μl of water, and 5 μl of venom solution. Cytidine 5′-phosphate was used as a control for 5′-nucleotidase activity and cytidine 2′(3′)-phosphate as a control for possible presence of nonspecific phosphatase. On incubation at 37°, the cytidine 5′-phosphate was quantitatively converted to cytidine in 1 hr, XIa to IVa in 2.5 hr, and XIb to IVb in 3.5 hr, as shown by chromatography (Table I). Cytidine 2′(3′)-phosphate exhibited only trace dephosphorylation after prolonged (24 hr) incubation.

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6-Phenyl-4,5-dihydro-3(2*H*)-pyridazinones. A Series of Hypotensive Agents

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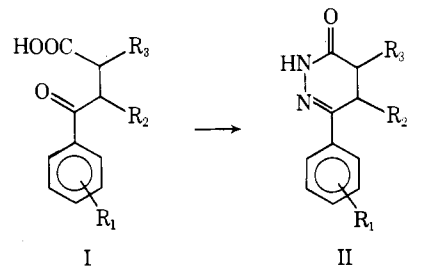
A variety of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones (II) have been synthesized and examined for hypotensive activity in the normotensive rat. Considerable activity in this area has been observed for a variety of substituents on the phenyl moiety. The compounds containing acetamido and cyano groups combined with a 5-methyl group (*e.g.*, II, R_1 = $NHCOCH_3$ or CN; R_2 = CH_3; R_3 = H) exhibit particularly potent and long-lasting hypotensive activity.

The finding that 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones (II) possessed reproducible activity in a rat hypotensive screening program prompted us to synthesize a number of derivatives in this area.

Chemistry. The synthesis of this series of compounds II is readily accomplished in high yields by refluxing the requisite γ-keto acid I with hydrazine hydrate in ethanol. (For reviews on pyridazine chemistry, see ref 1.) Therefore, the two synthetic approaches toward this series of compounds involve preparation of various substituted γ-keto acids I followed by ring closure and modification of the preformed pyridazinones II. Both of these approaches have been utilized. A listing of the compounds prepared is given in Tables I and II.

The standard synthesis of γ-keto acids such as I involves a Friedel–Crafts reaction between an aromatic compound and succinic anhydride in the presence of a Lewis acid such as aluminum chloride. (For comprehensive discussions of this reaction, see ref 2.) This results in para substitution in the case of simple monosubstituted benzene derivatives. A number of γ-keto acids were prepared *via* this route and converted to the desired pyridazinones as indicated in Table I. In those cases which produced new compounds and if there was any doubt as to the substitution pattern, nmr was utilized to establish the structures.



I II

Table I. Dihydropyridazinones[a]

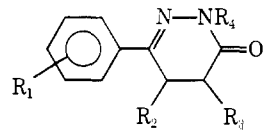
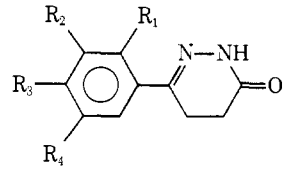
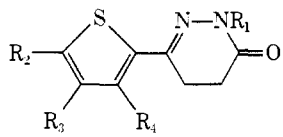
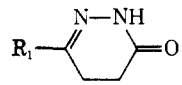
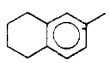
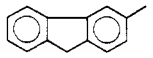
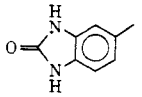
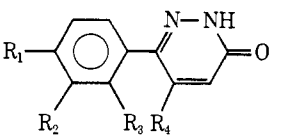
No.	R_1	R_2	R_3	R_4	Method[b]	% yield	Mp, °C	Formula	Hypotensive act. of MABP[c] (mm)
									
1	*p*-F	H	H	H	A[d]	98	190–192	$C_{10}H_9N_2OF$	90
2	*m*-NO_2	H	H	H	A (5)	91	232–235	$C_{10}H_9N_3O_3$	98
3	*p*-OH	H	H	H	A[e]	96	>270	$C_{10}H_{10}N_2O_2$	116
4	*p*-Br	H	H	CH_3	A[f]	56	115–118	$C_{11}H_{11}N_2OBr$	110
5	*p*-Cl	H	H	CH_3	A (7)	60	76–78	$C_{11}H_{11}N_2OCl$	115
6	*p*-Cl	H	H	*p*-ClC_6H_5	A (7)	88	92–93	$C_{16}H_{12}N_2OCl_2$	112
7	*p*-Cl	H	H	C_6H_5	A (7)	90	94–95	$C_{16}H_{13}N_2OCl$	110
8	*p*-Cl	H	H	$C_6H_5CH_2CH_2$	A (7)	95	93–94	$C_{18}H_{17}N_2OCl$	122
9	*p*-Cl	H	CH_3	H	A (7), B	89	137–138	$C_{11}H_{11}N_2OCl$	106
10	*p*-CN	H	H	H	A,[g] B	88	254–258	$C_{11}H_9N_3O$	82
11	*p*-ClC_6H_4-*p*-C_6H_4	H	H	H	A[g]	99	237–238	$C_{16}H_{13}N_2OCl$	132
12	*p*-Cl	CH_3	H	H	A[g]	90	136–139	$C_{11}H_{11}N_2OCl$	85
13	*p*-COOH	H	H	H	A,[g] B	50	>300	$C_{11}H_{10}N_2O_3$	114
14	*m*-CN	H	H	H	B[h]	65	188–189	$C_{11}H_9N_3O$	92
15	*p*-$(CH_3)_2NC(=O)S$	H	H	H	B[i]	10	191–194	$C_{13}H_{15}N_3O_2S$	98
16	*p*-$(CH_3)_2NC(=S)O$	H	H	H	B[i]	23	207–210	$C_{13}H_{15}N_3O_2S$	102
17	*p*-CH_3CONH	H	CH_3	H	A[g]	86	219–220	$C_{13}H_{15}N_3O_2$	100
18	*p*-$CONH_2$	H	H	H	B[k]	37	285–288	$C_{11}H_{11}N_3O_2$	98
19	*p*-NH_2	H	CH_3	H	B[l]	89	243–244	$C_{11}H_{13}N_3O$	102
20	*p*-CN	H	CH_3	H	B[h]	69	190–192	$C_{12}H_{11}N_3O$	90
21	*p*-NH_2	CH_3	H	H	B[m]	65	195–197	$C_{11}H_{13}N_3O$	68
22	*p*-CH_3CONH	CH_3	H	H	A[g]	60	235–236	$C_{13}H_{15}N_3O_2$	73
23	*m*-NO_2	CH_3	H	H	B[m]	18	191–194	$C_{11}H_{11}N_3O_3$	80
24	*p*-CN	CH_3	H	H	B[h]	75	194–196	$C_{12}H_{11}N_3O$	70
25	*p*-CN	H	H	CH_3	A[g]	84	138–140	$C_{12}H_{11}N_3O$	84
26	*m*-NH_2	CH_3	H	H	B[m]	46	143–145	$C_{11}H_{13}N_3O$	86
27	*p*-CH_3CONH	CH_3	H	CH_3	A[g]	94	145–147	$C_{14}H_{17}N_3O_2$	85
28	*p*-C_6H_4–	H	H	H	A[n]	92	197–198	$C_{16}H_{20}N_2O$	107
29	*p*-$CH_3OC_6H_4$	H	H	H	A[o]	74	245–250	$C_{17}H_{16}N_2O_2$	112
30	H	H	CH_3	H	A[g]	90	152–155	$C_{11}H_{12}N_2O$	103
31	*m*-CH_3CONH	CH_3	H	H	B[p]	72	216–219	$C_{13}H_{15}N_3O_2$	82
32	*m*-CN	CH_3	H	H	B[h]	68	187–189	$C_{12}H_{11}N_3O$	66
									
