1*H*-Pyrazolo[3,4-*b*]pyridines

H. Höhn, Th. Denzel and W. Janssen

Chemische Fabrik von Heyden GMBH, Regensburg, Germany

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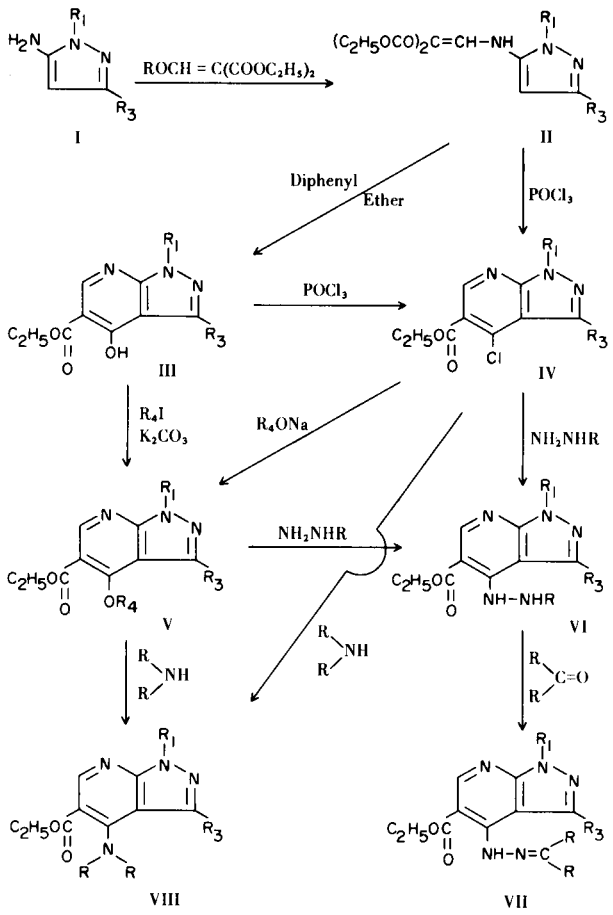
The synthesis of a number of new 1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid derivatives is described. Most of these compounds have either an alkoxy or a basic substituent in position 4.

Compounds containing a pyrazolo[3,4-*b*]pyridine nucleus have been described previously (1-12). In some of these publications it is stated that several of these compounds represent a new type of purine or pyrimidine antimetabolite (4,8-11). Moreover, a number of pyrazolo-[3,4-*b*]pyridines have been reported to possess hypotensive and vasodilator activity (12). In the course of the development of a synthetic program for various pyrazolopyridines, we have prepared a number of pyrazolo[3,4-*b*]pyridine-5-carboxylic acid derivatives, including compounds with various substituents in position 4. This type of compound has been found to be a potent inhibitor of various adenosine, cyclic 3′,5′-(hydrogen phosphate) [cyclic AMP] phosphodiesterases (13). In view of the current interest in the biological activities of adenosine, cyclic 3′,5′-(hydrogen phosphate), we wish to describe the properties of these novel pyrazolo[3,4-*b*]pyridine-5-carboxylic acid derivatives and general procedures for their preparation.

The general synthetic routes for the preparation of the various pyrazolo[3,4-*b*]pyridine-5-carboxylic acid derivatives are outlined in Scheme I. The preparation and properties of the required 5-aminopyrazoles (I) have been described previously (14). The condensation of the aminopyrazole with diethyl ethoxymethylenemalonate gave the desired diethyl 5-pyrazolylaminomethylenemalonates (II), listed in Table I. Heating these malonates in diphenyl ether at 230-260° resulted in ring-closure and the formation of ethyl 1-alkyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylates (III) listed in Table II. The cyclization may also be carried out using phosphorus oxychloride as the condensing agent, in which case the products bear a chlorine atom in position 4 instead of an hydroxyl group. These 4-chloro derivatives, IV, which are listed in Table III, may also be formed by the reaction of III with phosphorus oxychloride.

The alkylation of ethyl 4-hydroxy-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylates (III) was accomplished by reaction with an alkylating agent, such as an alkyl halide or an aralkyl halide in an inert solvent in the presence of potassium carbonate. The alkylation occurred as indicated since the same alkoxy compounds could be formed by the reaction of a 4-chloro derivative, IV, with the appropriate sodium alcoholate. The 4-alkoxy derivatives (V) are listed in Table IV.

SCHEME I



The alkoxy group in the 4-position of ethyl pyrazolo[3,4-*b*]pyridine-5-carboxylates is quite labile, since treatment with at least an equivalent amount of hydrazine or a substituted hydrazine in the presence of a catalytic amount of zinc chloride resulted in the formation of ethyl 4-hydrazinopyrazolo[3,4-*b*]pyridine-5-carboxylates (VI). These 4-hydrazino derivatives could also be prepared by the replacement of the chlorine atom in IV by the hydrazino group. Condensation of the unsubstituted 4-hydrazino derivatives with carbonyl compounds, both aldehydes and ketones, yielded the desired hydrazones (VII). The various hydrazines and hydrazones prepared are listed in Table V.

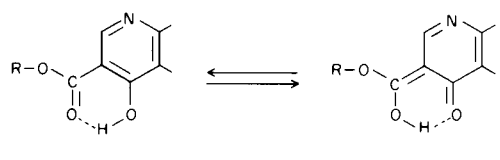
Similarly, derivatives in this series having an amino substituent in the 4 position could be prepared by the reaction of a primary or secondary amine with either a 4-alkoxy derivative (V) or a 4-chloro derivative (IV). These amino derivatives are listed in Table VI.

Various 5-carboxamides in this series were also prepared by hydrolysis of the ester to the acid, conversion to the acyl chloride and reaction with the appropriate amine. These amides are listed in Table VII.

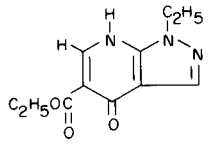
The nmr and ir spectral data (15) of a number of representative compounds are given in Table VIII to confirm the structural assignments made in this series. A report on the structure of diethyl 1-ethylpyrazolyl-5-aminomethylenemalonate (II, R_1 = ethyl, R_3 = H) and diethyl 1-ethyl-3-methylpyrazolyl-5-aminomethylenemalonate (II, R_1 = ethyl, R_3 = methyl) has been published recently (16).

The nmr spectra of the various compounds showed the expected signal for the 1-ethyl group and the O-ethyl group of the esters listed in Table VIII, a triplet at about 1.30-1.57 ppm and a quartet at 4.28-4.58 ppm. The aromatic proton at the 6-position was observed as a singlet at 8.67-9.35 ppm. The substituent at the 3-position was also observed as a singlet at 8.03-8.45 for hydrogen and 2.63-2.70 for the methyl protons, with the exception of compounds XX and XXIII in which the 4-substituent caused an upfield shift due to shielding by the *m*-trifluoroanilino and the diacetylhydrazino groups.

In the ir spectra of these representative compounds there are observed slightly broadened absorptions for the OH-stretching frequency. The low frequency shift to *ca.* 3400 cm^{-1} is typical for intramolecular hydrogen bonding with the ester carbonyl group (position 5) in a six-membered ring system of low energy (A and B). This is also indicated by the shift to lower frequency of the carbonyl absorption to approximately 1660-1680 cm^{-1} from 1720-1730 cm^{-1} for unassociated aryl ester carbonyl groups (17). Since the 4-chloro derivative (XIII) is incapable of this hydrogen bonding, it shows the normal carbonyl absorption at 1730 cm^{-1}. From these results it can be concluded that IX-XII exist as 4-hydroxypyrazolo[3,4-*b*]pyridines and not as the 4-pyridones. This conclusion is supported by the nmr spectra. In the 4-pyridone form (C) an interaction between the NH proton and the proton in position-6 would be expected, with a splitting of the signals of these protons (18,19). This is not seen in the nmr spectra, confirming the 4-hydroxy structure.



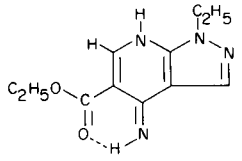
A B



C

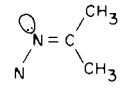
The carbonyl absorptions in compounds XIV and XV, in which no hydrogen bonding with the 4-substituent is possible, are more normal, appearing at 1765 cm^{-1} in XIV and at 1720 cm^{-1} in XV.

