1,3-Dipolar Addition of Pyridine *N*-Imine to Acetylenes and the Use of C-13 NMR in Several Structural Assignments

Paul L. Anderson, James P. Hasak, Alicia D. Kahle, Nicholas A. Paolella and Michael J. Shapiro*

Pharmaceutical Research, Sandoz, Inc., East Hanover, New Jersey 07936

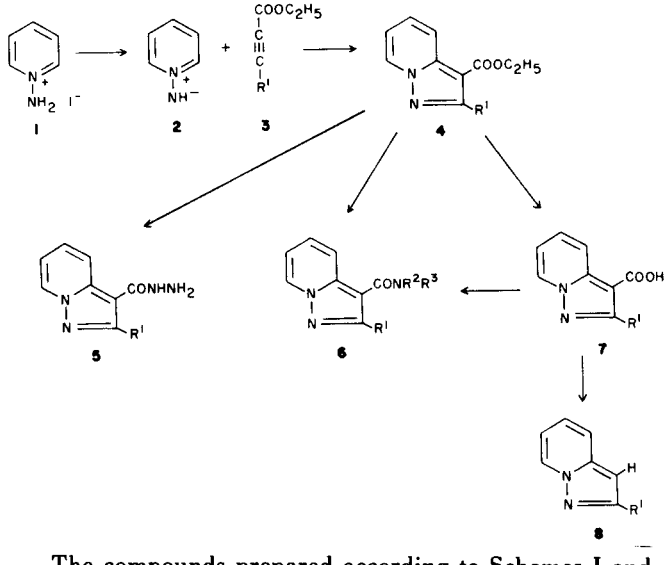
Received April 30, 1981

Addition of pyridine-*N*-imine to a variety of acetylenic mono- (Scheme I) and di- (Scheme II) carboxylic ester dipolarophiles was carried out. Several of the 3-azapyrrocoline esters obtained were further converted into acids, amides and hydrazides as shown in Schemes I and II.

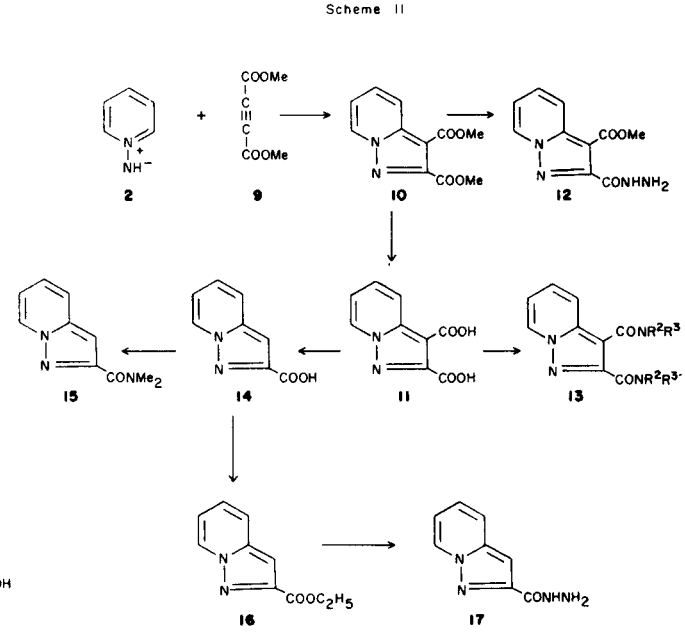
J. Heterocyclic Chem., **18**, 1149 (1981).

Since the pioneering work by Huisgen on azomethine imines (1), pyridine *N*-imine (2) has been one of the most utilized members of this class of compounds. In this paper, we wish to report the addition of this system to acetylenic esters and the preparation of a variety of derivatives from the initial products obtained. We also report the use of C-13 nmr in several structural assignments.

Scheme I



Scheme II



The compounds prepared according to Schemes I and II are shown in Table I. Structure elucidation of the 1,3-dipolar cycloadducts was accomplished by analysis of their nmr spectra.