33	Cl	H	H	Cl	A (2)	96	174–175	$C_{10}H_8N_2OCl_2$	99
34	OH	CH_3O	CH_3O	H	A[q]	92	223–227	$C_{12}H_{14}N_2O_4$	117
35	H	CN	CH_3	H	A[g]	94	204–206	$C_{12}H_{11}N_3O$	111
36	H	NH_2	CH_3	H	A[g]	90	244–248	$C_{11}H_{13}N_3O$	109
37	H	NO_2	CH_3	H	A (5)	92	215–217	$C_{11}H_{11}N_3O_3$	110
38	H	F	CH_3O	H	A[f]	85	178–179	$C_{11}H_{11}N_2O_2F$	115
									
39	H	Cl	H	H	A[r]	90	251–253	$C_8H_7N_2OSCl$	127
40	H	Br	H	H	A[r]	93	238–240	$C_8H_7N_2OSBr$	123
41	H	H	H	H	A[f]	92	124–125	$C_8H_8N_2OS$	108
42	H	CN	H	H	A[g]	97	238–240	$C_9H_7N_3OS$	85
43	CH_3	CN	H	H	A[g]	67	139–141	$C_{10}H_9N_3OS$	96
44	H	H	H	Br	A[g]	44	144–146	$C_8H_7N_2OSBr$	115
45	H	H	Br	H	A[g]	14	247–249	$C_8H_7N_2OSBr$	120
									
46					A[r]	96	141–142	$C_{14}H_{16}N_2O$	94

Table I (*Continued*)

No.	R_1	R_2	R_3	R_4	Method[b]	% yield	Mp, °C	Formula	Hypotensive act. of MABP[c] (mm)
47					A[n]	91	252–253	$C_{17}H_{14}N_2O$	112
48					A[o]	98	390	$C_{11}H_{10}N_4O_2$	115
49					A[s]		207–208	$C_{14}H_{20}N_2O$	112

[a]All new compounds reported in this paper gave acceptable elemental analyses (C, H, and N, and halogen and sulfur when present). Recrystallization solvents generally ethanol or ethanol–water for dihydropyridazinones. [b]A: synthesized by ring closure of the γ-keto acid with hydrazine hydrate or the appropriate substituted hydrazines. Several examples are included in the Experimental Section. Numbers in parentheses refer to reference source of keto acid. B: synthesized from a preformed dihydropyridazinone. Representative examples are given in the Experimental Section. [c]Mean arterial blood pressure of normotensive Wistar rats 4 hr after a single oral dose of 100 mg/kg. Control animals average 120 mm.[g] Under similar conditions hydralazine gives a value at 69. [d]L. F. Fieser and A. M. Seligman, *J. Amer. Chem. Soc.*, **60**, 170 (1938). [e]Acid hydrolysis of commercially available 3-(*p*-methoxybenzoyl)propionic acid. [f]Commercially available. [g]See Table III. [h]Prepared by Sandmeyer reaction. [i]Prepared by reaction of dimethylthiocarbamoyl chloride on the *p*-hydroxy compound. [j]Prepared by thermal rearrangement of compound **15**: M. S. Newman and H. A. Kornes, *J. Org. Chem.*, **31**, 3980. [k]Prepared by alkaline peroxide treatment of nitrile **10**. [l]Prepared by hydrolysis of corresponding acetamido compound. [m]See Experimental Section. [n]L. F. Fieser, *et al.*, *J. Amer. Chem. Soc.*, **70**, 3197 (1948). [o]L. F. Fieser and C. K. Bradsher, *J. Amer. Chem. Soc.*, **58**, 1738 (1936). [p]Prepared by acetylation of corresponding amino compound. [q]R. H. F. Manske and H. L. Holmes, *J. Amer. Chem. Soc.*, **67**, 95 (1945). [r]N. P. Buu-Hoi, N. Hoán, and N. P. Khôi, *Recl. Trav. Chim. Pays-Bas*, **69**, 1053 (1950). [s]Prepared *via* a malonic ester synthesis. No intermediates characterized.

Table II. Pyridazinones[a]



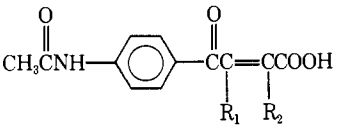
No.	R_1	R_2	R_3	R_4	Method[b]	% yield	Mp, °C	Formula	Hypotensive act. of MABP[c] (mm)
50	H	CN	H	H	A	50	291–294	$C_{11}H_7N_3O$	110
51	Cl	H	H	CH_3	A	90	224–225	$C_{11}H_9N_2OCl$	110
52	CN	H	H	H	A	56	335	$C_{11}H_7N_3O$	100
53	NH_2	H	H	CH_3	B	85	283–285	$C_{11}H_{11}N_3O$	106
54	CH_3CONH	H	H	CH_3	C	65	256–257	$C_{13}H_{13}N_3O_2$	107
55	CN	H	H	CH_3	B	80	255–260	$C_{12}H_9N_3O$	112

[a]All compounds recrystallized from aqueous ethanol. [b]A, bromine oxidation of dihydropyridazinone; B, basic hydrolysis of **54**; C, ring closure of unsaturated keto acid. [c]See footnote *c*, Table I.

The Friedel–Crafts reaction using methylsuccinic anhydride usually leads to a preponderance of the α-methylketo acids I (R_1, R_2 = H; R_3 = CH_3) and this was found to be the case in the reactions of it with chlorobenzene and acetanilide. The structure of the product obtained in the chlorobenzene reaction was established unequivocally by an alternate pathway via the malonic ester synthesis. (See ref 3. This work had to be repeated due to a discrepancy in melting points.) In the reaction of chlorobenzene with the methylsuccinic anhydride, a small amount of the β-methylketo acid and a bis compound were also isolated.

The reaction of citraconic anhydride (methylmaleic anhydride) with acetanilide afforded the β-methylacrylic acid III as the major product along with a small amount of the isomeric α-methyl compound IV. Both compounds were reduced to the saturated acids and one being identical with the product obtained from acetanilide and methylsuccinic anhydride (*vide supra*).

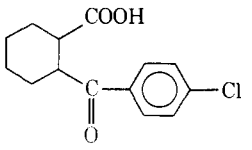
The essential diagnostic feature used to differentiate the α-methylketo acids from the corresponding β-methyl compounds was the nmr signal of the methine proton. In the β-methyl series this proton is always further downfield and separated from the methylene protons in contrast to the methine proton in the α-methyl analogs. This same feature was exhibited by the corresponding dihydropyridazinones.



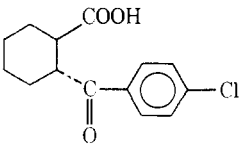
III, R_1 = CH_3; R_2 = H
IV, R_1 = H; R_2 = CH_3

The Friedel–Crafts reaction of chlorobenzene with cyclohexane-1,2-dicarboxylic anhydride afforded *cis*-2-(*p*-chlorobenzoyl)cyclohexanecarboxylic acid (V) in good yield which was readily isomerized to the trans compound VI by basic treatment. The structural assignments are based on nmr evidence and the method of preparation.

The Friedel–Crafts introduction of the keto acid side chain is not applicable to aromatic compounds containing



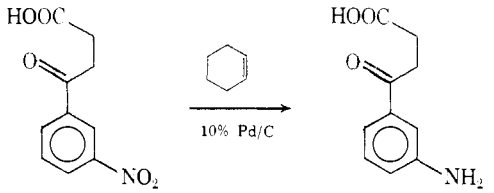
V



VI

electron-withdrawing groups; hence, this type of compound was prepared from preformed keto acids or pyridazinones. Thus, the *p*-amino compound VII was converted to the diazonum salt and treated with a mixture of cuprous and potassium cyanides to give the desired cyano derivative VIII. Alternatively, the amino acid X was diazotized and treated under Sandmeyer conditions to afford the cyano acid XI which was converted to the pyridazinone VIII in the usual way. The latter procedure gave a lower yield in the diazonium reaction. Cyanoacid XI was also synthesized *via* cuprous cyanide–dimethylformamide treatment[4] on the bromo acid XII; however, the yield was also low. Compound XI was converted to the diacid which was in turn cyclized to the pyridazinone IX. Treatment of the cyano compound VIII with hot, dilute sodium hydroxide also afforded the carboxy derivative IX. Alkaline hydrogen peroxide treatment of the cyano VIII gave the corresponding amide. These reactions are summarized in Scheme I.

