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Amine Functions of Reduced Basicity. Hypoglycemic and Natriuretic α-Alkoxybenzylamidoximes, Amidines, and Cycloamidines

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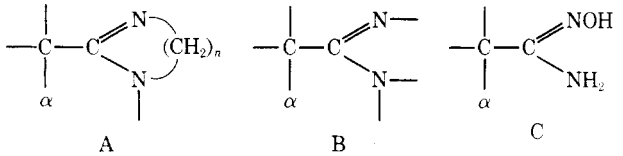
The introduction of α-alkoxybenzyl groups into carboxamidoximes, carboxamidines, 2-imidazolines, 1,4,5,6-tetrahydropyrimidines, and 4,5,6,7-tetrahydro-1*H*-1,3-diazepines predictively lowered the basicity of these nitrogen functions relative to the benzyl-substituted analogs. A general synthesis gave 2-alkoxy-2-arylacetonitriles which served as versatile intermediates for each of the series. Several of the compounds displayed potent natriuretic and/or hypoglycemic activity. One of these, 2-(α-ethoxybenzyl)-1,4,5,6-tetrahydropyrimidine (**32**), proved to be an inhibitor of hepatic drug metabolizing enzymes with a potency equal to or greater than SKF 525-A.

As part of a broad program, we were interested in devising means by which the tissue distribution of certain compounds bearing basic functional groups could be altered by reducing their ionization in solution, *i.e.*, by making them less basic.

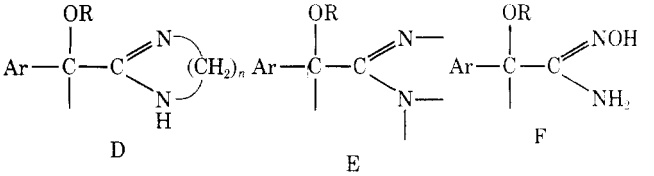
In order to preserve the integrity of the functional group being examined and to permit the flexibility for SAR studies, we considered juxtaposing a net "acidifying" function. The basic groups selected for examination were 2-imidazoline and ring homologs, *e.g.*, A (n = 2, 3, 4), amidines B, and amidoximes C. The "acidifying" function selected for this study was the α-alkoxy group.†



A B C

† The effect of the alkoxy moiety on amine basicity can be illustrated by a comparison of the pK_a values of ethylamine (10.81) and 2-methoxyethylamine (9.45).[1] For a discussion of the inductive and field effects of the alkoxy group and other functions see ref 2.

Finally, since such diverse biological activity has been attributed to 2-benzyl-2-imidazolines and 2-benzyl-1,4,5,6-tetrahydropyrimidines, an aryl group was added to provide the fundamental structures (D–F) in each series.



D E F

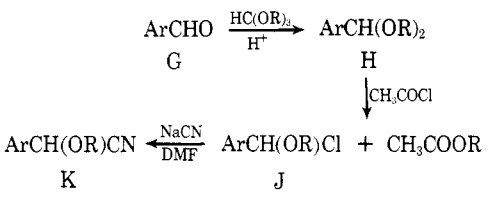
Chemistry. Attractive intermediates, useful for all three series, were the 2-alkoxy-2-arylacetonitriles K. Synthesis of the ethyl and methyl ethers of mandelonitrile was first accomplished by Hess and Dorner[3] who dehydrated the corresponding ethers of mandelamide with $SOCl_2$. This procedure was later improved by the use of P_2O_5 as a dehydrating agent.[4,5] Among the procedures considered by the earlier workers was the conversion of benzaldehyde to α-alkoxybenzyl chlorides with HCl and ROH,[3] followed by treatment of the chloro ether with KCN. Although this procedure in their hands was appar-