As in the case of the 4-hydroxy derivatives, the 4-amino derivatives XVIII-XX show an intramolecular hydrogen bonding as indicated by the shift of the carbonyl absorption to lower frequency, as well as a broad absorption band at 3220-3290 cm^{-1}, characteristic of associated NH protons. Compound XVIII also shows a sharp strong absorption at 3450 cm^{-1} typical of the unassociated NH stretching vibration. These compounds do not exist in the γ-imino form since the proton in position-6 is not split, as would be expected if, for example, compound XVIII existed as D.



D

We have observed a similar situation for the pyrazolopyridines substituted in position-4 by hydrazine groups (when N^1 is not further substituted). The NH-stretching vibration in XVI and XVII is shifted to a lower frequency and the C=O valence frequency of the ester carbonyl group drops to 1670 and 1665 cm^{-1}, respectively. The two methyl groups of the hydrazone XVII are not magnetically equivalent, since they are located in *cis/trans* position to the free electron pair of the sp^2-hybridized *N* atom and therefore, show different signals in the nmr.



A further question to be resolved was the position of the substituents on the hydrazino group in XXI-XXIII. The structural assignment as shown seem to be confirmed by the nmr and ir spectra. Thus, compound XXI shows two slightly broadened singlets at 6.55 and 10.40 ppm which disappear upon the addition of deuterium oxide. While the proton at 6.55 ppm exchanges rapidly, the proton at 10.40 was exchanged only after about 30 minutes, or the addition of deuteriotrifluoroacetic acid. In the ir spectra there is only one NH valence frequency and no NH_2 bands. Similar observations were made with compound XXII. From the method of synthesis it is possible that XXIII could be a 1,2-diacetyl hydrazino derivative. In a variety of solvents (benzene, toluene, DMSO, ether, pyridine) only one singlet is indicated for both of the methyl groups of the acetyl residues in the nmr. We can conclude that both the methyl groups are magnetically equivalent and that XXIII probably has the assigned structure.

EXPERIMENTAL

The procedures given below are representative for the compounds described in Tables I-VII. Melting points and boiling points are not corrected and yields are generally for unrecrystallized products.

Procedure A. Diethyl (1-Ethyl-5-pyrazolyl)aminomethylenemalonate.

A mixture of 245 g. (2.2 moles) of 1-ethyl-5-aminopyrazole and 469 g. (2.2 moles) of diethyl ethoxymethylenemalonate was heated at 120° (bath temperature) for 2 hours with stirring. The ethanol formed in the reaction was removed by vacuum distillation (water aspirator). Distillation of the reaction mixture under reduced pressure gave 520 g. (84%) of oil, b.p. 154-160°/0.1 mm, which crystallized quickly and melted at 50-53°. A sample recrystallized from *n*-hexane melted at 55-57°.

Procedure B. Ethyl 1-Ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A solution of 253 g. (0.9 mole) of diethyl (1-ethyl-5-pyrazolyl)-aminomethylenemalonate in 770 g. of diphenyl ether was heated to 235-250° (bath temperature) and maintained at this temperature for 1-2 hours, while the ethanol formed was allowed to distill from the reaction mixture. The last amount of alcohol was removed under reduced pressure. The mixture was fractionally distilled under reduced pressure; the ethyl 1-ethyl-4-hydroxy-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate boiled at 115-120°/0.05 mm and weighed 195 g. (92%), m.p. 85-87°. A sample crystallized from ligroin (90-100°) melted at 87-89°.

Procedure C. 4-Ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid.

A suspension of 26.3 g. (0.1 mole) of ethyl 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 375 ml. of aqueous sodium hydroxide (1.5 *N*) was stirred for 10 hours at room temperature. The clear solution was acidified with aqueous hydrochloric acid to yield 21.8 g. (92.5%) of compound, m.p. 198-199°.

Procedure D. *n*-Butyl 1-Ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylate.

A mixture of 10.3 g. (0.05 mole) of 1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 150 ml. of 1-butanol was heated under reflux for 4 hours, while a gentle stream of hydrogen chloride was passed into the solution. The solution was cooled and concentrated to dryness under reduced pressure. The residue was dissolved in about 50 ml. of water, the *p*H was adjusted to 8.0 with 10% aqueous ammonia, and a final adjustment of *p*H to 6.0 was achieved by the addition of 25% aqueous acetic acid. The precipitated butyl 1-ethyl-4-hydroxy-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate was filtered, washed with water and dried in a desiccator. The product weighed 9.8 g. (75%), m.p. 69-70°. A sample recrystallized from petroleum ether (60-70°), melted at 70-71°.

Procedure E. Ethyl 4-Chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A mixture of 23.5 g. (0.1 mole) of ethyl 1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and 150 ml. of phosphorus oxychloride was heated under reflux for 4 hours, and the excess phosphorus oxychloride was then removed by distillation under reduced pressure. As soon as the phosphorus oxychloride had been removed, the residue solidified. It was triturated with water and filtered to give 24.5 g. (94%) of product, m.p. 55-60°. The ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate, after recrystallization from *n*-hexane, melted at 62-63°.

This compound was also obtained by the following procedure: A mixture of 12 g. (0.043 mole) of diethyl (1-ethyl-5-pyrazolyl)-aminomethylenemalonate and 70 ml. of phosphorus oxychloride was heated under reflux for 10 hours. The excess phosphorus oxychloride was removed by distillation under reduced pressure, and the oily residue, when suspended in 50 ml. of water, became crystalline. The solid was filtered and dried in a desiccator to yield 8.5 g. (79%) of product, which melted at 62-63° after recrystallization from *n*-hexane.

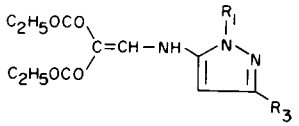
Procedure F. Ethyl 4-Ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

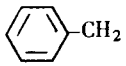
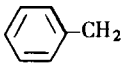
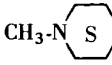
To a solution of 2.3 g. (0.1 mole) of sodium in 250 ml. of ethanol, there was added 25.4 g. (0.1 mole) of ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and the reaction mixture was allowed to remain at room temperature for 12 hours. The precipitated sodium chloride was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure. The product weighed 24.8 g. (94%), and after recrystallization from ligroin (90-100°), melted at 113-115°.

This compound was also obtained by the following procedure: To a well-stirred solution of 259 g. (1.1 moles) of ethyl 1-ethyl-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 1700 ml. of dimethylformamide there was added 400 g. of well-pulverized potassium carbonate and 300 g. of ethyl iodide. The reaction mixture was stirred at 65° for 7 hours and then filtered, while hot, to remove the inorganic material. The filtrate was allowed to cool overnight and the ethyl 4-ethoxy-1-ethyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate, which crystallized from the solution, was filtered. This first-crop material weighed 165 g.; a second crop of 80 g. was obtained by concentration of the mother liquor. The product, which weighed 245 g. (85%), melted at 112-

TABLE I

Diethyl 5-Pyrazolylaminomethylenemalonates

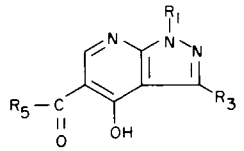


R_1	R_3	Procedure	Yield %	M.p.	Recryst. Solvent (a)	B.p.	Empirical Formula	Calcd., % C	H	N(Cl) (b)	Found, % C	H	N(Cl)
	H	A	85	65-67°	C		$C_{18}H_{21}N_3O_4$	62.97	6.16	12.24	62.85	6.01	12.44
	CH_3	A	92	86-87°	L		$C_{19}H_{23}N_3O_4$	63.83	6.48	11.77	63.97	6.67	11.77
CH_3-CH_2	H	A	84	55-57°	H	154-160°/0.1 mm	$C_{13}H_{19}N_3O_4$	55.50	6.80	14.93	55.42	6.94	14.74
CH_3-CH_2	CH_3	A	77	69-70°	L	152-153°/0.05 mm	$C_{14}H_{21}N_3O_4$	56.93	7.16	14.23	56.57	7.13	14.41
CH_3	H	A	83	40-41°	H	160-162°/0.1 mm	$C_{12}H_{17}N_3O_4$	53.92	6.41	15.72	54.05	6.36	15.64
$(CH_3)_2CH$	H	A	88	72-73°	H		$C_{14}H_{21}N_3O_4$	56.93	7.16	14.23	57.13	7.17	14.42
$(CH_3)_2CH$	CH_3	A	90	73-74°	H		$C_{15}H_{23}N_3O_4$	58.24	7.49	13.58	58.35	7.40	13.46
CH_3	CH_3	A	78	91°	E		$C_{13}H_{19}N_3O_4$	55.50	6.80	14.93	55.54	6.91	14.80
	H	A	96	95-96°	L		$C_{17}H_{19}N_3O_4$	61.99	5.81	12.76	62.43	5.66	12.74
CH_3-CH_2-CH_2-CH_2	H	A	73			150-154°/0.01 mm	$C_{15}H_{23}N_3O_4$	58.24	7.49	13.58	58.09	7.53	13.67
CH_3-CH_2-CH_2-CH_2	CH_3	A	72			180-183°/0.1 mm	$C_{16}H_{25}N_3O_4$	59.43	7.79	12.99	59.17	7.89	13.26
	H	A	82	98-99°	H		$C_{17}H_{26}N_4O_4$	58.26	7.47	15.99	58.00	7.43	16.29
CH_3-CH_2-CH_2	CH_3	A	68	45-47°	H	172-174°/0.8 mm	$C_{15}H_{23}N_3O_4$	58.24	7.49	13.58	58.21	7.48	13.84

