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Studies on Dihydropyridines. II.[1] Synthesis of 4,7-Dihydropyrazolo[3,4-*b*]-pyridines with Vasodilating and Antihypertensive Activities

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A series of 4-aryl-4,7-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylate derivatives (**72**—**149**) was prepared and the compounds were tested for Ca-blocking activity in isolated guinea pig portal vein, antihypertensive activity in spontaneously hypertensive rats, and coronary vasodilating effect in isolated guinea pig heart. A number of derivatives had potent antihypertensive and coronary vasodilating activities. The structure–activity relationships of the series indicated that a 3-cyclopentyl or 3-cyclohexyl substituent and a hydrophobic 5-ester moiety with moderate bulkiness were effective for increasing the pharmacological potencies.

Keywords——pyrazolo[3,4-*b*]pyridine; calcium antagonist; antihypertensive activity; vasodilating activity

The interesting biological properties of nifedipine, 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine,[2] have stimulated a variety of studies on the chemistry and pharmacology of the 1,4-dihydropyridines, as well as on the preparation of more potent analogues.[3] A number of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylate derivatives have been prepared and tested for cardiovascular activity. Some of them have been found to possess potent vasodilating activity due to their calcium (Ca)-blocking effect, and are now in clinical trials or therapeutic use for the treatment of cardiovascular diseases, such as several kinds of hypertension, angina, and cerebrovascular insufficiency. In trying to prepare new types of 1,4-dihydropyridine derivatives superior to nifedipine in biological activity, we synthesized a number of 4,7-dihydropyrazolo[3,4-*b*]pyridine derivatives, having a modified 1,4-dihydropyridine system with a fused pyrazole nucleus, and screened their antihypertensive and coronary vasodilating activities. The Ca-blocking activities of these compounds were estimated from their inhibitory effect on K-contracture of isolated guinea pig portal vein. Some of the compounds were found to be promising cardiovascular agents. This paper deals with the synthesis and biological activities of the title compounds.

Synthesis

A number of 4-aryl-4,7-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylate derivatives (**72**—**149**) were prepared by Michael addition of 5-aminopyrazoles (**1**—**33**) to α,β-unsaturated ketones (**34**—**71**), followed by cyclocondensation[4] (Chart 1). The requisite 5-aminopyrazole derivatives for the synthesis of the desired compounds were prepared by the method of Dorn *et al.*[5] (1) in Chart 2) and by cyclocondensation of alkyl and phenylhydrazines with acylacetonitriles (**154**)[6] (2) and 4) in Chart 2), as well as by the reaction of methylhydrazine sulfate with methyl cyanopyruvate sodium salt (**155**) (3) in Chart 2). Thirty-three 5-aminopyrazoles (**1**—**33**) were prepared by these methods. Thirty-six benzylideneacetoacetates (**34**—**69**) and two pyridylmethylideneacetoacetates (**70** and **71**) were readily obtainable by

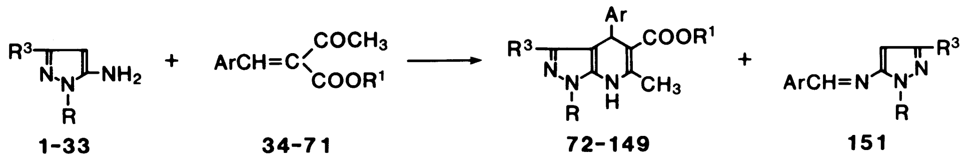


Chart 1

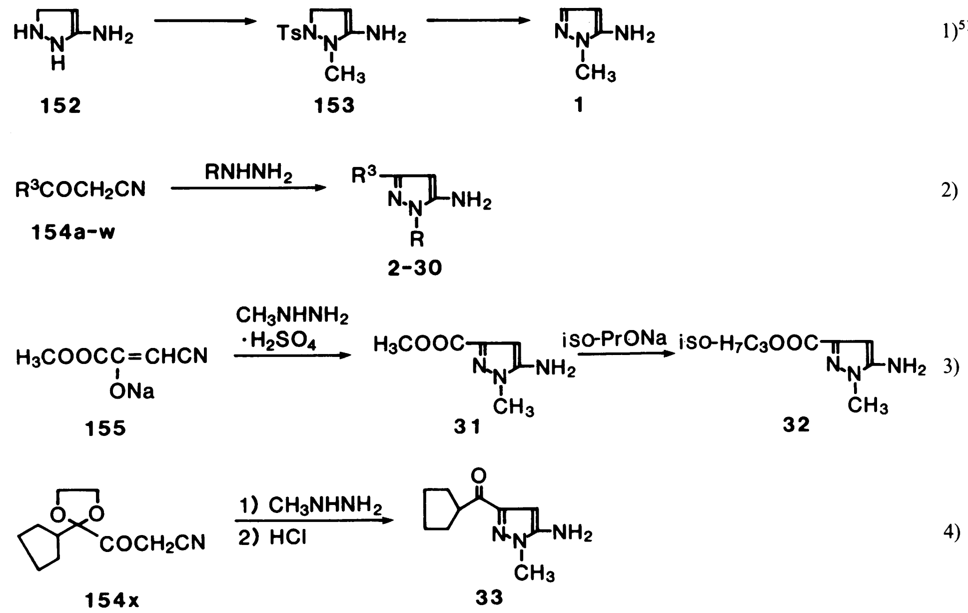


Chart 2

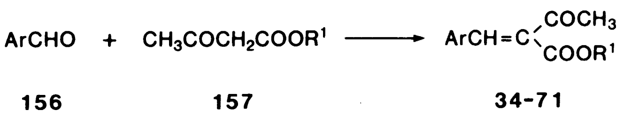


Chart 3

means of the Knoevenagel reaction[7] from the corresponding aldehydes (**156**) and alkyl acetoacetates (**157**), prepared by the reaction of diketene with alcohols[8] (Chart 3). Heating a solution of 5-amino-1-methylpyrazole (**1**) with methyl 2-nitrobenzylideneacetoacetate (**34**) in *tert*-butanol afforded methyl 4,7-dihydro-1,6-dimethyl-4-(2-nitrophenyl)pyrazolo[3,4-*b*]-pyridine-5-carboxylate (**72**) in 42.1% yield, together with a small amount of 1-methyl-5-(2-nitrobenzylidene)aminopyrazole (**151a**).[9] Similar treatment of 5-amino-3-cyclopentyl-1-methylpyrazole (**14**) with methyl 3-nitrobenzylideneacetoacetate (**58**) gave the 3-cyclopentyl-4-(3-nitrophenyl) derivative (**76**) in 94.0% yield. The compounds listed in Tables I and II were prepared from the corresponding 5-aminopyrazoles and acetoacetate derivatives in the same manner as described for the preparation of **72**. Reduction of **76** yielded the 4-(3-aminophenyl) derivative (**150**). Compounds **72**—**150** were characterized as having the 4-aryl-4,7-dihydro-6-methylpyrazolo[3,4-*b*]pyridine structure on the basis of their proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra, as well as carbon-13 nuclear magnetic resonance (^{13}C-NMR) data in some cases. However, the data did not completely rule out

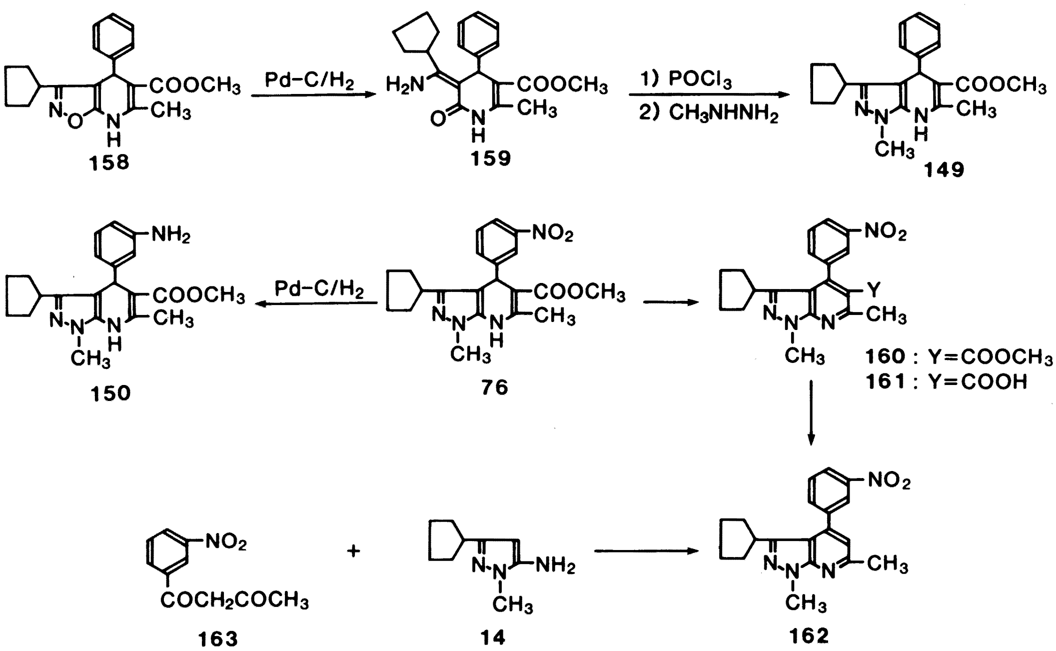


Chart 4

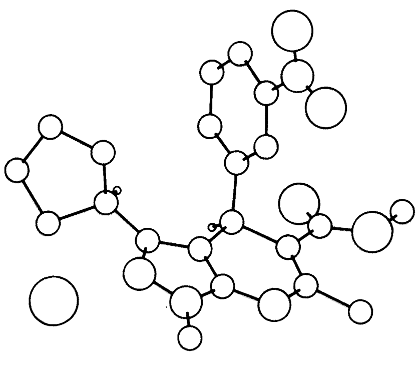


Fig. 1. X-Ray Crystallographic Structure of Methyl 3-Cyclopentyl-4,7-dihydro-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine-5-carboxylate Hydrochloride (**76**)

another structure, 6-aryl-1,2-dihydro-4-methylpyrazolo[3,4-*b*]pyridine form. In order to unequivocally establish the structure, the synthesis of **149** was successfully conducted *via* an alternative pathway starting from a known compound (**158**),[1a] as shown in Chart 4. Further, the product (**162**), which had been derived from **76** *via* oxidation followed by hydrolysis and decarboxylation, was identical with 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine, obtained by the reaction of **14** with 3-nitrobenzoylacetone (**163**).[10] Further confirmation of the structure came from an X-ray analysis of **76** hydrochloride[11] (Fig. 1).