The preparation of the meta derivatives was readily accomplished starting with 3-benzoylpropionic acid. Nitration of this compound using mixed acids gave the *m*-nitro compound XIII[5] which was smoothly reduced to the corresponding *m*-amino acid XIV using cyclohexene with 10%



XIII XIV

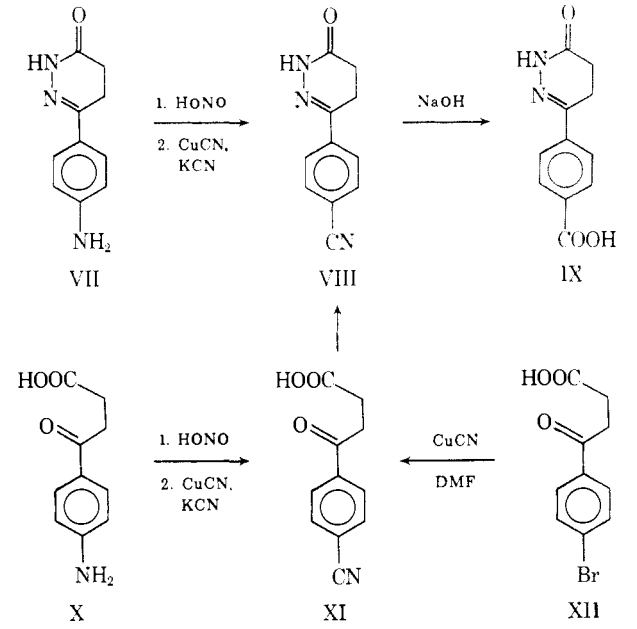
Pd/C. Ring closure to the pyridazinone followed by formation of the diazonium salt and treatment with cuprous cyanide afforded the *m*-cyano analog. 3-(*p*-Toluoyl)propionic acid was subjected to the same reaction sequence described above to give the related 6-(3-substituted 4-methylphenyl)-4,5-dihydro-3(2*H*)-pyridazinone compounds.

The novel tricyclic derivative XVIII and two similar compounds were prepared as shown in Scheme II. 6-Methoxytetralone XV was condensed with glyoxal, which was prepared *in situ* by sodium metaperiodate cleavage of tartaric acid, to give the unsaturated keto acid XVI.[6] Reduction with zinc and acetic acid afforded XVII followed by reaction with hydrazine hydrate which gave a good yield of compound XVIII.

The corresponding 4-methyl derivatives II (R_1 = *p*-CN; R_2 = H; R_3 = CH_3) and 5-methyl derivatives (R_1 = *p*-CN and *m*-CN; R_2 = CH_3; R_3 = H) were prepared by methods similar to those outlined above (see Scheme I). The starting keto acid for the *m*-5-methyl series, 3-benzoylbutyric acid, was synthesized *via* the malonic ester route (see Experimental Section).

Several thiophene derivatives were also prepared by methods similar to those described above. In addition, the reaction of 3-bromothiophene with succinic anhydride gave a mixture of two keto acids XIX and XX which was converted to the corresponding pyridazinones and separated by fractional crystallization (nmr provided structural assignments).

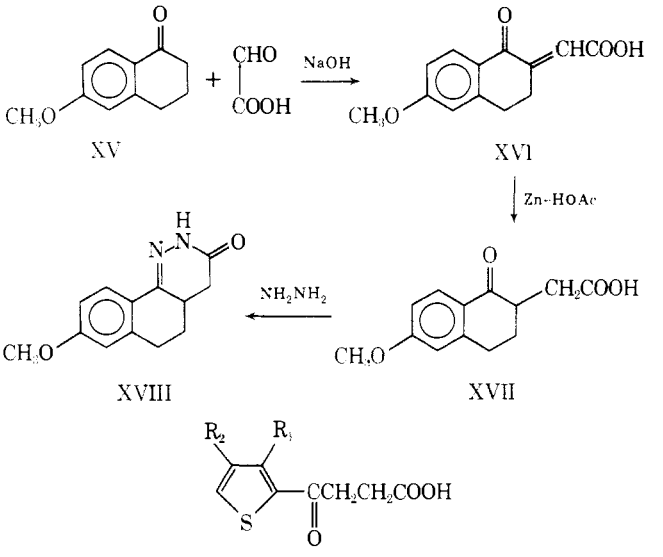
Scheme I



VII VIII IX

X XI XII

Scheme II



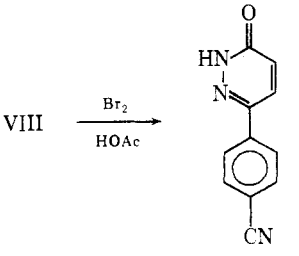
XV XVI

XVIII XVII

XIX, R_1 = Br; R_2 = H
XX, R_1 = H; R_2 = Br

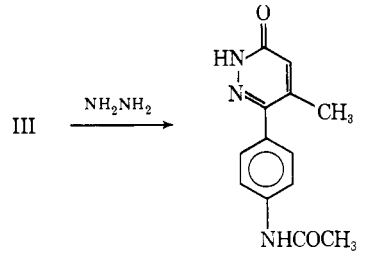
Conversion of the dihydropyridazine compounds to the corresponding aromatic derivatives is readily accomplished using bromide in acetic acid[7] as illustrated below for the *p*-cyano compound XXI. Several other analogs including the 5-methyl compound were prepared by this route.

Those dihydropyridazinone compounds containing activating substituents in the phenyl ring cannot be obtained



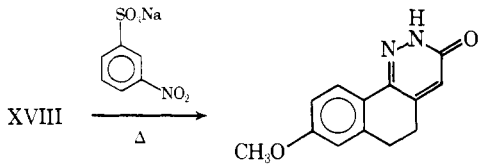
XXI

in this manner since bromination of the aromatic moiety will also occur. These compounds can be prepared from the unsaturated acids. Thus, keto acid III was cyclized to compound XXII with hydrazine. This product was also converted to the amino analog by the usual method.



XXII

Another method for the oxidation of compounds with activating groups on the aromatic ring is the recently described method of Bachman using sodium *m*-nitrobenzenesulfonate.[8] This route worked very well in the preparation of the tricyclic compound XXIII from XVIII. A list of aromatic pyridazinones is given in Table II.



XXIII

Biology. Approximately 20 of the dihydropyridazinones described herein were active in the normotensive rat screen. The criteria for activity is that the mean arterial blood pressure (mm) must be ≤90 4 hr after dosing for two rats and ≤95 on retest (two rats) compared to an average value of 120 for untreated controls.[9]

The single unifying feature of all the active compounds in this series is the presence of an aromatic substituent in the 6 position of the dihydropyridazinone.† Thus, the 6-methyl, *n*-propyl, isopropyl, and adamantyl were all inactive while the 20 active compounds were 6-substituted phenyl derivatives, with the exception of the 6-(5,6,7,8-tetrahydro-2-naphthyl), a borderline compound, and the 6-(5-cyano)-2-thienyl compound. The activity in the thiophene series was seen only in the latter compound, the corresponding 5-bromo, 5-chloro, and 5-unsubstituted derivatives all being inactive.

