(6) J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).
(7) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **73**, 1117 (1953).
(8) G. Bachmann, British Patent 1,168,291 (Oct 22, 1969).
(9) J. R. Cummings, A. M. Welter, J. L. Grace, Jr., and L. M. Lipchuck, *J. Pharmacol. Exp. Ther.*, **161**, 88 (1968).
(10) (a) G. Bachmann and A. Amann, U. S. Patent 3,475,431 (Oct 28, 1969); (b) G. Bachmann and A. Amann, British Patent 1,164,139 (Sept 17, 1969).
(11) J. P. English, R. C. Clapp, Q. P. Cole, and J. Krapcho, *J. Amer. Chem. Soc.*, **67**, 2263 (1945).
(12) E. A. Steck and F. C. Nachod., *J. Amer. Chem. Soc.*, **79**, 4408 (1957).
(13) R. E. Lutz, P. S. Bailey, C.-K. Dien, and J. W. Rinker, *J. Amer. Chem. Soc.*, **75**, 5039 (1953).
(14) H. M. Holava, Jr., and R. A. Partyka, *J. Med. Chem.*, **14**, 262 (1971).

6-(Substituted phenyl)-5-substituted-4,5-dihydro-3(2*H*)-pyridazinones. Antihypertensive Agents

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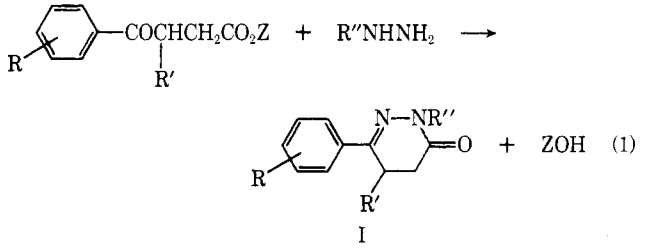
The preparation and antihypertensive properties of a series of 6-(substituted phenyl)-5-substituted-4,5-dihydro-3(2*H*)-pyridazinones are described. The structure–activity relationship in this series is discussed further. The consistent antihypertensive activity of the 6-(alkylaminophenyl) compounds and their acyl derivatives is noteworthy.

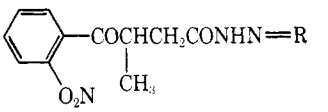
Previous reports from these laboratories have described the preparation and antihypertensive effects of a series of 6-(substituted phenyl)-4,5-dihydro-3(2*H*)-pyridazinones (I).[1] These studies indicated that the compounds having amino, acylamino, cyano, and halogen substituents on the phenyl ring were among those having the more interesting antihypertensive activity. Moreover, this action persisted for a longer duration in those compounds also possessing a 5-methyl substituent. In the present paper we describe the preparation and biological properties of additional members of this series. Specifically, we have prepared those compounds of structure I in which the phenyl substituent is alkylamino, *N*-alkylacylamino, and dimethylamino. Moreover, the effect of other 5 substituents on activity was investigated. A cursory examination of the effect on activity caused by alteration of substituents at the 2 position was made,† and certain 6-(o-substituted phenyl) derivatives also were prepared.

Chemistry. Most of the compounds of type I (see Table I) having 6-(alkylaminophenyl) (**1–12**), 6-(dimethylaminophenyl) (**13–18**), 6-(ortho-substituted phenyl) (**30, 32, 33**), and 5-alkyl and aryl (**41–51**) substituents were prepared by treatment of the appropriate γ-keto acid or γ-keto ester with hydrazine (eq 1).[2] The 6-(dimethylaminophenyl) compounds also could be prepared by Eschweiler-Clarke alkylation of the corresponding 6-(aminophenyl)-4,5-dihydropyridazinone, but this procedure is limited to those compounds with a 2 substituent, and the yield is poor (*cf.* **16**).



I

The yields for those dihydropyridazinones prepared by the procedure of eq 1 (methods A and A_1) generally were excellent, but the 6-(ortho-substituted phenyl) derivatives **30, 32,** and **33** were exceptions. Moderate yields were observed in the preparation of those dihydropyridazinones lacking a 5 substituent (**30** and **33**). However, the yield declined precipitously in the instance of the 6-(*o*-nitrophenyl)-5-methyl derivative **32,** and the isopropylidene hydrazide **58** was a more significant product. Presumably **58** arises by interaction of **59** with acetone utilized in the experimental procedure, and isolation of **58** suggests that formation of the dihydropyridazinone nucleus proceeds in this instance *via* intramolecular condensation of the acyl hydrazide onto the carbonyl function. Moreover, the presence of only end absorption in the electronic spectrum of **58** indicates preference for an "out-of-plane" conformation with respect to the carbonyl function and the aryl system. This preference is the apparent result of limitations on the degrees of freedom imposed by the steric requirements of the nitro and methyl substituents, and these constrictions make the tetrahedral intermediate in the conversion of **59** into **32** less attainable.

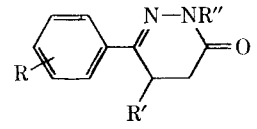


58, R = $C(CH_3)_2$
59, R = H_2

Modification of appropriate dihydropyridazinones afforded other members of the series. Thus, catalytic reduction of certain 6-(nitrophenyl) compounds gave excellent yields of the corresponding 6-(aminophenyl) derivatives **31** and **35.** The preparation of the 6-(*o*-aminophenyl)dihydropyridazinone (**31**) had been achieved earlier by treatment of β-(*o*-aminobenzoyl)propionic acid with hydrazine.[3] Acetylation of the requisite compounds gave the 6-(acylaminophenyl) derivatives **19–29, 48,** and **49.** The Sandmeyer procedure was used to prepare the *m*-hydroxy (**39**) and *m*-bromo (**40**) derivatives, and displacement[4] of bromide in the 6-bromophenyl derivatives **40** and **41** constituted an efficient alternative synthesis of the interesting *m*- (**43**) and *p*-cyanophenyl (**44**) compounds. Acid hydrolysis of **43** and **44** gave the carboxamides **55** and **56,** respectively, which were converted into their carboxylic acids by treatment with nitrosonium hexafluorophosphate. The carboxamide and carboxylic acid derivatives were of particular interest, inasmuch as they are possible metabolites of the more interesting carbonitriles. In addition to these transformations, 6-(*p*-aminophenyl)-4,5-dihydro-5-methyl-3-(2*H*)-pyridazinone[1] was converted into the sulfamoyl

†A more comprehensive study of this parameter was made by Drs. Goldman, Lin, and Stodja in these laboratories.