Pharmacological Results and Discussion

The Ca-blocking activity of each test compound was evaluated in terms of its inhibitory effect on the K-contracture of isolated guinea pig portal vein.[12] The values of the concentration required for 50% relaxation of the contracture (RC_{50}) by the compounds and two reference Ca-blockers, nifedipine and nicardipine hydrochloride, were calculated from

TABLE I. Alkyl (R^1) 4-Aryl-1-R-3-R^3-4,7-dihydro-

Compd. No.	Ar	R^3	R^1	R	mp (°C)	Recrystn. solvent	Yield (%)
72	2-NO_2-C_6H_4	H	CH_3	CH_3	213—214	iso-Pr_2O	42.1
73	3-NO_2-C_6H_4	CH_3	CH_3	CH_3	186—188	iso-Pr_2O	80.5
74	3-NO_2-C_6H_4	iso-C_3H_7	C_2H_5	CH_3	217—220	MeOH	92.6
75	3-NO_2-C_6H_4	*n*-C_4H_9	CH_3	CH_3	129—132	Et_2O	96.7
76	3-NO_2-C_6H_4	Cyclopentyl	CH_3	CH_3	172—173	iso-PrOH	94.0
77	3-NO_2-C_6H_4	Cyclopentyl	C_2H_5	CH_3	170—173	Acetone	78.4
78	3-NO_2-C_6H_4	Cyclopentyl	iso-C_3H_7	CH_3	190 (dec.)	iso-PrOH	68.2
79	2-NO_2-C_6H_4	Cyclopentyl	CH_3	CH_3	212—213	EtOH	77.6
80	2-NO_2-C_6H_4	Cyclopentyl	$CH_2CH_2OCH_3$	CH_3	197—198	EtOH	68.6
81	3-NO_2-C_6H_4	Cyclohexyl	CH_3	CH_3	230 (dec.)	MeOH	71.7
82	2-NO_2-C_6H_4	Cyclohexyl	CH_3	CH_3	217—219	MeCN	79.6
83	3-NO_2-C_6H_4	Cyclopentyl	CH_3	Cyclopentyl	175—176	EtOH	71.8
84	3-NO_2-C_6H_4	C_6H_5	C_2H_5	CH_3	157—158	CH_2Cl_2-Et_2O	83.7
85	3-NO_2-C_6H_4	C_6H_5	C_2H_5	C_6H_5	214—215	EtOAc	79.2
86	3-NO_2-C_6H_4	CO_2CH_3	CH_3	CH_3	208—209	EtOAc	59.8
87	3-NO_2-C_6H_4	CO_2-iso-C_3H_7	CH_3	CH_3	181—182	EtOAc	56.5
88	2-Cl-C_6H_4	Cyclopentyl	C_2H_5	CH_3	170 (dec.)	MeOH-acetone	59.0
89	2,6-Cl_2-C_6H_3	Cyclopentyl	C_2H_5	CH_3	147—148	iso-PrOH	15.7
	Nifedipine						
	Nicardipine hydrochloride						

Abbreviations used are: anti-HT activity, antihypertensive activity; SBP, systolic blood pressure; CVD effect, coronary vasodilating effect; CPF, coronary perfusion flow. *a*) RC_{50} values are the concentrations required for 50% relaxation of the contracture of isolated guinea-pig portal veins by KCl at 5×10^{-2} M. Usually 4 to 6 preparations were used for the determination of RC_{50} of test compounds except in the cases of **80** and **82** (2 preparations for each). *b*) For the determination of antihypertensive activities, test compounds were intraperitoneally administered at a dose of 3 mg/kg in 2 SHRs. Four SHRs were used for nifedipine

the concentration–response curves (Table I). Compound **72**, methyl 4,7-dihydro-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine-5-carboxylate, had no Ca-blocking effect, but the introduction of a 3-alkyl substituent into it increased its potency. Compounds **75**—**82** exhibited potent Ca-blocking activity, though they were less active than nifedipine and nicardipine hydrochloride. Similarly, the 3-phenyl and 3-isopropoxycarbonyl derivatives (**84** and **87**) as well as the 3-alkyl-4-(2-chlorophenyl) derivative (**88**) showed moderate potency.

6-methylpyrazolo[3,4-*b*]pyridine-5-carboxylates (**72**—**89**)

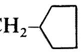
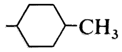
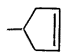
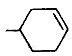
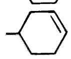
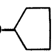
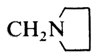
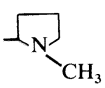
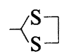
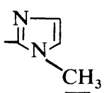
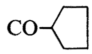
Formula	Analysis (%) Calcd (Found) C	H	N	Ca-blocking activity[a] RC_{50} ($\times 10^{-9}$ M)	Anti-HT activity[b] max. change of SBP (mmHg)	CVD effect[c] max. change of CPF (%)	Acute toxicity[d] LD_{50} (mg/kg)
$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	>10000	0	0	
	(58.68	4.89	17.14)				
$C_{17}H_{18}N_4O_4$	59.64	5.30	16.37	—[e]	−15	+11.3	
	(59.66	5.16	16.31)				
$C_{20}H_{25}ClN_4O_4$[f]	57.07	5.99	13.31	30	−5	+21.2	
	(56.93	5.97	13.36)				
$C_{20}H_{24}N_4O_4$	62.48	6.29	14.58	13	−46	+50.0 (5)	
	(62.52	6.31	14.46)				
$C_{21}H_{24}N_4O_4$	63.62	6.10	14.13	11	−66	+47.1 (20)	524
	(63.42	6.08	14.07)				
$C_{22}H_{27}ClN_4O_4$[f]	59.12	6.09	12.54	11	−42	+69.4 (9)	>1000
	(58.90	6.10	12.57)				
$C_{23}H_{29}ClN_4O_4$[f]	59.93	6.34	12.16	32	−16	+56.3 (6)	
	(59.92	6.00	12.03)				
$C_{21}H_{24}N_4O_4$	63.62	6.10	14.13	16	−90	0	239
	(63.50	6.15	14.10)				
$C_{23}H_{28}N_4O_5$	62.71	6.41	12.72	12.5	−45	+59.1 (8)	
	(62.69	6.20	12.82)				
$C_{22}H_{27}ClN_4O_4$[f]	59.13	6.09	12.54	26	−65	+49.7 (20)	
	(58.76	6.09	12.50)				
$C_{22}H_{26}N_4O_4$	64.37	6.39	13.65	20.5	−76	0	292
	(64.21	6.31	13.52)				
$C_{25}H_{30}N_4O_4$	66.65	6.71	12.44	>10000	0	0	
	(66.68	6.68	12.44)				
$C_{23}H_{22}N_4O_4$	66.01	5.30	13.39	50	0	+15.7	
	(65.94	5.16	13.33)				
$C_{28}H_{24}N_4O_4$	69.99	5.03	11.66	>10000	0	0	
	(70.28	5.09	11.68)				
$C_{18}H_{18}N_4O_6$	55.95	4.70	14.50	120	−19	0	
	(55.91	4.71	14.40)				
$C_{20}H_{22}N_4O_6$	57.96	5.35	13.52	39	−30	0	
	(57.73	5.36	13.30)				
$C_{22}H_{27}Cl_2N_3O_2$[f]	60.55	6.24	9.63	44	−4	+59.4 (6)	
	(60.63	6.31	9.75)				
$C_{22}H_{25}Cl_2N_3O_2 \cdot$	59.60	5.91	9.47	70	0	+50.1 (7)	
$1/2\,H_2O$	(59.56	6.04	9.41)				
				4.2	−45	+70.4 (7)	562
				4.8	−53	+91.0 (13)	

and **76**. *c*) The test compounds were intravascularly administered at a dose of 0.1 μg. Two to 4 preparations for each compound were used for the determination of CVD effect. The values in parentheses are the times (min) required for 50% recovery of the maximum change of CPF. *d*) LD_{50} values were determined after the oral administration of test compounds to 12 to 40 male slc. ddY mice. However, small number of mice was employed in some cases to obtain a rough indication of toxicity: **77**, **93**, **116**, **117**, **119**, **123** and **131**. *e*) Not tested. *f*) Hydrochloride.

Replacements with 1-phenyl and 1-cyclopentyl substituents resulted in a decrease of potency as seen in compounds **85** and **83**.

Antihypertensive activity was evaluated in conscious spontaneously hypertensive rats (SHR). Systolic blood pressure (SBP), recorded indirectly from the tail, was determined before dosing and at various time intervals during the ensuing 6 h after intraperitoneal administration of a test compound.[13] As can be seen in Table I, the compounds with potent

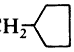
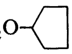
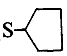
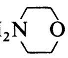
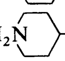
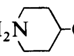
TABLE II. Alkyl (R^1) 4-Aryl-3-R^3-4,7-dihydro-1,6-

Compd. No.	Ar	R^1	R^3	mp (°C)	Recrystn. solvent
90	3-NO_2–C_6H_4	CH_3	iso-C_4H_9	114—115	EtOAc
91	3-NO_2–C_6H_4	CH_3	*tert*-C_4H_9	153—154	EtOAc
92	3-NO_2–C_6H_4	CH_3	$CH_2CH=CH_2$	102—105	Et_2O
93	2-NO_2–C_6H_4	CH_3	CH_2–	159—160	EtOAc–hexane
94	3-NO_2–C_6H_4	CH_3	$CH_2C_6H_5$	125—126	CH_2Cl_2–Et_2O
95	3-NO_2–C_6H_4	CH_3	Cyclopropyl	101—102	Et_2O
96	3-NO_2–C_6H_4	CH_3	Cyclobutyl	183—185	EtOAc
97	3-NO_2–C_6H_4	CH_3	Cycloheptyl	199—200	Et_2O
98	3-NO_2–C_6H_4	CH_3		197—198	iso-PrOH
99	3-NO_2–C_6H_4	CH_3		181—183	iso-PrOH
100	3-NO_2–C_6H_4	CH_3		196—197	EtOAc
101	2-NO_2–C_6H_4	CH_3		216—217	EtOH
102	3-NO_2–C_6H_4	CH_3	$CH_2CH_2OCH_3$	157—158	EtOAc
103	3-NO_2–C_6H_4	CH_3	CH_2O–	174—175	EtOAc
104	3-NO_2–C_6H_4	CH_3		230 (dec.)	MeOH
105	3-NO_2–C_6H_4	CH_3		158—160	EtOAc
106	3-NO_2–C_6H_4	CH_3		146—150	MeOH
107	3-NO_2–C_6H_4	CH_3	C_6H_3–3,5-Cl_2	263—264	THF–EtOH
108	3-NO_2–C_6H_4	CH_3	2-Pyridyl	213—214	iso-PrOH
109	3-NO_2–C_6H_4	CH_3	3-Furyl	197—198	EtOH
110	2-NO_2–C_6H_4	CH_3	2-Thienyl	185—188	EtOH
111	3-NO_2–C_6H_4	CH_3		207—208	MeOH
112	2-NO_2–C_6H_4	CH_3		204—205	EtOH
113	2-NO_2–C_6H_4	C_2H_5	Cyclopentyl	149—150	EtOAc

dimethylpyrazolo[3,4-*b*]pyridine-5-carboxylates (**90**—**150**)

Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Anti-HT activity[a] max. change of SBP (mmHg)	CVD effect[b] max. change of CPF (%)		Acute toxicity[c] LD_{50} (mg/kg)
59.0	$C_{20}H_{24}N_4O_4$	62.48 (62.12	6.29 6.12	14.58 14.76)	−55	+36.5	(7)	
38.8	$C_{20}H_{24}N_4O_4 \cdot 1/2\,H_2O$	61.06 (61.25	6.40 6.52	14.24 13.88)	−33	+21.6		
81.3	$C_{19}H_{20}N_4O_4$	61.94 (61.85	5.47 5.68	15.21 14.94)	−22	+15.5		
81.9	$C_{22}H_{26}N_4O_4$	64.37 (64.44	6.39 6.39	13.65 13.62)	−30	+71.4	(13)	1000
71.4	$C_{23}H_{23}ClN_4O_4 \cdot 1/2\,H_2O$[e]	59.54 (59.35	5.22 5.36	12.07 11.83)	0	0		
73.7	$C_{19}H_{20}N_4O_4$	61.94 (61.84	5.47 5.56	15.21 15.05)	−9	+20.3		
68.5	$C_{20}H_{22}N_4O_4$	62.81 (62.63	5.80 5.83	14.65 14.58)	−64	+36.9	(7)	720
95.2	$C_{23}H_{28}N_4O_4$	65.07 (65.13	6.65 6.77	13.20 13.10)	−38	+59.7	(14)	
53.2	$C_{23}H_{28}N_4O_4$	65.07 (65.09	6.65 6.60	13.20 13.05)	−2	+10.4		
78.7	$C_{21}H_{22}N_4O_4$	63.94 (64.01	5.62 5.50	14.21 13.93)	−60	+20.1		
81.7	$C_{22}H_{24}N_4O_4$	64.69 (64.61	5.92 5.70	13.72 13.74)	−40	+27.1		
70.1	$C_{22}H_{24}N_4O_4$	64.69 (64.61	5.92 5.82	13.72 13.50)	−65	0		
54.2	$C_{19}H_{22}N_4O_5$	59.06 (58.91	5.74 5.71	14.50 14.39)	0	0		
82.7	$C_{22}H_{26}N_4O_5$	61.96 (61.80	6.15 6.17	13.14 12.93)	−13	+23.8		
79.3	$C_{21}H_{26}ClN_5O_4$[e]	56.31 (56.12	5.85 5.83	15.64 15.59)	0	0		
21.5	$C_{21}H_{25}N_5O_4$	61.30 (61.19	6.12 6.26	17.02 16.89)	−9	0		
33.0	$C_{19}H_{21}ClN_4O_4S_2$[e]	48.66 (48.66	4.51 4.81	11.95 12.01)	−38	0		
84.5	$C_{22}H_{18}Cl_2N_4O_4$	55.82 (55.80	3.83 3.82	11.84 11.74)	0	0		
75.7	$C_{21}H_{19}N_5O_4$	62.21 (61.99	4.72 4.90	17.28 17.10)	−3	+15.5		
77.7	$C_{20}H_{18}N_4O_5$	60.91 (60.85	4.60 4.70	14.21 14.08)	−41	0		
53.5	$C_{20}H_{18}N_4O_4S \cdot C_2H_5OH$	57.88 (57.77	5.30 5.13	12.27 12.17)	−40	+15.4		
76.8	$C_{20}H_{20}N_6O_4 \cdot CH_3OH$	57.26 (57.10	5.49 5.48	19.08 19.05)	−19	0		
24.7	$C_{22}H_{24}N_4O_5$	62.25 (62.04	5.70 5.54	13.20 13.13)	−17	+29.6		
65.2	$C_{22}H_{27}ClN_4O_4$[e]	59.12 (58.86	6.09 6.03	12.54 12.37)	−58	+101.5	(14)	325

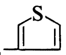
TABLE II.

Compd. No.	Ar	R^1	R^3	mp (°C)	Recrystn. solvent
114	$2\text{-}NO_2\text{–}C_6H_4$	C_2H_5	Cyclohexyl	148—151	EtOAc
115	$2\text{-}NO_2\text{–}C_6H_4$	$n\text{-}C_5H_{11}$	Cyclopentyl	112—113	EtOAc
116	$2\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2	Cyclopentyl	147—150	Acetone
117	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_5$	Cyclopentyl	181—182	Acetone
118	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_4\text{–}4\text{-}Cl$	Cyclopentyl	166—170	Acetone
119	$3\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_4\text{–}4\text{-}Cl$	Cyclopentyl	137—140	Acetone
120	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_4\text{–}4\text{-}Br$	Cyclopentyl	199—200	Acetone
121	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_4\text{–}3\text{-}CF_3$	Cyclopentyl	148—149	Acetone
122	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_3\text{–}3,4\text{-}(OCH_3)_2$	Cyclopentyl	129—130	Acetone
123	$3\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_3\text{–}3,4\text{-}(OCH_3)_2$	Cyclopentyl	151—152	EtOH
124	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2C_6H_3\text{–}3,4\text{-}Cl_2$	Cyclopentyl	125—126	Acetone
125	$2\text{-}NO_2\text{–}C_6H_4$	Cyclohexyl	Cyclopentyl	152—155	Acetone
126	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2OC_6H_5$	Cyclopentyl	172—173	CH_2Cl_2
127	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2OC_6H_5$	Cyclohexyl	127—130	Acetone
128	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2OC_6H_4\text{–}4\text{-}Cl$	Cyclopentyl	166—167	Acetone
129	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2CH_2O\text{iso-}C_3H_7$	Cyclopentyl	102—103	iso-Pr_2O
130	$2\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2O-	Cyclopentyl	119—121	Acetone
131	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2SCH_3$	Cyclopentyl	125—126	iso-Pr_2O
132	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2S\text{iso-}C_3H_7$	Cyclopentyl	152—155	Acetone
133	$2\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2S-	Cyclopentyl	149—150	Acetone
134	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2SC_6H_5$	Cyclopentyl	126—127	Acetone
135	$2\text{-}NO_2\text{–}C_6H_4$	$CH_2CH_2CH_2N(CH_3)_2$	Cyclopentyl	135—136	Acetone
136	$2\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2	Cyclopentyl	164—165	Acetone
137	$2\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2$\text{-}C_6H_5$	Cyclopentyl	169—170	EtOH
138	$3\text{-}NO_2\text{–}C_6H_4$	CH_2CH_2$\text{-}C_6H_5$	Cyclopentyl	112—113	Acetone–Et_2O

(continued)

Yield (%)	Formula	Analysis (%) Calcd (Found)			Anti-HT activity[a] max. change of SBP (mmHg)	CVD effect[b] max. change of CPF (%)	Acute toxicity[c] LD_{50} (mg/kg)
		C	H	N			
72.5	$C_{23}H_{29}ClN_4O_4$[e]	59.92 (59.55	6.34 6.25	12.16 12.37)	−38	+59.6 (20)	
72.8	$C_{25}H_{33}ClN_4O_4$[e]	61.40 (61.21	6.80 6.97	11.46 11.45)	−74	+64.0 (80)	
72.8	$C_{27}H_{35}ClN_4O_4$[e]	62.96 (62.64	6.85 6.97	10.88 10.80)	−64	+54.1 (60)	300
67.2	$C_{30}H_{32}N_4O_8 \cdot H_2O$[f]	60.60 (60.60	5.76 5.44	9.42 9.33)	−75	+118.7 (120)	>1000
76.0	$C_{28}H_{30}Cl_2N_4O_4$[e]	60.33 (60.10	5.42 5.52	10.05 9.85)	−114	+154.1 (>120)	65
73.2	$C_{28}H_{30}Cl_2N_4O_4$[e]	60.32 (60.20	5.42 5.65	10.05 9.68)	−74	+48.4 (>120)	>500
70.8	$C_{28}H_{30}BrClN_4O_4$[e]	55.82 (55.62	4.98 4.90	9.30 9.30)	−106	+160.0 (>120)	
67.8	$C_{29}H_{30}ClF_3N_4O_4$[e]	58.93 (58.78	5.12 4.96	9.48 9.40)	−102	+92.7 (>120)	
74.8	$C_{30}H_{35}ClN_4O_6$[e]	61.80 (61.52	6.05 6.20	9.61 9.32)	−119	+49.4 (>120)	64
56.6	$C_{30}H_{35}ClN_4O_6$[e]	61.80 (61.77	6.05 5.95	9.61 9.54)	−86	+33.2 (60)	>500
58.2	$C_{28}H_{29}Cl_3N_4O_4$[e]	56.81 (56.66	4.94 5.32	9.47 8.98)	−110	+158.0 (>120)	
64.3	$C_{28}H_{33}ClN_4O_4$[e]	62.33 (62.10	6.64 6.46	11.18 11.25)	−25	+12.0	
81.9	$C_{30}H_{32}N_4O_9 \cdot H_2O$[f]	59.01 (58.79	5.61 5.70	9.18 8.94)	−74	+65.9 (120)	129
81.7	$C_{29}H_{33}ClN_4O_5$[e]	62.98 (62.59	6.01 5.99	10.13 9.86)	−92	+119.8 (>120)	100
34.9	$C_{30}H_{31}ClN_4O_9 \cdot H_2O$[f]	55.86 (55.62	5.16 4.83	8.69 8.37)	−91	+147.1 (>120)	
75.4	$C_{26}H_{34}N_4O_5$	64.71 (64.89	7.10 7.07	11.61 11.53)	−53	+100.0 (30)	>1000
77.0	$C_{27}H_{35}ClN_4O_5$[e]	61.07 (59.75	6.64 6.55	10.55 10.28)	−53	+103.7 (100)	1000
31.5	$C_{25}H_{30}N_4O_8S$[f]	54.94 (54.68	5.53 5.38	10.25 10.05)	−20	+105.4 (30)	>1000
77.5	$C_{25}H_{33}ClN_4O_4S$[e]	57.63 (57.43	6.38 6.43	10.75 10.63)	−69	+121.3 (120)	
77.8	$C_{27}H_{35}ClN_4O_4S$[e]	59.28 (59.30	6.45 6.66	10.24 10.21)	−70	+68.3 (>120)	
71.4	$C_{28}H_{31}ClN_4O_4S$[e]	60.58 (60.60	5.63 5.91	10.09 9.73)	−82	+112.5 (100)	185
42.3	$C_{27}H_{35}N_5O_8 \cdot 2H_2O$[f]	54.63 (54.73	6.62 6.29	11.80 11.87)	−17	0	
66.9	$C_{26}H_{35}Cl_2N_5O_5 \cdot H_2O$[e]	53.24 (52.95	6.36 6.36	11.94 11.88)	−24	0	
43.8	$C_{33}H_{41}Cl_2N_5O_4$[e]	61.68 (61.43	6.43 6.73	10.90 10.56)	−103	+63.9 (>120)	
43.0	$C_{33}H_{39}N_5O_4$	69.57 (69.31	6.90 6.90	12.30 11.92)	−68	+64.3 (75)	

TABLE II.

