Synthesis of 3-Aryl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridines and 3-Aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines

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The synthesis and characterization of a number of 3-aryl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridines and 3-aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines from common precursors, 5-benzoyl-4-chloro-1*H*-pyrazolo-[3,4-*b*]pyridines, has been described. The structures were determined by unambiguous chemical synthesis and by isolation and ^{13}C nmr analysis of some key, isolated, intermediates. The ability of these compounds to displace [3*H*]flunitrazepam from CNS binding sites was also observed.

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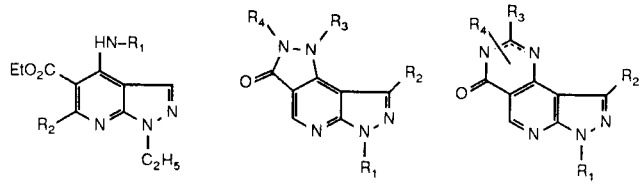
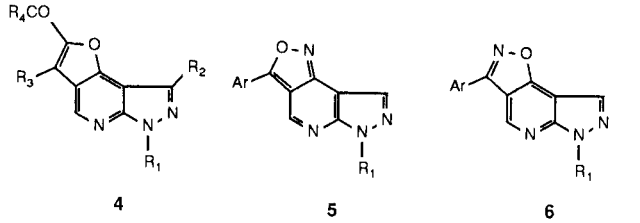
A number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity. Among these compounds are etazolate (**1a**) [1], tracazolate (**1b**) [2], and cartazolate (**1c**) [3]. Also displaying CNS activity are the related 1*H*,6*H*-dipyrazolo[3,4-*b*:3',4'-*d*]pyridin-3-ones **2** [4], the dihydro-4*H*-pyrazolo[4',3':5,6]pyrido[4,3-*d*]pyrimidin-4-ones **3** [5], and the furo[2,3-*d*]pyrazolo[3,4-*b*]pyridines **4** [6]. This information, taken together with our continuing interest in the biological properties of fused arylisoxazoles [7], suggested that the 3-aryl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridine **5** and 3-aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridine **6** ring systems might be biologically interesting as well as synthetically challenging. This paper describes the first examples of the ring systems **5** and **6**.



1a, R_1 = N=C(CH$_3$)$_2$, R_2 = H
1b, R_1 = n-C$_4$H$_9$, R_2 = CH$_3$
1c, R_1 = n-C$_4$H$_9$, R_2 = H

2 3



4 5 6

The synthesis of **5** and **6** is depicted in Scheme I. The substituted 5-benzoyl-4-chloro-1*H*-pyrazolo[3,4-*d*]pyridines **8** served as common intermediates in the synthetic pathways leading to both **5** and **6**. Compounds **8a-k** were conveniently prepared by the reaction of 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl chloride (**7**) [8] with substituted phenyl Grignard reagents at low temperature in tetrahydrofuran, as described by Sato *et al.* [9]. The preparation of analogous 5-benzoyl-4-methoxy-1*H*-pyrazolo-[3,4-*b*]pyridines has been described by Denzel and Hoehn [10], using the cadmium-Grignard method; we found the method of Sato *et al.* to be more convenient, however. The properties of compounds **8a-k** are given in Table 1.

We recently reported a synthesis of 1,2-benzisoxazoles by the treatment of 2-halobenzophenones with the potassium anion of acetone oxime and subsequent acid catalyzed transoximation of the intermediate [(isopropylidene)-amino]oxy compounds [11]. The application of these conditions to **8a** gave the [(isopropylidene)amino]oxy derivative **9a** which, upon acid catalyzed ring closure, gave 6-ethyl-3-phenyl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridine (**6a**) unambiguously. The compounds **6** synthesized by this route were always contaminated with some of the corresponding 5-benzoyl-1-ethyl-4-hydroxy-1*H*-pyrazolo-[3,4-*b*]pyridines **11**. This side reaction is due, possibly, to the acid catalyzed attack of water at the labile 4-position of **9**, initiated by protonation of the pyridine nucleus.