Table I. 6-Phenyl-4,5-dihydro-3(2*H*)-pyridazinones



Compd	R	R′	R″	Method	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses	Antihypertensive act., MABP[a] 4 hr	Antihypertensive act., MABP[a] 24 hr
						A. 6-(Alkylaminophenyl) Derivatives					
1	*p*-CH_3NH	H	H	A	90	EtOH	224–227	$C_{11}H_{13}N_3O$	C, H, N	++	+
2	*p*-C_2H_5NH	H	H	A	44	EtOH	210–213	$C_{12}H_{15}N_3O$	C, H, N	++	−
3	*p*-CH_3NH	CH_3	H	A	64	MeOH	213–215	$C_{12}H_{15}N_3O$	C, H, N	+++	+
4	*m*-CH_3NH	CH_3	H	A	47	EtOH	218–221 dec	$C_{12}H_{15}N_3O \cdot HCl$	C, H, Cl, N	++++	−
5	*p*-CH_3NH	H	CH_3	A	89	EtOH	199–200	$C_{12}H_{15}N_3O$	C, H, N	−	−
6	*p*-*n*-C_3H_7NH	H	H	A	83	EtOH	182–183	$C_{13}H_{17}N_3O$	C, H, N	+++	−
7	*p*-CH_3NH	CH_3	CH_3	A	63	EtOH	212–214	$C_{13}H_{17}N_3O$	C, H, N	++	−
				B_1	100	Acetone–hexane	213–215				
8	*p*-C_2H_5NH	CH_3	H	A	82	EtOH	192–194	$C_{13}H_{17}N_3O$	C, H, N	+++	+
9	*p*-CH_3NH	C_2H_5	H	A	52[b]	CH_2Cl_2–petr ether	142–144	$C_{13}H_{17}N_3O$	C, H, N	−	−
10	*m*-CH_3NH	CH_3	CH_3	A	83	EtOH	180–182 dec	$C_{13}H_{17}N_3O \cdot HCl$	C, H, Cl, N	−	−
11	*p*-C_2H_5NH	CH_3	CH_3	A	75	EtOH	165–167	$C_{14}H_{19}N_3O$	C, H, N	++	+
12	*p*-CH_3NH	C_2H_5	CH_3	A	51	Acetone–hexane	142–144	$C_{14}H_{19}N_3O$	C, H, N	−	−
						B. 6-(Dimethylaminophenyl) Derivatives					
13	*p*-$(CH_3)_2N$	H	H	A	86	CH_2Cl_2–petr ether	255–258	$C_{12}H_{15}N_3O$	C, H, N	−	−
14	*m*-$(CH_3)_2N$	CH_3	H	A	83	Acetone–hexane	146–148	$C_{13}H_{17}N_3O$	C, H, N	+++	−
15	*p*-$(CH_3)_2N$	CH_3	H	A	81	MeOH	208–210	$C_{13}H_{17}N_3O$	C, H, N	++	+
16	*p*-$(CH_3)_2N$	H	CH_3	H	9	Acetone–hexane	210–212	$C_{13}H_{17}N_3O$	C, H, N	−	−
17	*p*-$(CH_3)_2N$	CH_3	CH_3	A	90	CH_2Cl_2–petr ether	173–175	$C_{14}H_{19}N_3O$	C, H, N	+	+
18	*m*-$(CH_3)_2N$	CH_3	CH_3	A	68	MeOH–H_2O	83–85	$C_{14}H_{19}N_3O$	C, H, N	−	−
						C. 6-(Acylaminophenyl) Derivatives					
19	*p*-$N(CH_3)CHO$	H	H	G_1	53	EtOH	191–193	$C_{12}H_{13}N_3O_2$	C, H, N	++++	−
20	*p*-CF_3CONH	H	CH_3	M	95	Acetone	275–276	$C_{13}H_{12}F_3N_3O_2$	C, H, F, N	−	−
21	*p*-CF_3CONH	CH_3	H	M	100	Acetone–hexane	254–256	$C_{13}H_{12}F_3N_3O_2$	C, H, F, N	+++	++
22	*p*-$N(CH_3)COCH_3$	H	H	G	82	Acetone–hexane	184–186	$C_{13}H_{15}N_3O_2 \cdot 0.5H_2O$	C, H, N	++++	−
23	*p*-$N(CH_3)COCF_3$	CH_3	H	M	94	Acetone–petr ether	160–161	$C_{14}H_{14}F_3N_3O_2$	C, H, F, N	+++	+
24	*p*-CF_3CONH	CH_3	CH_3	M	80	Acetone–hexane	174–176	$C_{14}H_{14}F_3N_3O_2$	C, H, F, N	++	++
25	*p*-$N(CH_3)COCH_3$	CH_3	H	G	84	CH_2Cl_2–petr ether	218–220	$C_{14}H_{17}N_3O_2$	H, N; C[c]	++++	++
26	*p*-$N(CH_3)COC_2H_5$	H	H	G	89	EtOH–H_2O	108–110	$C_{14}H_{17}N_3O_2 \cdot H_2O$	C, H, N	++++	−
27	*p*-$N(C_2H_5)COCH_3$	H	H	G	83	Acetone–hexane	167–168	$C_{14}H_{17}N_3O_2$	C, H, N	++++	+
28	*p*-$N(CH_3)COCH_3$	CH_3	CH_3	G	83	Et_2O–petr ether	110–112	$C_{15}H_{19}N_3O_2$	H, N; C[d]	++++	−
29	*p*-$N(C_2H_5)COCH_3$	CH_3	H	G	64	Acetone–hexane	148–150	$C_{15}H_{19}N_3O_2$	C, H, N	++++	+
						D. (*o*-Substituted phenyl) Derivatives					
30	*o*-NO_2	H	H	A_1	47	Acetone–hexane	164–165	$C_{10}H_9N_3O_3$	C, H, N	+	−
31	*o*-NH_2	H	H	I	82	EtOH	171–173	$C_{10}H_{11}N_3O$	C, H, N	−	−
32	*o*-NO_2	CH_3	H	A_1	5	Acetone–hexane	159–161	$C_{11}H_{11}N_3O_3$	C, H, N	++	−
33	*o*-$NHCOCH_3$	H	H	A_1	40	MeOH	257–258	$C_{12}H_{13}N_3O_2$	C, H, N	−	−
						E. 2-Alkyl Derivatives					
34	*m*-NO_2	CH_3	CH_3	A	69	MeOH–H_2O	196–197	$C_{12}H_{13}N_3O_3$	C, H, N	++++	+
35	*m*-NH_2	CH_3	CH_3	I	93	H_2O	123–124	$C_{12}H_{15}N_3O$	C, H, N	−	−
36	*m*-CN	CH_3	CH_3	B	74	Et_2O–petr ether	80–81	$C_{13}H_{13}N_3O$	C, H, N	++++	+

