PYRAZOLO[1,5-*a*]PYRIDO[3,4-*e*]PYRIMIDINE: A NEW HETEROCYCLIC RING SYSTEM

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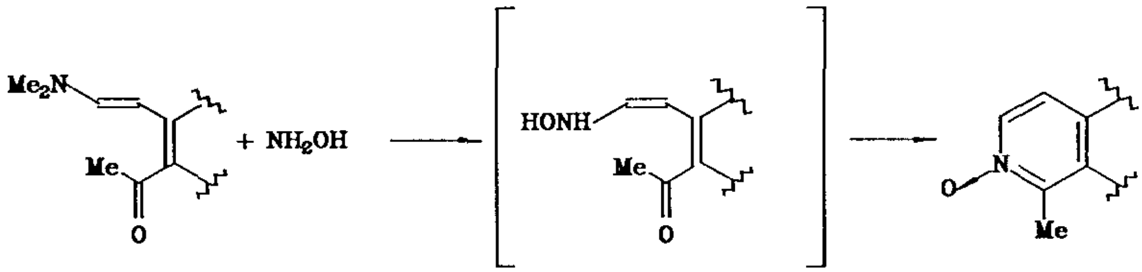
Abstract - Treatment of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidine (**1**) with hydroxylamine afforded in high yields the pyridine *N*-oxide (**2**), a key intermediate in the preparation of new functionalized pyrazolo[1,5-*a*]pyrido[3,4-e]pyrimidines as well as in the synthesis of the parent ring system (**8**).

Previous studies in our laboratories led us to describe a new pathway to various pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines;[1] following our interest on hetero-condensed five-membered heterocycles,[2] we wish to report here the synthesis of the parent ring system together with some new derivatives.

After compound (**1**) became recently available,[1] we decided to investigate its behavior toward hydroxylamine, in an effort to expand the scope of the above reaction. Like ammonia, a nucleophile such hydroxylamine is likely to show a similar behavior on an enamine moiety (**A**) giving rise to a *cis*-intermediate (**B**) having the requisite stereochemical configuration to cyclize to the pyridine *N*-oxide (**C**) as outlined in Scheme 1. In fact, refluxing compound (**1**)[1] with hydroxylamine hydrochloride in acetic acid-sodium acetate afforded nearly quantitatively the *N*-oxide (**2**), thus providing an easy and direct route to this compound which could be also prepared in much lower yield from the derivative (**7**) and peracetic acid (see Experimental). ^{1}H-Nmr data of compound (**2**) agree well with those reported for similar compounds;[3] in particular, besides the expected low frequency shift observed for H-8, it is worthy to note the effect of the electronegative oxygen atom on the vicinal coupling between H-8 and H-9 which,



A B C

Scheme 1

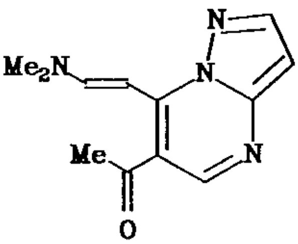
according to the findings of Castellano and Kostelnik,[4] increases on going from compound (**7**) to the *N*-oxide (**2**) (5.8 Hz[1] vs 7.4 Hz).

On treatment with acetic anhydride 6-methylpyrazolo[1,5-*a*]pyrido[3,4-e]pyrimidine-7-oxide (**2**) underwent the well-known side-chain acyloxylation reaction[5] to give the derivative (**3**) (Scheme 2) whose structure was derived from spectroscopic data. In particular, the complete attribution of carbon resonances was achieved both by an heteronuclear COSY experiment which with the proton assignments firmly established allowed the distinction of the various C-H signals, and on the basis of the fully coupled ^{13}C-nmr spectrum. A careful examination of the latter endorsed the distinction between the quaternary C-3a and C-9a showing for the former a coupling of 13.8 Hz; such a coupling constant, absent in the multiplet at δ 141.01 ppm, must be ascribed to the C3a-H5 pathway as confirmed by a long-range HETCOR experiment.