Compd. No.	Ar	R^1	R^3	mp (°C)	Recrystn. solvent
139	$2\text{-}NO_2\text{-}C_6H_4$	CH_2CH_2– 	Cyclopentyl	140—141	Acetone
140	$2\text{-}NO_2\text{-}C_6H_4$	$CH_2CH_2C_6H_5$	2-Thienyl	144—145	$EtOH\text{-}Et_2O$
141	$2\text{-}NO_2\text{-}C_6H_4$	$CH_2CH_2C_6H_4\text{-}4\text{-}Cl$	2-Thienyl	183—184	EtOAc
142	$2\text{-}NO_2\text{-}C_6H_4$	CH_2CH_2O– 	2-Thienyl	158—160	EtOH
143	$2\text{-}NO_2\text{-}C_6H_4$	$CH_2CH_2C_6H_4\text{-}4\text{-}Cl$	CO– 	205—206	EtOH
144	$3\text{-}CF_3\text{-}C_6H_4$	CH_3	Cyclopentyl	183 (dec.)	MeOH
145	$2,3\text{-}(CH_3O)_2C_6H_3$	CH_3	Cyclopentyl	182—184	EtOH
146	$2,3\text{-}Cl_2\text{-}C_6H_3$	$CH_2CH_2C_6H_4\text{-}4\text{-}Cl$	2-Thienyl	143—144	EtOAc
147	2-Pyridyl	CH_3	Cyclopentyl	217 (dec.)	MeOH
148	3-Pyridyl	CH_3	Cyclopentyl	225—227	MeOH
149	C_6H_5	CH_3	Cyclopentyl	201—202	iso-PrOH
150	$3\text{-}NH_2\text{-}C_6H_4$	CH_3	Cyclopentyl	106—110	EtOH

a—e) See footnotes *b—f* in Table I. *f*) Oxalate. *g*) The yield from **76**.

Ca-blocking activity showed a marked antihypertensive effect. Maximal decreases in SBP for compounds **76**, **79**, **81** and **82** observed at 1—2 h post administration were greater than those caused by nifedipine.

Coronary vasodilating activity was measured in isolated guinea pig heart by Langendorff's method.[14] The values shown in Table I were obtained by measuring the volume of the coronary arterial perfusates after intracoronary administration of the test compounds. Increases in coronary arterial flow were induced by the 4-(3-nitrophenyl) derivatives (**76** and **81**), in accordance with their Ca-blocking and antihypertensive activities, and the durations of action of these compounds were longer than those of the reference drugs. On the other hand, the 4-(2-nitrophenyl) derivatives (**79** and **82**), which showed stronger antihypertensive activity than **76** and nifedipine, did not exhibit a coronary vasodilating effect. Potent effects were observed with **80**, a 5-(2-methoxy)ethoxycarbonyl analogue of **79**, and also with the 4-(2-chlorophenyl) derivative (**88**), which had only weak potency for lowering SBP.

On the basis of these findings on the structure–activity relationships, pyrazolo[3,4-*b*]pyridines were further modified to improve the pharmacological effects. First, 3-alkyl and 3-aryl substituents were introduced into compound **72**. Table II lists a series of methyl 3-substituted-4,7-dihydro-1,6-dimethyl-4-(2- or 3-nitrophenyl)pyrazolo[3,4-*b*]pyridine-5-carboxylates (**90**—**112**) and their antihypertensive and coronary vasodilating activities. Compounds **90**, **96**, **99** and **101**, which have 3-isobutyl, 3-cyclobutyl, 3-cyclopentenyl and 3-

(continued)

Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Anti-HT activity[a] max. change of SBP (mmHg)	CVD effect[b] max. change of CPF (%)		Acute toxicity[c] LD_{50} (mg/kg)
81.1	$C_{26}H_{29}ClN_4O_4S$[e]	59.03	5.53	10.59	−88	+97.1	(50)	316
		(58.73	5.20	10.55)				
67.7	$C_{27}H_{24}N_4O_4S$	64.78	4.83	11.19	−43	+37.7	(24)	
		(64.74	4.79	11.11)				
47.4	$C_{27}H_{23}ClN_4O_4S$	60.61	4.33	10.47	−73	+22.2		
		(60.68	4.41	10.41)				
61.5	$C_{26}H_{28}N_4O_5S$	61.40	5.54	11.01	−36	+60.0	(16)	
		(61.28	5.48	11.01)				
24.7	$C_{29}H_{29}ClN_4O_5$	63.44	5.32	10.21	−75	+124.0	(120)	>1000
		(63.30	5.16	10.07)				
88.0	$C_{22}H_{25}ClF_3N_3O_2$[e]	57.96	5.53	9.22	−8	0		
		(57.86	5.45	9.34)				
18.4	$C_{23}H_{30}ClN_3O_4$[e]	61.67	6.75	9.38	0	0		
		(61.55	6.78	9.38)				
35.5	$C_{29}H_{24}Cl_3N_3O_6S$[f]	53.68	3.73	6.48	−63	0		
		(53.29	3.80	6.26)				
51.0	$C_{20}H_{24}N_4O_2$	68.16	6.86	15.90	−10	0		
		(68.12	6.84	15.80)				
84.2	$C_{20}H_{24}N_4O_2$	68.16	6.86	15.90	−17	0		
		(67.96	7.07	15.63)				
75.0	$C_{21}H_{26}ClN_3O_2$[e]	65.02	6.76	10.83	—[d]	—[d]		
		(64.97	6.85	10.61)				
84.1[g]	$C_{21}H_{26}N_4O_2$	68.83	7.15	15.29	0	0		
		(68.58	7.30	14.92)				

cyclohexenyl substituents, respectively, showed relatively potent antihypertensive activity. The 3-cyclopentylmethyl derivative (**93**) showed potent coronary vasodilating activity, comparable to that of nifedipine, but its antihypertensive effect was weak. The second modification focused on the 5-ester group in **76**, **79** and **82**, which showed potent Ca-blocking and antihypertensive activities. Table II lists a series of 3-cyclopentyl- or 3-cyclohexyl-4,7-dihydro-1,6-dimethyl-4-(2- or 3-nitrophenyl)pyrazolo[3,4-*b*]pyridine derivatives (**113**—**139**) having various 5-ester substituents and their biological activities. Most of these compounds exhibited potent antihypertensive and coronary vasodilating activities with long-lasting actions. Compounds **117**—**124**, which had phenethyloxycarbonyl or substituted phenethyloxycarbonyl substituents at the C-5 position, showed remarkably strong potencies with long durations of action. Some 5-aryloxyethyl esters (**126**—**128**), as well as 5-isopropoxy- and 5-cyclopentyloxyethyl esters (**129** and **130**) also showed strong potencies. On the other hand, **125**, which had a bulkier cyclohexyloxycarbonyl group at the C-5 position, showed lesser potency. Table II also includes compounds having other substituents at the C-3 and C-4 positions of the 4,7-dihydropyrazolo[3,4-*b*]pyridine system and their pharmacological activities. Compound **143** showed good potency, comparable to the reference compounds. However, compounds **144**—**148** and **150**, which had other substituents in place of the 2- or 3-nitrophenyl groups at the C-4 position, showed lesser potencies, probably because of their chemical instability.

Although a precise relationship can not yet be established between chemical structure and biological activity, fusion of the pyrazole nucleus to 1,4-dihydropyridine seems to satisfy the structure requirements for enhancing the Ca-blocking activity. The results also indicate that the potency is enhanced in those compounds which have a 3-cycloalkyl substituent and a hydrophobic 5-ester moiety with moderate bulkiness. The nitro group on the 4-phenyl substituent seems to be necessary not only to increase the pharmacological activities but also to increase the stability of the compounds.

Finally, the acute toxicity in mice was determined for several compounds which showed potent antihypertensive and coronary vasodilating activities. The LD_{50} values were calculated by the Bliss method[15] for the 24 h after oral administration (Tables I and II).

On the basis of these results, five compounds (**76**, **117**, **129**, **130** and **143**), which showed potent antihypertensive and coronary vasodilating actions and were less toxic in mice, were selected as promising agents. Further pharmacological evaluations of these compounds are in progress.

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were recorded with a Varian EM390 spectrometer in the indicated solvents. Chemical shifts are represented by δ-values using tetramethylsilane as an internal standard and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Mass spectra (MS) were obtained on an RMU-8GN mass spectrometer. After the reactions were run as indicated, thin-layer chromatography (TLC) was conducted on Merck Silica gel F_{254} plates. Standard work-up procedures were as follows: the reaction mixture was partitioned between the indicated solvent and water, and the organic extract was washed successively with water, $NaHCO_3$ solution (aq. $NaHCO_3$), NaOH solution (aq. NaOH) and hydrochloric acid (aq. HCl), and then dried over $MgSO_4$, filtered and evaporated *in vacuo*. Chromatographic separation was carried out on Merck Silica gel 60 using the indicated eluents.