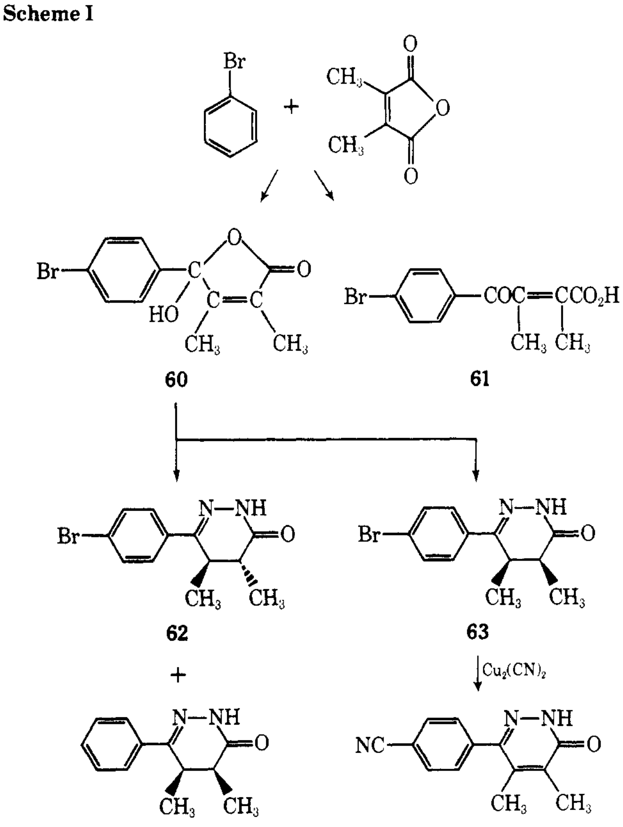
37	*p*-CN	CH_3	CH_3	B	100	CH_2Cl_2–petr ether	172–174	$C_{13}H_{13}N_3O$	C, H, N	++++	+
38	*p*-CN	CH_3	C_2H_5	B	100	Acetone–hexane	92.5–93.0	$C_{14}H_{15}N_3O$	C, H, N	++++	+++
						F. 5-Alkyl and 5-Phenyl Derivatives					
39	*m*-OH	CH_3	H	C	37	Acetone–C_6H_6	155	$C_{11}H_{12}N_2O_2$	C, H, N	–	–
40	*m*-Br	CH_3	H	C	26	Acetone–hexane	162–164	$C_{11}H_{11}BrN_2O$	C, H, Br, N	+++	+++
41	*p*-Br	CH_3	H	A	92	EtOH	196–197	$C_{11}H_{11}BrN_2O$	C, H, Br, N	++	–
42	*p*-F	CH_3	H	A	81	EtOH	170–172	$C_{11}H_{11}FN_2O$	C, H, F, N	+++	–
43	*m*-CN	CH_3	H	D	73		184–188[e]	$C_{12}H_{11}N_3O$		++++	–
44	*p*-CN	CH_3	H	D	85	CH_2Cl_2–C_6H_6	196–198[f]	$C_{12}H_{11}N_3O$		++++	+++
45	*p*-F	C_2H_5	H	A	63	EtOH	153–154	$C_{12}H_{13}FN_2O$	C, H, F, N	–	–
46	*p*-NH_2	C_2H_5	H	A	91	EtOH	155–157	$C_{12}H_{15}N_3O$	C, H, N	+++	–
47	*p*-NH_2	*n*-C_3H_7	H	A	87	EtOH	171–173	$C_{13}H_{17}N_3O$	C, H, N	–	–
48	*p*-$NHCOCH_3$	C_2H_5	H	M	90	Acetone–petr ether	239–240	$C_{14}H_{17}N_3O$	C, H, N	+	–
49	*p*-$NHCOCH_3$	*n*-C_3H_7	H	M	87	Acetone–hexane	217–218	$C_{15}H_{19}N_3O$	C, H, N	–	–
50	*p*-F	C_6H_5	H	A	70	EtOH	245–247	$C_{16}H_{13}FN_2O$	C, H, F, N	–	–
51	H	C_6H_5	H	A	73	EtOH	225–227	$C_{16}H_{14}N_2O$	C, H, N	–	–
52	$NHSO_2N_3$	CH_3	CH_3		7	Et_2O–petr ether	137–139	$C_{11}H_{12}N_6O_3S$	C, H, N, S		
53	*m*-CO_2H	CH_3	H	F	44	Acetone–C_6H_6	238–243	$C_{12}H_{12}N_2O_3$	C, H, N	–	–
54	*p*-CO_2H	CH_3	H	F	63	Acetone–H_2O	270–273	$C_{12}H_{12}N_2O_3$	C, H, N	+	–
55	*m*-$CONH_2$	CH_3	H	E	77	Acetone–H_2O	218–220	$C_{12}H_{13}N_3O_2$	C, H, N	++++	–
56	*p*-$CONH_2$	CH_3	H	E	85	MeOH	216–218	$C_{12}H_{13}N_3O_2 \cdot CH_3OH$	C, H, N	+++	–
57	–SO_2–	CH_3	CH_3		22	DMF–H_2O	246–248	$C_{22}H_{22}N_4O_4S_2$	C, H, N, S	–	–

[a]Control animals have a MABP of 120 mm; ++++ = 65–75 mm; +++ = 76–85 mm; ++ = 86–95 mm; + = 96–105 mm; – ≥ 106 mm. Hydralazine (25 mg/kg) lowers the MABP to 69 mm at 4 hr and 107 mm at 24 hr. [b]After elution from a magnesia–silica gel adsorbent with 6% acetone in CH_2Cl_2. [c]C: calcd, 64.84; found, 64.40. [d]C: calcd, 65.91; found, 66.38. [e]Lit.[1] mp 187–189°. [f]Lit.[1] mp 193.5–195.5°.

azide **52** since previous reports indicate potent hypotensive properties among organic sulfamoyl azides.[5] The sulfone derivative **57** was a major side product in the synthesis of **52**. The preparation of the 2-alkyl derivatives **34–38** was accomplished by procedures requiring no comment.