(a) Recrystallization solvents used in Tables I-VII: A = acetonitrile; Ac = acetic acid; At = acetone; B = benzene; C = cyclohexane; E = ether; Ea = ethyl acetate; Et = ethyl alcohol; H = *n*-hexane; L = ligroin (90-100°); M = methyl alcohol; P = petroleum ether (60-70°). (b) (Cl) Chlorine values are given in place of nitrogen for all compounds containing chlorine in Tables III-VII.

TABLE II

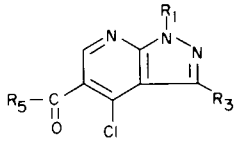
4-Hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Derivatives



R_1	R_3	R_5	pro-cedure	Yield %	M.p.	recryst. solvent	B.p.	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3	H	OC_2H_5	B	77	141-143°	L		$C_{10}H_{11}N_3O_3$	54.28	5.01	18.99	54.62	5.05	18.90
CH_3-CH_2	H	OC_2H_5	B	82	87-89°	L		$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.57	5.25	17.60
CH_3-CH_2	H	OH	C	92	201-202°	G		$C_9H_9N_3O_3$	52.19	4.38	20.28	52.16	4.35	19.90
CH_3-CH_2	CH_3	OC_2H_5	B	75	93-94°	L	125-129°/0.05 mm	$C_{12}H_{15}N_3O_3$	57.83	6.06	16.86	57.78	6.04	16.94
CH_3-CH_2	CH_3	OH	C	97	212-213°	Et		$C_{10}H_{11}N_3O_3$	54.28	5.01	18.99	54.37	4.97	18.85
CH_3-CH_2	CH_3	O-CH_2-CH_2-CH_3	D	76	64-65°	H		$C_{14}H_{19}N_3O_3$	60.63	6.90	15.15	60.73	6.75	15.46
$(CH_3)_2CH$	H	OC_2H_5	B	85	103-105°	L	122-125°/0.1 mm	$C_{12}H_{15}N_3O_3$	57.83	6.06	16.86	57.57	5.83	17.05
$(CH_3)_2CH$	CH_3	OC_2H_5	B	70	114-116°	H	130-135°/0.1 mm	$C_{13}H_{17}N_3O_3$	59.29	6.51	15.96	59.41	6.49	16.05
$(CH_3)_2CH$	CH_3	OH	C	90	202-203°	Et		$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	55.99	5.58	18.02
CH_3-CH_2-CH_2	CH_3	OC_2H_5	B	90			127-135°/0.05 mm	$C_{13}H_{17}N_3O_3$	59.29	6.51	15.96	59.53	6.62	16.11
CH_3-CH_2-CH_2	CH_3	OH	C	85	200-201°	G		$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	55.94	5.33	18.09
CH_3-CH_2-CH_2		OC_2H_5	B	67	121-123°	L		$C_{18}H_{19}N_3O_3$	66.45	5.88	12.91	66.51	5.87	12.91
CH_3-CH_2-CH_2-CH_2	H	OC_2H_5	B	76	47-49°	H	138-140°/0.1 mm	$C_{13}H_{17}N_3O_3$	59.29	6.51	15.96	59.3	6.52	16.22
CH_3-CH_2-CH_2-CH_2	CH_3	OC_2H_5	B	92			163-165°/0.05 mm	$C_{14}H_{19}N_3O_3$	60.63	6.90	15.15	60.82	7.03	15.25
	H	OC_2H_5	B	80	152-154°	L		$C_{15}H_{13}N_3O_3$	63.59	4.62	14.83	63.48	4.61	14.97
 -CH_2	H	OC_2H_5	B	78	117-119°	L		$C_{16}H_{15}N_3O_3$	64.63	5.08	14.13	64.53	5.25	14.23
 -CH_2	H	OH	C	92	197-198°	M		$C_{14}H_{11}N_3O_3$	62.45	4.11	15.61	62.52	4.33	15.24
 -CH_2	CH_3	OC_2H_5	B	79	103-104°	L	196-199°/0.2 mm	$C_{17}H_{17}N_3O_3$	65.50	5.50	13.49	65.90	5.28	13.48
CH_3	H	OH	C	98	213°	Et		$C_8H_7N_3O_3$	49.74	3.65	21.75	49.49	3.66	21.91
CH_3-CH_2	H	OCH_2-CH_2-CH_2-CH_3	D	75	70-71°	P		$C_{13}H_{17}N_3O_3$	59.29	6.51	15.96	59.42	6.59	16.21
CH_3-CH_2	H	O-$(CH_2)_8CH_3$	D	83	71-73°	H		$C_{18}H_{27}N_3O_3$	64.84	8.16	12.6	64.57	8.21	12.83

TABLE III

4-Chloro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Derivatives



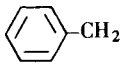
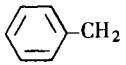
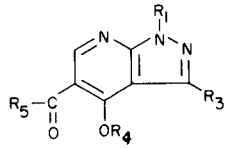
R_1	R_3	R_5	pro-cedure	Yield %	M.p.	recryst. solvent	B.p.	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	(NCl)
CH_3-CH_2	H	OC_2H_5	E	94	62-63°	H		$C_{11}H_{12}ClN_3O_2$	52.07	4.7	(13.97)	52.05	4.84	(13.94)
CH_3-CH_2	CH_3	OC_2H_5	E	93	78-80°	H		$C_{12}H_{14}ClN_3O_2$	53.83	5.27	(13.24)	54.04	5.32	(13.21)
$(CH_3)_2CH$	CH_3	OC_2H_5	E	80	84-85°	H		$C_{13}H_{16}ClN_3O_2$	55.42	5.72	(12.58)	55.37	5.73	(12.67)
CH_3-CH_2-CH_2	CH_3	OC_2H_5	E	82	52-54°	H		$C_{13}H_{16}ClN_3O_2$	55.42	5.72	(12.58)	55.52	5.81	(12.71)
CH_3-CH_2-CH_2		OC_2H_5	E	93	87-89°	H		$C_{18}H_{18}ClN_3O_2$	62.87	5.27	(10.31)	62.90	5.23	(10.15)
CH_3-CH_2-CH_2-CH_2	H	OC_2H_5	E	80			128°/0.05 mm	$C_{13}H_{16}ClN_3O_2$	55.42	5.72	(12.58)	55.31	5.59	(12.49)
CH_3-CH_2-CH_2-CH_2	CH_3	OC_2H_5	E	78			192°/0.2 mm	$C_{14}H_{18}ClN_3O_2$	56.86	6.13	(11.99)	56.60	6.22	(12.24)
CH_3-CH_2-CH_2-CH_2	CH_3	OH	C	97	178-180°	A		$C_{12}H_{14}ClN_3O_2$	53.83	5.27	(13.24)	54.08	5.27	(13.41)
	H	OC_2H_5	E	95	100-102°	H		$C_{15}H_{12}ClN_3O_2$	59.71	4.00	(11.75)	59.55	4.09	(11.99)
	H	OC_2H_5	E	94	82-84°	C		$C_{16}H_{14}ClN_3O_2$	60.87	4.47	(11.23)	60.68	4.40	(11.31)
	CH_3	OC_2H_5	E	95	94-96°	H		$C_{17}H_{16}ClN_3O_2$	61.91	4.89	(10.75)	62.4	4.91	(10.42)
CH_3	H	OC_2H_5	E	50	84-86°	H		$C_{10}H_{10}ClN_3O_2$	50.11	4.20	(14.78)	50.06	4.23	(15.05)
CH_3-CH_2	CH_3	Cl	P	85	68-70°	C		$C_{10}H_9Cl_2N_3O$	46.53	3.51	(27.47)	46.91	3.53	(27.13)
$(CH_3)_2CH$	CH_3	Cl	P	90	81-83°	H		$C_{11}H_{11}Cl_2N_3O$	48.55	4.07	(26.06)	48.14	3.81	(25.98)