Table I. 2-Alkoxy-2-arylacetonitriles, ArCH(OR)CN

Compd	Ar	R	Bp, °C (Torr)	% yield	Analyses[a]
1[b]	C_6H_5	CH_3	64–67 (0.25)	50	
2[b]	C_6H_5	C_2H_5	106–114 (9)	76	
3	C_6H_5	C_3H_7	100–103 (2)	65	C, H, N
4	C_6H_5	C_4H_9	106–108 (1.5)	65	C, H, N
5	o-ClC_6H_4	C_2H_5	96–97 (1.4)	67	N, Cl
6	m-ClC_6H_4	C_2H_5	89–91 (0.14)	48	N, Cl
7	p-ClC_6H_4	C_2H_5	103–105 (1.3)	58	N, Cl
8	3,4-$Cl_2C_6H_3$	C_2H_5	123–124 (1.3)	51	Cl; N[c]
9	2,6-$Cl_2C_6H_3$	C_2H_5	95–99 (0.03–0.04)	69	N, Cl
10	m-FC_6H_4	C_2H_5	75–78 (0.17)	36	C, H, N
11	o-$(CH_3O)C_6H_4$	C_2H_5	111–113 (1.3)	66	C, H, N
12	p-$(CH_3O)C_6H_4$	C_2H_5	118–125 (1.5)	78	C, H, N
13	3-F-4-$(CH_3O)C_6H_3$	C_2H_5	127–129 (1.4)	62	C, H, N
14	p-$CH_3C_6H_4$	C_2H_5	134–135 (9)	55	C, H, N
15	p-i-PrC_6H_4	C_2H_5	86–92 (0.1)	60	C, H, N
16	C_6H_9[d]	C_2H_5	97–99 (8)	26	C, H, N
17	α-$C_{10}H_7$[e]	CH_3	124–126 (0.28)	44	C, H, N
18	α-$C_{10}H_7$[e]	C_2H_5	137–139 (0.1)	74	C, H, N
19	β-$C_{10}H_7$[e]	C_2H_5	52–54[f]	61	C, H, N
20	C_9H_9[g]	C_2H_5	122–126 (1.4)	40	C, H, N

[a] Analyses were within ±0.4% of theory for indicated elements. [b] Reference 3. [c] Calcd, 6.09; found, 6.81. [d] 3-Cyclohexene. [e] Naphthalene. [f] Melting point from Et_2O. [g] 5-Indan.

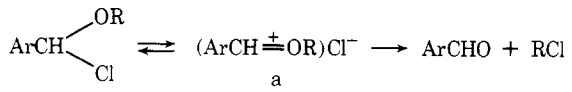
ently inferior to the amide dehydration sequence, we found it to be the most general and effectual method of generating the desired intermediates for our studies. In our procedure, the chloro ethers, generated from the acetals with AcCl,[6,7] were isolated without purification and were treated immediately with NaCN in DMF.[8,‡] The products were usually obtained as distillable oils which showed no C≡N absorption in the ir.[10,11] Raman spectroscopy, however, clearly showed strong C≡N bands in the region of 2240 cm^{-1}.§



Although the 2-alkoxy-2-phenylacetonitriles were readily alkylated using t-BuOK in THF, subsequent reactions of the hindered nitrile products were very sluggish. Conversion of the nitriles (Table I) into the corresponding cyclic derivatives (Table II) was readily accomplished by heating them with an excess of diamine using a few drops of CS_2 as catalyst.[12] The amidoximes (Table III) were prepared in the usual way (see Experimental Section) from the nitriles and hydroxylamine.[13] The amidines (Table IV) and compound **31** were available through the appropriate imidate salts[14,15] or *via* imidoyl chlorides[16] (Scheme I).

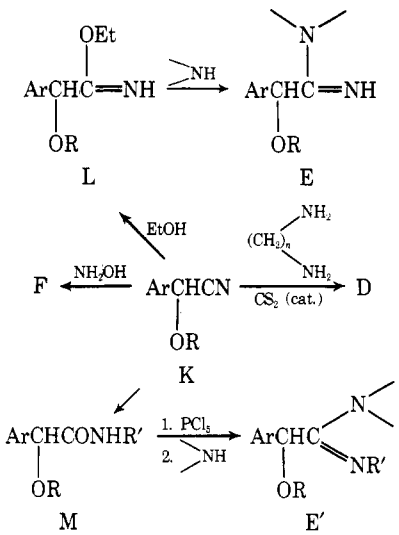
Attempts to utilize nitro-substituted benzaldehydes in the 2-alkoxy-2-arylacetonitrile sequence failed due to the extreme reactivity of the α-chloro ether intermediates. Direct nitration of the preformed cyano ethers **1** or **2** failed, but similar treatment of **32** gave a mixture of ortho and para isomers, **46**. The tetrahydropyrimidine **62** gave a single isomer, presumably the 3-nitro derivative, on treatment with potassium nitrate in sulfuric acid. Surprisingly, reduction of the latter compound with hydrazine and Raney nickel stopped at the hydroxylamine stage to give **67**. Catalytic reduction over palladium or platinum produced mixtures due to concomitant hydrogenolysis of both the ether and the halogen function.