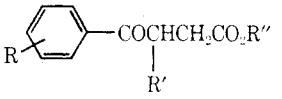
The earlier studies in these laboratories with the dihydropyridazinones indicated that while a 5-methyl substituent had a desirable effect on activity, placement of a methyl group at the 4 position gave substances with weaker antihypertensive properties. Nevertheless, it was of interest to prepare a 4,5-dimethyl-4,5-dihydropyridazinone for testing. Since the 6-(*p*-cyanophenyl) derivative **44** was one of the most interesting members, the preparation of its 4-methyl derivative was undertaken. Our attempted synthesis of this substance began with the reported Friedel–Crafts acylation of bromobenzene with dimethylmaleic anhydride, which in this laboratory gave lactol **60**, mp 102–103°, rather than the reported crotonic acid **61**, mp 120–121° (see Scheme I).[6] Reduction of the olefinic center in **60** was accomplished with zinc in acetic acid. However, the extended reaction time required for efficient reduction caused partial hydrogenolysis of the bromo substituent. The crude reduction products were treated with hydrazine and liquid–liquid partition chromatography resolved the mixture of dihydropyridazinones **62–64**. The composition of this mixture indicated that cis addition of the elements of hydrogen to **60** predominated by a ratio of 5:1. Surprisingly, the displacement of bromide in **63** by cyanide was accompanied by dehydrogenation to give pyridazinone **65**. This dehydrogenation in the 4,5-dimethyl series on treatment with cuprous cyanide contrasts sharply with the smooth conversion of **41** into **44** by this reagent in the 5-methyl series (see above), and the ferric chloride used to destroy the cuprous halide–nitrile adduct[4] apparently functions as the oxidizing agent.

Scheme I



Two procedures were used to prepare the γ-keto acids required as intermediates for the preparation of dihydropyridazinones **1–29**. The monoalkylaminophenyl-

Table II. 4,5-Dihydro-3(2*H*)-pyridazinone Intermediates

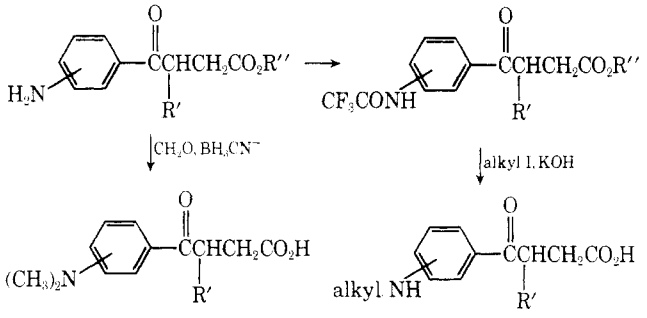


Compd	R	R′	R″	Method	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
66	*p*-NH_2	H	CH_3	J	87	Acetone–C_6H_6	164–167	$C_{11}H_{13}NO_3$	C, H, N
67	*p*-NH_2	CH_3	CH_3	J	66	MeOH–H_2O	118–120	$C_{12}H_{15}NO_3$	C, H, N
68	*p*-NH_2	C_2H_5	CH_3	J	67	Et_2O–petr ether	68–69	$C_{13}H_{17}NO_3$	C, H, N
69	*m*-NH_2	CH_3	C_2H_5	I	86	Acetone–H_2O	65–67	$C_{13}H_{17}NO_3$	C, H, N
70	*p*-CF_3CONH	H	CH_3	M	95	Acetone–hexane	183–184	$C_{13}H_{12}F_3NO_4$	C, H, F, N
71	*p*-CF_3CONH	CH_3	CH_3	M	100	Et_2O–petr ether	67–70	$C_{14}H_{14}F_3NO_4$	C, H, F, N
72	*p*-CF_3CONH	C_2H_5	CH_3	M	86	Et_2O–petr ether	68–70	$C_{15}H_{16}F_3NO_4$	C, H, F, N
73	*m*-CF_3CONH	CH_3	C_2H_5	M	80	Et_2O–petr ether	70–73	$C_{16}H_{18}F_3NO_4$	C, H, F, N
74	*p*-CH_3NH	H	H	N	93	MeOH	203–205 dec	$C_{11}H_{13}NO_3$	C, H, N
75	*p*-C_2H_5NH	H	H	N	35	Acetone–hexane	189–190 dec	$C_{12}H_{15}NO_3$	C, H, N
76	*p*-*n*-C_3H_7NH	H	H	N	12	MeOH–H_2O	196–198 dec	$C_{13}H_{17}NO_3$	C, H, N
77	*p*-CH_3NH	CH_3	H	N	76	Acetone–C_6H_6	172–174	$C_{12}H_{15}NO_3$	C, H, N
78	*p*-C_2H_5NH	CH_3	H	N	54	MeOH–H_2O	162–165 dec	$C_{13}H_{17}NO_3$	C, H, N
79	*m*-CH_3NH	CH_3	H	N	98		Oil[a]	$C_{12}H_{15}NO_3$	
80	*p*-CH_3NH	C_2H_5	H	N	80	Et_2O–petr ether	90–92	$C_{13}H_{17}NO_3$	C, H, N
81	*p*-$(CH_3)_2N$	H	H	K	100	Acetone–hexane	178–179	$C_{12}H_{15}NO_3$	C, H, N
82	*p*-$(CH_3)_2N$	CH_3	H	K	59	Acetone–hexane	129–130	$C_{13}H_{17}NO_3$	C, H, N
83	*m*-$(CH_3)_2N$	CH_3	H	K	96		Oil[a]	$C_{13}H_{17}NO_3$	
84	*m*-NH_2	CH_3	H	I	96		91–95[a]	$C_{11}H_{13}NO_3$	

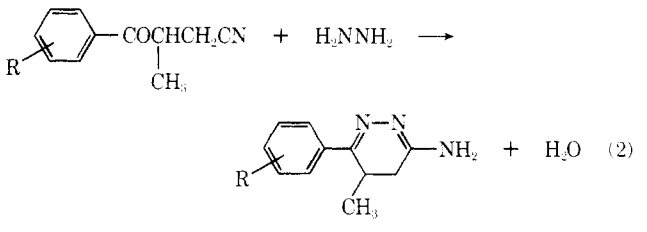
[a] This substance could not be purified; the yield cited is for material that was used in a subsequent transformation.