In the 6-substituted phenyl class the substituents included both electron-withdrawing (F, Cl, Br, I, NO_2, and CN) and electron-releasing ($-NH_2$ and $-NHCOCH_3$) groups. The most striking feature was the effect of methyl groups in the 4 and 5 position of the dihydropyridazinone ring. In every case the introduction of a 5-methyl group produced an active compound. In contrast to this, all of the corresponding 4-methyl derivatives with the exception of the *p*-cyano compound were completely inactive. Substitution of the 2 position with methyl, phenyl, or phenethyl gave inactive compounds in the *p*-chlorophenyl and *p*-bromophenyl series but the 2-methyl analogs of the *p*-cyanophenyl and of the 5-methyl-6-(*p*-acetamidophenyl) were quite active. Putting a methyl group on the phenyl moiety along with the cyano substituent, *e.g.*, the 6-(3-cyano-4-methylphenyl) derivative, resulted in loss of all activity. Similarly, the 6-(3-fluoro-4-methoxyphenyl) analog was inactive. From the foregoing discussion it is quite obvious that no simple steric or electronic effect is discernible to account for the biological activity of this class of compounds.

Another interesting observation regarding structure-activity relationships is that all of the aromatic pyridazinones (those derivatives listed in Table II which contain a double bond at the 4,5 position) were devoid of hypotensive activity. Even the compounds derived from the most active dihydropyridazinone were not active.

The cyano, acetamido, and amino groups in the para or meta position and the *m*-nitro group combined with the 5-methyl moiety on the dihydropyridazinone afford the most active compounds. In addition, most of the 5-methyl compounds have a longer lasting hypotensive effect than the corresponding 5-unsubstituted derivatives. The amino and acetamido compounds in the 5-unsubstituted series were reported in recent patents.[10] Finally, it should be noted that those compounds not listed in Tables I and II, *e.g.*, XVIII and XXIII, did not show any hypotensive activity.

Unfortunately, preliminary toxicity experiments in several species including mice, dogs, and monkeys revealed the presence of hemorrhagic patches in the heart area when the animals were treated with any of the active members of this series of compounds.

Experimental Section

The numbering of the compounds corresponds to Tables I–III and to the figures in the text when applicable.

γ,2-Dioxo-5-benzimidazolinebutyric Acid (69). A mixture of 45 g (0.33 mol) of 2-hydroxybenzimidazole, 34 g (0.34 mol) of succinic anhydride, and 150 g (1.1 mol) of $AlCl_3$ in 600 ml of tetrachloroethane was stirred slowly at 5–10° until the violent reaction subsided. Stirring was continued until the temperature rose to 25° and the mixture congealed. After standing at room temperature for 3 hr the complex was decomposed with concentrated HCl and water. The solid material was washed with benzene and tetrachloroethane and extracted with $NaHCO_3$ solution. Acidification of the $NaHCO_3$ solution gave a precipitate which was recrystallized from DMSO–water to give 35 g (46%) of white crystals, mp 298–298.5° (lit.[11] 298°).

3-(2,5-Dichlorobenzoyl)propionic Acid (56). Succinic anhydride (100 g, 1 mol), 270 g (2 mol) of $AlCl_3$, and 400 g of *p*-dichlorobenzene were treated as described for compound **69**. Treatment with ice and concentrated HCl was followed by benzene extraction. The benzene layer was reextracted with aqueous $NaHCO_3$ which was acidified to pH 5.5. A dark solid separated which was recrystallized several times from benzene to afford 8.7 g (3.5%) of white crystals, mp 109–111°. *Anal.* ($C_{10}H_8Cl_2O_3$) C, H, Cl.

4′-Chloro-γ-oxo-4-biphenylbutyric Acid (61). To 200 ml of cold CS_2 were added 95 g (0.5 mol) of *p*-chlorobiphenyl, 50 g (0.5 mol) of succinic anhydride, and 147 g (1.1 mol) of $AlCl_3$. The mixture was stirred under reflux for 21 hr and cooled, and the solvent was decanted. The residue was decomposed with ice and concentrated HCl, and the reaction mixture was extracted with benzene and filtered. The insoluble material was extracted with hot $CHCl_3$ which was chilled to give 20 g of product, mp 185.5–186.5°. *Anal.* ($C_{16}H_{13}ClO_3$) C, H, Cl.

3-(*p*-Chlorobenzoyl)-2-methylpropionic Acid (63), 3-(*p*-Chlorobenzoyl)butyric Acid, and 4,4-Bis(*p*-chlorophenyl)-2-methyl-3-butenoic Acid. To a solution of 114 g (1 mol) of methylsuccinic anhydride in 400 ml of chlorobenzene was added carefully 270 g (2 mol) of $AlCl_3$. The mixture was heated to 65° for 1.5 hr, cooled, quenched with ice and concentrated HCl, and then extracted with benzene. The benzene layer was extracted with aqueous $NaHCO_3$. Concentrated HCl was added slowly over a period of several hours with stirring to the $NaHCO_3$ solution. At pH 5.7, 78 g (34%) of white crystals was collected, mp 126–130°. Recrystallization of a 34-g portion from EtOH–H_2O gave 33 g of pure 3-(*p*-chlorobenzoyl)-2-methylpropionic acid: mp 129.5–131.0°; nmr ($DCCl_3$ + DMSO-d_6) δ 1.3 (d, 3, J_{ab} = 7 Hz, $-CHCH_3$), 3.2 (m, 3, $-CH_2CH-$). *Anal.* ($C_{11}H_{11}ClO_3$) C, H, Cl.

The material which separated at pH 5.5, 21 g of oil and 12 g of white crystals, mp 76–79° (15%), could not be purified by crystal-

†The numbering of dihydropyridazinones is

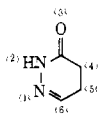
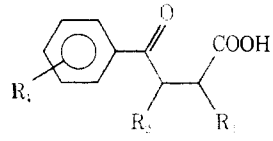
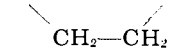
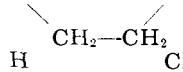
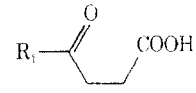
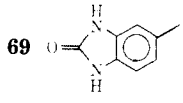
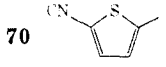


Table III. Intermediate Keto Acids

No.	R_1	R_2	R_3	Method[a]	% yield	Mp, °C	Formula	Recrystn solvent
								
56	2,5-Cl_2	H	H	A	3.5	109–111	$C_{10}H_8O_3Cl_2$	Benzene
57	*m*-NH_2	H	H	B	50	123–126	$C_{10}H_{11}NO_2$	EtOH
58	*p*-COOH	H	H	F	38	242–246	$C_{11}H_{10}O_5$	EtOH–CH_3CN
59	*p*-CN	H	H	C	43	161–163.5	$C_{11}H_9NO_3$	EtOAc
60	*p*-Cl	CH_2	CH_2 (cis)	A	37	147–149	$C_{11}H_{11}O_3Cl$	EtOAc
								
61	*p*-(*p*-ClC_6H_5)	H	H	A	38	185.5–186.5	$C_{15}H_{13}O_3Cl$	$CHCl_3$
62	*p*-Cl	CH_2	CH_2 (trans)	D	90	156.5–158	$C_{11}H_{11}O_3Cl$	$CHCl_3$–hexane
								
63	*p*-Cl	H	CH_3	A	34	129.5–131	$C_{11}H_{12}O_3Cl$	EtOH–H_2O
64	3-CN, 4-CH_3	H	H	C	32	145–147	$C_{12}H_{11}NO_3$	EtOH
65	3-NH_2, 4-CH_3	H	H	B	74	144–147	$C_{11}H_{13}NO_3$	EtOH
66	*p*-CH_3CONH	H	CH_3	A	31	208–209	$C_{13}H_{15}NO_4$	EtOH
67	*p*-CH_3CONH	CH_3	H	E	92	147–149	$C_{13}H_{15}NO_4$	EtOH
68	H	CH_3	H	F	90	52–57	$C_{11}H_{12}O_3$	
								
69				A	46	298–298.5	$C_{11}H_{10}N_2O_4$	DMSO–H_2O
70				G	38	135–137	$C_9H_7NO_3S$	$CHCl_3$–hexane

[a] A, Friedel–Crafts reaction; B, reduction of corresponding nitro compound; C, Sandmeyer reaction; D, isomerization of cis compound; E, reduction of unsaturated acid; F, malonic ester synthesis; G, cuprous cyanide and DMF treatment.

lization but afforded upon reaction with hydrazine the pure 6-(*p*-chlorophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (80%).