Alkanoylacetonitriles and Aroylacetonitriles (**154a**—**w**) were prepared by means of the literature method.[16]

2-Cyanoacetyl-2-cyclopentyl-1,3-dioxolane (154x)——Methyl methylsulfinylmethyl sulfide (FAMSO) (4.95 g, 39.9 mmol) was added dropwise to a mixture of *tert*-BuOK (8.95 g, 79.8 mmol) and tetrahydrofuran (THF) (45 ml) under cooling at 0 °C. After stirring of the mixture for 15 min, a solution of ethyl cyclopentylcarboxylate (67 g, 39.9 mmol) in THF (15 ml) was added dropwise. The reaction mixture was stirred at 20 °C for 14 h, and then cooled, quenched with aq. HCl, and extracted with CH_2Cl_2. The extract, after removal of the solvent, was chromatographed on silica gel with CH_2Cl_2–Et_2O (1 : 1) to give cyclopentylcarbonyl-FAMSO (6.85 g, 78.0%) as a mixture of both isomers in the ratio of 4 : 6. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (8H, m), 2.15, 2.21 (3H, s), 2.62, 2.77 (3H, s), 3.22 (1H, m), 4.41, 4.52 (1H, s). A mixture of the product (5.4 g, 24.5 mmol), $CuCl_2 \cdot 2H_2O$ (5.03 g, 24.5 mmol) and EtOH (54 ml) was stirred for 21 h at 25 °C. The solvent was evaporated off, and the residue was extracted with benzene. After removal of the solvent, the extract was chromatographed on silica gel with hexane–ethyl acetate (EtOAc) (20 : 1) to give ethyl cyclopentylpyruvate (2.75 g, 65.8%) as a colorless liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (8H, m), 1.34 (3H, t, J=7 Hz), 3.49 (1H, m), 4.32 (2H, q, J=7 Hz). A solution of the pyruvate (1.58 g, 9.3 mmol), ethyleneglycol (0.7 g, 11.3 mmol) and boron trifluoride diethylether complex (44 ml) in benzene (6 ml) was stirred at 25 °C for 20 h. The mixture was quenched with aq. $NaHCO_3$, washed with NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in MeCN (0.7 g, 17 mmol)–THF (8 ml), and the solution was added to a mixture of *tert*-BuOK (1.9 g, 17 mmol) and THF (10 ml) under cooling at 0 °C. The mixture, after stirring for 6 h at 25 °C, was quenched with aq. HCl, and extracted with benzene. Chromatography of the extract on silica gel with CH_2Cl_2 gave **154x** (1.02 g, 60.1%) as a colorless liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (8H, m), 2.37 (1H, m), 3.67 (2H, s), 3.99 (4H, m).

5-Amino-1-methyl-3-R^3-pyrazoles (1—28)——**1** (R^3 = H),[5] **2** (R^3 = Me),[6c] **3** (R^3 = iso-Pr),[6d] **4** (R^3 = Ph),[6e] and **5** (R^3 = 2-pyridyl)[6f] were prepared by the literature methods. The pyrazoles (**6**—**28**) were prepared by the following general procedure. A solution of **154** (20 mmol) and methylhydrazine (0.92 g, 20 mmol) in EtOH (15 ml) was heated under reflux for 3—5 h, and then evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–MeCN (19 : 1) to give the product. Futher purification was done by recrystallization from the appropriate solvents. **6** (R^3 = *n*-Bu): 89.1% yield, liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (9H, m), 3.51 (2H, br s), 3.53 (3H, s), 5.29 (1H, s). **7** (R^3 = iso-Bu): 55.1% yield, mp 102—104 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.86 (1H, m), 2.35 (2H, d, J=6 Hz), 3.55 (5H, br s). **8** (R^3 = *tert*-Bu): 79.4% yield, mp 156—157 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (9H, m), 3.52 (2H, br s), 3.60 (3H, s), 5.38 (1H, s). **9** (R^3 = allyl): 16.3% yield, mp 52—55 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 3.23 (2H, m), 3.57 (3H, s), 3.62 (2H, br s), 5.09 (2H, m), 5.33 (1H, s), 5.99 (1H, m). **10** (R^3 = cyclopentylmethyl): 64.9% yield, mp 106—107 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (9H, m), 2.47 (2H, m), 3.51 (3H, s), 3.60 (2H, br s), 5.28 (1H, s). **11** (R^3 = benzyl): 89.2% yield, mp 130—131 °C from iso-Pr_2O. ^{1}H-NMR

($CDCl_3$) δ: 3.40 (2H, br s), 3.53 (3H, s), 3.78 (2H, s), 5.22 (1H, s), 7.23 (5H, s). **12** (R^3 = cyclopropyl): 53.6% yield, mp 123—125 °C from Et_2O. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (4H, m), 1.85 (1H, m), 3.52 (5H, br s), 5.12 (1H, s). **13** (R^3 = cyclobutyl): 68.2% yield, mp 117—118 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (7H, m), 3.54 (3H, s), 3.60 (2H, br s), 5.38 (1H, s). **14** (R^3 = cyclopentyl): 74.4% yield, mp 149—150 °C from PrOH. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (8H, m), 2.63 (1H, m), 3.57 (5H, br s), 5.32 (1H, s). **15** (R^3 = cyclohexyl): 71.7% yield, mp 173—174 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (11H, m), 3.43 (2H, br s), 3.57 (3H, s), 5.32 (1H, s). **16** (R^3 = cycloheptyl): 82.9% yield, mp 162—163 °C from Et_2O. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (13H, m), 3.48 (2H, br s), 3.55 (3H, s), 5.30 (1H, s). **17** (R^3 = 4-methylcyclohexyl): 60.4% yield, mp 170—175 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (13H, m), 3.50 (2H, br s), 3.57 (3H, s), 5.33 (1H, s). **18** (R^3 = 3-cyclopentenyl): 59.3% yield, mp 102—105 °C from iso-Pr_2O–hexane. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (7H, m), 3.57 (3H, s), 5.35 (1H, s), 5.71 (2H, m). **19** (R^3 = 3-cyclohexenyl): 75.0% yield, mp 146—148 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 1.99 (6H, m), 2.75 (1H, m), 3.58 (3H, s), 3.72 (2H, s), 5.36 (1H, s), 5.72 (2H, m). **20** (R^3 = 2-methoxyethyl): 80.7% yield, liquid. ^{1}H-NMR ($CDCl_3$) δ: 2.73 (2H, t, J = 6 Hz), 3.47 (2H, br s), 3.55 (3H, s), 3.60 (5H, m), 5.35 (1H, s). **21** (R^3 = cyclopentyloxymethyl): 24.6% yield, mp 112—114 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (8H, m), 3.47 (2H, br s), 3.60 (3H, s), 4.00 (1H, m), 4.31 (2H, s), 5.55 (1H, s). **22** (R^3 = pyrrolidinomethyl): 49.5% yield, liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (4H, m), 3.05 (4H, m), 3.62 (3H, s), 3.85 (2H, s), 5.68 (1H, s), 6.87 (2H, br s). **23** (R^3 = 1,3-dithiolan-2-yl): 47.5% yield, mp 77—78 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (6H, m), 3.56 (3H, s), 5.33 (1H, s), 5.60 (1H, s). **24** (R^3 = 1-methylpyrrolidin-2-yl): 54.7% yield, mp 138—139 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (9H, m), 3.10 (1H, m), 3.53 (2H, br s), 3.58 (3H, s), 5.47 (1H, s). **25** (R^3 = 3,5-Cl_2-Ph): 99.1% yield, mp 155—156 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (5H, br s), 5.72 (1H, s), 7.34 (3H, m). **26** (R^3 = 3-furyl): 14.2% yield, mp 118—120 °C from iso-Pr_2O. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (2H, br s), 3.65 (3H, s), 5.63 (1H, s), 7.19 (3H, m). **27** (R^3 = 2-thienyl): 58.1% yield, mp 135—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (3H, s), 3.60 (2H, br s), 5.68 (1H, s), 7.08 (3H, m). **28** (R^3 = 1-methylimidazol-2-yl): 51.6% yield, mp 164—165 °C from EtOAc. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (2H, br s), 3.67 (3H, s), 3.93 (3H, s), 6.03 (1H, s), 6.83 (1H, d, J = 1 Hz), 7.00 (1H, d, J = 1 Hz).

Methyl 5-Amino-1-methylpyrazole-3-carboxylate (31)——A solution of methyl cyanopyruvate sodium-enolate[17] (**155**, 10.0 g, 60 mmol) with methylhydrazine sulfate (9.0 g, 60 mmol) was stirred for 72 h at room temperature, and then evaporated. The residue was extracted with $CHCl_3$, and the extract was washed with aq. NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel with EtOAc to give **31** (6.54 g, 70.3%). Recrystallization from EtOH gave colorless needles, mp 101—102 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s), 3.90 (2H, br s), 3.86 (3H, s), 6.05 (1H, s).

iso-Propyl 5-Amino-1-methylpyrazole-3-carboxylate (32)——A solution of **31** (2.0 g, 12.9 mmol) and iso-PrONa (0.1 g) in iso-PrOH (40 ml) was heated under reflux for 20 h. After removal of the solvent, the residue was extracted with $CHCl_3$, and the extract was washed with water, dried over $MgSO_4$, filtered, and evaporated. The crystalline residue was recrystallized from iso-PrOH to give **32** (1.72 g, 72.9%) as colorless needles, mp 86—87 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J = 6 Hz), 3.72 (3H, s), 3.75 (2H, br s), 5.23 (1H, s).

5-Amino-3-cyclopentylcarbonyl-1-methylpyrazole (33)——A solution of **154x** (2.35 g, 11.2 mmol) and methylhydrazine (0.52 g, 11.3 mmol) in MeOH (20 ml) was stirred at 25 °C for 7 h, and then evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–EtOH (20 : 1) to give **33**-ethyleneketal (1.45 g, 54.5%) as colorless crystals, mp 158—159 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (8H, m), 3.53 (2H, br s), 3.62 (3H, s), 3.96 (4H, m), 5.49 (1H, s). A solution of the ketal (3.88 g, 16.3 mmol) and 10% aq. HCl (40 ml) in dioxane (40 ml) was stirred at room temperature for 72 h, and then evaporated. The residue was extracted with CH_2Cl_2, and the extract was washed with aq. $NaHCO_3$, then dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on slica gel with CH_2Cl_2–Et_2O (1 : 1) to give **33** (2.29 g, 72.6%) as a pale yellow liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (8H, m), 3.68 (3H, s), 3.76 (1H, m), 3.85 (2H, br s), 5.94 (1H, s).

5-Amino-1,3-diphenylpyrazole (29)——**29** was prepared by a literature method.[10]

5-Amino-1,3-dicyclopentylpyrazole (30)——A solution of cyclopentylcarbonylacetonitrile (**154h**, 0.69 g, 5 mmol) and cyclopentylhydrazine[18] (0.5 g, 5 mmol) in EtOH (5 ml) was stirred for 16 h at 25 °C and then evaporated. The residue was chromatographed on silica gel with benzene–EtOAc (19 : 1) to give **30** (0.79 g, 71.5%) as pale yellow crystals. Recrystallization from iso-Pr_2O–hexane gave colorless prisms, mp 92—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (16H, m), 2.97 (1H, m), 3.42 (2H, br s), 4.35 (1H, m), 5.33 (1H, s).