For this reason, an alternate route to **6** was developed, using the hydroxyketones, **11**, as intermediates. Treatment of **8a** with aqueous potassium hydroxide in dimethyl sulfoxide gave a good yield of **11a**, which, when reacted with hydroxylamine hydrochloride in refluxing pyridine, gave a product that was identical to the **6a** isolated by the previous method. By varying the experimental conditions (see Experimental section), the isomeric hydroxyloximes **12** and **13** [12] were isolated and then subsequently converted to **6a** under the reaction conditions, further substantiating the structure of **6a**. The 3-aryl-6-ethyl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines **6b-i** were synthesized by this latter method; their properties are given in Table II. Hydroxyketones **11b-i**, the precursors to compounds **6b-i**, were used without recrystallization.

Treatment of **8a** with hydroxylamine hydrochloride in refluxing acetic acid containing a little concentrated hydrochloric acid gave 6-ethyl-3-phenyl-6*H*-isoxazolo[3,4-*d*]-pyrazolo[3,4-*b*]pyridine, **5a**. The structure of **5a** was established by comparison with **6a**, whose synthesis from the

Scheme 1

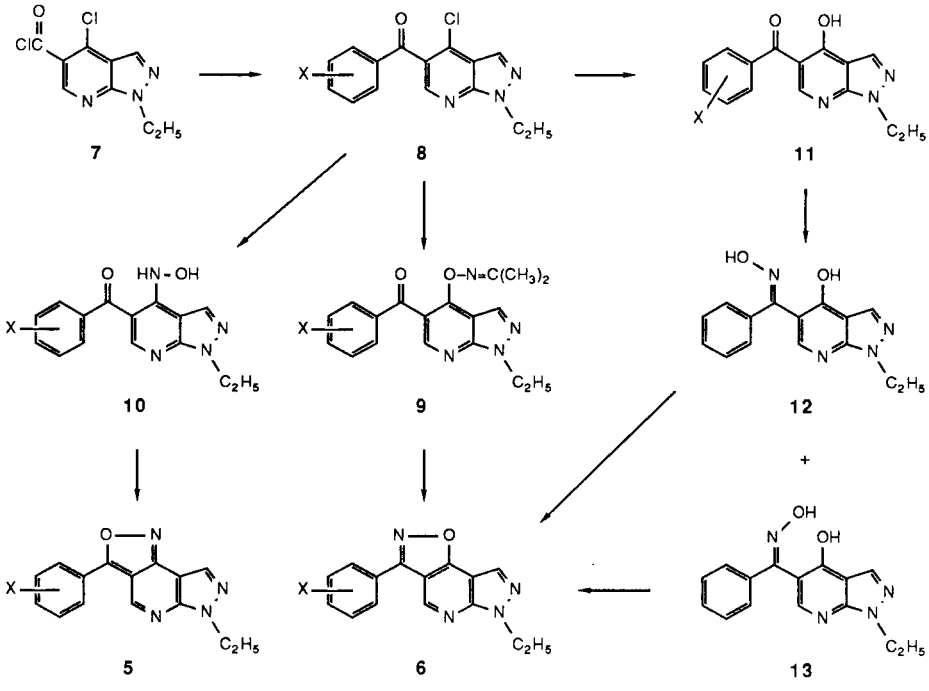
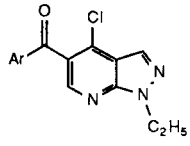


Table I

5-Benzoyl-4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridines



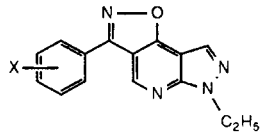
Compound	Ar	Mp°C	Yield %	Molecular Formula	Analysis % Calcd. (Found) C	H	N
8a	C_6H_5	138-140 [a]	74	$C_{15}H_{12}ClN_3O$	—	—	—
8b	3-ClC_6H_4	88-90 [b]	58	$C_{15}H_{11}Cl_2N_3O$	56.27 (56.47	3.46 3.65	13.13 13.05)
8c	4-ClC_6H_4	133-134 [b]	38	$C_{15}H_{11}Cl_2N_3O$	56.27 (55.97	3.46 3.50	13.13 13.25)
8d	3-FC_6H_4	123-125 [c]	66	$C_{15}H_{11}FClN_3O$	59.31 (59.34	3.65 3.66	13.84 13.94)
8e	4-FC_6H_4	134-135 [c]	39	$C_{15}H_{11}FClN_3O$	59.31 (59.38	3.65 3.72	13.84 13.87)
8f	2-$CH_3C_6H_4$	145-146 [c]	76	$C_{16}H_{14}ClN_3O$	64.10 (64.48	4.71 4.75	14.02 14.43)
8g	3-$CH_3C_6H_4$	100-102 [c]	80	$C_{16}H_{14}ClN_3O$	64.10 (64.59	4.71 4.74	14.02 14.36)
8h	4-$CH_3C_6H_4$	105-106 [c]	59	$C_{16}H_{14}ClN_3O$	64.10 (63.80	4.71 4.69	14.02 14.25)
8i	2-$CH_3OC_6H_4$	96-98 [d]	76	$C_{16}H_{14}ClN_3O_2$	60.86 (60.42	4.47 4.52	13.31 13.49)