When the diester **10** was treated with hydrazine, the monohydrazide **12** was obtained. Assignment of the structure of this ester hydrazide **12** was based on analysis of the C-13 nmr spectrum. In order to ascertain the regiospecificity of the reaction it was necessary to obtain and compare the nmr data for the various monosubstituted compounds. The chemical shifts and substitutent chemical shifts for the pertinent compounds are shown in Table II. The numbering sequence used for the pyrazolo[1,5-*a*]-pyridines is as shown in Table II. The carbon-13 spectral assignments for the parent compound ($R^1 = R^2 = H$) have been described previously by Grant (5). Using these shift assignments and their "finger prints" obtained from the proton-coupled carbon spectrum (see Figure 1), the carbon resonances for all of the derivatives were readily assigned (6). It became apparent from this data that there were three critical differences in the carbon shifts depending on the substitution of R^1 or R^2. These are the C_3, C_6 and C_7 resonances. Using the substitutuent shifts generated from the monosubstituted compounds, the calculated values for the hydrazide ester **12** could be obtained. The calculated shift values for these critical carbon resonances are (7) $C_3 = 6.3$, $C_6 = 7.0$ and $C_7 = 8.0$ ppm and $C_3 = 4.5$, $C_6 = 11.9$ and $C_7 = 2.4$ ppm. The actual values for the hydrazide ester **12** are $C_3 = 5.1$, $C_6 = 3.1$ and $C_7 = 8.2$ ppm and compare very favorably with the values for $R^1 = CO_2CH_2CH_3$ and $R^2 = CONHNH_2$. The difference in calculated *versus* observed for C_6 probably stems from steric and compressional effects which give rise to an up-

0022-152X/81/061149-04$02.25

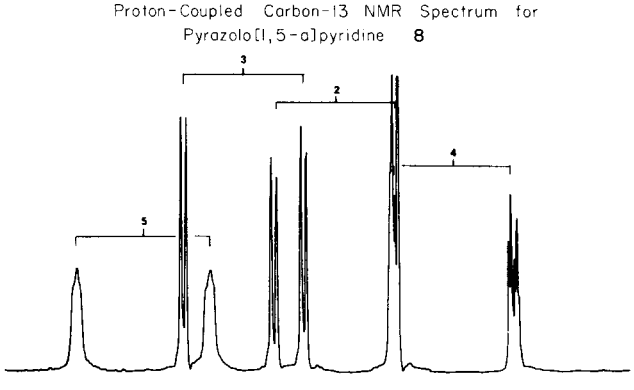
Table I (a)