Alkyl (R^1) 2-Nitrobenzylideneacetoacetates (34—57)——**34**—**57** were prepared by the following general procedure.[7a] A solution of 2-nitrobenzaldehyde (**156a**, 15.0 g, 0.1 mol), alkyl (R^1) acetoacetate[8] (**157**, 0.1 mol), AcOH (3 ml) and piperidine (0.8 ml) in benzene (40 ml) was stirred for 24 h at 30—45 °C. After cooling, the mixture was washed with aq. $NaHCO_3$, followed by aq. NaOH, then dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–MeCN (9 : 1) to give the product as a mixture of the *cis* and *trans* isomers. **34** (R^1 = Me)[7b]: 90% yield. **35** (R^1 = Et)[7b]: 19.2% yield. **36** (R^1 = pentyl): 89.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (9H, m), 2.20, 2.47 (3H, s), 3.98, 4.27 (2H, t, J = 7 Hz), 7.81 (5H, m). **37** (R^1 = 2-cyclopentylethyl): 97.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (14H, m), 3.98, 4.27 (2H, t, J = 7 Hz), 7.77 (5H, m). **38** (R^1 = phenethyl): 88.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.40 (3H, s), 2.68, 3.00 (2H, t, J = 7 Hz), 4.22, 4.47 (2H, t, J = 7 Hz), 7.53 (10H, m). **39** (R^1 = 4-chlorophenethyl): 96.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.10, 2.43 (3H, s), 2.68, 3.00 (2H, t, J = 7 Hz), 4.20, 4.48 (2H, t, J = 7 Hz), 7.58 (9H, m). **40** (R^1 = 4-bromophenethyl): 76.5% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.40 (3H, s), 2.63, 2.95

(2H, t, $J=7$ Hz), 4.18, 4.43 (2H, t, $J=7$ Hz), 7.50 (9H, m). **41** (R^1=3-trifluoromethylphenethyl): 54.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.10, 2.40 (3H, s), 2.77, 3.08 (2H, t, $J=7$ Hz), 4.23, 4.48 (2H, t, $J=7$ Hz), 7.68 (9H, m). **42** (R^1=3,4-dimethoxyphenethyl): 96.8% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.08, 2.40 (3H, s), 2.62, 2.93 (2H, t, $J=7$ Hz), 3.78, 3.83, 3.85 (6H, s), 4.18, 4.45 (2H, t, $J=7$ Hz), 7.16 (8H, m). **43** (R^1=3,5-dichlorophenethyl): 93.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.43 (3H, s), 2.67, 2.97 (2H, t, $J=7$ Hz), 4.20, 4.45 (2H, t, $J=7$ Hz), 7.49 (8H, m). **44** (R^1=cyclohexyl): 97.3% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (10H, m), 2.22, 2.47 (3H, s), 4.87 (1H, m), 7.78 (5H, m). **45** (R^1=2-methoxyethyl)[7b]: 90.2% yield. **46** (R^1=2-phenoxyethyl): 94.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.18, 2.42 (3H, s), 4.20 (4H, m), 7.42 (10H, m). **47** [R^1=2-(4-chloro)phenethyl]: 95.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.17, 2.47 (3H, s), 4.23 (4H, m), 7.39 (9H, m). **48** (R^1=3-isopropoxypropyl): 50.7% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (6H, d, $J=6$ Hz), 1.79 (2H, m), 2.47 (3H, s), 3.80 (5H, m), 7.76 (5H, m). **49** (R^1=2-cyclopentyloxyethyl): 84.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (8H, m), 2.23, 2.49 (3H, s), 3.82 (5H, m), 7.84 (5H, m). **50** (R^1=2-methylthioethyl): 86.7% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.00, 2.17 (3H, s), 2.22, 2.48 (3H, s), 2.45, 2.83 (2H, t, $J=7$ Hz), 4.17, 4.45 (2H, t, $J=7$ Hz), 7.77 (5H, m). **51** (R^1=2-isopropylthioethyl): 93.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.32 (6H, d, $J=6$ Hz), 2.23, 2.50 (3H, s), 2.51, 2.87 (2H, t, $J=7$ Hz), 2.97 (1H, m), 4.15, 4.42 (2H, t, $J=7$ Hz), 7.78 (5H, m). **52** (R^1=2-cyclopentylthioethyl): 92.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (8H, m), 2.23, 2.48 (3H, s), 2.52, 2.87 (2H, t, $J=7$ Hz), 3.03 (1H, m), 4.17, 4.40 (2H, t, $J=7$ Hz), 7.82 (5H, m). **53** (R^1=2-phenylthioethyl): 84.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.17, 2.42 (3H, s), 2.82, 3.18 (2H, t, $J=7$ Hz), 4.12, 4.37 (2H, t, $J=7$ Hz), 7.62 (10H, m). **54** (R^1=3-dimethylaminopropyl): 53.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (4H, m), 2.13 (6H, s), 2.47 (3H, s), 4.15, 4.33 (2H, t, $J=7$ Hz), 7.79 (5H, m). **55** (R^1=2-morpholinoethyl): 85.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.22, 2.49 (3H, s), 2.53 (6H, m), 3.67 (4H, m), 4.15, 4.42 (2H, t, $J=7$ Hz), 7.82 (5H, m). **56** [R^1=2-(4-phenylpiperidino)ethyl]: 54.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (14H, m), 4.15, 4.41 (2H, t, $J=7$ Hz), 7.69 (9H, m). **57** [R^1=2-(2-thienyl)ethyl]: 94.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.43 (3H, s), 2.73, 3.07 (2H, t, $J=7$ Hz), 4.23, 4.48 (2H, t, $J=7$ Hz), 7.52 (8H, m).

Alkyl (R^1) 3-Nitrobenzylideneacetoacetates (58—63)——**58**—**63** were prepared in a similar manner to that described for **34**. **58** (R^1=Me)[7c]: 80.2% yield. **59** (R^1=Et)[7c]: 87.5% yield. **60** (R^1=iso-Pr)[7c]: 32.4% yield. **61** (R^1=4-chlorophenethyl): 98.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.25, 2.37 (3H, s), 2.95 (2H, m), 4.46 (2H, m), 7.60 (9H, m). **62** (R^1=3,5-dimethoxyphenethyl): 90.4% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.27, 2.38 (3H, s), 2.91 (2H, m), 3.77, 3.80, 3.83, 3.87 (6H, s), 4.46 (2H, m), 7.43 (8H, m). **63** [R^1=2-(4-phenylpiperidino)ethyl]: 17.8% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (14H, m), 4.43, 4.47 (2H, t, $J=7$ Hz), 7.73 (10H, m).

The acetoacetates (**64**—**71**) were prepared in a similar manner to that described for **34**. Ethyl 2-Chlorobenzylideneacetoacetate (**64**)[7d]: 78.4% yield. 2-Chlorophenethyl 2,3-Dichlorobenzylideneacetoacetate (**65**): 94.5% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.40 (3H, s), 2.76, 2.97 (2H, t, $J=7$ Hz), 4.30, 4.42 (2H, t, $J=7$ Hz), 7.35 (8H, m). Ethyl 2,6-Dichlorobenzylideneacetoacetate (**66**): 83.5% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.00, 1.38 (3H, t, $J=7$ Hz), 2.33, 2.50 (3H, s), 4.08, 4.33 (2H, q, $J=7$ Hz), 7.18 (5H, m). Methyl 2-Trifluoromethylbenzylideneacetoacetate (**67**)[7d]: 94.0% yield. Methyl 2,3-Dimethoxybenzylideneacetoacetate (**68**): 93.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.78 (6H, s), 3.87 (3H, s), 7.43 (5H, m). Methyl 2-Pyridylmethylideneacetoacetate (**70**): 52.1% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.43, 2.51 (3H, s), 3.84, 3.90 (3H, s), 7.93 (5H, m). Methyl 3-Pyridylmethylideneacetoacetate (**71**): 91.7% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.87 (3H, s), 8.01 (5H, m). Methyl Benzylideneacetoacetate (**69**)[7a]: 90.5% yield.

Alkyl (R^1) 4-Aryl-1-R-3-R^3-4,7-dihydro-6-methylpyrazolo-[3,4-*b*]pyridine-5-carboxylates (72—149)——**72**—**149**, prepared by the following general procedure, are listed in Tables I and II. A solution of a 5-aminopyrazole (**1**—**33**, 5 mmol) and an alkyl arylmethylideneacetoacetate (**34**—**71**, 5 mmol) in *tert*-BuOH (10 ml) was heated at 80 °C for 24 h under N_2. After removal of the solvent, the residue was chromatographed on silica gel using benzene–EtOAc (2 : 1) and EtOAc as the eluants. The benzene–EtOAc eluate was evaporated to obtain the Schiff base (**151**). The product from the EtOAc eluate was recrystallized from the indicated solvents to obtain the corresponding 4,7-dihydropyrazolo[3,4-*b*]pyridine (**72**—**149**). When an oily product was obtained, it was converted into the hydrochloride or oxalate in the usual manner. The IR and ^{1}H-NMR spectra of the products are shown in Table III.

Methyl 4-(3-Aminophenyl)-3-cyclopentyl-4,7-dihydro-1,6-dimethylpyrazolo[3,4-*b*]pyridine-5-carboxylate (150)——A solution of **76** (1.0 g, 2.52 mmol) in MeOH (10 ml) was hydrogenated in the presence of 10% Pd–C (0.1 g) under atmospheric pressure. After absorption of H_2 (166 ml), the reaction was worked up, and the mixture was filtered and evaporated. The residue was chromatographed on silica gel with EtOAc and gave **150** (0.78 g, 84.1%). Recrystallization from EtOH gave colorless prisms, mp 106—110 °C (Table II). IR (Nujol): 3430, 3300, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (12H, m), 3.35 (2H, br s), 3.45 (3H, s), 3.55 (3H, s), 5.00 (1H, s), 6.68 (4H, m), 7.58 (1H, br s).