8j	3-$CH_3OC_6H_4$	72-74 [b]	71	$C_{16}H_{14}ClN_3O_2$	60.86 (60.85	4.47 4.67	13.31 13.34)
8k	4-$CH_3OC_6H_4$	144-145 [c]	63	$C_{16}H_{14}ClN_3O_2$	60.86 (60.86	4.47 4.47	13.31 13.56)

[a] Lit [10] mp 140-142°. [b] Recrystallized from hexane. [c] Recrystallized from methanol. [d] Recrystallized from cyclohexane.

Table II

3-Aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines



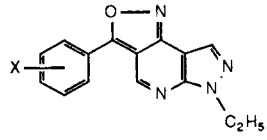
Compound	X	Mp°C	Yield % [a]	Molecular Formula	Analysis % Calcd. (Found) C	H	N
6a	H	151-153 [b]	73	$C_{15}H_{12}N_4O$	68.17 (68.23	4.58 4.65	21.20 21.15)
6b	3-Cl	178-179 [c]	45	$C_{15}H_{11}ClN_4O$	60.31 (60.10	3.71 3.68	18.76 18.89)
6c	4-Cl	195-197 [d]	44	$C_{15}H_{11}ClN_4O$	60.31 (60.68	3.71 3.83	18.76 18.64)
6d	3-F	136-137 [e]	78	$C_{15}H_{11}FN_4O$	63.82 (63.92	3.93 4.05	19.85 19.90)
6e	4-F	175-176 [f]	86	$C_{15}H_{11}FN_4O$	63.82 (63.80	3.93 3.92	19.85 20.10)
6f	3-CH_3	122-123 [e]	63	$C_{16}H_{14}N_4O$	69.05 (68.78	5.07 5.19	20.13 20.24)
6g	4-CH_3	173-175 [g]	87	$C_{16}H_{14}N_4O$	69.05 (68.88	5.07 5.14	20.13 20.23)
6h	3-CH_3O	130-131 [e]	83	$C_{16}H_{14}N_4O_2$	65.29 (65.16	4.79 4.75	19.04 19.15)
6i	4-CH_3O	156-157 [g]	79	$C_{16}H_{14}N_4O_2$	65.29 (64.87	4.79 4.84	19.04 19.08)

[a] Yield of **6a** calculated from **9**. Yields of **6b-i** calculated from **11b-i**. [b] Recrystallized from: methanol/ethyl acetate. [c] ethyl acetate. [d] hexane. [e] methanol. [f] ethyl acetate/hexane. [g] dichloromethane/hexane.

[(isopropylidene)amino]oxy compounds was unambiguous. The other 3-aryl-6-ethyl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]-pyridines, **5b-k**, were synthesized in like manner. Their properties are given in Table III. In one instance, under less vigorous experimental conditions (see Experimental section), a compound of molecular weight 282 was isolated whose ^1H nmr fit the benzoyl hydroxyamine, **10**. In recognition of the possibility that **10** was one of the isomeric 5-benzoyl-1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine oximes (**12** or **13** [13]), ethyl 1-ethyl-4-hydroxyamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**14**) was synthesized so that it and **10** could be compound by ^{13}C nmr with the corresponding 4-hydroxy compounds, **11a** and ethyl 1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate [8]. The results of this study are shown in Table IV. It is clear that the structures of **10** and **14** are as assigned: the ester and ketone carbonyls are clearly present in each (166.9 ppm and 195.5 ppm, respectively) and the chemical shift of C-4 is consistent with a change from *O*- to *N*-substitution (170.5 ppm going to 151.0 ppm and 166.7 ppm going to 150.8 ppm [14]). The conversion of **10** to **5a** under acid catalyzed conditions further substantiated the structure of **5a**.