3-Azapyrrocolines Prepared

Reactants		Product (b)	Mp, °C	Yield %	Molecular Formula	Calcd. % (Found) C	H	N
2 + **3a** (R^1 = Ph)	**4a** (c)	(R^1 = Ph)	80-82	47	$C_{16}H_{14}N_2O_2$	72.2	5.3	10.5
						(72.2)	(5.1)	(10.4)
2 + **3b** (R^1 = CH_3)	**4b**	R^1 = CH_3)	89-91	43	$C_{11}H_{12}N_2O_2$	64.7	5.9	13.7
						(64.6)	(5.6)	(13.7)
2 + **3c** (R^1-H)	**4c** (d)	(R^1 = H) (f)		33	$C_{10}H_{10}N_2O_2$			
4c + NH_2NH_2	**5**	(R^1 = H)	202.5-204	69	$C_5H_6N_4O$	54.5	4.6	31.8
						(54.5)	(4.6)	(31.5)
4a + $H_2N(CH_2)_3OH$	**6a**	(R^1 = Ph, R^2 = H, R^3 = $(CH_2)_3OH$)	136-139	73	$C_{17}H_{17}N_3O_2$	69.1	5.8	14.2
						(68.7)	(6.0)	(13.8)
4a + $H_2NCH_2CHOHC_2H_5$	**6b**	(R^1 = Ph, R^2 = H, R^3 = $CH_2CHOHC_2H_5$)	143-147	81	$C_{18}H_{19}N_3O_2$	69.9	6.2	13.6
						(70.1)	(6.2)	(13.5)
7b + $(COCl)_2$ + NH_2CH_3	**6c**	(R^1 = CH_3, R^2 = H, R^3 = CH_3)	161-163	93	$C_{10}H_{11}N_3O$	63.5	5.9	22.2
						(63.2)	(6.1)	(22.0)
4b + $H_2NCH_2CHOHC_2H_5$	**6d**	(R^1 = CH_3, R^2 = H, R^3 = $CH_2CHOHC_2H_5$)	80-82	38	$C_{13}H_{17}N_3O_2$	63.1	6.9	17.0
						(63.4)	(7.0)	(17.1)
7c + $(COCl)_2$ + $H_2NCH_2CH_2OH$	**6e**	(R^1 = H, R^2 = H, R^3 = CH_2CH_2OH)	158-160	39	$C_{10}H_{11}N_3O_2$	58.5	5.4	20.5
						(58.3)	(5.7)	(20.7)
7c + $(COCl)_2$ + 2-$H_2NCH_2C_5H_4N$	**6f**	(R^1 = H, R^2 =H, R^3 = 2-$CH_2C_5H_4N$)	230-240	90	$C_{12}H_{12}N_4O\cdot HCl$	58.2	4.5	19.4
						(58.5)	(4.8)	(19.5)
7b + $(COCl)_2$ + o-$H_2NC_6H_5CH_2CH_2OH$	**6g**	(R^1 = CH_3, R^2 = H, R^3 = o-$C_6H_5CH_2CH_2OH$)	171-174	44	$C_{17}H_{17}N_3O_2$	69.1	5.8	14.2
						(69.3)	(6.0)	(13.8)
4a + KOH	**7a**	(R^1 = Ph)	203-205	94	$C_{14}H_{10}N_2O_2$	70.6	4.2	11.8
						(70.3)	(4.3)	(11.4)
4b + NaOH	**7b**	(R^1 = CH_3)	243-245	97	$C_9H_8N_2O_2$	61.3	4.6	15.9
						(61.0)	(4.7)	(15.5)
4c + NaOH	**7c** (d)	(R^1 = H)	222.5-224.5	93	$C_8H_6N_2O_2$			
7c + PPA	**8** (d)	(R^1 = H)	oil	89	$C_7H_6N_2$			
2 + **9**	**10** (e)		64-68	24	$C_{11}H_{10}N_2O_4$			
10 + NaOH	**11** (e)		288-290	64	$C_9H_6N_2O_4\cdot 2H_2O$			
10 + NH_2NH_2	**12**		190-193	89	$C_{10}H_{10}N_4O_3$	51.3	4.3	23.9
						(51.7)	(4.4)	(23.6)
11 + $(COCl)_2$ + NH_2CH_3	**13a**	(R^2 = H, R^3 = CH_3)	165-166	97	$C_{11}H_{12}N_4O_2$	56.9	5.2	24.1
						(56.7)	(5.2)	(23.9)
11 + $(COCl)_2$ + $H_2NC_6H_5$	**13b**	(R^2 = H, R^3 = C_6H_5)	207-208	90	$C_{21}H_{16}N_4O_2$	70.8	4.5	15.7
						(70.6)	(4.9)	(15.6)
11 + $(COCl)_2$ + $HN(CH_3)_2$	**13c**	(R^2 = R^3 = CH_3)	80-85	79	$C_{13}H_{16}N_4O_2$	60.0	6.2	21.5
						(59.8)	(6.3)	(21.9)
11 + PPA	**14**		190-191.5	97	$C_8H_6N_2O_2$	59.3	3.7	17.3
						(59.0)	(4.0)	(17.2)
14 + $(COCl)_2$ + $HN(CH_3)_2$	**15**	(R^2 = R^3 = CH_3)	73-75	33	$C_{10}H_{11}N_3O$	63.5	5.9	22.2
						(63.6)	(6.0)	(22.4)
14 + EtOH	**16**		40-43	76	$C_{10}H_{10}N_2O_2$	63.1	5.3	14.7
						(63.3)	(5.0)	(14.5)
16 + H_2NNH_2	**17**		155-159	62	$C_8H_8N_4O$	54.5	4.6	31.8
						(54.2)	(5.0)	(32.0)