Table 1. ^{13}C-Nmr data

Compd.	C-2	C-3	C-3a	C-5	C-5a	C-6	C-8	C-9	C-9a	Others
3	144.71	101.24	145.99	148.02	112.20	155.71	151.39	108.94	141.01	170.31(s, CO) , 64.67 (t, OCH_2), 20.80(q, Me)
4	144.81	101.32	146.38	146.73	110.26	158.96	150.38	108.32	140.91	61.54(t, OCH_2)
6	144.97	101.67	145.74	149.25	113.25	147.96	150.80	111.75	141.46	164.74(s, CO), 53.63(t, OMe)
8	144.51	101.05	146.42	150.14	113.91	151.07	152.49	108.41	140.30	

Various attempts to oxidize compound (**7**) failed to give the desired acid (**5**) resulting only in products deriving from ring opening. On the other hand, compound (**3**) underwent rapid deacylation with alkali to give the hydroxy derivative (**4**) which could be oxidized nearly quantitatively (93%) by a dilute permanganate solution to the requisite carboxylic acid (5). This latter has been then converted into the corresponding methyl ester (6) by treatment with ethereal diazomethane.



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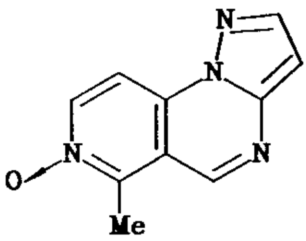

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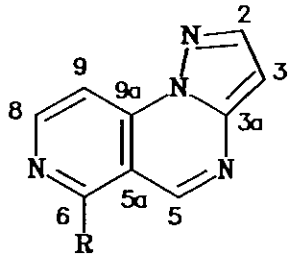

3 R = CH_2OCOMe

4 R = CH_2OH

5 R = CO_2H

6 R = CO_2Me

7 R = Me

8 R = H

Scheme 2

As expected, the acid (5) could be easily decarboxylated by heating near its melting point to the parent ring system pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine (8) whose structure was established on the basis of analytical and spectroscopic evidence; to this end, a detailed analysis of the ^{1}H- and ^{13}C-nmr spectra was undertaken. The proton spectrum (Table 2) was unambiguous except for the assignment of H-5 and H-6 both showing a small coupling with H-9 (which appeared as a doublet of pseudo triplets), removed by selective irradiation of this latter. This ambiguity could be removed utilizing the decoupled and coupled carbon spectra; the methine ^{13}C resonances were easily recognized and the signals of C-8, C-6, C-5,and C-2 were identified on the basis of chemical shift considerations between δ 153 and 143 ppm. Their assignment was then achieved by means of long-range couplings and of an HETCOR experiment. In fact, although the coupled spectrum did not allow the relative assignment, it made possible the distinction between the resonances of C-8 and C-6 and those of C-5 and C-2; the two doublets at higher frequency (^1J = 186.0 and 182.2 Hz) showed a fine structure of doublet of doublets and this pattern revealed, besides a small coupling (J = 2.4 and 2.2 Hz), a large, diagnostic one (J = 12.4 and 11.6 Hz) through a nitrogen atom which can be attributed only to $^3J_{C8\text{-}H6}$ and $^3J_{C6\text{-}H8}$. Now, being H-8 and H-2 firmly