TABLE IV

4-Alkoxy-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Derivatives



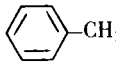
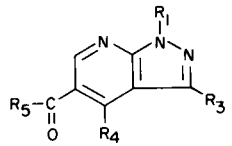
R_1	R_3	R_4	R_5	pro-cedure	Yield %	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3	H	CH_3-CH_2	OC_2H_5	F	91	128-129°	L	$C_{12}H_{15}N_3O_3$	57.81	6.06	16.86	57.96	5.98	16.83
CH_3-CH_2	H	CH_3-CH_2	OC_2H_5	F	94	113-115°	L	$C_{13}H_{17}N_3O_3$	59.31	6.51	15.96	59.18	6.48	16.08
CH_3-CH_2	H	CH_3-CH_2	OH	C	93	198-199°	Et	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.42	5.76	18.01
CH_3-CH_2	H	CH_3-$(CH_2)_8$	OC_2H_5	F	86	70°	P	$C_{20}H_{31}N_3O_3$	66.46	8.64	11.62	66.65	8.61	11.76
CH_3-CH_2	H	CH_3-CH_2-CH_2-CH_2	OC_2H_5	F	85	70-71°	L	$C_{15}H_{21}N_3O_3$	61.86	7.26	14.42	61.59	7.07	14.21
CH_3-CH_2	H	CH_3-$(CH_2)_3$	O-$(CH_2)_3$-CH_3	D	79	65-66°	L	$C_{17}H_{25}N_3O_3$	63.94	7.89	13.16	63.75	7.68	13.25
CH_3-CH_2	H	CH_3-$(CH_2)_3$	OH	C	62	148°	B	$C_{13}H_{17}N_3O_3$	59.31	6.51	15.96	59.06	6.41	16.36
CH_3-CH_2	H	CH_3-$(CH_2)_8$	O-$(CH_2)_8$-CH_3	D	88	53-55°	H	$C_{27}H_{45}N_3O_3$	70.53	9.87	9.14	70.61	9.78	9.38
CH_3-CH_2	H	 -CH_2	OC_2H_5	F	91	128°	L	$C_{18}H_{19}N_3O_3$	66.45	5.88	12.91	66.38	5.95	13.19
CH_3-CH_2	H	CH_3-CH_2	Cl	P	96	122-124°	C	$C_{11}H_{12}ClN_3O_2$	52.09	4.76	(13.98)	52.21	4.84	(14.03)
CH_3-CH_2	H	CH_3-CH_2	O-$(CH_2)_2N(C_2H_5)_2 \cdot 2HCl$	Q	77	129-130°	Ea/Et	$C_{17}H_{28}Cl_2N_4O_3$	50.12	6.92	(17.41)	50.28	7.07	(17.18)
CH_3-CH_2	H	CH_3	OCH_3	D	95	91-93°	M	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.24	5.37	17.85
CH_3-CH_2	CH_3	CH_3-CH_2	$OC_2H_5 \cdot HCl$	F	60	98° dec.	Ea	$C_{14}H_{20}ClN_3O_2$	53.59	6.24	(11.30)	53.77	6.27	(11.59)
CH_3-CH_2	CH_3	CH_3-CH_2	OH	C	92	201-202°	Et	$C_{12}H_{15}N_3O_3$	57.81	6.06	16.86	58.06	6.08	16.70
CH_3-CH_2	CH_3	CH_3	OH	C	94	189-190°	Et	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.18	5.50	18.06
CH_3-CH_2	CH_3	CH≡C-CH_2	OC_2H_5	F	50	112°	L	$C_{15}H_{17}N_3O_3$	62.70	5.97	14.62	62.60	6.01	14.70
CH_3-CH_2	H	CH_2=CH-CH_2	OC_2H_5	F	71	85-87°	P	$C_{14}H_{17}N_3O_3$	61.06	6.22	15.26	61.08	5.87	14.98
$(CH_3)_2CH$	CH_3	CH_3-CH_2	OH	C	90	154-156°	L	$C_{13}H_{17}N_3O_3$	59.31	6.51	15.96	59.41	6.42	15.81
$(CH_3)_2CH$	H	CH_3-CH_2	OC_2H_5	F	84	104-105°	L	$C_{14}H_{19}N_3O_3$	60.63	6.90	15.15	60.76	6.81	15.3
CH_3-CH_2	CH_3	$(CH_3)_2CH$	$OC_2H_5 \cdot HCl$	F	70	108-109°	Ea	$C_{15}H_{22}ClN_3O_3$	54.95	6.77	(10.81)	54.83	6.87	(10.78)
CH_3-CH_2-CH_2-CH_2	H	CH_3-CH_2	OC_2H_5	F	86	74-76°	L	$C_{15}H_{21}N_3O_3$	61.84	7.26	14.42	61.65	7.19	14.53
	H	CH_3	OCH_3	D	83	135-136°	L	$C_{15}H_{13}N_3O_3$	64.62	5.08	14.13	63.91	4.56	14.66
 -CH_2	H	CH_3-CH_2	OC_2H_5	F	87	94-96°	L	$C_{18}H_{19}N_3O_3$	66.45	5.88	12.91	66.32	5.93	13.05

TABLE IV (Continued)

R_1	R_3	R_4	R_5	pro-cedure	Yield %	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
	H	CH_3-CH_2	OH	C	93	181-182°	Et	$C_{16}H_{15}N_3O_3$	64.63	5.08	14.13	64.68	5.02	14.09
	CH_3	CH_3-CH_2	OC_2H_5	F	79	77-78°	H	$C_{19}H_{21}N_3O_3$	67.25	6.23	12.38	66.86	6.14	12.61
CH_3-CH_2	H	CH_3	Cl	P	89	141-143°	C	$C_{10}H_{10}ClN_3O_2$	50.12	4.20	(14.79)	50.45	4.16	(14.91)
	H	CH_3	Cl	P	96	169-170°	C	$C_{14}H_{10}ClN_3O_2$	58.44	3.50	(12.32)	58.63	3.47	(12.50)
CH_3-CH_2	CH_3	CH_3	OCH_3	D	94	51-53°	H	$C_{12}H_{15}N_3O_3$	57.81	6.06	16.86	57.97	6.01	17.13
CH_3-CH_2	H	CH_3	OH	C	82	216-217°	Et	$C_{10}H_{11}N_3O_3$	54.29	5.01	19.00	54.18	5.03	18.93
CH_3-CH_2-CH_2-CH_2	H	CH_3-CH_2	OH	C	97	162°	Et	$C_{13}H_{17}N_3O_3$	59.31	6.51	15.96	59.19	6.46	16.25

TABLE V

4-Hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Derivatives



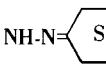
R_1	R_3	R_4	R_5	pro-cedure	Yield %	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3	H	NH-NH_2·HCl	OC_2H_5	G	90	208-209°	Et	$C_{10}H_{14}ClN_5O_2$	44.20	5.19	(13.05)	44.45	4.99	(13.02)
CH_3	H	NH-N=$C(CH_3)_2$·HCl	OC_2H_5	I	86	212-213°	Et	$C_{13}H_{18}ClN_5O_2$	50.00	5.81	(11.37)	50.14	5.71	(11.43)
CH_3-CH_2	H	NH-N=$C(CH_3)_2$	OH	C	94	225°	Et	$C_{12}H_{15}N_5O_2$	55.16	5.78	26.81	55.38	5.69	26.70
CH_3-CH_2	H	NH-NH_2	OC_2H_5	G	84	139-140°	L/B	$C_{11}H_{15}N_5O_2$	53.01	6.06	28.10	52.92	5.97	27.79
CH_3-CH_2	H	NH-N=$C(CH_3)_2$·HCl	OC_2H_5	I	96	193-195° 210-220°	Ea/Et	$C_{14}H_{20}ClN_5O_2$	51.63	6.18	(10.88)	51.62	6.09	(10.88)
CH_3-CH_2	H	NH-N=  ·HCl	OC_2H_5	I	85	198-199°	Ea/Et	$C_{17}H_{24}ClN_5O_2$	55.81	6.61	(9.69)	55.99	6.47	(9.59)