Table III

3-Aryl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridines

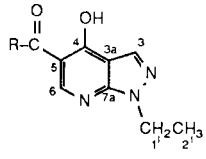


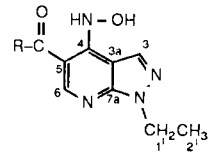
Compound	X	Mp°C	Yield %	Molecular Formula	Analysis % Calcd. (Found) C	H	N	[3H]Flunitrazepam Binding Assay IC_{50}, *M* [f]
5a	H	175-176 [a]	52	$C_{15}H_{12}N_4O$	68.17 (68.04	4.58 4.57	21.20 20.97)	4.7×10^{-7}
5b	3-Cl	207-209 [b]	49	$C_{15}H_{11}ClN_4O$	60.31 (60.06	3.71 3.77	18.86 18.68)	4.4×10^{-6}
5c	4-Cl	248-250 [c]	43	$C_{15}H_{11}ClN_4O$	60.31 (60.16	3.71 3.73	18.76 19.03)	4.0×10^{-7}
5d	3-F	183-184 [b]	74	$C_{15}H_{11}FN_4O$	63.82 (63.75	3.93 4.05	19.85 19.97)	2.3×10^{-6}
5e	4-F	222-223 [d]	52	$C_{15}H_{11}FN_4O$	63.82 (64.07	3.93 4.07	19.85 20.13)	5.3×10^{-7}
5f	2-CH_3	170-171 [b]	44	$C_{16}H_{14}N_4O$	69.05 (68.94	5.07 5.15	20.13 20.17)	$>10^{-5}$
5g	3-CH_3	180-181 [b]	75	$C_{16}H_{14}N_4O$	69.05 (69.03	5.07 5.06	20.13 20.33)	$>10^{-5}$
5h	4-CH_3	221-222 [d]	61	$C_{16}H_{14}N_4O$	69.05 (69.13	5.07 5.24	20.13 20.14)	9.9×10^{-7}
5i	2-CH_3O	126-127 [e]	63	$C_{16}H_{14}N_4O_2$	65.29 (65.63	4.79 4.99	19.04 19.39)	2.0×10^{-6}
5j	3-CH_3O	169-171 [b]	65	$C_{16}H_{14}N_4O_2$	65.29 (65.44	4.79 4.94	19.04 19.20)	8.6×10^{-7}
5k	4-CH_3O	215-216 [b]	53	$C_{16}H_{14}N_4O_2$	65.29 (65.24	4.79 4.68	19.04 19.11)	1.2×10^{-6}

Recrystallized from: [a] Methanol. [b] Ethyl acetate. [c] 1,2-Dichloromethane. [d] Pentane wash. [e] Ethyl acetate/pentane. [f] Chlordiazepoxide $IC_{50} = 3.4 \times 10^{-7}$.

Table IV

^{13}C Chemical Shifts of Some Pyrazolo[3,4-*b*]pyridines





Carbon	R = C_2H_5O [a,b]	R = C_6H_5 (**11a** [b])	R = C_2H_5O (**14** [c])	R = C_6H_5 (**10** [c])
3	131.7	132.2	135.6	136.1
3a	106.2 [d]	109.8 [d]	101.1 [d]	104.6 [d]
4	170.5	166.7	151.0	150.8
5	102.3 [d]	106.5 [d]	95.8 [d]	100.8 [d]
6	151.1	154.5	151.8	155.2

7a	153.3	152.8	152.0	151.2
C=O	164.2	200.8	166.9	195.5
1′	42.3	42.3	41.2	41.1
2′	14.8 [d]	14.9	14.7 [d]	14.6
R	61.7 (OCH_2)	137.2 (C-1)	60.0 (OCH_2)	139.6 (C-1)
	14.3 (CH_3 [d])	129.1 (*o* [d])	14.3 (CH_3 [d])	128.4 (*o* [d])
		128.6 (*m* [d])		128.2 (*m* [d])
		132.5 (*p*)		130.7 (*p*)

[a] Ref [8]. [b] Spectrum recorded in deuteriochloroform (ppm from TMS). [c] Spectrum recorded in DMSO-d_6 (ppm from TMS). [d] Tentative assignment.

