperature for 2 days. The separated product **8** (R = Me; R_1 = MeCO) (0.175 g, 38%) had mp 147–151 °C (M^+ 261) and was used without purification in the next step. The obtained acetoxy compound (90 mg) was heated in water (5 mL) under reflux for 1 h, the solvent was evaporated, and the residue was crystallized from cyclohexane (12 mg, 17%): mp 188–189 °C; M^+ 201; ^1H NMR (CD_3SOCD_3) δ 8.77 (s, H_2), 8.45 (dd, H_5), 7.49 (dd, H_6), 9.30 (dd, H_7), 2.80 (s, Me) ($J_{5,6}$ = 7.4, $J_{6,7}$ = 6.2, $J_{5,7}$ = 1.0 Hz).

Anal. Calcd for $C_9H_7H_5O$: C, 53.73; H, 3.51. Found: C, 53.74; H, 3.75.

8-Carboxamido-*s*-triazolo[1,5-*a*]pyridine (10, R = $CONH_2$). Compound **11** (R = H) (0.15 g) was treated with aqueous NaOH (5 mL of 5%) and the mixture left at room temperature for 32 h. The separated product was collected and crystallized from H_2O (68 mg, 52%): mp 250–260 °C; M^+ 162; ^1H NMR (CD_3SOCD_3) δ 8.85 (s, H_2), 9.35 (dd, H_5), 7.49 (dd, H_6), 8.47 (dd, H_7) ($J_{5,6}$ = 7.5, $J_{6,7}$ = 7.0, $J_{5,7}$ = 1.5 Hz).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73. Found: C, 52.12; H, 4.06.

4-Aminopyrido[2,3-*d*]pyrimidine (12, R = H). Method A. A mixture of 2-amino-3-cyanopyridine (1 g) and triethyl orthoformate (10 mL) was heated under reflux for 8 h. The solvent was evaporated and the residue dissolved in $CHCl_3$, charcoaled, and filtered into petroleum ether. Upon cooling to −80 °C 2-(ethoxymethyleneamino)-3-cyanopyridine was separated and collected (0.685 g, 47%), mp 53–56 °C; M^+ 175. This compound (0.5 g) was dissolved in methanol (200 mL) saturated with ammonia. The mixture was left at room temperature for 24 h, the solvent was removed, and the residue (0.345 g, 83%) was crystallized from ethanol, mp 305–310 °C dec (lit.[2] mp 297–300 °C). This compound gave: M^+ 146; ^1H NMR (CD_3SOCD_3, 90 °C) δ 8.60 (s, H_2), 8.71 (dd, H_5), 7.47 (dd, H_6), 9.01 (dd, H_7), 7.85 (broad s, NH_2) ($J_{5,6}$ = 8.2, $J_{6,7}$ = 4.5, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.60; H, 4.11; N, 38.15.

Method B. The *N*-oxide (**4**, R = H) (0.1 g) was suspended in water (5 mL) and under stirring an aqueous solution of $TiCl_3$ (10%) was added dropwise until the color of the reagent persisted. The solution was treated with solid $NaHCO_3$ to destroy the reagent and the mixture was evaporated to dryness. The residue was extracted with hot absolute ethanol and the product crystallized from ethanol (16 mg, 18%). The compound was identical with the product of method A.

4-[(Hydroxyimino)methyleneamino]pyrido[2,3-*d*]pryimidine (12, R = CH=NOH). The amino compound (**12**, R = H) (0.625 g) and *N*,*N*-dimethylformamide dimethyl acetal (1 mL) were heated under reflux for 2 h. Excess of the reagent was distilled in vacuo and the residue was crystallized from $CHCl_3$ and petroleum ether (0.715, 83%) to give the 4-[(*N*,*N*-dimethylamino)methyleneamino] derivative: mp 164–166 °C; M^+ 201; ^1H NMR ($CDCl_3$) δ 8.87 and 8.96 (s, H_2 and CH), 8.82 (dd, H_5), 7.38 (dd, H_6), 9.09 (dd, H_7), 3.23 and 3.26 (s, NMe_2) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 4.0, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81. Found: C, 59.46; H, 5.83; N, 34.70.

This compound (0.432 g) was then treated with hydroxylamine hydrochloride (0.21 g) in methanol (10 mL) and the mixture was stirred for 6 h at room temperature. The product was collected (0.307 g, 76%). For analysis it may be crystallized from methanol, but it is slowly decomposed, mp over 320 °C.

Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73. Found: C, 50.81; H, 3.75.