A 1.5-g portion of the above oil was separated into two fractions by partition column chromatography on neutral (acid-washed) Celite using a system of heptane–ethyl acetate–MeOH–water (80:20:20:6). Obtained were a major component (a mixture of 1.1 g, mp 75–110°) and 270 mg of a minor component, 4,4-bis(*p*-chlorophenyl)-2-methyl-3-butenoic acid, which had mp 134–136°; nmr ($CDCl_3$) δ 1.3 (d, 3, J_{ab} = 7 Hz, $-CH_bCH_3$), 3.3 (m, 1, J_{bc} = 10.5 Hz, $-CH_bCH_3$), 6.1 (d, 1, $=CH_c-$), 7.2 (m, 8, arom); mass spectrum *m/e* 320, 275, 226, 208, 191, 173. *Anal.* ($C_{17}H_{14}Cl_2O_2$) C, H, Cl.

Below pH 4.5, 320 mg of crystalline 3-(*p*-chlorobenzoyl)-butyric acid was obtained, mp 80.5–82.5°. A sample recrystallized from water gave mp 82.5–83.0°; nmr ($DCCl_3$ + DMSO-d_6) δ 1.2 (d, 3, J_{ad} = 7 Hz, $-CHCH_3$), 2.4 (octet, 1, J_{bd} = 5.5 Hz, J_{bc} = 17 Hz, $-CH_bCOOH$), 2.8 (octet, 1, J_{bc} = 8 Hz, $-CH_cCOOH$), 3.8 (m, 1, $-CH_dCH_3$). *Anal.* ($C_{11}H_{11}O_3Cl$) C, H, Cl.

3-(*p*-Acetamidobenzoyl)-2-methylpropionic Acid (66). Method A. A suspension of 500 g (3.8 mol) of $AlCl_3$ in 540 ml of CS_2 was allowed to react with 135 g (1 mol) of acetanilide and 114 g (1 mol) of methylsuccinic anhydride according to the usual procedure. The $NaHCO_3$ extract was acidified with concentrated HCl and the crude product was collected, mp 196–202°. Recrystallization from EtOH gave 78 g (31%): mp 208–209°; nmr (DMSO-d_6) δ 1.2 (d, 3, J_{ab} = 7.5 Hz, $-CHCH_3$), 2.1 (s, 3, $-NHCOCH_3$), 3.1 (m, 3, $-CH_2CHCH_3$). *Anal.* ($C_{13}H_{15}NO_4$) C, H, N.

Method B. A solution of 100 mg (0.4 mol) of 3-(*p*-acetamidobenzoyl)-2-methylacrylic acid (IV) and 60 μl of glacial HOAc in 1.5 ml of water was heated with 60 mg of zinc dust on a steam bath for 30 min. Ethanol was added to dissolve the white crystals which had formed and the mixture was filtered. The filtrate was evaporated to give 60 mg (60%) of white crystals: mp 205–206°; nmr identical with that of the sample prepared by method A.

3-(*p*-Acetamidobenzoyl)crotonic Acid (III) and 3-(*p*-Acetamidobenzoyl)-2-methylacrylic Acid (IV). Ground acetanilide (135 g, 1 mol) was added to a cold, mechanically stirred suspension of 490 g (3.6 mol) of $AlCl_3$ in 650 ml of CS_2 followed by the addition of 112 g (90 ml, 1 mol) of citraconic anhydride. The mixture was refluxed with stirring until the stirrer stopped and then allowed to stand at room temperature for 5 days. The CS_2 was decanted and the complex was decomposed using ice and concentrated HCl. The aqueous layer and solid were extracted with benzene which was in turn extracted with aqueous $NaHCO_3$. The $NaHCO_3$ solution was treated with Darco and acidified to pH 2 to precipitate a brown gum. This gum was set aside and the aqueous solution remaining gave yellow crystals on standing which were recrystallized from acetone–water to give 580 mg of yellow crystals, mp 207–209°, of 3-(*p*-acetamidobenzoyl)-2-methylacrylic acid: nmr ($CDCl_3$ + DMSO-d_6) δ 2.14 (d, 3, J_{ab} = 1.5 Hz, $=CCH_3$), 2.10 (s, 3, $O=CCH_3$), 7.7 (q, 1, $-CH=$). *Anal.* ($C_{13}H_{13}NO_4$) C, H, N.

The gum was stirred with ethyl acetate and evaporated to an oil which was crystallized from acetone–water in three crops to give 51 g (20%) of 3-(*p*-acetamidobenzoyl)crotonic acid as off-white crystals, mp 130–136°. A portion was recrystallized three more times from acetone–water to give white crystals, mp 134–142°. However, a small impurity was still observed on silica gel thin-layer plates with benzene–methanol (3:1): nmr ($CDCl_3$ + DMSO-d_6) δ 1.9 (d, 3, J_{ab} = 1.5 Hz, $=CCH_3$), 2.0 [s, 3, $-C(=O)CH_3$], 5.8 (q, 1, $-CH=$).

An analytical sample of compound III was prepared when a 1-g sample of the crude brown gum was subjected to partition column chromatography on Celite using a system heptane–ethyl acetate–MeOH–water (55:45:17:4) to give 415 mg of white crystals, mp 132.5–135°. *Anal.* ($C_{13}H_{13}NO_4$) C, H, N.

3-(*p*-Acetamidobenzoyl)butyric Acid (67). To a solution of 5.0 g (0.02 mol) of 3-(*p*-acetamidobenzoyl)crotonic acid in 45 ml of water and 3.0 ml of acetic acid was added 3.0 g of zinc dust and the mixture was heated on a steam bath for 30 min and then filtered. The filtrate was acidified with concentrated HCl to give an oil which was crystallized from EtOH–water: yield 4.6 g (92%) of white crystals: mp 94.5–103.0°. Recrystallization from a small vol-

ume of EtOH gave 2.6 g: mp 147–149°; nmr ($CDCl_3$ + DMSO-d_6) δ 1.2 (d, 3, J_{ad} = 7.5 Hz, $-CHCH_3$), 2.1 (s, 3, $-NHCOCH_3$), 2.4 (octet, 1, J_{bd} = 6 Hz, J_{bc} = 17 Hz, $-CH_bCOOH$), 2.9 (octet, 1, J_{cd} = 8 Hz, $-CH_cCOOH$), 3.9 (m, 1, $-CH_dCH_3$). *Anal.* ($C_{13}H_{15}NO_4$) C, H, N.

6-(3-Bromo-2-thienyl)-4,5-dihydro-3(2*H*)-pyridazinone (44) and 6-(4-Bromo-2-thienyl)-4,5-dihydro-3(2*H*)-pyridazinone (45). 3-Bromothiophene (65 g, 0.4 mol), 44 g (0.44 mol) of succinic anhydride, 120 g (0.9 mol) of $AlCl_3$, and 400 ml of nitrobenzene were allowed to react as in the above procedure to give 98 g (92%) of a product which could not be purified by recrystallization: mp 102–126°; nmr ($CDCl_3$ + DMSO-d_6) showed 65% of 3-bromo-γ-oxo-2-thiophenebutyric acid (XIX) [δ 7.18 (d, 1, $J_{4,5}$ = 5 Hz, H_4), 7.64 (d, 1, $J_{4,5}$ = 5 Hz, H_5)] and 35% of 4-bromo-γ-oxo-2-thiophenebutyric acid (XX) [δ 7.66 (d, 1, $J_{3,5}$ = 1.5 Hz, H_5), 7.70 (d, 1, $J_{3,5}$ = 1.5 Hz, H_3)]. *Anal.* ($C_8H_7BrO_3S$) Br.