‡ Prolonged standing or warming of the α-chloro ethers resulted in regeneration of the starting aldehyde *via* the carboxonium chloride a.[9]



§ We are grateful to Professor Samuel C. Wait, Jr., of the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, N. Y., for providing these measurements.

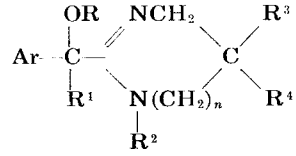
Scheme I



pK$_a$ Data. Table V summarizes a comparison of the pK_a data for some of the α-alkoxy derivatives prepared here and their desethoxy counterparts. In all cases, the substitution of an α-alkoxy group resulted in the expected lowering of pK_a values. We have no explanation for the differences in the magnitude of the changes in basicity among the four series.

Biological Data. Tolazoline (2-benzyl-2-imidazoline) exhibits depressor activity in cats due to peripheral vasodilation[17] while 2-benzyl-1,4,5,6-tetrahydropyrimidine is reported to produce pressor effects in the same animal.[18] The simple α-alkoxy analogs in these two ring series (**21–23** and **32**) were examined in renal hypertensive (RH) rats. At a screening dose of 100 mg/kg ip, these compounds were found to have no effect on blood pressure. Further examination of the autonomic properties of **32** in the anesthetized cat and dog revealed that the compound had weak ganglionic blocking activity with an iv ED_{50} of *ca.* 10 mg/kg in both species.

Table II. α-Alkoxybenzylimidazolines, 1,4,5,6-Tetrahydropyrimidines, and 4,5,6,7-Tetrahydro-1*H*-1,3-diazepines