(a) Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. (b) All products exhibited satisfactory spectra in accord with the assigned structure. (c) Known compound, see reference 9. (d) Known compound, see reference 3. (e) Known compound, see reference 4. (f) bp = 80-84° (0.1 to 0.05 torr).

FIGURE I

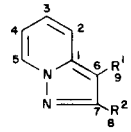


field shift in the observed value for the hydrazide ester **12** (8). Similar observations can be made for the diester **10.**

Supporting evidence for the stereochemical assignment can be found in the one bond CH coupling constants obtained for the compounds given in Table III. It is clear that there is a difference between C_2 and C_5 depending on the position of the ester function. When R^1 = H, R^2 = CO_2Et, the JCH is smaller than R^1 = CO_2Et, R^2 = H. The larger values of ^{1}JCH for C_2 and C_5 in the ester hydrazide **12** is consistent with the proposed structure.

Table II

Chemical Shifts and Substituent Chemical Shifts for the Pyrazolo[1,5-*a*]pyridines (c)



Compound No.	R^1, R^2	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
8	H, H (b)	140.4	118.3	123.3	111.8	128.8	96.9	142.1	—	—
17	H, $CONHNH_2$ (a)	140.8	119.2	124.6	114.2	129.1	97.4	147.6	161.6	—
	$\Delta\delta$ (d)	0.4	0.9	1.3	2.4	0.3	0.5	5.5		
5	$CONHNH_2$, H (a)	140.2	119.0	126.9	113.9	129.7	105.4	141.3	—	163.3
	$\Delta\delta$	−0.2	0.7	3.6	2.1	0.9	8.5	−0.8		
4c	CO_2Et, H (b)	140.4	118.4	128.3	114.4	130.1	103.4	144.6	162.9	—
	$\Delta\delta$	0.0	0.1	5.0	2.6	2.3	6.5	2.5		
16	H, CO_2Et (b)	141.2	119.4	124.2	114.3	129.1	100.3	145.3	—	163.1
	$\Delta\delta$	0.8	1.1	0.9	2.5	1.3	3.4	3.2		
10	CO_2CH_3, CO_2CH_3 (a)	140.6	118.9	129.3	115.8	130.2	101.2	147.8	162.3	163.9
	$\Delta\delta$	0.2	0.6	6.0	4.0	1.4	4.3	5.7		
12	CO_2CH_3, $CONHNH_2$ (a)	140.8	118.7	128.4	115.0	129.5	100.4	150.3	161.4	162.9
	$\Delta\delta$	0.4	0.4	5.1	3.2	0.7	3.1	8.2		

(a) DMSO-d_6. (b) Deuteriochloroform (c) In ppm from TMS. (d) $\Delta\delta = (\delta$ (**8**) $- \delta$ (substituted)).

Table III

Carbon-Hydrogen Coupling Constants for the Pyrazolo[1,5-*a*]pyridines (a)

Compound No.	R^1, R^2	C_2	C_3	C_4	C_5	C_6	C_7
8	H, H	167.2 (H_2)	165.6 (H_3)	166.6 (H_4)	185.0 (H_5)	183.6 (H_6)	188.8 (H_7)
		7.4 (H_4)	7.2 (H_5)	8.2 (H_2)		6.3 (H_7)	10.1 (H_6)
17	H, $CONHNH_2$	169.9	167.4	168.7	188.4	182.2 (H_6)	4.6 (H_6)
		7.5	7.0	8.7	(11.4) (b)		
5	$CONHNH_2$, H	166.5	166.4	167.7	187.8	9.8	187.1
		(8.5) (c)		8.5	(11.6)		
4c	CO_2Et, H	173.7	168.0	170.1	189.1	8.9	187.8
		7.4	7.3	8.5	(11.9)		
16	H, CO_2Et	169.2	167.0	168.3	186.8	182.7	3.8
		7.6	7.2	8.6	(11.1)		
10	CO_2CH_3, CO_2CH_3	174.4	168.8	172.2	190.8		
		7.5	7.2	8.3	(11.7)		
12	CO_2CH_3, $CONHNH_2$ (d)	173.8	168.2	171.4	189.7		
		7.7	7.1	8.3	6.7 (H_4)		
					5.1 (H_3)	(11.8)	
					1.7 (H_2)		