γ-keto acids **74–80** were prepared by the method of Johnstone and his coworkers (see Scheme II).[7] Thus, the aminobenzoyl esters **66–69** were converted into the trifluoroacetamides **70–73.** Alkylation of these last substances with the appropriate alkyl iodide in the presence of potassium hydroxide and subsequent saponification of the ester function furnished the required acids. The dimethylaminophenyl-γ-keto acids **81–83** were prepared by saponification of the corresponding crude esters which were obtained by treatment of the aminobenzoyl esters **66, 67,** and **69** with formalin and cyanoborohydride as described by Borch and Hassid.[8] The synthesis of the remaining γ-keto acids required for the preparation of other dihydropyridazinones of Table II has been described elsewhere.[9]

Scheme II



Finally, the preparation of two 6-amino-4,5-dihydropyridazines **85** was accomplished by treatment of a γ-keto nitrile with hydrazine (eq 2). Spectral data for the products clearly exclude the alternate 6-imino structure.



85

series **a**, R = *p*-AcNH; **b**, R = *m*-NO_2

Biology. The effect of the dihydropyridazinones on blood pressure was determined in normotensive rats of the Wistar strain as described by Cummings and his coworkers.[10] Mean arterial blood pressure (MABP, mm) was measured at 4 and 24 hr following a single oral dose of 100 mg/kg of the candidate agent. The data are summarized in Table I; comparable data for the highly interesting *m*- (**43**) and *p*-cyano (**44**) derivatives[1] are included. 2-Alkyl derivatives **36–38** of these compounds also cause dramatic lowering of blood pressure and possess a long duration (24 hr) of action following administration of a single dose.

The results expressed in Table I in conjunction with those obtained earlier for members of the series[1] indicate that among the 5-substituted derivatives the greatest lowering of the blood pressure is seen with the 5-methyl derivatives. Representative 5-ethyl (**9, 12, 45, 46, 48**), propyl (**47, 49**), and phenyl (**50, 51**) members were also examined.

Consistent, highly effective antihypertensive activity was found in 6-(alkylaminophenyl) derivatives **1–4, 6–8,** and **11.** Substitution at the 2 position in this series (**5, 9, 12**) by an alkyl group reduced their effectiveness, but acylation of the amino function gave compounds **19–29** generally possessing equal or greater effectiveness. The acetyl derivatives usually proved more active than the corresponding trifluoroacetyl compounds.

Our studies indicate that 6-(halophenyl) and 6-(hydroxyphenyl) derivatives are less interesting with respect to their antihypertensive properties. The potent antihypertensive effect of the carboxamido derivatives **55** and **56** is of interest, since these compounds represent potential metabolites of the benzonitriles **43** and **44,** respectively. The activity of the carboxamides may account, in part, for the sustained effect of the nitriles. Interestingly, the corresponding carboxylic acids **53** and **54** have little effect as antihypertensive agents.

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried and concentrated under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were

within ±0.4% of the theoretical values. The petroleum ether used was that fraction with bp 30–60°.

Preparation of the 6-(Substituted phenyl)-4,5-dihydro-3(2*H*)-pyridazinones (I). Method A. A solution of 34.85 g (0.128 mol) of β-(*p*-bromobenzoyl)butyric acid[9] and 10.0 g (0.21 mol, 10 ml) of hydrazine hydrate in 300 ml of EtOH was stirred at reflux temperature for 3 hr. A solid began separating after 5 min. The mixture was chilled and filtered to give 31.57 g (92%) of **6-(*p*-bromophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (41)** as white crystals, mp 197–199°. The characterization of this substance and others prepared in a similar manner is given in Table I.

Method A_1. A solution of 4.68 g (20 mmol) of methyl 3-(*o*-nitrobenzoyl)propionate, 2.1 ml (40.5 mmol) of hydrazine hydrate, and 1.65 ml of HOAc in 25 ml of EtOH was heated at reflux temperature for 18 hr. Removal of the solvent gave a residue that was distributed between CH_2Cl_2 and H_2O. The material in the organic layer crystallized from CH_2Cl_2–petroleum ether to give 2.03 g (46%) of **4,5-dihydro-6-(*o*-nitrophenyl)-3(2*H*)-pyridazinone (30)** as yellow crystals, mp 162–165°.

Method B. A stirred mixture of 1.00 g (4.65 mmol) of 6-(*p*-cyanophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (**44**) and 1.29 g of powdered KOH in 30 ml of acetone was treated with 3.0 ml of MeI. The mixture was heated at reflux temperature for 40 min, and the solvent was removed. The residue was triturated with H_2O and filtered to give **6-(*p*-cyanophenyl)-4,5-dihydro-2,5-dimethyl-3(2*H*)-pyridazinone (37)**, mp 172–174°. The characterization of this substance is given in Table I.

Method B_1. Application of method B to 670 mg (2.14 mmol) of 4,5-dihydro-2,5-dimethyl-6-(*p*-2,2,2-trifluoroacetamidophenyl)-3(2*H*)-pyridazinone (**24**), 0.60 ml (8.5 mmol) of CH_3I, and 475 mg (8.5 mmol) of powdered KOH in 12 ml of acetone afforded 490 mg of 4,5-dihydro-2,5-dimethyl-6-(*p*-methylaminophenyl)-3(2*H*)-pyridazinone (**7**). See Table I for its characterization.