Compd	Ar	R	R^1	R^2	R^3	R^4	*n*	Mp, °C (solv)[a] or bp, °C (Torr)	% yield	Analyses[b]	Hypoglycemic response[c]	Natriuretic effect CD_{50},[d] mg/kg	Natriuretic effect Max[e]	24-hr ALD_{50} po, mg/kg (species)[f]
21	C_6H_5	CH_3	H	H	H	H	0	78–80 (A–B)	43	C, H, N	0	Inactive		*g*
22	C_6H_5	C_2H_5	H	H	H	H	0	123–125 (A–B)	37	C, H, N	0	Inactive		*g*
23	C_6H_5	C_3H_7	H	H	H	H	0	82–84 (B)	64	C, H, N	45	7.1	(—)	350 (R)
24	*o*-ClC_6H_4	C_2H_5	H	H	H	H	0	84–87 (C–D)	51	N, Cl	23	Inactive		*g*
25	3,4-$Cl_2C_6H_3$	C_2H_5	H	H	H	H	0	75–76 (C–D)	36	C, H, N	*h*	3.8	NSD	150 (M)
26	2,6-$Cl_2C_6H_3$	C_2H_5	H	H	H	H	0	104–107 (G–D)	55	N; Cl[i]	29	Inactive		*g*
27	C_6H_5	C_2H_5	H	C_4H_9	H	H	0	100–110 (0.025)	61	C, H, N	35	Inactive		110 (M)
28	C_6H_5	C_2H_5	H	H	CH_3	H	0	102–106 (C–D)	30	C, H	43	>11	(—)	1000 (R)
29	C_6H_5	C_2H_5	H	H	CH_3	CH_3	0	73–74 (E)	35	C, H, N	54	5.1	(—)	510 (R)
30	3,4-$Cl_2C_6H_3$	C_2H_5	H	H	CH_3	CH_3	0	111–114 (D)	61	N, Cl	56	1.5	(—)	110 (R)
31[j]	C_6H_5	H	H	H	H	H	1	223–226[k] (L)	21		0	Inactive		*g*
32	C_6H_5	C_2H_5	H	H	H	H	1	101–104 (A–D)	56	C, H, N	53	10.5	(—)	1540[l] (R)
33	C_6H_5	C_3H_7	H	H	H	H	1	86–88 (B)	61	C, H, N	63	3.2	(—)	625 (R)
34	C_6H_5	C_4H_9	H	H	H	H	1	54–62 (F–D)	74	C, H, N	54	4.2	(—)	310 (R)
35	*o*-ClC_6H_5	C_2H_5	H	H	H	H	1	101–104 (C–D)	47	N, Cl	59	8.6	(—)	>1000 (R)
36	*m*-ClC_6H_5	C_2H_5	H	H	H	H	1	86–87 (D)	41	C, H, N	50	5	NSD	695 (R)
37	*p*-ClC_6H_4	C_2H_5	H	H	H	H	1	93–96 (C–D)	42	C, H, N	69	3.5	NSD	875 (R)
38	3,4-$Cl_2C_6H_3$	C_2H_5	H	H	H	H	1	90–92 (B)	35	N, Cl	37	1.7	NSD	370 (R)
39	2,6-$Cl_2C_6H_3$	C_2H_5	H	H	H	H	1	120–123 (C–D)	16	C, H, N	67	4.3	NSD	625 (R)
40	*m*-FC_6H_4	C_2H_5	H	H	H	H	1	92–94 (B)	59	C, H, N	57	0.5	(—)	1000 (R)
41	*o*-$(CH_3O)C_6H_4$	C_2H_5	H	H	H	H	1	80–82 (D)	38	C, H, N	0	Inactive		>1000 (R)
42	*p*-$(CH_3O)C_6H_4$	C_6H_4	H	H	H	H	1	52–56[m]	24	C, H, N	23	7.4	(—)	1000 (R)
43	3-F-4-$(CH_3O)C_6H_3$	C_6H_5	H	H	H	H	1	77–79[m]	38	C, H, N	0	Inactive		1000 (R)
44	*p*-$CH_3C_6H_4$	C_2H_5	H	H	H	H	1	72–73 (D)	38	C, H, N	22	Inactive		500 (M)
45	*p*-*i*-PrC_6H_4	C_2H_5	H	H	H	H	1	105–108 (H)	43	C, H, N	20	Inactive		625 (M)
46	*x*-$NO_2C_6H_4$[n]	C_2H_5	H	H	H	H	1	202–208[k] (H–I)	25	C, H, N	45	Inactive		*g*
47	C_6H_9[o]	C_2H_5	H	H	H	H	1	76–77[m]	31	C, H, N	30	Inactive		*g*
48	C_6H_{11}	C_2H_5	H	H	H	H	1	99–100 (D)	45	C, H, N	46	Inactive		*g*
49	C_6H_5	C_2H_5	C_2H_5	H	H	H	1	78–81 (D)	68	C, H, N	37	1.2	NSD	750 (R)
50	C_9H_9[p]	C_2H_5	H	H	H	H	1	69–75 (B–D)	59	C, H, N	34	13	(—)	750 (R)
51	α-$C_{10}H_7$[q]	CH_3	H	H	H	H	1	102–104 (G–J)	37	C, H, N	46	Inactive		435 (R)
52	α-$C_{10}H_7$[q]	C_2H_5	H	H	H	H	1	101–103 (D)	53	C, H, N	75	8.6	(—)	375 (R)
53	β-$C_{10}H_7$[q]	C_2H_5	H	H	H	H	1	115–117 (K)	70	C, H, N	36	Inactive		375 (M)
54	C_6H_5	C_2H_5	H	CH_3	H	H	1	93–95 (0.02)	56	C, H, N	0	Inactive		*g*
55	C_6H_5	C_2H_5	H	C_4H_9	H	H	1	103–110 (0.01)	64	C, H, N	34	3.6	NSD	220 (R)
56	C_6H_5	C_2H_5	H	C_4H_9	CH_3	H	1	97–98 (D)	24	C, H, N	56	8.1	(—)	875 (R)
57	*p*-ClC_6H_4	C_2H_5	H	H	CH_3	H	1	80–81 (D)	16	C, H, N	57	0.8	(+)	750 (R)
58	3,4-$Cl_2C_6H_3$	C_2H_5	H	H	CH_3	H	1	100–102 (K)	36	N, Cl	*g*	0.3	NSD	256 (M)
59	C_6H_5	C_2H_5	H	H	CH_3	CH_3	1	92–94 (D)	59	C, H, N	43	1.5	NSD	875 (R)
60	*o*-ClC_6H_4	C_2H_5	H	H	CH_3	CH_3	1	115–116 (B–D)	40	C, H, N	56	1.4	(—)	310 (R)
61	*m*-ClC_6H_4	C_2H_5	H	H	CH_3	CH_3	1	82–83 (D)	42	N, Cl	*h*	0.6	(+)	95 (R)
62	*p*-ClC_6H_4	C_2H_5	H	H	CH_3	CH_3	1	114–115 (B–D)	41	N, Cl	49	3.7	NSD	190 (R)
63	*m*-FC_6H_4	C_2H_5	H	H	CH_3	CH_3	1	88–89 (D)	27	C,H, N	56	1.8	NSD	750 (R)