(a) ±1.2 Hz, precision ±0.6 Hz. (b) $J_{3,5} + J_{4,5}$. (c) Precision outside of experimental error. (d) ±0.2 Hz.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Ir spectra were taken on a Perkin-Elmer Model 257 or 457.

The proton nmr spectra were recorded on a Varian T-60 or EM-360 spectrometer. All shifts are referenced to internal TMS. The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 20% w/v in deuteriochloroform or deuteriodimethyl sulfoxide in 10 mm outside diameter sample tubes. General nmr spectral and instrumental parameters employed are: internal deuterium lock to the solvent; spectral width of 5120 Hz for decoupled spectra and 5000 Hz for proton-coupled spectra. Sample 8 was run at a spectral width of 850 Hz; a pulse width of 25 ys, corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds for the decoupled spectra. For all spectra 8K time domain data points were used. All shifts reported are referenced to internal TMS, and are estimated to be accurate to ±0.05 ppm.

The carbon numbering system is as shown in Table II.

General Method for Addition of Acetylenic Mono and Dicarboxylic Esters to Pyridine *N*-Imine.

To a stirred solution of aminopyridinium iodide (**1**, 10.4 g, 50 mmoles) in 100 ml of dry dimethylformamide were added 9 g pulverized anhydrous potassium carbonate and 100 mmoles of the mono- or di-ester. The mixture was stirred about 18 hours and then poured into about 600 ml of ice-

water and the precipitated product filtered and dried.

Pyrazolo[1,5-*a*]pyridine-3-carboxhydrazide (**5**).

To a stirred solution of 5.7 g (30.0 mmoles) of ethyl pyrazolo[l,5-*a*]pyridine-3-carboxylate (**4c**) in 50 ml of absolute ethanol was added 7.0 ml of anhydrous hydrazine. After stirring 6 days at room temperature, 145 ml of ice-water was added and the precipitate collected, washed with 50 ml water and dried to obtain 3.63 g (69%) of product, mp 202.5-204°; nmr (DMSO-d_6): δ 4.45 (s, 2, NH_2), 7.06 (t, 1, C_4-H), 7.48 (t, l, C_3H),8.28 (d, l, C_2H), 8.54 (s, l, C_7-H), 8.83 (d, 1, C_5-H), 9.55 (s, 1, NH); ir (potassium bromide): 3314, 3280, 3225 (NHs), 1630 (C=O), 1617 (C=N).

General Method for Preparation of Pyrazolo[1,5-*a*]-pyridine-3-carboxylic Acid Amides (**6**) from Esters (**4**).

To a pyrazolo[1,5-*a*]pyridine-3-carboxylic acid ester **4** (3.0 g) was added 30 ml of the amine. The solution was stirred and heated at 150° for two days and then poured on water. The precipitate which formed was collected, washed and dried to obtain the desired amide.

2-Phenylpyrazolo[1,5-*a*]pyridine-3-(3-hydroxy)propylamide (**6a**).