TABLE V (Continued)

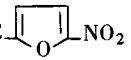
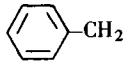
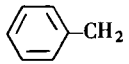
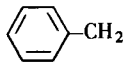
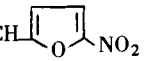
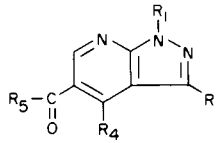
R_1	R_3	R_4	R_5	procedure	Yield %	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3-CH_2	H	NH-N=C[$(CH_2)_3CH_3$]$_2$·HCl	OC_2H_5	I	95	156°	L/B	$C_{20}H_{32}ClN_5O_2$	58.59	7.86	(8.65)	58.19	7.86	(8.68)
CH_3-CH_2	H	NH-NH_2	O-$(CH_2)_3CH_3$	G	83	86-88°	L	$C_{13}H_{19}N_5O_2$	56.30	6.90	25.25	56.44	6.91	25.13
CH_3-CH_2	H	NH-N=C$(CH_3)_2$·HCl	O-$(CH_2)_3CH_3$	I	79	149°	B	$C_{16}H_{24}ClN_5O_2$	54.31	10.02	(6.83)	53.89	10.25	(6.72)
CH_3-CH_2	H	NH-N=C$(CH_2OH)_2$	OC_2H_5	I	92	175-177°	Et	$C_{14}H_{19}N_5O_4$	52.33	5.96	21.79	52.31	5.99	21.94
CH_3-CH_2	H	NH-N=C(CH_3)-CH_2-CH$(OCH_3)_2$	OC_2H_5	I	65	76-77°	P	$C_{17}H_{25}N_5O_4$	56.18	6.93	19.27	56.28	6.94	19.53
CH_3-CH_2	H	NH-NH- 	OC_2H_5	H	78	176-177°	Et	$C_{17}H_{19}N_5O_2$	62.76	5.88	21.53	62.76	5.87	21.35
CH_3-CH_2	H	NH-N=HC- 	OC_2H_5	G	95	228-229°	Ea	$C_{16}H_{16}N_6O_5$	51.61	4.33	22.57	51.23	4.17	22.37
CH_3-CH_2	H	NH-NH-CO-CH_3	OC_2H_5	K	85	226-227°	Et	$C_{13}H_{17}N_5O_3$	53.59	5.88	24.04	53.56	5.89	24.11
CH_3-CH_2	H	NH-N$(CO$-$CH_3)_2$	OC_2H_5	L	10	113-114°	H	$C_{15}H_{19}N_5O_4$	54.04	5.73	21.01	53.84	5.89	20.95
CH_3-CH_2	CH_3	NH-NH_2	NH-NH_2	G	68	192-193°	Ea/Et	$C_{10}H_{15}N_7O$	48.19	6.06	39.34	48.18	6.04	38.96
$(CH_3)_2CH$	H	NH-NH_2	OC_2H_5	G	85	136-138°	L/B	$C_{12}H_{17}N_5O_2$	54.75	6.51	26.61	54.70	6.67	26.62
$(CH_3)_2CH$	H	NH-N=C$(CH_3)_2$·HCl	OC_2H_5	I	83	215-216°	A	$C_{15}H_{22}ClN_5O_2$	53.01	6.52	(10.43)	53.04	6.48	(10.42)
$(CH_3)_2CH$	CH_3	NH-NH_2	OC_2H_5	G	56	163°	L	$C_{13}H_{19}N_5O_2$	56.30	6.90	25.25	56.10	7.05	25.27
$(CH_3)_2CH$	CH_3	NH-N=C$(CH_3)_2$	OC_2H_5	I	92	160°	L	$C_{16}H_{23}N_5O_2$	60.54	7.30	22.07	60.51	7.21	22.29
 -CH_2	H	NH-NH_2	OC_2H_5	G	76	159-161°	Et	$C_{16}H_{17}N_5O_2$	61.72	5.50	22.49	61.67	5.53	22.52
 -CH_2	H	NH-N=C$(CH_3)_2$·HCl	OC_2H_5	I	74	178-180°	At	$C_{19}H_{22}ClN_5O_2$	58.83	5.45	18.05	58.95	5.74	17.99
 -CH_2	H	NH-N=CH- 	OC_2H_5	I	91	205-207°	Ea	$C_{21}H_{18}N_6O_5$	58.05	4.17	19.34	58.13	4.16	19.18
CH_3-CH_2	CH_3	NH-NH_2	OC_2H_5	G	84	156-158°	L	$C_{12}H_{17}N_5O_2$	54.75	6.51	26.61	54.38	6.57	26.86
CH_3-CH_2	CH_3	NH-N=C$(CH_3)_2$·HCl	OC_2H_5	I	74	197-199° 204-205°	Ea	$C_{15}H_{22}ClN_5O_2$	53.01	6.52	(10.43)	53.19	6.43	(10.16)

TABLE VI

4-Amino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Derivatives



R_1	R_3	R_4	R_5	procedure	Yield %	M.p.	salt	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3	H	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	52		hydrochloride	180-181°	Ea/E	$C_{14}H_{21}ClN_4O_2$	53.75	6.76	(11.33)	53.86	6.56	(11.47)
CH_3	H	NH-CH_2-CH_2-CH_2-CH_3	OH	C	95	217-218°			Et	$C_{12}H_{16}N_4O_2$	58.04	6.49	22.56	58.31	6.46	22.54
CH_3-CH_2	H	NH_2	OC_2H_5	N	77	181-182°			Et	$C_{11}H_{14}N_4O_2$	56.40	6.02	23.92	56.63	5.86	23.93
CH_3-CH_2	CH_3	NH_2	OC_2H_5	N	90	177-179°			Et	$C_{12}H_{16}N_4O_2$	58.04	6.49	22.56	58.00	6.52	22.39
CH_3-CH_2	H	NH_2	OH	C	96	248-249°			Et	$C_9H_{10}N_4O_2$	52.42	4.88	27.17	52.46	4.91	27.48
CH_3-CH_2	H	$N(C_2H_5)_2$	OC_2H_5	N	54		hydrochloride	104-105°	Ea	$C_{15}H_{23}ClN_4O_2$	55.12	7.09	(10.84)	55.24	7.15	(10.63)
CH_3-CH_2	CH_3	$N(C_2H_5)_2$	OC_2H_5	N	75		hydrochloride	102°	Ea/E	$C_{16}H_{25}ClN_4O_2$	56.38	7.39	(10.40)	56.14	7.58	(10.08)
CH_3-CH_2	H	NH-CH_2-CH_2-CH_3	OC_2H_5	N	88		hydrochloride	174-175°	Ea/Et	$C_{14}H_{21}ClN_4O_2$	53.75	6.76	(11.33)	53.92	6.66	(11.12)
CH_3-CH_2	H	NH-$CH(CH_3)_2$	OC_2H_5	N	94		hydrochloride	191-192°	Ea/Et	$C_{14}H_{21}ClN_4O_2$	53.75	6.76	(11.33)	53.76	6.72	(11.34)
CH_3-CH_2	H	NH-CH_2-CH=CH_2	OC_2H_5	N	91	90-92°			L	$C_{14}H_{18}N_4O_2$	61.29	6.61	20.42	61.05	6.60	20.59
CH_3-CH_2	H	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	92	82-83°			H	$C_{15}H_{22}N_4O_2$	62.05	7.63	19.30	62.17	7.64	19.49
CH_3-CH_2	CH_3	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	95		hydrochloride	152-153°	Ea	$C_{16}H_{25}ClN_4O_2$	56.38	7.39	(10.40)	56.40	7.30	(10.69)
CH_3-CH_2	CH_3	NH-CH_2-CH_2-CH_2-CH_3	OH	C	89	200-201°			Et	$C_{14}H_{20}N_4O_2$	60.84	7.29	20.27	60.85	7.32	20.58
CH_3-CH_2	H	$NHC(CH_3)_3$	OC_2H_5	N	73	117-119°			H	$C_{15}H_{22}N_4O_2$	62.05	7.63	19.30	61.88	7.58	19.59
CH_3-CH_2	H	NH-CH_2-$CH(CH_3)_2$	OC_2H_5	N	64	92-93°			H	$C_{15}H_{22}N_4O_2$	62.05	7.63	19.30	62.10	7.71	19.61
CH_3-CH_2	H	NH-$CH(CH_3)$-CH_2-CH_3	OC_2H_5	N	50		hydrochloride	171-172°	Ea	$C_{15}H_{23}ClN_4O_2$	55.12	7.09	(10.84)	55.10	7.09	(11.08)
CH_3-CH_2	H	NH-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	97	57-59°			H	$C_{17}H_{26}N_4O_2$	64.14	8.23	17.60	64.22	8.12	17.55
CH_3-CH_2	H	NH-CH_2- 	OC_2H_5	N	80	128-129°			H	$C_{18}H_{20}N_4O_2$	66.64	6.21	17.27	66.30	6.23	17.50
CH_3-CH_2	H	NH-CH_2-CH_2- 	OC_2H_5	N	81	97-99°			Et	$C_{19}H_{22}N_4O_2$	67.43	6.55	16.56	67.29	6.64	16.55
CH_3-CH_2	H	NH-$(CH_2)_3$-$N(C_2H_5)_2$	OC_2H_5	N	70	63-65°	dihydrochloride	195-196°	P	$C_{18}H_{31}Cl_2N_5O_2$	51.43	7.43	(16.87)	51.58	7.62	(16.98)
CH_3-CH_2	H	NH-$(CH_2)_2$-$N(C_2H_5)_2$	OC_2H_5	N	94	55-57°	dihydrochloride	157-158°	P	$C_{17}H_{29}Cl_2N_5O_2$	50.25	7.19	(17.45)	49.97	7.39	(17.22)