Method C. A solution of 5.22 g (25.8 mmol) of 6-(*m*-anilino)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone[1] in 18 ml of H_2O and 11 ml of 48% HBr was stirred at 0°. A solid separated, and 1.79 g (26 mmol) of $NaNO_2$ was added in portions to the slurry, the temperature being maintained at 0–3°. Solution occurs, and then a solid separates. The slurry was added dropwise to a cold solution of 4.05 g (14 mmol) of Cu_2Br_2 in 13 ml of 48% HBr. The mixture was stirred at 0° for 30 min, allowed to warm to 20°, and then stirred at 40° for 1 hr. The mixture was cooled and diluted with 90 ml of H_2O. The precipitate was collected, dried, and extracted with two 100-ml portions of CH_2Cl_2. Evaporation of the solvent gave a glass which was dissolved in 5% acetone in CH_2Cl_2 and filtered through a synthetic magnesia–silica adsorbent. The solid was washed liberally with the same solvent mixture. Evaporation of the solvent from the filtrate gave a solid which was recrystallized from acetone–hexane to give 1.75 g of 6-(*m*-bromophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (**40**) as white crystals, mp 160–163°. See Table I for its characterization.

Method D. A mixture of 20.43 g (76.5 mmol) of 6-(*p*-bromophenyl)-4,5-dihydro-5- methyl-3(2*H*)-pyridazinone (**41**) and 9.10 g (51 mmol) of $Cu_2(CN)_2$ in 70 ml of DMF was stirred at reflux temperature for 5.5 hr. The hot mixture was poured into a stirred solution of 46 ml of ethylenediamine in 230 ml of H_2O; stirring was continued for 20 min, whereafter the mixture was filtered to give 14.20 g (87%) of **6-(*p*-cyanophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (44)**, mp 194–197°. See Table I for other compounds prepared similarly.

Method E. A solution of 500 mg (2.35 mmol) of *p*-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)benzonitrile (**41**) in 5 ml of concentrated H_2SO_4 was allowed to stand at room temperature for 18 hr and then was diluted with 45 ml of iced H_2O to afford 460 mg (85%) of ***p*-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)benzamide (56)** as a white solid, mp 215–216°. See Table I for the characterization of this substance.

Method F. To a solution of 360 mg (2.06 mmol) of nitrosonium hexafluorophosphate in 10 ml of acetonitrile cooled to ice-bath temperature was added with stirring 395 mg (1.71 mmol) of *p*-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)benzamide (**56**). The solution was stirred at 0° for 10 min, at 25° for 20 min, and at 50° for 30 min. Water (0.3 ml) was added to the reaction, and the solid was collected to give 250 mg (63%) of ***p*-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)benzoic acid (54)** as white crystals, mp 266–270°.

Method G. A mixture of 500 mg (2.2 mmol) of 6-(*p*-ethylaminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**2**) and 1 ml of acetic anhydride was stirred at room temperature for 1 hr. Water was added to destroy the excess anhydride, after which time the solid ***N*-ethyl-4′-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)acetanilide (27)** (470 mg, 83%) was collected to give white crystals, mp 167–168°. See Table I for its characterization.

Method G_1. A mixture of 400 mg (1.97 mmol) of 4,5-dihydro-6-(*p*-methylaminophenyl)- 3(2*H*)-pyridazinone (**1**) and 1 ml of 97% HCO_2H in 10 ml of toluene was heated at reflux temperature for 17 hr; separated H_2O was collected in a modified Dean–Stark H_2O trap. The solvent was removed, and the product, ***N*-methyl-4′-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)formanilide (19)**, was purified as indicated in Table I.

Method H. A solution of 1.71 g (8.4 mmol) of 6-(*p*-anilino)-4,5-dihydro-2-methyl-3(2*H*)-pyridazinone, 0.55 g (18.5 mmol, 1.4 ml) of 37% formalin, and 1.83 g (42 mmol, 1.5 ml) of 97% HCO_2H was heated on a steam bath for 17 hr. The volatile material was removed, and the residue was distributed between CH_2Cl_2 and H_2O. The material in the organic layer was chromatographed on a synthetic magnesia–silica adsorbent. The fractions eluted by CH_2Cl_2 contained the product, the characterization of which is given in Table I.

Method I. A mixture of 2.56 g (10.4 mmol) of 4,5-dihydro-2,5-dimethyl-6-(*m*-nitrophenyl)-3(2*H*)-pyridazinone (**34**) and 250 mg of 10% Pd/C in 50 ml of EtOH was shaken under hydrogen until the pressure became constant (13 min). The solution was filtered and evaporated to furnish a gum which crystallized from Et_2O–petroleum ether to give 2.10 g (93%) of **6-(*m*-anilino)-4,5-dihydro-2,5-dimethyl-3(2*H*)-pyridazinone (35)** as white crystals, mp 120–122°.

Preparation of Esters of 3-(Substituted benzoyl)alkanoic Acids. Method J. A solution of 3.00 g (13.5 mmol) of 3-(*p*-aminobenzoyl)butyric acid[9] and 0.12 ml of H_2SO_4 in 60 ml of MeOH was heated at reflux temperature for 18 hr. The solution was cooled and added to 1.0 g of anhydrous NaOAc and diluted with 60 ml of H_2O, and the MeOH was removed until crystals separated. The mixture was cooled in an ice bath, and the solid was collected, affording 2.20 g (66%) of **methyl 3-(*p*-aminobenzoyl)butyrate (67)** as crystals, mp 116–118°. The characterization of this substance and the preparation of other esters by this procedure are given in Table II.

Method K. To a mixture of 1.49 g (7.20 mmol) of methyl 3-(*p*-aminobenzoyl)propionate (**66**) and 6.2 ml of 37% formalin in 30 ml of MeCN was added 1.37 g (23.2 mmol) of sodium cyanoborohydride. To the stirred mixture was added 0.77 ml of HOAc over a period of 7 min. Stirring was continued for 2 hr, and an additional 0.77 ml of HOAc added. After stirring for an additional 30 min, the solution was diluted with 100 ml of Et_2O and washed with 1 *N* NaOH solution. The organic solution was dried and evaporated leaving 1.69 g of amber gum. This material was heated at reflux temperature for 90 min with 20 ml of 6 *N* HCl solution, and the hot solution was filtered through diatomaceous earth. Evaporation of the filtrate gave a residue that was triturated with 25 ml of acetone to give 1.62 g (100%) of crude **3-(*p*-dimethylaminobenzoyl)propionic acid (81)** as a white solid, mp 172–175°. See Table II for the characterization of this substance and those prepared in similar fashion.