Conversion of Methyl 3-Cyclopentyl-4,7-dihydro-6-methyl-4-phenylisoxazolo[5,4-*b*]pyridine-5-carboxylate (158) into 149—A solution of **158**[1)] (2.67 g, 8.0 mmol) in EtOAc (25 ml) was hydrogenated over PtO_2 (0.3 g) in H_2 at room temperature for 6 h. The precipitated crystals were dissolved by addition of CH_2Cl_2. The solution, after removal of the catalyst by filtration, was evaporated and the residue was crystallized from EtOAc, giving **159** (2.5 g, 93.6%) as colorless prisms, mp 222—224 °C. IR (Nujol): 3450, 1695, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (8H, m), 2.27 (3H, s), 3.09 (1H, m), 3.70 (3H, s), 4.98 (1H, s), 7.19 (5H, m). *Anal.* Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.39; H, 7.00; N, 8.13. $POCl_3$ (6 ml) was added dropwise to a solution of **159** (2.0 g, 6.84 mmol) in CH_2Cl_2 (6 ml) under cooling, and the solution was stirred at 25 °C for 20 h. After removal of the solvent, the residue was

TABLE III. IR and ^{1}H-NMR Data for 4,7-Dihydropyrazolo[3,4-*b*]pyridines (**72**—**149**)

Compd. No.	IR (Nujol) (cm^{-1}) NH	CO	NO_2	^{1}H-NMR (in $CDCl_3$) δ
72	3280	1680	1350	2.45 (3H, s), 3.40 (3H, s), 3.70 (3H, s), 5.70 (1H, s), 7.34 (6H, m)
73	3275	1645	1352	1.87 (3H, s), 2.42 (3H, s), 3.57 (3H, s), 3.65 (3H, s), 5.20 (1H, s), 7.59 (5H, m)
74	3290	1690	1350	1.00 (6H, d, J=7 Hz), 1.21 (3H, t, J=7 Hz), 2.40 (3H, s), 2.52 (1H, m), 3.71 (3H, s), 4.05 (2H, q, J=7 Hz), 5.32 (1H, s), 7.54 (5H, m)
75	3350	1693	1345	1.03 (7H, m), 2.20 (2H, m), 2.40 (3H, s), 3.59 (3H, s), 3.68 (3H, s), 5.25 (1H, s), 7.68 (5H, m)
76	3375	1700	1380	2.00 (12H, m), 3.58 (3H, s), 3.67 (3H, s), 5.25 (1H, s), 7.40 (5H, m)
77	3270	1690	1350	1.90 (12H, m), 2.38 (3H, s), 3.67 (3H, s), 4.03 (2H, q, J=7 Hz), 5.25 (1H, s), 7.62 (5H, m)
78	2560	1693	1353[a]	1.14 (6H, d, J=7 Hz), 2.07 (12H, m), 3.65 (3H, s), 4.90 (2H, q, J=7 Hz), 5.23 (1H, s), 7.67 (5H, m)[b]
79	3290	1673	1355	1.99 (12H, m), 3.32 (3H, s), 3.67 (3H, s), 5.62 (1H, s), 7.47 (5H, m)
80	3260	1690	1360	1.50 (8H, m), 2.33 (3H, s), 2.92 (1H, m), 3.27 (3H, s), 3.51 (2H, m), 3.63 (3H, s), 4.13 (2H, m), 5.92 (1H, s), 7.20 (5H, m)
81	2495	1699	1352[a]	3.17 (14H, m), 3.62 (3H, s), 3.70 (3H, s), 5.31 (1H, s), 7.64 (5H, m)
82	3320	1685	1360	1.79 (14H, m), 3.50 (3H, s), 3.67 (3H, s), 5.87 (1H, s), 7.42 (5H, m)
83	3350	1695	1340	1.71 (16H, m), 2.40 (3H, s), 2.62 (1H, m), 3.58 (3H, s), 4.35 (1H, m), 5.25 (1H, s), 7.20 (5H, m)
84	3280	1678	1350	1.18 (3H, t, J=7 Hz), 2.43 (3H, s), 3.77 (3H, s), 4.07 (2H, q, J=7 Hz), 5.50 (1H, s), 7.41 (10H, m)
85	3360	1698	1345	1.13 (3H, t, J=7 Hz), 2.43 (3H, s), 4.02 (2H, q, J=7 Hz), 5.62 (1H, s), 7.47 (15H, m)[b]
86	3320	1700	1355	2.39 (3H, s), 3.58 (3H, s), 3.75 (3H, s), 3.78 (3H, s), 5.50 (1H, s), 7.57 (5H, m)
87	3370	1693	1350	1.26 (6H, d, J=6 Hz), 2.38 (3H, s), 3.63 (3H, s), 3.78 (3H, s), 5.17 (1H, m), 5.58 (1H, s), 7.71 (5H, m)
88	2360	1701[a]		1.17 (3H, t, J=7 Hz), 2.20 (12H, m), 3.52 (3H, s), 4.02 (2H, q, J=7 Hz), 5.62 (1H, s), 7.12 (5H, m)
89	3280	1670		1.07 (3H, t, J=7 Hz), 2.04 (12H, m), 3.57 (3H, s), 3.99 (2H, q, J=7 Hz), 6.08 (1H, s), 7.12 (5H, m)
90	3220	1690	1347	0.77 (6H, d, J=6 Hz), 1.82 (3H, m), 2.40 (3H, s), 3.57 (3H, s), 3.67 (3H, s), 5.20 (1H, s), 7.08 (1H, br s), 7.62 (4H, m)
91	3300	1700	1350	1.08 (9H, s), 2.42 (3H, s), 3.72 (3H, s), 3.78 (3H, s), 5.45 (1H, s), 6.57 (1H, br s), 7.67 (4H, m)
92	3220	1690	1348	2.39 (3H, s), 2.99 (2H, m), 3.58 (3H, s), 3.68 (3H, s), 4.92 (2H, m), 5.20 (1H, s), 5.74 (1H, m), 7.59 (4H, m), 7.80 (1H, br s)
93	3350	1700	1350	1.42 (9H, m), 2.19 (2H, m), 2.40 (3H, s), 3.57 (3H, s), 3.66 (3H, s), 5.22 (1H, s), 7.48 (5H, m)
94	3200	1690	1350	2.30 (3H, s), 3.52 (3H, s), 3.60 (5H, s), 5.00 (1H, s), 7.48 (10H, m)
95	3225	1695	1350	0.97 (5H, m), 2.40 (3H, s), 3.57 (3H, s), 3.60 (3H, s), 5.28 (1H, s), 7.54 (5H, m)
96	3375	1705	1350	2.59 (10H, m), 3.56 (3H, s), 3.65 (3H, s), 5.16 (1H, s), 7.64 (5H, m)
97	3355	1700	1350	1.85 (16H, m), 3.58 (3H, s), 3.67 (3H, s), 5.25 (1H, s), 7.54 (5H, m)
98	3340	1695	1340	1.56 (16H, m), 3.59 (3H, s), 3.68 (3H, s), 5.27 (1H, s), 7.47 (5H, m)
99	3380	1700	1345	2.63 (7H, m), 3.59 (3H, s), 3.68 (3H, s), 3.08 (1H, m), 5.23 (1H, s), 5.60 (2H, s), 7.52 (5H, m)
100	3340	1695	1345	1.86 (7H, m), 2.39 (3H, s), 3.59 (3H, s), 3.69 (3H, s), 5.28 (1H, s), 5.66 (2H, m), 7.52 (5H, m)
101	3310	1670	1355	1.66 (6H, m), 2.36 (3H, s), 2.85 (1H, m), 3.48 (3H, s), 3.68 (3H, s), 5.61 (2H, m), 5.86 (1H, s), 7.30 (5H, m)
102	3270	1690	1345	2.40 (3H, s), 3.24 (3H, s), 3.58 (3H, s), 3.65 (3H, s), 2.49 (2H, t, J=6 Hz), 3.40 (2H, m), 5.27 (1H, s), 7.00 (1H, br s), 7.73 (4H, m)
103	3225	1690	1345	1.59 (8H, m), 2.43 (3H, s), 3.54 (3H, s), 3.66 (3H, s), 3.86 (1H, m), 4.01 (2H, m), 5.30 (1H, s), 6.52 (1H, br s), 7.74 (4H, m)
104	3430	1690	1350	1.72 (4H, m), 2.38 (7H, m), 3.18 (2H, m), 3.53 (3H, s), 3.65 (3H, s), 5.28 (1H, s), 7.63 (5H, m)

TABLE III. (continued)