The above [(*N*,*N*-dimethylamino)methyleneamino] derivative is decomposed either in hot water or in the presence of base or acid into the amino compound (**12**, R = H).

4-Amino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (13). Method A. The amino compound **12** (R = H) (60 mg) and palladized

charcoal (50 mg of 10%) were suspended in methanol (30 mL) and the mixture was shaken in an atmosphere of hydrogen for 2 days. Upon filtration and evaporation of the solvent the product was crystallized from methanol and diethyl ether (49 mg, 80%): mp 233–236 °C; M^+ 150; ^1H NMR (CD_3SOCD_3) δ 7.74 (s, H_2), 2.33 (m, 5-CH_2), 1.78 (m, 6-CH_2), 3.20 (m, 7-CH_2).

Anal. Calcd for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.95; H, 6.92; N, 37.51.

Method B. In a similar manner the compound was obtained by hydrogenation of the *N*-oxide (**4**, R = H) in 82% yield and was found to be identical with the product obtained in method A.

Method C. By the same catalytic hydrogenation (1 atm) the hydroxylamino compound **14** was transformed into **13** in 54% yield.

4-(Hydroxylamino)pyrido[2,3-*d*]pyrimidine (14, R = R_1 = H). The *N*-oxide **4** (R = H) 1 g) was suspended in water (20 mL) and the mixture heated under reflux for 7 h. Upon cooling the separated product was collected (0.38 g, 38%) and crystallized from water, mp 226–227 °C. This compound gave: M^+ 162; ^1H NMR (CD_3SOCD_3) δ 7.84 (s, H_2), 8.25 (dd, H_5), 7.35 (dd, H_6), 8.70 (dd, H_7), 10.60 and 11.1 (broad s, NH, OH) ($J_{5,6}$ = 8.5, $J_{6,7}$ = 5.0, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.60; H, 3.87; N, 34.53.

The filtrate from the above reaction was evaporated to dryness and extracted with hot $CHCl_3$ to give 2-amino-3-cyanopyridine (0.1 g, 13%). The $CHCl_3$ insoluble residue was crystallized from H_2O and some more hydroxylamino compound (95 mg, 10%) was obtained.

The hydroxylamino compound forms a hydrochloride salt, mp 237–242 °C dec from methanol and ether, and with 10% NaOH it is transformed at room temperature into 2-aminonicotinic acid (**16**). However, with hot dilute hydrochloride acid (1:1) the compound **14** (R = R_1 = H) is in 10 min transformed into **15**, identified with the aid of an authentic sample.[14]

4-(Acetoxyamino)-2-methylpyrido[2,3-*d*]pyrimidine (14, R = MeCO, R_1 = Me). Method A. A mixture of the amidoxime **2** (R = H) (0.152 g) and acetic anhydride (2 mL) was heated under reflux for 75 min. The solvent was evaporated and the residue was suspended in ethyl acetate (2 mL). Upon cooling, the product was collected and crystallized from ethyl acetate (56 mg, 26%): mp 210–212 °C; M^+ 218; ^1H NMR (CD_3SOCD_3) δ 8.28 (dd, H_5), 7.32 (dd, H_6), 8.63 (dd, H_7), 2.18 and 2.33 (s, Me and COMe) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 2.0 Hz).

Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.10; H, 4.70; N, 25.73.

Method B. In a similar manner the compound was obtained from the acetoxy derivative **2** (R = MeCO) and acetic anhydride in 18% yield.

2-(Acetylamino)-3-cyanopyridine (17). A mixture of compound **1** (1.2 g) and acetic anhydride (6 mL) was heated under reflux for 2 h. The solvent was evaporated, the residue was treated with ethyl acetate (4 mL), and the insoluble part was filtered. The product (1.1 g, 68%) was recrystallized from ethyl acetate: mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 8.04 (dd, H_4), 7.26 (dd, H_5), 8.63 (dd, H_6), 2.36 (s, Me), 8.95 (s, NH) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz.

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.64; H, 4.40; N, 25.99.

4-Amino-2-methylpyrido[2,3-*d*]pyrimidine 3-Oxide (18). A mixture of the above compound **17** (0.161 g), hydroxylamine hydrochloride (0.2 g), toluene (10 mL), and 5 drops of pyridine was heated under reflux for 1 h, absolute ethanol (5 mL) was added, and heating was continued for 1 h. Upon cooling, the product was collected, dissolved in water (1 mL), and neutralized with $NaHCO_3$ and the separated product (23 mg, 13%) was filtered. The toluene solution was evaporated in vacuo, the residue was neturalized with aqueous $NaHCO_3$, and the mixture was evaporated to dryness. Upon extraction with hot ethanol the obtained extract was evaporated to 1–2 mL, a few drops of water were added, and upon chilling the product filtered (21 mg, 12%). Compound **18** had mp over 310 °C; M^+ 176.