Method L. A solution of 4.08 g (20 mmol) of 3-(*o*-nitrobenzoyl)-propionitrile[9] in 100 ml of methanol saturated with hydrogen chloride at 0° was heated at reflux temperature for 3 hr. Most of the solvent was removed, and the residue was distributed between methylene chloride and water. The dried organic solution was evaporated to give 4.68 g (99%) of yellow liquid: ir max 5.75–5.81, 6.60, 7.45 μ; tlc in EtOAc–heptane (1:1) R_f 0.65. The esters prepared in this manner were used for the preparation of the dihydropyridazinones without further purification.

Method M. A mixture of 11.80 g (53.4 mmol) of methyl 3-(*p*-aminobenzoyl)butyrate (**66**) and 25 ml of trifluoroacetic anhydride was stirred for 1 hr, diluted with 370 ml of ice–water, and stirred for an additional 1 hr. The mixture was extracted with CH_2Cl_2, and the extracts were washed successively with 1 *N* HCl, saline, saturated $NaHCO_3$ solution, and saline. The dried solution was evaporated to give 15.97 g (100%) of methyl 3-(*p*-2,2,2-trifluoroacetamidobenzoyl)butyrate (**71**) as a gum that crystallized on trituration with Et_2O–petroleum ether to give a white solid, mp 67–70°. See Table II for its characterization.

Preparation of the 3-(Alkylaminobenzoyl)alkanoic Acids. Method N. The following preparation of 3-(*p*-methylaminobenzoyl)butyric acid (**77**) illustrates the general procedure. To a stirred solution of 15.0 g (47.4 mmol) of methyl 3-(*p*-2,2,2-trifluoroacetamidobenzoyl)butyrate (**71**) and 30.8 g (13.5 ml, 0.21 mol) of iodomethane in 300 ml of acetone was added 14.2 g (0.25 mol) of powdered KOH. The mixture was stirred at reflux temperature for 5 min and then the solvent was removed. Water (200 ml) was

added to the residue, and the mixture was heated at reflux temperature for 10 min. The mixture was cooled and washed with CH_2Cl_2. The alkaline solution was stirred in an ice bath and rendered acidic (pH ~4) by the dropwise addition of 1 *N* HCl. The product was collected as tan crystals, mp 170–172°. The characterization of this acid and others prepared in a similar manner is described in Table II.

3-(*p*-Bromobenzoyl)-2-methylcrotonic Acid Lactone (60). A solution of 13.75 g (9.2 ml, 87.5 mmol) of bromobenzene in 10 ml of CS_2 was added dropwise over a period of 60 min to a stirred mixture of 49.7 g (0.186 mol) of $AlBr_3$ and 9.80 g (78 mmol) of 2,3-dimethylmaleic anhydride. The mixture was heated at reflux for 4 hr and then poured onto iced 37% HCl. The mixture was extracted with CH_2Cl_2 and the extracts were washed with saline solution, dried, and evaporated. The residue was subjected to steam distillation, collecting 350 ml of distillate. The pot residue was extracted with CH_2Cl_2 and the extracts were washed, dried, and evaporated. The residual gum was triturated with heptane to give 11.10 g (50%) of white solid, mp 92–96°. One crystallization from CH_2Cl_2–heptane gave 9.45 g of white crystals: mp 100–102°; uv max 228 mμ (ε 14,300); ir max 2.95, 5.73, 5.90, 6.25 μ; δ^{TMS} ($CDCl_3$) 1.76 (s, 6, CH_3), 3.42 (s, 1, OH), 7.27, 7.48 (d, 2 each, aryl A_2B_2), exchange with CD_3OD erased the 3.42 signal.

***cis*- and *trans*-6-(*p*-Bromophenyl)-4,5-dihydro-4,5-dimethyl-3(2*H*)-pyridazinone.** A hot solution of 5.50 g (19.5 mmol) of 3-(*p*-bromobenzoyl)-2-methylcrotonic acid lactone (**60**) in 75 ml of HOAc and 30 ml of H_2O was treated with 2.73 g (41.8 mg-atoms) of Zn dust. The mixture was stirred at reflux temperature for 30 min. An additional 2.73 g of Zn dust was added and the heating continued for 3.5 hr. The mixture was cooled, and the supernatant was decanted from the Zn and concentrated. The concentrate was diluted with H_2O, and the mixture was extracted with CH_2Cl_2. The extracts were washed with saline, dried, and evaporated. Toluene was added to the residue and removed under reduced pressure to give 5.18 g of crude 3-(*p*-bromobenzoyl)-2-methylbutyric acids which were converted into the pyridazinones by method A.

The crude product (5.20 g) was subjected to partition chromatography on diatomaceous silica using a heptane–MeCN–H_2O (200:55:45) system and monitoring the effluent for material with uv absorption at 292 mμ. The material with peak hold-back volume 4.4 (V_m/V_s = 3.46) was crystallized from Et_2O–petroleum ether to give 840 mg (15%) of cis isomer **63**: mp 174–176°; δ^{TMS} ($CDCl_3$) 1.10 (d, 3, J = 8.0 Hz, 4-CH_3), 1.30 (d, 3, J = 8.0 Hz, 5-CH_3), 2.78 (d of q, 1, $J(H_a-H_b) \sim 7$ Hz, $J(H_a-CH_3)$ = 8.0 Hz, 4-H), 3.16 (d of q, 1, $J(H_a-H_b) \sim 7$ Hz, $J(H_b-CH_3)$ = 8.0 Hz, 5-H), 7.57, 7.62 (each d, 1 each, J = 10 Hz, aryl A_2B_2), 9.15 (s, 1, NH). *Anal.* ($C_{12}H_{13}BrN_2O$) C, H, Br, N.

The material eluted at peak hold-back volume 6.3 crystallized from Et_2O–petroleum ether to give 280 mg (5%) of trans isomer **62**: mp 174–175°; δ^{TMS} ($CDCl_3$) 1.19, 1.22 (overlapping d, 3 each, J = 8 Hz, CH_3), 2.54 (d of q, 1, $J(H_a-CH_3)$ = 8 Hz, $J(H_a-H_b) \sim$ 1.5 Hz, 4-H), 3.02 (d of q, 1, 5-H), 7.56, 7.61 (aryl-A_2B_2, 4), 9.11 (s, 1, NH). *Anal.* ($C_{12}H_{13}BrN_2O$) C, H, N; Br: calcd, 28.43; found; 28.94.