A 1.0-g sample of the above crude was heated with 0.2 ml of 95% hydrazine in 4 ml of ethanol for 2 hr and the resulting crystals were filtered from the hot solution and recrystallized from ethanol to give 150 mg of pale yellow crystals of **45**: mp 247–249°; nmr ($CDCl_3$ + DMSO-d_6) δ 7.3 (d, 1, $J_{3,5}$ = 1.5 Hz, H_3), 7.5 (d, 1, H). *Anal.* ($C_8H_7BrN_2OS$) C, H, N, S, Br.

The mother liquor was cooled and filtered to give 90 mg, mp 147–189°. The filtrate was concentrated to give more crystals which were recrystallized from ethanol–H_2O: 475 mg of 44; mp 144–146.5°; nmr ($CDCl_3$ + DMSO-d_6) δ 7.0 (d, 1, $J_{4,5}$ = 5 Hz, H_4), 7.3 (d, 1, H_5). *Anal.* ($C_8H_7BrN_2OS$) C, H, N, Br, S.

3-(5-Cyano-2-thenoyl)propionic Acid (70). A mixture of 5.2 g (0.02 mol) of 3-(5-bromo-2-thenoyl)propionic acid, 3.6 g (0.04 mol) of CuCN, and 20 ml of *N*-methylpyrrolidinone was heated with stirring with a preheated mantle for 20 min at *ca.* 200°. The solution was then cooled and diluted with 250 ml of H_2O containing 16 g of $FeCl_3$ and 4.6 ml of concentrated HCl. The mixture was heated on a steam bath for 30 min, cooled, and filtered and 5 *N* NaOH was added to a pH 2. An orange solid was collected: 3.1 g; mp 125–127°. This was extracted with hot chloroform and filtered, and hexane was added to the filtrate to afford white crystals: yield 1.6 g (38%); mp 135–137°; ir 4.5 μ (C≡N). A sample recrystallized from $CHCl_3$–hexane gave mp 137–139°. *Anal.* ($C_9H_7NO_3S$) C, H, N, S.

6-(*p*-Aminophenyl)-4,5-dihydro-4-methyl-3(2*H*)-pyridazinone (19). A solution of 20 g (0.82 mol) of 6-(*p*-acetamidophenyl)-4-methyl-4,5-dihydro-3(2*H*)-pyridazinone, 170 ml of 10 *N* NaOH, and 170 ml of methanol was heated on a steam bath for 2.5 hr. The methanol was evaporated, and the solution was cooled, diluted with 400 ml of water, and neutralized to pH 4 to afford 14.9 g (89%) of white crystals, mp 242–243°. *Anal.* ($C_{11}H_{13}N_3O$) C, H, N.

3-(*p*-Cyanobenzoyl)propionic Acid (59). Method A. To a cold, stirred solution of *p*-aminobenzoylpropionic acid (25.0 g, 0.13 mol) in 600 ml of water containing 100 ml of concentrated HCl was added a cold solution of $NaNO_2$ (9.1 g, 0.132 mol) in 60 ml of water over 15 min. The solution was carefully neutralized with Na_2CO_3 and then added in several portions to a cold, stirred solution of CuCN (14.0 g, 0.156 mol) and KCN (20.0 g, 0.307 mol) in 400 ml of water which was covered with 100 ml of toluene. The mixture was stirred in the cold for 0.5 hr and then at room temperature overnight. A small amount of yellow solid was filtered and the filtrate was acidified with 50 ml of concentrated HCl (hood). The resulting dark brown solid was collected and extracted with a boiling solution of 800 ml of $CHCl_3$–benzene (1:1). The extract deposited orange crystals on cooling; 11.2 g (43%); mp 157–161°. For analytical purposes a sample was recrystallized from ethyl acetate using Norit. The melting point was raised to 161–163.5°; ir 4.5 μ (C≡N). *Anal.* ($C_{11}H_9NO_3$) C, H, N.

Method B. A mixture of *p*-bromobenzoylpropionic acid (5.0 g, 19.8 mmol) and CuCN (2.0 g, 22 mmol) in 12 ml of DMF was refluxed for 3.75 hr and then poured into a solution of 12 ml of H_2O containing 8.0 g of $FeCl_3 \cdot 6H_2O$ and 1.0 ml of concentrated HCl. The mixture was heated on a steam bath for 20 min and then with 100 ml of water to give a crystalline product which was collected, dried, and recrystallized from $CHCl_3$ using Norit: yield 1.2 g; mp 154–156°. The ir of this material was essentially the same as that prepared by method A.

6-(*p*-Cyanophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (10). Method A. To a stirred solution of 6-(*p*-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (3.8 g, 0.02 mol) in 150 ml of water containing 15 ml of concentrated HCl in an ice bath was added a cold solution of $NaNO_2$ (1.4 g, 0.02 mol) in 10 ml of water. The mixture was stirred in the cold for 10 min and then neutralized with Na_2CO_3. The solution was added to a stirred, cold solution of CuCN (2.24 g, 0.025 mol) and KCN (4.0 g) in 100 ml of water covered with 50 ml of toluene. The mixture was stirred in the cold for 0.5 hr and then overnight at room temperature to give an orange crystalline product which was collected and dried: yield 3.2 g; mp 245–255° dec (80%). For analytical purposes a portion of this material was recrystallized from EtOH–CH_3CN: mp 254–258° dec; ir 4.5 μ (C≡N); uv max (MeOH) 298 mμ (ε 2.4 × 10^4). (For a discussion of the uv absorption spectra of some 3(2*H*)-pyridazinones, see ref 12). *Anal.* ($C_{11}H_9N_3O$) C, H, N.

Method B. A solution of 3-(*p*-cyanobenzoyl)propionic acid (5.0 g, 0.625 mol) and 2.0 ml (0.041 mol) of hydrazine hydrate in 50 ml of EtOH was refluxed for 1.0 hr, chilled, and collected: 4.6 g (94%) of orange crystals; mp 252–257°.

3-(*m*-Aminobenzoyl)propionic Acid (57). A mixture of 3-(*m*-nitrobenzoyl)propionic acid[5] (39.7 g, 0.167 mol), 10% Pd/C, 500 ml of cyclohexene, and 1.0 l. of EtOH was refluxed for 42 hr and then filtered through a pad of Celite. The filtrate was evaporated to a crystalline residue and recrystallized from hot EtOH using Norit to afford 16.2 g (50%) of product, mp 122.5–126° (lit.[13] mp 131–132°).

***cis*-2-(*p*-Chlorobenzoyl)cyclohexane-1-carboxylic Acid (60).** $AlCl_3$ (60 g, 0.45 mol) was added in three portions over 15 min to a stirred solution of 1,2-cyclohexanedicarboxylic anhydride (32 g, 0.21 mol) in 250 ml of chlorobenzene at room temperature. The mixture was stirred overnight, heated on a steam bath for 15 min, cooled, and poured onto ice. The resulting solution was extracted with three 250-ml portions of ether which were combined, washed with water, and extracted with five 100-ml portions of 10% NaOH solution. The combined basic extracts were washed with ether and then acidified with concentrated HCl (ice bath). The solid was filtered, washed with water, then dissolved in 700 ml of ethyl acetate, and dried over $MgSO_4$. The solvent was evaporated and residue dissolved in 200 ml of hot ethyl acetate and filtered from some insoluble material. The filtrate deposited some amorphous solid which was filtered and discarded. The filtrate deposited white crystals on cooling: 11.2 g; mp 147–149°. An additional crop of 9.4 g (37% total yield), mp 142–145°, was obtained by concentrating the filtrate: nmr ($CDCl_3$) δ 2.8 (m, 1, $-CH_aCOOH$), 3.85 [m, 1, $-CH_bC(=O)-$, $J_{a,b}$ = 4.5 Hz]. *Anal.* ($C_{14}H_{15}ClO_3$) C, H, Cl.