All compounds **5** and **6** were tested in the [3*H*]flunitrazepam binding assay [15] as an indication of their potential anxiolytic activity. The 3-aryl-6*H*-isoxazolo[5,4-*d*]pyrazolo-[3,4-*b*]pyridines **6** were only weakly active ($IC_{50} > 10^{-5}$ *M*) but a number of the 3-aryl-6*H*-isoxazolo[3,4-*d*]pyrazolo-[3,4-*b*]pyridines **5** showed good activity (Table III), comparable to Chlordiazepoxide.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam SP3-200 grating spectrophotometer. Nuclear magnetic resonance spectra were taken on a JEOL C-60HL instrument. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. The mass spectra were obtained from a Finnigan Model 4000 spectrophotometer with an INCOS data system at 70 eV by direct insertion. Thin-layer chromatography (tlc) was preformed on precoated glass plates (E. Merck 5.0 × 10.0 cm, silica gel 60, F-254). E. Merck 230-400 mesh silica gel was used for flash chromatography. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Il.

5-Benzoyl-4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**8a**).

4-Chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl chloride [8] (**7**, 11.72 g, 0.048 mole) was dissolved in 250 ml of tetrahydrofuran and cooled to −65°. Phenyl magnesium bromide (21.3 ml of 2.3*M* [16], 0.049 mole) was added dropwise and the reaction was allowed to stir for 30 minutes in the cold. At the end of this time the cold bath was removed and the reaction mixture was allowed to come to room temperature overnight. It was then distributed between ether and saturated ammonium chloride solution. The organic phase was separated, dried and evaporated, giving a residue that was triturated with hexane and filtered off to give 10.2 g (74%) of **8a**, mp 138-140° (lit [10] mp 140-142°); ir (chloroform): μ cm^{-1}, 1660 (C=O); ^1H nmr (deuteriochloroform): δ 1.50 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.50 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.15-7.80 (m, 5H, C_6H_5), 8.05 (s, 1H, H-3), 8.43 (s, 1H, H-6); ms: m/e 287, 285 (M^+). Combustion analysis data for compounds **4b-k** are tabulated in Table I.

5-Benzoyl-1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine (**11a**).

Compound **8a** (10.05 g, 0.035 mole) was stirred for 1 hour at 55° in a solution of 75 ml of dimethyl sulfoxide and 10 ml of 20% aqueous sodium hydroxide solution. At the end of this time the reaction mixture was distributed between water and dichloromethane. The organic phase was then separated, dried and evaporated and the crude product recrystallized from ether to give 8.40 g (89%) of **11a**, mp 147-148°, (lit [10] mp 151-153°); ir (chloroform): ν cm^{-1}, 1630 (C=O); ^1H nmr (deuteriochloroform): δ 1.50 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.50 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.34-7.75 (m, 5H, C_6H_5), 8.20 (s, 1H, H-3), 8.70 (s, 1H, H-6); 14.0 (s, 1H, exchanges with deuterium oxide, OH); ms: m/e 267 (M^+).

5-Benzoyl-1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine Oximes **12** and **13**.

Compound **11a** (8.15 g, 0.031 mole) was refluxed for 15 minutes in 75 ml of pyridine containing 2.2 g of hydroxyamine hydrochloride (0.032 mole). At the end of this time the pyridine was evaporated and the residue was distributed between dichloromethane and 5% aqueous hydrochloric acid to give a precipitate which was filtered off. Tlc analysis of the precipitate showed a two component mixture (50% ethyl acetate/hexane, R_f = 0.38 and R_f = 0.12), which was separated into its components by flash chromatography (20% ethyl acetate/dichloromethane). The high R_f product **12** [12] amounted to 2.39 g (28%) after recrystallization from ethyl acetate/hexane, mp 178-179°; ir (potassium bromide): ν cm^{-1}, 1600 (C=N); ^1H nmr (DMSO-d_6): δ 1.50 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.50 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.40-7.80 (m, 5H, C_6H_5), 8.05 (s, 1H, H-3), 8.30 (s, 1H, H-6), 11.3 (s, 1H, exchanges with deuterium oxide, OH), 13.5 (s, 1H, exchanges with deuterium oxide, =N-OH); ms: m/e 282 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.47; H, 5.06; N, 19.67.