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.23; H, 4.68; N, 32.11.

2-[(Methoxyimino)methyleneamino]-3-cyanopyridine (19). A solution of compound **5** (0.875 g) in methanol (15 mL) was treated with *O*-methylhydroxylamine hydrochloride (4.2 g) in methanol (5 mL). Upon standing at room temperature for 2 h the solvent was evaporated and the residue treated with iced water (30 mL). The product was collected and crystallized from water (0.68 g, 77%): mp 104–105 °C; M^+ 176; ^1H NMR (CD_3SOCD_3) δ 8.10 (dd, H_4), 7.05 (dd, H_5), 8.40 (dd, H_6), 7.84 (s, CH), 3.81 (s, OMe) ($J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: 54.95; H, 4.55; N, 31.42.

Registry No.—**1**, 24517-64-4; **2**, R = H, 68640-74-4; **2**, R = COMe, 68640-75-5; **3**, R = Me; R_1 = H, 68640-76-6; **3**, R = Me; R_1 = CHO, 68640-82-4; **3**, R = R_1 = H, 68640-84-6; **3**, R = H; R_1 = CHO, 68640-85-7; **4**, R = H, 68640-78-8; **5**, 68640-77-7; **6**, 68640-79-9; **7**, 68640-81-3; **8**, R = R_1 = H, 68640-80-2; **8**, R = Me; R_1 = MeCO, 69277-98-1; **9**, R = CHO, 68640-83-5; **9**, R = H 6752-16-5; **10**, R = CN, 69277-99-2; **10**, R = $CONH_2$, 69278-00-8; **11**, R = H, 69278-01-9; **11**, R = Me, 69278-02-0; **12**, R = H, 37538-65-1; **12**, R = CH=NOH, 69278-03-1; **13**, 69278-04-2; **14**, R = R_1 = H, 69278-05-3; **14** (R = R_1 = H) HCl, 69278-06-4; **14**, R = MeCO; R_1 = Me, 69278-07-5; **15**, 24410-19-3; **16**, 5345-47-1; **17**, 69278-08-6; **18**, 69278-09-7; **19**, 69278-10-0; 2-(ethoxymethyleneamino)-3-cyanopyridine, 69278-11-1; 2,3-diaminopyridine, 452-58-4; hydroxylamine, 7803-49-8; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; formic acid, 64-18-6; hydroxylamine hydrochloride, 5470-11-1; *O*-methylhydroxylamine hydrochloride, 593-56-6; 4-[(*N,N*-dimethylamino)methyleneamino]pyrido[2,3-*d*]-pyrimidine, 69278-12-2.

References and Notes

(1) Heterocycles 182. Part of this paper appeared as a short communication in *Heterocycles*, **9**, 1327 (1978).
(2) M. Debeljak-Šuštar, B. Stanovnik, M. Tišler, and Z. Zrimšek, *J. Org. Chem.*, **43**, 393 (1978).
(3) The X-ray structure determination was performed by I. Leban and full details will be published elsewhere.
(4) L. B. Clapp in "Advances in Heterocyclic Chemistry", Vol. 20, A. R. Katritzky and A. J. Boulton Ed., Academic Press, New York, 1976, p 65.
(5) F. Eloy, R. Lenaers, and C. Moussebois, *Chem. Ind. (London)*, 292 (1961).
(6) C. Moussebois, R. Lenaers, and F. Eloy, *Helv. Chim. Acta*, **45**, 446 (1962).
(7) M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **82**, 1148 (1960).
(8) C. Ainsworth, W. E. Buting, J. Davenport, M. E. Callender, and M. C. McCowen, *J. Med. Chem.*, **10**, 208 (1967).
(9) K. Kasuga, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, **94**, 945 (1974).
(10) S. Polanc, B. Verček, B. Šek, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **39**, 2143 (1974).
(11) K. Babič, S. Molan, S. Polanc, B. Stanovnik, J. StresBratoš, M. Tišler, and B. Verček, *J. Heterocycl. Chem.*, **13**, 487 (1976).
(12) J. Bradač, Z. Furek, D. Janežič, S. Molan, I. Smerkolj, B. Stanovnik, M. Tišler, and B. Verček, *J. Org. Chem.*, **42**, 4197 (1977).
(13) T. L. P. Hatt and J. D. R. Vaas, *Chem. Commun.*, 293 (1966).
(14) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955).