Table 2. ^{1}H-Nmr data for compounds **2-6** and **8**

Compd.	δ_H*(300 MHz, CDCl₃)*
2	2.948(s, 3H, 6-Me), 6.881(d, J_{H3-H2} = 2.2 Hz, 1H, H-3), 8.161(d, J_{H2-H3} = 2.2 Hz, 1H, H-2), 8.239(dd, J_{H9-H8} = 7.4 Hz, J_{H9-H5} = 0.8 Hz, 1H, H-9), 8.590(d, J_{H8-H9} = 7.4 Hz, 1H, H-8), and 9.011(d, J_{H5-H9} = 0.8 Hz, 1H, H-5)
3	2.153(s, 3H, CO*Me*) 5.680(s, 2H, OCH_2), 6.883(d, J_{H3-H2} = 2.2 Hz, 1H, H-3), 8.175(d, J_{H2-H3} = 2.2 Hz, 1H, H-2), 8.276(dd, J_{H9-H8} = 5.8 Hz, J_{H9-H5} = 0.8 Hz, 1H, H-9), 8.882(d, J_{H8-H9} = 5.8 Hz, 1H, H-8), and 9.183(d, J_{H5-H9} = 0.8 Hz, 1H, H-5)
4	4.504(t exch., J_{OH-CH_2} = 4.2 Hz, 1H, OH), 5.297(d, J_{CH_2-OH} = 4.2 Hz, 2H, CH_2), 6.893(d, J_{H3-H2} = 2.1 Hz, 1H, H-3), 8.187(d, J_{H2-H3} = 2.1 Hz, 1H, H-2), 8.243(ddt, J_{H9-H8} = 5.8 Hz, J_{H9-H5} = 0.8 Hz, J_{H9-CH_2} = 0.8 Hz, 1H, H-9), 8.846(d, J_{H8-H9} = 5.8 Hz, 1H, H-8), and 9.013(d, J_{H5-H9} = 0.8 Hz, 1H, H-5)
5	6.948(d, J_{H3-H2} = 2.1 Hz, 1H, H-3), 8.209(d, J_{H2-H3} = 2.1 Hz, 1H, H-2), 8.611(dd, J_{H9-H8} = 5.7 Hz, J_{H9-H5} = 0.8 Hz, 1H, H-9), 8.884(d, J_{H8-H9} = 5.7 Hz, 1H, H-8), and 10.417(d, J_{H5-H9} = 0.8 Hz, 1H, H-5)
6	4.104(s, 3H, OMe), 6.868(d, J_{H3-H2} = 2.1 Hz, 1H, H-3), 8.147(d, J_{H2-H3} = 2.1 Hz, 1H, H-2), 8.446(dd, J_{H9-H8} = 5.6 Hz, J_{H9-H5} = 0.8 Hz, 1H, H-9), 8.953(d, J_{H8-H9} = 5.6 Hz, 1H, H-8), and 9.814(d, J_{H5-H9} = 0.8 Hz, 1H, H-5)
8	6.845(d, J_{H3-H2} = 2.1 Hz, 1H, H-3), 8.148(d, J_{H2-H3} = 2.1 Hz, 1H, H-2), 8.215(ddd, J_{H9-H8} = 5.8 Hz, J_{H9-H6} = 0.8 Hz, J_{H9-H5} = 0.8 Hz, 1H, H-9), 8.910(d, J_{H8-H9} = 5.8 Hz, 1H, H-8), 8.928(d, J_{H5-H9} = 0.8 Hz, 1H, H-5), and 9.210(d, J_{H6-H9} = 0.8 Hz, 1H, H-6)

assigned from the proton spectrum, the carbon resonances were unambiguously established and it became possible to make unequivocal attribution of the H-5 and H-6 proton signals by means of an HETCOR experiment. Finally, the quaternary carbon assignments were based both on chemical shift arguments (C-5a) and the magnitude of long-range couplings as previously described for C-3a and C-9a in compound (**3**).

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were measured for potassium bromide discs with a Perkin-Elmer 283 spectrophotometer. ^{1}H- And ^{13}C-nmr spectra were recorded in $CDCl_3$ on a Varian VXR-300 instrument; chemical shifts are reported in ppm high frequency from tetramethylsilane as secondary reference standard and coupling constants in Hz. Silica gel plates

(Merck F_{254}) were used for analytical tlc. Solvents were removed under reduced pressure.