To ethyl 2-phenylpyrazolo[1,5-*a*]pyridine-3-carboxylate (**4a**) (2.9g, 10.9 mmoles) was added 3-amino-1-propanol and the resulting solution stirred and heated at 150° for two days. The solution was then poured into water and the resultant precipitate collected, washed and dried to obtain 2.19 g of product. A second crop of 0.24 g was also collected. The total yield was 2.4 g (73%), mp 137-141°, nmr (deuteriochloroform): δ 1.58 (m, 2, C-CH_2-C), 3.50 (m, 5, -NCH_2-C-CH_2 + OH), 5.86 (m, 1, NH), 6.75 to 8.50 (m, 9, C_6H_5 + C_5NH_4); ir (chloroform): 3632 (OH), 3450 (NH), 1634 (C=O), 1615 (C=N).

General Method for the Hydrolysis of the Mono and Diesters **4** and **10** to the Carboxylic Acids **7** and **11**.

To 400 g of 50% aqueous sodium hydroxide solution was added with stirring 91.7 mmoles of the mono or diester. The mixture was stirred at reflux for 30 minutes, cooled, and 300 ml of 95% ethanol added. The mixture was stirred at reflux during 20 minutes more and then cooled in an ice bath and neutralized slowly with concentrated hydrochloric acid. The precipitated product was collected, washed with water and dried.

General Method for the Mono Decarboxylation of the Carboxylic Acids **7** and **14**.

To 2.90 g of the carboxylic acid derivative was added 150 ml of polyphosphoric acid. The solution was heated at 80° for 16 hours, cooled and poured into 1500 ml of ice water. The resultant precipitate was filtered, washed with water and dried to obtain 2.05 g of the product.

3-Carbomethoxypyrazolo[1,5-*a*]pyridine-2-carboxylic Acid Hydrazide (**12**).

To 11.7 g of dimethyl pyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (**10**) in 150 ml of absolute ethanol was added 2.0 ml of anhydrous hydrazine with sstirring at room temperature. The solution was stirred for 48 hours and the resulting precipitate filtered, washed with ethanol and dried to obtain 10.37 g (89%) of the product, mp 190-195°; nmr (DMSO-d_6 + deuteriochloroform): δ 3.31 (s, 1, NH_2), 3.89 (s, 3, CH_3), 4.59 (s, 1, NH_2), 7.19 (t, 1, C_4-H), 7.61 (t, 1, C_3-H), 8.15 (d, 1, C_2-H), 8.79 (d, 1, C_5-H), 10.10 (s, 1, NH); ir (potassium bromide): 3320, 3280, 3225 (NHs), 1680 (ester C=O), 1650 (amide C=O).

General Method for the Preparation of Mono- and Diamides from Mono- and Dicarboxylic Acids. Illustrated by Preparation of 2-Methylpyrazolo-[1,5-*a*]pyridine-3-(*N*-methyl)carboxamide (**6c**).

To a stirred suspension of 13.4 g, 2 methylpyrazolo[1,5-*a*]pyridine-3-carboxylic acid (**7b**) in 40 ml of toluene under nitrogen was slowly added 25.6 ml of oxalyl chloride. Mild heat was applied to initiate the reaction but heating was discontinued as soon as bubbling began. After the bubbling ceased, the mixture was gradually warmed to 60°. After 4.5 hours, the carboxylic acid had all gone into solution. The solvent and excess oxalyl chloride were then removed under reduced pressure and the resultant light tan solid dissolved in 40 ml dichloromethane. This solution was cooled to −60° and 40 ml of methylamine in 40 ml of dichloromethane was slowly added. After addition was complete, the solution was allowed to warm to room temperature and the methylene chloride and the excess methylamine were removed under reduced pressure. To the resultant solid was added 800 ml of chloroform and 600 ml of water. The layers were separated and the aqueous layer extracted with 4 × 200 ml of chloroform. The combined organic extracts were washed with 300 ml of water and 300 ml of saturated salt solution and dried over calcium chloride. The solvent was then removed under reduced pressure and the resultant solid dried to obtain 13.33 g (93%) of product, mp 161-163°; nmr (deuteriochloroform): δ 2.59 (s, 3, 7-CH_3), 3.00 (d, 2, J = 2.0 Hz, NCH_3), 6.05 (m, 1, NH), 6.80 (t, 1, J = 3.5 Hz, C_4-H), 7.15 (t, 1, J = 3.5 Hz, C_3-H), 8.05 (d, 1, J = 4.0 Hz, C_2-H), 8.35 (d, 1, J = 4.0 Hz, C_5-H); ir (chloroform): 3480 (NH), 1650 (C=O), 1635 (C=N).