TABLE VI (Continued)

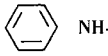
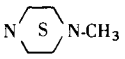
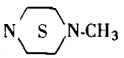
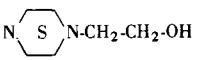
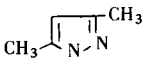
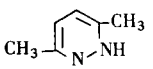
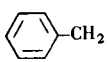
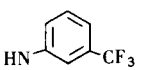
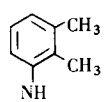
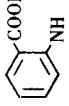
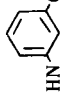
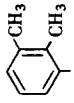
R_1	R_3	R_4	R_5	procedure	Yield %	M.p.	salt	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3-CH_2-CH_2	CH_3	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	75		hydrochloride	118-121°	Ea	$C_{17}H_{27}ClN_4O_2$	57.53	7.67	(9.99)	57.28	7.61	(10.13)
CH_3-CH_2-CH_2		NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	83		½ oxalate	107-109°	H	$C_{23}H_{29}N_4O_4$	64.93	6.87	13.17	64.55	6.70	13.51
CH_3-CH_2-CH_2-CH_2	H	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	96		hydrochloride	174-175°	Ea	$C_{17}H_{27}ClN_4O_2$	57.53	7.67	(9.99)	57.74	7.53	(10.34)
CH_3-CH_2-CH_2-CH_2	CH_3	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	53		hydrochloride	128-130°	Ea/H	$C_{18}H_{29}ClN_4O_2$	58.60	7.92	(9.61)	58.35	7.98	(9.76)
	H	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	92	96-98°			C	$C_{19}H_{22}N_4O_2$	67.43	6.55	16.56	67.48	6.46	16.86
CH_3-CH_2	H		OC_2H_5	N	92	105-106°	hydrochloride	190-191°	C	$C_{15}H_{21}ClN_4O_2$	55.49	6.51	(10.91)	55.73	6.48	(10.93)
CH_3-CH_2	CH_3		OC_2H_5	N	94		hydrochloride	199-200°	B	$C_{16}H_{23}ClN_4O_2$	56.71	6.84	(10.46)	56.96	6.78	(10.51)
CH_3-CH_2	H		OC_2H_5	N	91		hydrochloride	174-175°	Ea/Et	$C_{16}H_{23}ClN_4O_2$	56.71	6.84	(10.46)	56.94	6.75	(10.57)
CH_3-CH_2	CH_3		OC_2H_5	N	86		hydrochloride	152-153°	Ea	$C_{17}H_{25}ClN_4O_2$	57.86	7.14	(10.04)	57.91	7.32	(10.06)
CH_3-CH_2	H		OC_2H_5	N	85		dihydrochloride	232-235°	Et	$C_{16}H_{25}Cl_2N_5O_2$	49.23	6.45	(18.16)	49.01	6.38	(17.83)
CH_3-CH_2	CH_3		OC_2H_5	N	88		dihydrochloride	174-176° 206°	Et/Ea	$C_{17}H_{27}Cl_2N_5O_2$	50.49	6.73	(17.53)	50.27	6.63	(17.41)
CH_3-CH_2	H		OC_2H_5	N	86	103-104°			C	$C_{17}H_{25}N_5O_3$	58.77	7.25	20.16	58.67	7.27	19.99
CH_3-CH_2	H		OC_2H_5	R	95	61-63°			H	$C_{16}H_{19}N_5O_2$	61.33	6.11	22.35	61.26	6.09	22.50
CH_3-CH_2	H		OC_2H_5	R	85	155-157°			Et	$C_{17}H_{21}N_5O_2$	62.38	6.46	21.39	62.50	6.41	21.61
	H	NH-CH_2-CH_2-CH_2-CH_3	OC_2H_5	N	64	97-98°			Et	$C_{20}H_{24}N_4O_2$	68.74	6.92	15.17	68.53	7.12	14.93
CH_3-CH_2	H		OC_2H_5	O	75	96-97°			Et/H_2O	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.74	5.57	18.5
CH_3-CH_2	H		OC_2H_5	N	67	101.5-102°			Et/H_2O	$C_{18}H_{17}F_3N_4O_2$	57.13	4.53	14.81	57.35	4.47	14.90
CH_3-CH_2	H		OC_2H_5	N	70	99-101°			Et/H_2O	$C_{19}H_{22}N_4O_2$	67.44	6.55	16.56	67.56	6.30	16.01

TABLE VI (Continued)

R_1	R_3	R_4	R_5	pro-cedure	Yield %	M.p.	salt	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3-CH_2	H		OC_2H_5	N	25	193-196°			Et/H_2O	$C_{18}H_{18}N_4O_4$	61.00	5.12	15.81	60.85	5.06	16.20
CH_3-CH_2	H	NH-CH_2-CH_2-CH_2-CH_3	OH	C	50	213-214°			Et	$C_{13}H_{15}N_4O_2$	59.52	6.91	21.36	59.36	6.88	21.48
CH_3-CH_2	H		OH	C	73	237-238°			Ac	$C_{15}H_{14}N_4O_2$	63.82	5.00	19.85	63.61	4.76	19.58
CH_3-CH_2	H		OH	C	75	250°			Ac	$C_{16}H_{13}F_3N_4O_2$	54.86	3.74	15.99	54.44	3.66	15.51
CH_3-CH_2	H		OH	C	78	212-213°			Et	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.56	5.74	17.80
CH_3-CH_2	H	N_3	OC_2H_5	J	85	73-74°			A/H_2O	$C_{11}H_{12}N_6O_2$	50.76	4.64	32.29	51.06	4.60	32.57
CH_3-CH_2	H	NH-CH_2-CH_2-CH_2-CH_3	Cl	P	95	134-136°			B	$C_{13}H_{17}ClN_4O$	55.62	6.10	(12.63)	55.40	6.02	(12.78)

115°, and, after recrystallization from ligroin (90-100°), melted at 113-115°.

Procedure G. Ethyl 1-Ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

To a solution of 5.08 g. (0.02 mole) of ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 50 ml. of benzene there was added 2.5 g. (0.05 mole) of 100% hydrazine hydrate. The reaction mixture was stirred for 4 days, and then filtered to remove the hydrazine hydrochloride. The filtrate was concentrated to dryness under reduced pressure, and, after recrystallization from a benzene-ligroin mixture (1:3), melted at 139-140°.

The hydrochloride was formed by adding 5 ml. of a 6.3 *N* ethanolic hydrogen chloride solution to a cooled solution of 5 g. of ethyl 1-ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 100 ml. of absolute ethanol. The hydrochloride precipitated as a white solid immediately. The mixture was diluted with anhydrous ether and filtered. The solid was washed with anhydrous ether, air-dried overnight, and, after recrystallization from a mixture of acetonitrile and absolute ethanol, melted at 210-212°.