The low R_f product **13** amounted to 2.59 g (30%) after recrystallization from methanol, mp 210-212°; ir (potassium bromide): ν cm^{-1}, 1600 (C=N); ^1H nmr (DMSO-d_6): δ 1.40 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.40 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.20-7.70 (m, 5H, C_6H_5), 8.00 (s, 1H, H-3); 8.20 (s, 1H, H-6), 11.5 (s, 2H, exchanges with deuterium oxide, OH and =N-OH); ms: m/e 282 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.49; H, 5.06; N, 20.05.

6-Ethyl-3-phenyl-6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridine (**6a**).

Compound **11a** (5.28 g, 0.02 mole) was refluxed overnight in 100 ml of pyridine containing 4.5 g of hydroxylamine hydrochloride (0.065 mole). At the end of this time the solvent was evaporated and the residue triturated with 5% aqueous hydrochloric acid to give crude **6a**, which was filtered off. After flash chromatography to get rid of a trace of **5a** and recrystallization from methanol/ethyl acetate, 3.83 g (73%) of **6a** was obtained, mp 151-153°; ^1H nmr (deuteriochloroform): δ 1.61 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.65 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.42-7.60 (m, 3H, phenyl H-3,4, and 5), 7.70-8.05 (m, 2H, phenyl H-2 and 6), 8.30 (s, 1H, H-4), 9.00 (s, 1H, H-8); ms: m/e 264 (M^+).

Combustion analysis data for compounds **6a-i** are tabulated in Table II.

5-Benzoyl-1-ethyl-4-[[(isopropylidene)amino]oxy]-1*H*-pyrazolo[3,4-*b*]pyridine (**9a**).

In 25 ml of dry tetrahydrofuran was dissolved 1.60 g (0.022 mole) of acetone oxime, followed by 2.46 g (0.022 mole) of potassium *t*-butoxide. After this mixture had stirred for 30 minutes, **8a** (5.0 g, 0.017 mole) was added as a solution in 50 ml of tetrahydrofuran. After an additional 30 minutes the reaction mixture was quenched by the addition of 5 ml of saturated ammonium chloride solution and then extracted with ether. Evaporation of the dried organic phase and recrystallization of the resi-

due from ethanol gave 4.1 g (75%) of **9a**, mp 115-116°; ir (chloroform): ν cm^{-1}, 1650 (C=O), 1600 (C=N); ^1H nmr (deuteriochloroform): δ 1.45 (s, 3H, $N=C(CH_3)_2$), 1.60 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.00 (s, 3H, $N=C(CH_3)_2$), 4.60 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.31-7.49 (m, 3H, phenyl H-3, 4 and 5), 7.59-7.92 (m, 2H, phenyl H-2 and 6), 8.32 (s, 1H, H-3), 8.55 (s, 1H, H-6).

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 66.80; H, 5.73; N, 17.29.

Synthesis of **6a** from **9a**.

Compound of **9a** (2.50 g, 0.0078 mole) was refluxed for 2 hours in a mixture of 10 ml of 5% aqueous hydrochloric acid and 15 ml of ethanol. The reaction mixture was then extracted into ether and washed consecutively with 5% aqueous sodium hydroxide and then water. Evaporation of the organic phase and recrystallization from methanol/ethyl acetate gave 1.5 g (73%) of **6a**, mp 151-153°, that was identical in all respects to the **6a** isolated above.

Acidification of the sodium hydroxide wash, extraction with ether and evaporation gave 0.22 g (11%) of **11a** that was identical by nmr (deuteriochloroform) and ms to the **11a** isolated above.

6-Ethyl-3-phenyl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridine (**5a**): Isolation of 5-Benzoyl-1-ethyl-4-hydroxyamino-1*H*-pyrazolo[5,4-*b*]pyridine (**10**).