Ethyl Pyrazolo[l,5-*a*]pyridine-2-carboxylate (**16**).

A solution of 8.1 g pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (**14**), 50 ml of absolute ethanol and 0.2 g of *p*-toluenesulfonic acid monohydrate was refluxed in a flask fitted with a soxhlet extractor containing 50 g of 3 angstrom molecular sieves (Linde). The solution was refluxed 24 hours, cooled and diluted with 200 ml of water. The solution was then extracted three times with 100 ml portions of chloroform and the chloroform extracts washed successively with 200 ml of water, 200 ml of 1*N* sodium bicarbonate solution, 200 ml of water and 200 ml of a mixture of 150 ml of saturated salt solution and 50 ml of water. The chloroform solution was then dried over sodium sulfate and the solvent removed to give 11.3 g of an orange oil. The oil was distilled under reduced pressure and the fraction boiling at 80-90° (0.05 torr) was collected. This colorless oil crystallized on standing to give 7.26 g (76%) of colorless product, mp 40-43°; nmr (deuteriochloroform): δ 1.43 (t, 3, J = 3 Hz, CH_3), 4.50 (q, 2, J = 3.5 Hz, CH_2), 7.10 (m, 2, C_4-H + C_3-H), 7.12 (s, 1, C_6-H), 7.64 (d, 1, J = 4 Hz, C_2-H), 8.59 (d, 1, J = 3.5 Hz, C_5-H); ir (chloroform); 1720 (C=O), 1636 (C=N).

Pyrazolo[1,5-*a*]pyridine-2-carboxhydrazide (**17**).

To 3.00 g of ethyl pyrazolo[1,5-*a*]pyridine-2-carboxylate (**16**)was added 5 ml of anhydrous hydrazine and the solution was stirred at room temperature for 16 hours. The resulting precipitate was filtered and dried to obtain 1.73 g (62°) of the product, mp 155-159°; nmr (DMSO-d_6): δ 4.0 (broad s, 2, NH_2), 7.0 (s, 1, C_6-H), 7.17 (m, 2, C_3-H + C_4-H), 7.81 (d, 1, C_2H), 8.72 (d, 1, C_5-H), 9.72 (s, 1, NH); ir (potassium bromide):3400, 3315 (NHs), 1671 (C=O), 1638 (C=N).

REFERENCES AND NOTES

(1) For an excellent review of the early work done, see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

(2) R. Huisgen, R. Grashey and R. Krischke, *Tetrahedron Letters*, 387 (1962).

(3) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).

(4)R. Krischke, R. Grashey and R. Huisgen, *Ann. Chem.*, 498 (1977).

(5) R. J. Pugmire, M. J. Robins, D. M. Grant and R. K. Robins, *J. Am. Chem. Soc.*, **93**,1887 (1971).

(6a) M. J. Shapiro, *J. Org. Chem.*,**43**, 3769 (1978); (b) H. Gunther, H. Schmickler and G. Jikeli, *J. Magn. Reson.*, **11**, 344 (1973).

(7) The Δδ-values shown were obtained by summation of the Δδ-values observed for the appropriate monosubstituted systems. For example, the predicted C_3 Δδ-value of 6.3 ppm of one isomer (R^1 = CO_2Et, R^2 = $CONHNH_2$) is obtained by summation of the Δδ-value of 1.3 ppm arising from **17** and the Δδ-value of 5.0 ppm arising from **4c**.

(8) For example, see (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N. Y., 1972, p. 95. (b) L. Ernst, *J. Magn. Reson.*, **20**, 544 (1975).

(9) A. Kakehi and S. Ito, *J. Org. Chem.*, **39**, 1542, (1974).