Compd. No.	IR (Nujol) (cm^{-1}) NH	CO	NO_2	^{1}H-NMR (in $CDCl_3$) δ
105	3240	1685	1350	1.60 (4H, m), 2.07 (3H, s), 2.39 (3H, s), 3.00 (3H, m), 3.54 (3H, s), 3.67 (3H, s), 5.28 (1H, s), 7.16 (5H, m)
106	3420	1690	1350	2.37 (3H, s), 3.27 (4H, m), 3.59 (3H, s), 3.69 (3H, s), 5.23 (1H, s), 7.70 (5H, m)
107	3355	1683	1350	2.40 (3H, s), 3.53 (3H, s), 3.83 (3H, s), 5.47 (1H, s), 7.60 (8H, m)
108	3360	1695	1355	2.45 (3H, s), 3.70 (3H, s), 3.85 (3H, s), 5.80 (1H, s), 7.75 (9H, m)
109	3360	1701	1350	2.39 (3H, s), 3.64 (3H, s), 3.74 (3H, s), 5.36 (1H, s), 7.57 (8H, m)
110	3330	1695	1345	2.30 (3H, s), 3.51 (3H, s), 3.72 (3H, s), 6.21 (1H, s), 7.29 (8H, m)
111		1667	1347	2.65 (3H, s), 3.18 (3H, s), 3.44 (3H, s), 3.60 (3H, s), 5.38 (1H, s), 7.73 (7H, m)
112	3270	1685	1350	1.54 (8H, m), 2.30 (3H, s), 3.51 (3H, s), 3.68 (1H, m), 3.77 (3H, s), 6.31 (1H, s), 7.28 (5H, m)
113	2510	1700	1373[a]	2.07 (12H, m), 2.37 (3H, s), 3.68 (3H, s), 3.93 (2H, q, $J=7$ Hz), 5.68 (1H, s), 7.59 (5H, m)
114	2200	1700	1355[a]	1.82 (17H, m), 3.67 (3H, s), 3.95 (2H, q, $J=7$ Hz), 5.93 (1H, s), 7.63 (5H, m)
115	2570	1697	1357[a]	1.97 (21H, m), 3.63 (3H, s), 3.91 (2H, m), 5.92 (1H, s), 7.36 (5H, m)
116	2520	1700	1358[a]	1.94 (23H, m), 3.45 (2H, m), 3.62 (3H, s), 5.90 (1H, s), 7.28 (5H, m)
117	2300	1700	1375[a]	1.55 (8H, m), 2.27 (3H, s), 2.92 (3H, m), 3.62 (3H, s), 4.23 (2H, m), 5.93 (1H, s), 7.64 (9H, m)
118	2370	1705	1360[a]	2.15 (12H, m), 2.73 (2H, t, $J=7$ Hz), 3.67 (3H, s), 4.13 (2H, m), 5.88 (1H, s), 7.24 (9H, m)
119	3270	1685	1350	1.59 (8H, m), 2.35 (3H, s), 2.60 (1H, m), 2.82 (2H, m), 3.66 (3H, s), 4.21 (2H, m), 5.12 (1H, s), 7.18 (9H, m)
120	2380	1713	1355[a]	1.54 (8H, m), 2.27 (3H, s), 2.72 (2H, t, $J=7$ Hz), 2.95 (1H, m), 3.62 (3H, s), 5.87 (1H, s), 7.33 (8H, m)
121	2590	1715	1338[a]	1.60 (8H, m), 2.25 (3H, s), 2.78 (1H, m), 2.83 (2H, t, $J=7$ Hz), 3.62 (3H, s), 4.17 (2H, t, $J=7$ Hz), 5.87 (1H, s), 7.40 (8H, m)
122	2360	1699	1348[a]	2.15 (9H, m), 2.70 (2H, t, $J=7$ Hz), 3.30 (3H, s), 3.64 (3H, s), 3.82 (6H, s), 4.11 (2H, m), 5.90 (1H, s), 6.72 (3H, s), 7.12 (5H, m)
123	3280	1685	1350	1.43 (8H, m), 2.36 (3H, s), 2.58 (1H, m), 2.83 (2H, m), 3.67 (3H, s), 3.85 (6H, s), 4.24 (2H, m), 5.20 (1H, s), 7.34 (8H, m)
124	2670	1700	1375[a]	2.19 (14H, m), 3.67 (3H, s), 4.17 (2H, t, $J=7$ Hz), 5.90 (1H, s), 7.55 (8H, m)
125	2525	1702	1355[a]	1.97 (22H, m), 3.63 (3H, s), 4.62 (1H, m), 6.03 (1H, s), 7.33 (5H, m)
126	2300	1700	1378[a]	1.49 (8H, m), 2.33 (3H, s), 2.88 (1H, m), 3.63 (3H, s), 4.12 (4H, m), 5.95 (1H, s), 7.24 (10H, m)
127	2590	1679	1357[a]	1.80 (14H, m), 3.63 (3H, s), 4.00 (2H, m), 4.33 (2H, m), 5.91 (1H, s), 7.23 (10H, m)
128	3280	1685	1355	1.46 (8H, m), 2.32 (3H, s), 2.94 (1H, m), 3.61 (3H, s), 4.17 (4H, m), 5.91 (1H, s), 7.17 (9H, m)
129	3240	1692	1355	1.49 (16H, m), 2.37 (3H, s), 2.89 (1H, m), 3.33 (3H, m), 3.67 (3H, s), 4.04 (2H, t, $J=7$ Hz), 5.90 (1H, s), 7.23 (5H, m)
130	3430	1690	1355	1.57 (16H, m), 2.36 (3H, s), 2.89 (1H, m), 3.66 (3H, s), 3.81 (3H, m), 5.91 (1H, s), 7.02 (5H, m)
131	2300	1702	1378[a]	2.10 (17H, m), 3.65 (3H, s), 4.08 (2H, m), 5.90 (1H, s), 7.52 (4H, m)
132	2670	1705	1363[a]	2.10 (21H, m), 3.67 (3H, s), 4.08 (2H, m), 5.90 (1H, s), 7.38 (5H, m)
133	2480	1701	1359[a]	2.17 (23H, m), 3.68 (3H, s), 4.10 (2H, m), 5.91 (1H, s), 7.33 (5H, m)
134	2700	1694	1352[a]	1.47 (8H, m), 2.30 (3H, s), 2.95 (3H, m), 3.60 (3H, s), 4.08 (2H, m), 5.85 (1H, s), 7.45 (9H, m)
135	3430	1695	1355	2.04 (22H, m), 3.70 (3H, s), 3.94 (3H, m), 5.91 (1H, s), 7.38 (4H, m)
136	2660	1712	1352[a]	2.09 (18H, m), 3.60 (3H, s), 3.65 (4H, m), 4.07 (2H, m), 5.92 (1H, s), 7.39 (5H, m)
137	3300	1695	1355	2.12 (23H, m), 3.64 (3H, s), 4.09 (2H, m), 5.93 (1H, s), 7.39 (10H, m)
138	3260	1680	1349	2.23 (23H, m), 3.70 (3H, s), 4.18 (2H, t, $J=7$ Hz), 5.28 (1H, s), 7.10 (10H, m)
139	2520	1703	1370[a]	1.68 (8H, m), 2.28 (3H, s), 2.98 (3H, m), 3.62 (3H, s), 4.17 (2H, m), 5.90 (1H, s), 7.30 (8H, m)

TABLE III. (continued)

Compd. No.	IR (Nujol) (cm^{-1}) NH	CO	NO_2	^{1}H-NMR (in $CDCl_3$) δ
140	3275	1670	1345	2.23 (3H, s), 2.83 (2H, t, $J=7$ Hz), 3.73 (3H, s), 4.20 (2H, m), 6.26 (1H, s), 7.25 (13H, m)
141	3280	1685	1345	2.24 (3H, s), 2.80 (2H, t, $J=7$ Hz), 3.74 (3H, s), 4.17 (2H, t, $J=7$ Hz), 6.23 (1H, s), 7.21 (12H, m)
142	3230	1673	1350	1.57 (11H, m), 3.73 (3H, s), 3.92 (5H, m), 6.27 (1H, s), 7.32 (8H, m)
143	3350	1675	1355	1.61 (8H, m), 2.38 (3H, s), 2.76 (2H, t, $J=7$ Hz), 3.62 (1H, m), 3.77 (3H, s), 4.17 (4H, t, $J=7$ Hz), 6.24 (1H, s), 7.21 (9H, m)
144	3430	1690		1.47 (8H, m), 2.32 (3H, s), 2.47 (1H, m), 3.53 (3H, s), 3.58 (3H, s), 5.17 (1H, s), 7.22 (5H, m)
145	3430	1690		1.54 (8H, m), 2.38 (3H, s), 2.80 (1H, m), 3.53 (3H, s), 3.70 (3H, s), 3.80 (3H, s), 5.66 (1H, s), 6.69 (4H, m)
146	3290	1695		2.23 (3H, s), 2.78 (2H, t, $J=7$ Hz), 3.58 (3H, s), 4.18 (2H, m), 5.68 (1H, s), 7.31 (11H, m)
147	3220	1655		1.44 (8H, m), 2.00 (3H, s), 2.58 (1H, m), 3.11 (3H, s), 3.54 (3H, s), 5.36 (1H, s), 7.96 (5H, m)
148	3240	1665		1.63 (8H, m), 2.33 (3H, s), 2.62 (1H, m), 3.59 (3H, s), 3.61 (3H, s), 5.14 (1H, s), 7.81 (5H, m)
149	2460	1698[a]		1.63 (8H, m), 2.29 (3H, s), 2.62 (1H, m), 3.42 (3H, s), 3.55 (3H, s), 5.12 (1H, s), 7.13 (5H, s)

a) Hydrochloride. *b*) In DMSO-d_6.

dissolved in CH_2Cl_2 (10 ml) and then methylhydrazine (1 ml) was added dropwise under cooling. The mixture was stirred at 25 °C for 20 h, and then refluxed for 4 h. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–EtOAc (10 : 1) to give a yellow liquid (0.4 g, 40%), which, when treated with EtOH–HCl, gave colorless crystals. This product was identified as **149** (Table II) by comparison of the IR spectrum with that of an authentic sample.

Methyl 3-Cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine-5-carboxylate (160)——$NaNO_2$ (0.26 g) was added portionwise to a solution of **76** (0.5 g, 1.26 mmol) in acetic acid (5 ml) at 20 °C. After stirring for 5 min, the mixture was poured into ice-water, and the precipitated crystalline solid was collected by filtration. Recrystallization from EtOH gave **160** (0.33 g, 66.4%) as colorless needles, mp 133—134 °C. IR (Nujol): 1722, 1345 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (9H, m), 2.72 (3H, s), 3.57 (3H, s), 4.11 (3H, s), 8.03 (4H, m). *Anal.* Calcd for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 64.00; H, 5.45; N, 14.22.

Hydrolysis of 160——A solution of **160** (0.5 g, 1.27 mmol) and KOH (0.13 g) in 70% aq. MeOH (10 ml) was refluxed for 43 h. After evaporation of the solvent, the residue was dissolved in water. This solution was washed with ether, then acidified with aq. HCl. A crystalline solid which precipitated was obtained by filtration and recrystallized from MeOH, giving 3-cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (**161**, 0.44 g, 91.7%) as yellow prisms, mp 284—286 °C. IR (Nujol): 2540, 1710, 1345 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.98 (9H, m), 2.68 (3H, s), 4.00 (3H, s), 8.10 (4H, m). *Anal.* Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.08; N, 14.73.

3-Cyclopentyl-1,6-dimethyl-4-(3-nitrophenyl)pyrazolo[3,4-*b*]pyridine (162)——A mixture of **161** (0.25 g, 0.66 mmol), $CuCO_3$ (0.03 g, 0.13 mmol) and quinoline (1.5 ml) was heated at 220 °C for 0.5 h under stirring. After cooling, the mixture was diluted with ether and the insoluble materials were filtered off. The filtrate was washed with aq. HCl and water, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–MeCN (9 : 1), giving **162** (0.18 g, 80.1%), which was recrystallized from EtOH. Yellow plates, mp 116—117 °C. MS *m/z*: 336 (M^+). IR (Nujol): 1353 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (12H, m), 4.10 (3H, s), 6.87 (1H, s), 7.99 (4H, m). *Anal.* Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.99; H, 6.11; N, 16.58.

Reaction of 3-Nitrobenzoylacetone (163)[10] with 14——A solution of **163** (0.414 g, 2 mmol) with **14** (0.33 g, 2 mmol) in diphenylether (1 ml) was heated at 180 °C for 5 h, then cooled, and chromatographed on silica gel with CH_2Cl_2–EtOAc (4 : 1). The yellow crystalline product (0.5 g, 74.7%) obtained was identified as **162** by comparison of the IR spectrum with that of an authentic sample.

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4) The reaction may proceed *via* a course similar to that of the reaction of 5-aminoisoxazoles with α,β-unsaturated ketones to give 4,7-dihydroisoxazolo[5,4-*b*]pyridines, the mechanism of which has been described in our preceding paper.[1a)]
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