This compound was also prepared by the following procedure: To a solution of 316 g. (1.2 moles) of ethyl 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 4800 ml. of absolute ethanol, there was added 72 g. (1.44 moles) of hydrazine hydrate (100%) and 0.4 g. of zinc chloride. The reaction mixture was heated under reflux for 4 hours, and the hot solution was filtered. The filtrate was concentrated to dryness under reduced pressure, and, after recrystallization from a benzene-ligroin mixture (1:3), weighed 250 g. (84%), m.p. 139-140°.

Procedure H. Ethyl 1-Ethyl-4-(2-phenylhydrazino)-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate.

A solution of 25.3 g. (0.1 mole) of ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and 21.6 g. (0.2 mole) of phenylhydrazine in 200 ml. of benzene was heated under reflux for 4 hours. The reaction mixture was cooled, filtered to remove the phenylhydrazine hydrochloride, and then concentrated to dryness under reduced pressure. The residue was recrystallized from 95% ethanol to give 25.4 g. (78%) of product, m.p. 176-177°.

Procedure I. Ethyl 1-Ethyl-4-isopropylidenehydrazino-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate Hydrochloride.

A solution of 8.4 g. (0.034 mole) of ethyl 1-ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 100 ml. of acetone was heated under reflux for 1 hour. To the cooled solution, there was added 10 ml. of a 6.7 *N* ethanolic hydrogen chloride solution, resulting in the precipitation of a white crystalline solid. The mixture was diluted with 150 ml. of anhydrous ether and filtered. The solid was washed with anhydrous ether and dried overnight at 110° at 1 mm. The product, which weighed 10.5 g. (96%), melted with decomposition at 193-195°, resolidified at 198°, and then remelted at 210-220°.

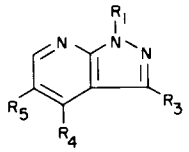
The free base, m.p. 92-93°, was obtained by concentrating the original reaction mixture to dryness under reduced pressure.

Procedure J. Ethyl 4-Azido-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A solution of 345 mg. (5 mmoles) of sodium nitrite was added slowly below the surface of a stirred solution of 1.47 g. (5 mmoles) of ethyl 4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate, hydrochloride in 20 ml. of water at room temperature. A white solid precipitated immediately. After the reaction mixture

TABLE VII

1H-Pyrazolo[3,4-b]pyridine-5-carboxamides



R_1	R_3	R_4	R_5	pro-cedure	Yield %	M.p.	salt	M.p.	recryst. solvent	Empirical Formula	Calcd., % C	H	N(Cl)	Found, % C	H	N(Cl)
CH_3-CH_2	H	OC_2H_5	CO-N(S)N-CH_3	Q	50		dihydro-chloride	202-205°	Ea/Et	$C_{16}H_{25}Cl_2N_5O_2$	49.23	6.45	(18.16)	48.82	6.54	(18.29)
CH_3-CH_2	H	OC_2H_5	CO-N(S)	Q	74	85-87°	hydro-chloride	140-142°	C	$C_{15}H_{21}ClN_4O_2$	55.46	6.51	(10.91)	55.24	6.44	(10.88)
CH_3-CH_2	H	OC_2H_5	CONH-CH_2-CH_2-CH_2-CH_3	Q	92	122-124°			C/B	$C_{15}H_{22}N_4O_2$	62.05	7.63	19.30	61.86	7.65	19.38
CH_3-CH_2	H	OC_2H_5	CO-NH-CH_2-CH_2-N(C_2H_5)$_2$	Q	77	109-111°			C	$C_{17}H_{27}N_5O_2$	61.23	8.16	21.00	61.48	8.22	21.01
CH_3-CH_2	H	OC_2H_5	CO-N(S)N-CH_2-CH_2-OH	Q	89	106-108° (a)			Ea	$C_{17}H_{25}N_5O_3$	58.77	7.25	20.16	58.68	7.27	20.37
CH_3-CH_2	CH_3	Cl	CO-N(S)N-CH_3	Q	75	152°			L	$C_{15}H_{20}ClN_5O$	55.98	6.26	(11.01)	55.71	6.34	(11.21)
CH_3-CH_2	H	OC_2H_5	CO-N(S)	Q	83	123-124°			C	$C_{16}H_{22}N_4O_2$	63.56	7.33	18.53	63.83	7.39	18.61
CH_3-CH_2	H	OC_2H_5	CO-NH_2	S	71	184-185°			B	$C_{11}H_{14}N_4O_2$	56.38	6.02	23.92	56.16	6.00	23.75
CH_3-CH_2	CH_3	OC_2H_5	CO-N(S)	Q	82		hydro-chloride	153-154°	Ea/Et	$C_{17}H_{25}ClN_4O_2$	57.86	7.14	(10.04)	58.15	7.01	(10.07)
CH_3-CH_2	CH_3	OC_2H_5	CO-N(S)	Q	83		hydro-chloride	158-160°	Ea/E	$C_{16}H_{23}ClN_4O_2$	56.71	6.84	(10.46)	56.53	6.71	(10.30)

(a) Dihydrochloride, m.p. 154-155°.

TABLE VIII

Spectroscopic Properties of Representative Compounds

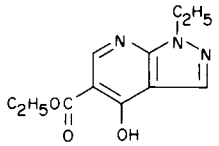
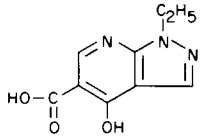
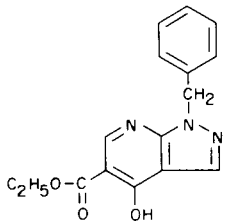
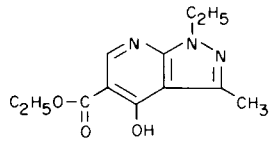
Compound Number	Structure	NMR (a) R^1 ppm (e)	R^3/H^3 ppm	H^6 ppm	R^4 ppm	R^5 ppm (e)	IR (c) OH	NH	C=O
IX		1.35 (t) 4.45 (q)	8.07	8.90	12.30	1.53 (t) 4.50 (q)	3430	----	1670
X (b)		1.48 (t) 4.48 (q)	8.33	8.80	9.98 (broad)	9.98 (broad)	3450	----	1660
XI		5.68 7.35	8.22	9.02	12.48 (broad)	1.43 (t) 4.48 (q)	3440	----	1670
XII		1.43 (t) 4.43 (q)	2.63	8.95	12.35 (broad)	1.48 (t) 4.45 (q)	3440	----	1675

TABLE VIII (Continued)

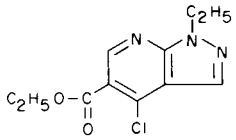
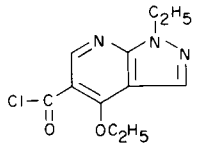
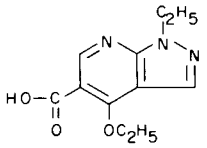
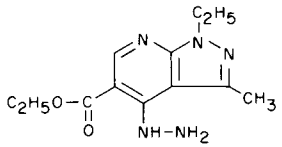
Compound Number	Structure	NMR (a) R^1 ppm (e)	R^3/H^3 ppm	H^6 ppm	R^4 ppm	R^5 ppm (e)	IR (c) OH	NH	C=O
XIII		1.45 (t) 4.47 (q)	8.17	8.98	---	1.57 (t) 4.58 (q)	----	----	1730
XIV		1.55 (t) 4.62 (q)	8.27	9.35	1.72 (t) 4.83 (q)	----	----	----	1765
XV (b)		1.47 (t) 4.53 (q)	8.45	9.02	1.53 (t) 4.78 (q)	9.47 (broad)	3450	----	1720
XVI (b)		1.30 (t) 4.28 (q)	2.68	8.67	3.77 (very broad) 10.25 (broadened)	1.33 (t) 4.28 (q)	----	3290 3180	1670

TABLE VIII (Continued)