***trans*-2-(*p*-Chlorobenzoyl)cyclohexane-1-carboxylic Acid (62).** The cis acid (1 g) was dissolved in 40 ml of 1 *N* NaOH and heated on a steam bath for 1 hr; it was then acidified, cooled, and filtered to give white crystals (0.9 g) of the trans acid, mp 155–158°. This product was recrystallized from $CHCl_3$–hexane to afford 0.8 g: mp 156.5–158°; nmr ($CDCl_3$) δ 2.9 (m, 1, $-CH_aCOOH$), 3.5 [m, 1, $-CH_bC(=O)-$, $J_{a,b}$ = 11 Hz]. *Anal.* ($C_{14}H_{15}ClO_3$) C, H, Cl.

***p*-(3-Carboxypropionyl)benzoic Acid (58).** The *p*-cyano acid XI (4.0 g, 0.02 mol) was added to a solution of 170 ml of dilute H_2SO_4 (1:1) and heated on a steam bath for 10 hr. The solution was diluted with water, and brown crystals were filtered and recrystallized from EtOH–CH_3CN (1:1) to afford 0.5 g, mp 253–256° dec. An additional crop of 1.2 g (38% total yield), mp 242–246°, was obtained from the filtrate. *Anal.* ($C_{11}H_{10}O_5$) C, H.

***p*-(1,4,5,6-Tetrahydro-6-oxo-3-pyridazinyl)benzoic Acid (13).** A mixture of 0.8 g (4 mmol) of the *p*-cyano compound VIII and 50 ml of 1 *N* NaOH was heated on a steam bath for 4.0 hr, followed by the addition of 10 ml of 10 *N* NaOH and an additional 1.5 hr of heating. The solution was treated with Norit, filtered, and acidified with 15 ml of HOAc to afford 0.45 g of product which was presumably the sodium salt (unmelted at 380°). This material was dissolved in 40 ml of hot water and acidified to pH 2 with concentrated HCl. The resulting white crystalline product was collected and recrystallized from aqueous EtOH to afford 0.15 g (17%) of the acid, mp 303–306° dec. *Anal.* ($C_{11}H_{10}N_2O_3$) C, H, N.

3-(3-Amino-*p*-toluoyl)propionic Acid (65). A mixture of the nitro compound[5] (10 g, 42.4 mmol), 1.5 g of 10% palladium on carbon, 84 ml of cyclohexane, and 250 ml of ethanol was refluxed for 20.5 hr, filtered, and evaporated to give 6.5 g (74% of a white crystalline product), mp 144–146.5° (lit.[5] 148–149°).

***p*-(1,6-Dihydro-6-oxo-3-pyridazinyl)benzonitrile (52).** Bromine (0.56 ml, 11 mmol) was added to a hot solution of the *p*-cyano compound (2.0 g, 10 mmol) in 40 ml of HOAc. The solution was heated for 5 min on a steam bath, cooled to room temperature, filtered, and washed with ether and water. Recrystallization from aqueous dioxane using Norit gave 1.1 g (56%) of pink crystals: mp 333–336° dec; uv max (MeOH–methyl cellosolve) 258 mμ (ε 2.3 × 10^4) and 272 (2.2 × 10^4).[12] *Anal.* ($C_{11}H_7N_3O$) C, H, N.

***O*-[*p*-(1,4,5,6-Tetrahydro-6-oxo-3-pyridazinyl)phenyl] Dimethylthiocarbamate (16).** NaH (2.6 g, 54 mmol of 57% disper-

sion) was added to a mixture of 5.1 g (26.9 mmol) of the pyridazinone **3** in 100 ml of DMF and stirred for 20 min. Dimethylthiocarbamoyl chloride (5.0 g, 40.3 mmol) was added and the mixture was stirred at room temperature for 0.5 hr, then heated on a steam bath for 1.0 hr, cooled, poured into 400 ml of water, and extracted with three 100-ml portions of benzene which were combined and washed with saturated salt solution and dried ($MgSO_4$). Evaporation of the solvent to about 50 ml afforded 2.2 g of brown crystals, mp 195–200°, which was recrystallized from aqueous EtOH using Norit: yield 1.7 g (23%); mp 207–214°. *Anal.* ($C_{13}H_{15}N_3O_2S$) C, H, N, S.

S-[*p*-(1,4,5,6-Tetrahydro-6-oxo-3-pyridazinyl)phenyl] Dimethylthiocarbamate (15). The thio compound **16** (0.5 g, 1.8 mmol) was heated in an oil bath at 250° for 1.0 hr and cooled and the resulting oil crystallized from EtOH to give 0.15 g, mp 185–193°. Recrystallization from EtOH (Norit) afforded 50 mg (10%): mp 191–194°; ir (KBr) 5.94 (pyridazine C=O), 6.0 μ (thio C=O). *Anal.* ($C_{13}H_{15}N_3O_2S$) C, H, N, S.

p-(1,4,5,6-Tetrahydro-6-oxo-3-pyridazinyl)benzamide (18). A mixture of 1.5 g (7.5 mmol) of the nitrile **10**, 3.0 ml of 30% H_2O_2, 25 ml of EtOH, and 1 ml of 5 *N* NaOH was stirred at room temperature for 3 hr. The resulting crystals were filtered, washed with water, and dried to give 0.65 g, mp 270–280°. Recrystallization from EtOH–H_2O (Norit) afforded 0.25 g of light yellow crystals: mp 285–288°; ir 5.93 (C=O) and 6.0 μ (C=O); uv max (MeOH) 296 mμ (ϵ 23,000); mass spectrum (70 eV) *m/e* 217 (molecular ion). An additional crop of 0.35 g (37% total yield), mp 270–280°, was obtained from the mother liquors. *Anal.* ($C_{11}H_{11}N_3O_2$) C, H, N.

Diethyl α-Methylphenacylmalonate. Sodium (9.2 g, 0.4 mol) was dissolved in a solution of 80 ml of benzene and 100 ml of diethyl malonate by refluxing for several hours. α-Bromopropiophenone (84 g, 0.39 mol) was added and the mixture was heated on a steam bath for 2 hr, poured into water, and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated and the residue was distilled through a Bantamware Vigreux column. Two fractions were collected: 14.1 g, bp 136 (0.6 mm) to 151° (0.75 mm), $n^{23}D$ 1.4994; and 43.2 g, bp 151 (0.6 mm) to 168° (1.4 mm), $n^{23}D$ 1.4972. The ir of these two fractions were practically identical and both exhibited carbonyl bands at 5.75 (ester C=O) and 5.95 μ (ketone C=O).

α-Methylphenacylmalonic Acid. A mixture of the malonic ester derivative described above (35 g, 0.12 mol), KOH (15 g), 35 ml of EtOH, and 15 ml of water was refluxed for 5 hr and then evaporated at reduced pressure to remove most of the EtOH. Water (450 ml) was added to the residue and filtered to remove precipitated glass. The filtrate was acidified with 40 ml of concentrated HCl to afford an oil which crystallized on cooling: yield 14.2 g. This product was recrystallized from ethyl acetate–hexane using Norit to give 11.3 g (40%), mp 143–149°, with gas evolution. For analytical purposes a sample was recrystallized again from ethyl acetate–hexane to give a product melting at 147–149.5°. *Anal.* ($C_{12}H_{12}O_5$) C, H.