***cis*-4,5-Dihydro-4,5-dimethyl-6-phenyl-3(2*H*)-pyridazinone (64)** was eluted at peak hold-back volume 10.0. Recrystallization from acetone–hexane gave 421 mg (11%) of white crystals; mp 124–125°; δ^{TMS} ($CDCl_3$) 1.12, 1.30 (each d, 3, $J \sim 7$ Hz, CH_3), 2.78 (d of q, 1, $J(H_a-CH_3) = J(H_a-H_b) \sim 7$ Hz, 4-H) , 3.22 (d of q, 1, 5-H), 7.42 (m, 3, *m*- and *p*-H of Ph), 7.77 (m, 2, *o*-H of Ph), 9.09 (s, 1, NH). *Anal.* ($C_{12}H_{14}N_2O$) C, H, N.

6-(*p*-Cyanophenyl)-4,5-dimethyl-3(2*H*)-pyridazinone (65). A mixture of 1.28 g (4.55 mmol) of *cis*-6-(*p*-bromophenyl)-4,5-dihydro-4,5-dimethyl-3(2*H*)-pyridazinone (**63**) and 1.72 g (9.6 mmol) of $Cu_2(CN)_2$ in 5 ml of DMF was stirred and heated at reflux temperature for 5 hr. The hot solution was poured into a solution of 4.4 g of $FeCl_3$ and 3.4 ml of 37% HCl in 12 ml of water and heated on the steam bath for 30 min. The solution was cooled, diluted with H_2O, and filtered to give 1.30 g of brown solid. This solid was extracted with CH_2Cl_2, and the extracts were evaporated. The residual solid was recrystallized from acetone to give 270 mg (26%) of white crystals: mp 258–262°; uv max 242 mμ (ε 23,900). *Anal.* ($C_{13}H_{11}N_3O$) C, H, N.

4′-(6-Amino-4,5-dihydro-4-methyl-3-pyridazinyl)acetanilide (82a). A mixture of 1.28 g (5.6 mmol) of 4′-(3-cyano-2-methylpropionyl)acetanilide,[9] 0.58 ml of hydrazine hydrate, and 0.47 ml of HOAc in 7 ml of EtOH was stirred and heated at reflux temperature for 1 hr. The mixture was cooled, and the yellow crystals were collected and washed successively with methanol, methylene chloride, and acetone to give 635 mg (46%) of yellow crystals, mp 254–256°. *Anal.* ($C_{13}H_{16}N_4O$) C, H, N.

6-Amino-4,5-dihydro-4-methyl-3-(*m*-nitrophenyl)pyridazine (82b). In the manner described above a mixture of 920 mg (4.2 mmol) of 3-*m*-nitrobenzoylbutyronitrile,[9] 0.44 ml of hydrazine hydrate, and 0.35 ml of HOAc in 10 ml of EtOH gave 500 mg (51%) of crystals, mp 200–210°. A sample recrystallized from acetone–hexane had mp 200–208°. *Anal.* ($C_{11}H_{12}N_4O_2$) C, H, N.

3-(*o*-Nitrobenzoyl)butyric Acid Isopropylidenehydrazide (58). Using method A, 7.32 g (29.5 mmol) of methyl 3-(*o*-nitrobenzoyl)butyrate and 7 ml of hydrazine hydrate in 75 ml of MeOH gave 6.87 g of a gum after solvent removal. An acetone–ether solution of this material deposited 1.68 g (20%) of the hydrazide as yellow crystals, mp 140–143°, on standing at room temperature. Recrystallization of a sample from CH_2Cl_2–petroleum ether gave yellow crystals, mp 143–144°. *Anal.* ($C_{14}H_{17}N_3O_4$) C, H, N. The filtrate was evaporated to give 4.57 g of a residue from which **32** was isolated by partition chromatography.

Reaction of Chlorosulfonyl Azide with 6-(*p*-Aminophenyl)-4,5-dihydro-2,5-dimethyl-3(2*H*)-pyridazinone. A stirred, ice-cooled solution of 2.17 g (10 mmol) of 6-(*p*-aminophenyl)-4,5-dihydro-2,5-dimethyl-3(2*H*)-pyridazinone (crude material prepared from 3-(*p*-aminobenzoyl)butyric acid[9] and methylhydrazine using procedure A) and 1.4 ml (10.2 mmol) of triethylamine in 20 ml of CH_3CN was treated with a solution of chlorosulfonyl azide[11] in acetonitrile (prepared as described by Griffiths[12] from 5.0 mmol of sulfuryl chloride and 5.0 mmol of sodium azide). The reaction was concentrated to a volume of 5 ml, and the products were isolated with EtOAc in the usual manner. After removal of the solvent, the residue was crystallized from acetone–hexane to give **57** as tan crystals.

Evaporation of the filtrate gave a residue that was chromatographed on a synthetic magnesia–silica adsorbent. The material eluted by 8% acetone in methylene chloride crystallized from Et_2O–petroleum ether to give **52**. Characterization of **52** and **57** is given in Table I.

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References

(1) W. V. Curran and A. Ross, *J. Med. Chem.*, **17**, 273 (1974).
(2) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **75**, 1117 (1953), and references cited therein.
(3) M. Morishita and F. Sakiyama, *Bull. Chem. Soc. Jap.*, **43**, 524 (1970).
(4) (a) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961); (b) M. S. Newman and H. Boden, *ibid.*, **26**, 2525 (1961).
(5) W. L. Matier, W. T. Comer, and D. Deitchman, *J. Med. Chem.*, **15**, 538 (1972), and references cited therein.
(6) R. E. Lutz and M. Couper, *J. Org. Chem.*, **6**, 77 (1941).
(7) R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc. C*, 2223 (1969).
(8) R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972).
(9) F. J. McEvoy and G. R. Allen, Jr., *ibid.*, **38**, 4044 (1973).
(10) J. R. Cummings, A. N. Welter, J. L. Grace, Jr., and L. M. Lipchuck, *J. Pharmacol. Exp. Ther.*, **161**, 88 (1968).
(11) R. J. Shozda and J. A. Vernon, *J. Org. Chem.*, **32**, 2876 (1967).
(12) J. Griffiths, *J. Chem. Soc. C*, 3191 (1971).