64	*p*-$(CH_3O)C_6H_4$	C_2H_5	H	H	CH_3	CH_3	1	138–140 (0.02)	37	C, H, N	42	8.8	(—)	625 (R)
65	3-F-4-$(CH_3O)C_6H_3$	C_2H_5	H	H	CH_3	CH_3	1	83–85[m]	55	N, F	39	4.4	(—)	320 (R)
66	*p*-*i*-Pr-C_6H_4	C_2H_5	H	H	CH_3	CH_3	1	137–139 (0.04)	49	C, H, N	35	3.7	NSD	220 (R)
67	4-Cl-3-(HONH)C_6H_3	C_2H_5	H	H	CH_3	CH_3	1	172–174 (L)	59	C, H, N	*g*	11	(—)	*g*
68	*p*-ClC_6H_4	C_2H_5	C_2H_5	H	CH_3	CH_3	1	124–125 (D)	14	N, Cl	*g*	0.6	NSD	58 (R)
69	α-$C_{10}H_7$[n]	C_2H_5	H	H	CH_3	CH_3	1	106–107 (D)	27	C, H, N	*h*	1.5	NSD	55 (R)
70	C_6H_5	C_2H_5	H	H	CH_3	C_2H_5	1	132–135 (0.15)	60	C, H, N	44	1.3	NSD	220 (R)
71	*m*-ClC_6H_4	C_2H_5	H	H	CH_3	C_2H_5	1	142–145 (0.03)	52	N, Cl	45	0.6	(+)	88 (R)
72	*p*-ClC_6H_4	C_2H_5	H	H	CH_3	C_2H_5	1	86–87 (D)	24	N, Cl	*h*	0.6	(+)	110 (R)
73	*m*-FC_6H_4	C_2H_5	H	H	CH_3	C_2H_5	1	59–61[m]	70	C, H, N	42	0.6	NSD	165 (R)
74	3-F-4-$(CH_3O)C_6H_3$	C_2H_5	H	H	CH_3	C_2H_5	1	156–157 (0.1)	52	N, F	45	4.6	(—)	*g*
75	C_6H_5	C_2H_5	H	H	C_2H_5	C_2H_5	1	68–70[m]	50	C, H, N	45	0.9	(+)	250 (R)
76	*m*-ClC_6H_4	C_2H_5	H	H	C_2H_5	C_2H_5	1	136–138 (0.01)	34	N, Cl	46	1.8	(+)	110 (R)
77	*p*-ClC_6H_4	C_2H_5	H	H	C_2H_5	C_2H_5	1	68–70 (D)	26	N, Cl	32	1.6	(+)	375 (R)
78	C_6H_5	C_2H_5	H	H	OH	H	1	152–156[k] (L–B)	67	C, H, N	0	Inactive		1750 (R)
79	C_6H_5	C_2H_5	H	H	OCH_3	H	1	140–146 (0.1)	35	C, H, N	28	Inactive		875 (R)
80	C_6H_5	C_2H_5	H	H	H	H	2	110–113 (0.06)	59	C, H, N	43	Inactive		375 (R)
81	*p*-ClC_6H_4	C_2H_5	H	H	H	H	2	142–144 (0.03)	78	N, Cl	40	1.3	(+)	370 (R)
82	*o*-ClC_6H_4	C_2H_5	H	H	H	H	2	128–130[r] (I)	49	N	41	3.4	NSD	190 (M)