6-Methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine-7-oxide **2**

a)The enamine (**1**) (2.3 g; 10 mmol) and hydroxylamine hydrochloride (0.7 g; 10.1 mmol) were refluxed under stirring for 1.5 h in acetic acid (30 ml) containing anhydrous sodium acetate (2 g; 24.4 mmol). The orange residue left by removal of the solvent was treated with water and filtered to afford compound (**2**) as yellow crystals (1.81 g, 91%), mp 269-270 °C (recrystallized from water). Ir ν_{max}: 3080, 3060, 1555, 1290, 1245, and 830 cm^{-1}. Anal. Calcd for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 60.08; H, 4.00; N, 27.85.

b)Hydrogen peroxide (30%; 10 ml) was added to a solution of compound (**7**) (0.18 g; 1 mmol) in acetic acid (10 ml) and the mixture was kept at room temperature for 3 days. After concentration the orange precipitate was filtered, dried, and recrystallized from water to give the *N*-oxide (**2**) (0.1 g, 50%), identical (mp, ir, and ^{1}H-nmr spectra) with the material reported above.

6-Acetoxymethylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine **3**

The oxide (**2**) (2 g; 10 mmol) was refluxed with acetic anhydride (5 ml) for 5 min. After concentration of the mixture, dilution with ethanol afforded compound (**3**) as a yellowish solid (1.7 g, 70%), mp 113-114 °C (recrystallized from *i*-PrOH). Ir ν_{max}: 3140, 1738, 1605, and 1250 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.24; H, 4.12; N, 23.07.

6-Hydroxymethylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine **4**

Compound (**3**) (2.68 g; 11.1 mmol) in methanol (50 ml) was added to a solution of freshly prepared sodium methoxide (0.25 g of Na in 70 ml of MeOH) and the mixture was stirred at room temperature for 30 min. After neutralization with acetic acid the white solid which separated was filtered off and dried to give the derivative (**4**) (1.9 g); evaporation to dryness of the mother liquors afforded a second crop of the same material (ir and ^{1}H-nmr) (0.23 g, overall 96%). An analytical sample (white needles) obtained by recrystallization from EtOH melted at 188-189 °C. Ir ν_{max}: 3300br(OH), 3140, 3100, 3030, 1600, and 1020 cm^{-1}. Anal. Calcd for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.92; H, 4.08; N, 27.81.

Pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidin-6-carboxylic Acid **5**

Compound (**4**) (1 g; 5 mmol) was suspended in water (5 ml) and an aqueous solution of potassium permanganate (2.6% w/v, 40 ml) was added dropwise. The mixture was stirred at 40-50 °C for 1 h and filtered. Acidification with hydrochloric acid (6 N, pH 2) precipitated the acid (**5**) as a yellowish solid (1 g, 93%), mp 186 °C (decomp), which was not further purified. Ir ν_{max}: 3500-2200vbr (CO_2H), 1740, and 1605 cm^{-1}. Anal. Calcd for $C_{10}H_6N_4O_2$: C, 56.08; H, 2.82; N, 26.16. Found: C, 56.32; H, 2.70; N, 26.35.

Methyl Pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidin-6-carboxylate **6**

A suspension of compound (**5**) (0.64 g; 3 mmol) in ether (40 ml) was treated with an excess of ethereal diazomethane and set aside overnight. The solid formed (0.6 g, 88%) was separated by filtration and consisted almost exclusively [tlc (chloroform-methanol 20:1 v/v) and ^{1}H-nmr] of the ester (**6**) with a small amount of the starting material; an analytical sample obtained by recrystallization from MeOH melted at 168-169 °C. Ir ν_{max}: 3130, 3100, 3080, 2960, 1730, 1600, and 1590 cm^{-1}. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.81; H, 3.62; N, 24.70.

Pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine **8**

The acid (**6**) (0.4 g; 1.9 mmol) was deposited in a sublimation apparatus which was dipped in an oil bath at 200 °C. When the inner temperature reached 185 °C, the sample softened and decarboxylation slowly occurred, giving rise to a yellowish fluid. After cooling, the solid mass was sublimed at 150 °C/20 mmHg to afford compound (**8**) as white crystals (0.23 g, 72%), mp 182-183 °C. Ir ν_{max}: 3110, 3080, 1610, and 1600 cm^{-1}. Anal. Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.92. Found: C, 63.30; H, 3.51; N, 32.64.

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