A solution of hydroxylamine in methanol was prepared by titrating 5.0 g of hydroxylamine hydrochloride (0.0719 mole) in 50 ml of methanol with methanolic potassium hydroxide to a phenophthalein end point and then filtering off the potassium chloride. To this was added **8a** (5.0 g, 0.0175 mole) as a slurry in 50 ml of methanol. After stirring overnight the precipitated **5a** was filtered off and dried to give 1.65 g, mp 175-176°. The methanol filtrate contained, by tlc analysis, additional **5a** (50% ethyl acetate/hexane, R_f = 0.53) and a new product, R_f = 0.24. The methanol was evaporated and the residue was purified by flash chromatography (5% ethyl acetate/dichloromethane) to give fractions that contained pure **5a**, fractions that contained pure R_f = 0.24 product, and fractions that had both. The fractions containing pure R_f = 0.24 product were evaporated and analyzed by nmr and ms, indicating that the new product was indeed **10**; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 1.40 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.40 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.45-7.55 (m, 5H, C_6H_5), 8.43 (s, 2H, H-3 and H-6), 10.25 (br s, 1H, NHOH, exchanges with deuterium oxide), 11.85 (br s, 1H, NHOH, exchanges with deuterium oxide); ms: m/e 282.

Compound **10** obtained in this manner was combined with the material obtained from the fractions that contained both **10** and **5a** and refluxed for 1 hour in 50 ml of toluene containing 0.05 g of *p*-toluenesulfonic acid. At the end of this time the reaction mixture was distributed between ether and aqueous sodium bicarbonate, and then the organic phase was separated, dried and evaporated to give a residue that was flushed over a short silica gel column (5% ethyl acetate/dichloromethane) to give, after evaporation of the product-containing fractions, an additional 0.73 g of **5a**, mp 175-176°, for a total yield of 2.38 g (52%). Material for analysis was recrystallized from methanol, but the melting point was unchanged; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 1.60 (t, J = 7.5 Hz, 3H, CH_2CH_3), 4.68 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.61-7.79 (m, 3H, phenyl H-3,4 and 5), 8.05-8.22 (m, 2H, phenyl H-2 and 6), 8.35 (s, 1H, H-3), 9.20 (s, 1H, H-6); ms: m/e 264 (M^+).

Combustion analysis data for compounds **5a-k** are tabulated in Table III.

Hydroxylamine Hydrochloride/Acetic Acid Method.

Compound **8a** (4.26 g, 0.0149 mole) and hydroxylamine hydrochloride (14.0 g, 0.02 mole) were refluxed in a solution of 250 ml of acetic acid and 4 ml of concentrated hydrochloric acid. After 2 hours the solvent was evaporated and the residue was distributed between dichloromethane and sodium bicarbonate solution. The organic phase was evaporated and the crude product was purified by flash chromatography (10% ethyl acetate/dichloromethane). Evaporation of the product-containing fractions and trituration with pentane gave 2.2 g (52%) of analyticaly pure **5a**, mp 175-176°, that was identical in all respects to the **5a** isolated in the previous procedure.

Ethyl 1-Ethyl-4-hydroxyamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**14**).

Ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate [17] (5.0 g, 0.0197 mole) was dissolved in 25 ml of methanol and added dropwise to 0.08 mole of hydroxylamine in 200 ml of methanol, generated as in the synthesis of **10** above. After stirring for 4 days, the reaction mixture was filtered from a small amount of a precipitate and then the solvent was evaporated. The crude **14** was dissolved in 5% aqueous hydrochloric acid and filtered again. Pure **14** was obtained by carefully adjusting the *p*H to 7-8, filtering, and recrystallizing from ethanol to give 2.20 g (45%), mp 202-204°; ir: ν cm^{-1}, 1680 (C=O); ^1H nmr (DMSO-d_6): δ 1.31-1.60 (m, 6H, CH_2CH_3), 4.22-4.71 (m, 4H, CH_2CH_3), 8.42 (s, 1H, H-3), 8.78 (s, 1H, H-6); 10.0 (s, 1H, exchanges with deuterium oxide, NHOH), 10.5 (s, 1H, exchanges with deuterium oxide, NHOH).

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.74; H, 5.64; N, 22.39. Found: C, 52.92; H, 5.56; N, 22.27.

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[13] Tlc analysis of these compounds was inconclusive and the infrared spectra were ambiguous.

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