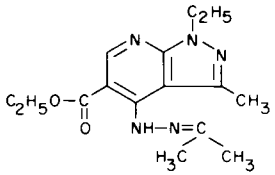
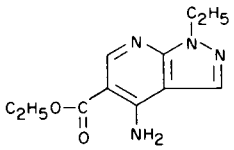
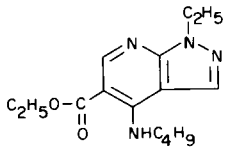
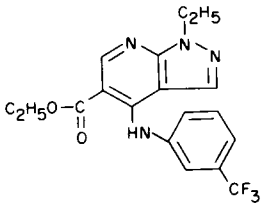
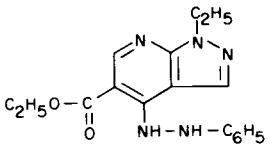
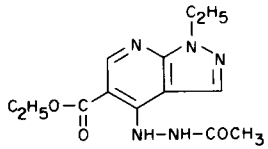
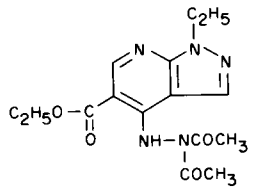
Compound Number	Structure	NMR (a) R^1 ppm (e)	R^3/H^3 ppm	H^6 ppm	R^4 ppm	R^5 ppm (e)	OH	IR (c) NH	C=O
XVII (b)		1.40 (t) 4.48 (q)	2.70	8.67	11.28 (broad) 2.00 2.13	1.43 (t) 4.48 (q)	----	3160	1665
XVIII		1.42 (t) 4.40 (q)	8.05	8.97	4.48 (broad)	1.58 (t) 4.55 (q)	----	3450 3290	1682
XIX		1.38 (t) 4.35 (q)	8.03	8.85	0.80-2.10 (m) 3.65 (sex) 9.17 (t, broad)	1.50 (t) 4.48 (q)	----	3280	1673
XX (b)		1.37 (t) 4.38 (q)	6.62	9.05	7.42 (s, broad) 7.82 (s, broad)	1.37 (t) 4.38 (q)	----	3220	1680

TABLE VIII (Continued)

Compound Number	Structure	NMR (a) R^1 ppm (e)	R^3/H^3 ppm	H^6 ppm	R^4 ppm	R^5 ppm (e)	IR (c) OH	NH	C=O
XXI		1.38 (t) 4.38 (q)	8.32	9.13	6.55, 10.40 broadened 6.77-7.53 (m)	1.47 (t) 4.50 (q)	3290	----	1675
XXII (b)		1.42 (t) 4.48 (q)	8.40	8.85	10.07, 10.65 broadened 2.18	1.47 (t) 4.57 (q)	3310	----	1680
XXIII		1.43 (t) 4.40 (q)	7.77	9.18	10.80 (broadened) 2.53	1.50 (t) 4.50 (q)	3300	----	1710

(a) 20% solution in deuteriochloroform; (b) 20% solution in DMSO-d_6; (c) Taken in potassium bromide pellet or as melted film; (e) Superscript indicates position in pyrazolopyridine ring. In the case of some compounds, it is not possible to distinguish with certainty between R^1 and R^5 in the nmr spectrum. We have arbitrarily assigned the downfield signal to the R^1 position in these cases. s = singlet; d = doublet; t = triplet; q = quartet; sex = sextet; m = multiplet.

had been stirred for 1 hour at room temperature, 25 ml. of 10% sodium hydroxide solution was added, and the stirring was continued for an additional 30 minutes. The solid was filtered, washed with water, and air-dried. It weighed 1.1 g. (85%), m.p. 68-70°.

Procedure K. Ethyl 4-(2-Acetylhydrazino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

To a solution of 4 g. of acetic anhydride in 50 ml. of chloroform, there was added 5.0 g. (0.02 mole) of ethyl 1-ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate, and the mixture was heated under reflux for 1.5 hours. The solution was concentrated to dryness under reduced pressure, and the residue was recrystallized from ethanol. The product, which weighed 4.9 g. (85%), melted at 226-227°.

Procedure L. Ethyl 4-(2,2-Diacetylhydrazino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A mixture of 3 g. (0.012 mole) of ethyl 1-ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and 25 ml. of acetic anhydride was heated at 100° for 1 hour, cooled and filtered to remove the monoacetylated derivative (2.0 g.). The filtrate was stirred with 100 ml. of ice water to hydrolyze the unreacted acetic anhydride. The precipitated solid was filtered, washed with water, air-dried, and recrystallized from *n*-hexane to give 0.4 g. (10%) of product, m.p. 113-114°.

Procedure M. Ethyl 4-Amino-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A mixture of 10.4 g. (0.04 mole) of ethyl 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and 50 ml. of an ethanolic solution of ammonia (56.5 g. of ammonia in 1 liter of ethanol) was heated in an autoclave at 65° for 15 hours. The reaction mixture was cooled to room temperature and filtered. The solid was washed with a small amount of cold ethanol and dried at 80°. The product, which weighed 7.4 g. (79%), m.p. 180-182°, melted at 181-182° after recrystallization from absolute ethanol. An additional 0.8 g. of crude product was obtained by concentration of the filtrate, for a combined yield of 88%.

Procedure N. Ethyl 4-*n*-Butylamino-1-ethyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylate.

To a solution of 5.08 g. (0.02 mole) of ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 20 ml. of benzene, there was added 2.92 g. (0.04 mole) of *n*-butylamine, and the reaction mixture was allowed to remain at room temperature for 2 days. The precipitated *n*-butylamine hydrochloride was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure. The residue, which weighed 5.3 g. (92%), after recrystallization from *n*-hexane melted at 82-83°.

Procedure O. Ethyl 1-Ethyl-4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A mixture of 10.1 g. (0.04 mole) of ethyl 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and 20 ml. of aniline was stirred for 2 hours at 110°, and the unreacted aniline was then removed by distillation under reduced pressure. The residue was suspended in aqueous sodium bicarbonate solution, and the mixture was extracted with chloroform (3 x 100 ml.). The combined chloroform extracts were dried with sodium sulfate and then concentrated under reduced pressure. The residue, which solidified upon cooling, was recrystallized from aqueous ethanol to give 9.2 g. (75%) of product, m.p. 96-97°.

Procedure P. 4-Ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Chloride.

A mixture of 26.5 g. (0.11 mole) of 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 150 ml. of thionyl chloride was heated under reflux for 7 hours. The residue, after removal of the excess thionyl chloride by distillation under reduced pressure, weighed 27 g. (96%) and melted at 116-120°. This material was sufficiently pure to use in subsequent reactions, but it could be recrystallized from cyclohexane, and then melted at 122-124°.

Procedure Q. 4-Ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-*n*-butylcarboxamide.

To a suspension of 7.5 g. (0.03 mole) of 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid chloride in 60 ml. of benzene, there was added slowly, with cooling, 4.4 g. (0.06 mole) of *n*-butylamine. After a short time, the solid dissolved and the solution became clear. The reaction mixture was allowed to remain at room temperature for 24 hours, during which time a precipitate formed. The mixture was filtered, and the solid was washed with water to remove the *n*-butyl amine hydrochloride. The residue, which weighed 3 g. was combined with an additional 5 g. obtained by concentration of the benzene filtrate, for a total yield of 8 g. (92%), m.p. 119-121°. The product, after recrystallization from a mixture of cyclohexane and benzene, melted at 122-124°.

Procedure R. Ethyl 4-[1-(3,6-Dimethyl-1*H*-pyridazinyl)]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate.

A solution of 5 g. (0.02 mole) of ethyl 1-ethyl-4-hydrazino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate in 75 ml. of absolute ethanol was treated with 5 ml. of an 8.2 *N* ethanolic hydrogen chloride solution, followed by the addition of 2.3 g. (0.02 mole) of 2,5-hexanedione. The reaction mixture was heated under reflux for 3 hours and then allowed to remain at room temperature for 2 days. The mixture was filtered to remove an insoluble precipitate, and the filtrate was concentrated to dryness under reduced pressure. The residue was suspended in aqueous sodium carbonate solution to liberate the free base, which was then filtered and washed with water and with ether. The solid, which weighed 5.6 g. (86%), melted at 152-155°. The product, after recrystallization from absolute ethanol, melted at 155-157°.

Procedure S. 4-Ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide.

To 700 ml. of concentrated aqueous ammonia, there was added, with vigorous stirring, 34.4 g. (0.136 mole) of 4-ethoxy-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid chloride. The solid appeared to go into solution, and a new crystalline solid then precipitated. The reaction mixture was stirred for 3 hours at room temperature and filtered. The solid was washed with water and air-dried; it weighed 22.7 g. (71%), m.p. 183-185°. After recrystallization from benzene, the product melted at 184-185°.

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