3-Benzoylbutyric Acid (68). α-Methylphenacylmalonic acid (5.5 g, 23 mmol) was heated in an oil bath at 170–175° for 45 min, cooled, and added to petroleum ether (bp 30–60°). The mixture was stored in a freezer overnight and then filtered to give 4 g (90%) of the acid, mp 52–57.5° (lit.[13] 59–60°).

4,5-Dihydro-5-methyl-6-(*m*-nitrophenyl)-3(2*H*)-pyridazinone (23). 3-Benzoylbutyric acid (2.5 g, 13 mmol) was dissolved in 20 ml of concentrated HNO_3, cooled, and added to 20 ml of concentrated H_2SO_4 over 30 min with stirring. The mixture was then stirred at room temperature for 1.5 hr and then poured onto ice. The resulting gum was extracted with $CHCl_3$ which was washed with saturated salt solution and then dried ($MgSO_4$). Evaporation of the $CHCl_3$ gave an amber oil which resisted crystallization.

The above oil was refluxed for 1.0 hr in 20 ml of EtOH containing 1.0 ml of $NH_2NH_2 \cdot H_2O$, treated with Norit, and filtered. The filtrate deposited 0.55 g (18%) of crystals of the pyridazinone, mp 189–192°. For analytical purposes this product was recrystallized from EtOH to afford light yellow crystals, mp 191–194°. *Anal.* ($C_{11}H_{11}N_3O_3$) C, H, N.

6-(*m*-Aminophenyl)-5,6-dihydro-5-methyl-3(2*H*)pyridazinone (26). A mixture of the nitro compound **23** (0.5 g, 2.4 mmol), 0.25 g of 10% palladium on carbon, 20 ml of EtOH, and 10 ml of cyclohexene was refluxed for 18 hr, filtered, and evaporated to give an oil which crystallized. Recrystallization from ethyl acetate–hexane followed by EtOH afforded 0.2 g (46%) of the amino compound, mp 143–145°. *Anal.* ($C_{11}H_{13}N_3O$) C, H, N.

3′-(1,4,5,6-Tetrahydro-4-methyl-6-oxo-3-pyridazinyl)acetanilide (31). A mixture of the aminopyridazinone **26** (250 mg, 1.23 mmol) was heated on a steam bath for 5.0 min in 1.0 ml of acetic anhydride, cooled, and filtered to afford 196 mg (69%), mp 216–219°. *Anal.* ($C_{13}H_{15}N_3O_2$) C, H, N.

1,2,3,4-Tetrahydro-5-methoxy-1-oxo-2-naphthylideneacetic Acid. Sulfuric acid (5.7 ml) was added to an ice-cooled solution of sodium metaperiodate (62.2 g, 0.29 mol) in 340 ml of water, followed by a solution of tartaric acid (43.2 g, 0.288 mol) in 85 ml of water over 15 min. The solution was stirred at room temperature for 30 min and the 5-methoxytetralone (50.0 g, 0.284 mol) was added followed by a solution of NaOH (43.5 g, 1.09 mol) in 770 ml of water and finally 170 ml of EtOH. The reaction mixture was stirred at room temperature overnight, heated on a steam bath for 40 min, cooled, and diluted with water (1500 ml). The mixture was extracted with 800 ml of ether and then the aqueous portion was acidified with 400 ml of 3 *N* HCl to give a 31.8 g of a tan crystalline solid, mp 130–142°. Recrystallization from ethyl acetate using Norit afforded 18.7 g (29%) of tan crystals, mp 150–152.5°. *Anal.* ($C_{13}H_{12}O_4$) C, H.

1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthaleneacetic Acid (XVII). A mixture of the acid XVI[6] (1.86 g, 8 mmol), 12 ml of acetic acid, 5 ml of water, and 1.0 g (18.4 mmol) of zinc dust was heated on a steam bath for 0.5 hr, then filtered, and diluted with water (40 ml). The solution was chilled and the white crystalline product collected and recrystallized from EtOH–H_2O to afford 1.5 g (80%) of the keto acid, mp 161–164°. *Anal.* ($C_{13}H_{14}O_4$) C, H.

5,6-Dihydro-8-methoxybenzo[*h*]cinnolin-3(2*H*)-one (XXIII). A mixture of the dihydro compound XVIII (1.0 g, 4.35 mmol), sodium *m*-nitrobenzenesulfonate (1.0 g, 4.45 mmol), NaOH (0.75 g, 18.8 mmol), and 40 ml of water was heated on a hot plate with stirring for 40 min. The resulting brown solution was treated with Norit and filtered and the filtrate acidified with 2 ml of concentrated HCl to give 0.9 g of tan crystals; mp 240–243°. Recrystallization from EtOH–H_2O afforded 0.65 g (63%) of white crystals: mp 246–248°; uv max (MeOH) 272 mμ (ϵ 36,400), 325 (5450). *Anal.* ($C_{13}H_{12}N_2O_2$) C, H, N.

1,2,3,4-Tetrahydro-5-methoxy-1-oxo-2-naphthaleneacetic Acid. This compound was prepared in 85% yield by the same procedure as described for the corresponding 6-methoxy analog XVII, mp 168–171°. *Anal.* ($C_{13}H_{14}O_4$) C, H, N.

4,4a,5,6-Tetrahydro-8-methoxybenzo[*h*]cinnolin-3(2*H*)-one (XVIII). (The demethoxy analog of this compound has recently been reported; see ref 14.) A solution of XVII (10 g, 42.7 mmol) and 2.5 ml of hydrazine hydrate (52 mmol) in 75 ml of ethanol was refluxed for 1.5 hr, cooled, and filtered to afford 8.7 g (88%) of XVIII: mp 199–201°; uv max (MeOH) 230 mμ (ϵ 1.5×10^4), 296 (2.9×10^4), 313 (3.2×10^4). *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

4,4a,5,6-Tetrahydro-7-methoxybenzo[*h*]cinnolin-3(2*H*)-one[14] was prepared in 90% yield as described for XVIII, mp 230–231.5°. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

4′-(1,6-Dihydro-4-methyl-6-oxo-3-pyridazinyl)acetanilide (XXII). 3-(*p*-Acetamidobenzoyl)crotonic acid (4 mmol) and 0.2 ml of 95% hydrazine in 4 ml of EtOH were heated 4 hr on a steam bath, cooled, and recrystallized from EtOH–H_2O to give 0.65 g (65%) of white crystals, mp 256.5–257.0°. *Anal.* ($C_{13}H_{13}N_3O_2$) C, H, N.

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

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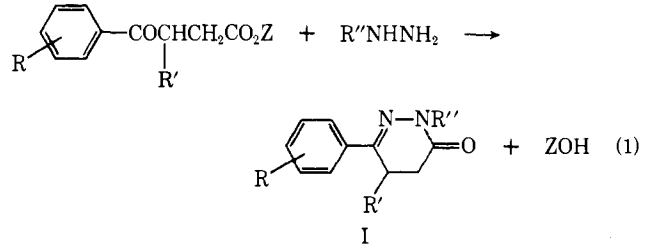
The preparation and antihypertensive properties of a series of 6-(substituted phenyl)-5-substituted-4,5-dihydro-3(2*H*)-pyridazinones are described. The structure-activity relationship in this series is discussed further. The consistent antihypertensive activity of the 6-(alkylaminophenyl) compounds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

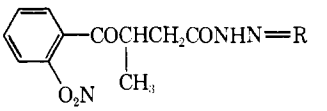
Previous reports from these laboratories have described the preparation and antihypertensive effects of a series of 6-(substituted phenyl)-4,5-dihydro-3(2*H*)-pyridazinones (I).[1] These studies indicated that the compounds having amino, acylamino, cyano, and halogen substituents on the phenyl ring were 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.