[a]Recrystallization solvent: A, CH_2Cl_2; B, Et_2O; C, PhH; D, hexane; E, pentane; F, EtOAc; G, THF; H, MeOH; I, Me_2CO; J, *i*-PrOAc; K, cyclohexane; L, EtOH. [b]Analyses were within ±0.4% of theory for indicated elements. [c]Maximum per cent decrease in circulating blood glucose levels in glucose primed rats during 5-hr observation period; screening dose 100 mg/kg po. [d]Comparative po dose required to produce one-half the natriuretic effect of a maximally effective (2.38 mg/kg po) dose of HCT. [e]Efficacy of test agent less than (—), not significantly different from (NSD), or greater than (+) HCT. [f]Approximate LD_{50}; R = rat, M = mouse. [g]No data. [h]Lethal. [i]Calcd, 25.96; found, 26.46. [j]Prepared by method of ref 28. [k]HCl salt. [l]LD_{50}. [m]Crystallized after distillation. Bp, °C (Torr): **42**, 145 (0.06); **43**, 137–140 (0.065); **47**, 93–95 (0.015); **65**, 148–149 (0.08); **73**, 129–132 (0.03); **75**, 130–134 (0.03). [n]Mixture of ortho and para isomers. [o]3-Cyclohexene. [p]5-Indan. [q]Naphthalene. [r]Cyclohexanesulfamate salt.

The most interesting activities that these compounds exhibited were hypoglycemic and/or natriuretic actions. Thus, certain compounds were able to elicit significant decreases in blood glucose levels in fasted, glucose-primed rats while others produced natriuresis in rats equal to or greater than that produced by a maximally effective dose of hydrochlorothiazide (HCT). Although most of the test agents produced both effects, the levels of activities were not maximized in the same compound. The highest levels of activity were found in the imidazoline and, especially, the tetrahydropyrimidine series (Table II).‡ It was interesting to note that replacement of the ether function by hydroxyl (**31**) abolished both activities. Other examples of this class of compounds have been shown to have pK_a values not significantly different from the α-unsubstituted analogs.[24]

In a quantitation experiment in rats comparing 5-hr cumulative hypoglycemic activity, compounds **33, 37,** and **39** were found to have potencies relative to tolbutamide of 1.2, 1.5, and 1.7, respectively. In this series, **57, 61, 71, 72, 75, 76,** and **77** all produced a natriuretic effect greater than that resulting from a maximally effective (2.4 mg/kg po) dose of HCT. The latter activity, however, was usually associated with a high degree of toxicity.

Compound **32** (hypoglycemic potency 0.6 of tolbutamide) had the greatest separation of antidiabetic activity and toxicity and was examined more extensively. At a dose of 25 mg/kg po, **32** produced a long-acting hypoglycemic response in the glucose fed rat (*ca.* 40% decrease in blood glucose levels at 5 hr postmedication). By contrast, blood glucose levels in the same animals medicated with 25 mg/kg of tolbutamide had returned to control levels by 5 hr. In fasted beagle dogs, at 25 mg/kg po, **32** produced a 51% decrease in blood glucose levels but a 100 mg/kg dose proved fatal to 4/5 animals. Hypoglycemia was significant and prolonged in fasted monkeys medicated with single oral doses of 25 and 75 mg/kg (decreases in blood glucose levels 21 and 39%, respectively, at 5 hr postmedication). During preliminary dose ranging for toxicity in this species, single oral doses of 1000 mg/kg of **32** were well tolerated. In the rat, the single dose oral LD_{50} was found to be 1540 mg/kg while in the mouse this value was considerably lower (360 mg/kg).

To study the effects of combinations of **32** and β-diethylaminoethyl 2,2-diphenylvalerate (SKF 525-A), animals treated with combinations of these agents were killed 5.5 hr postmedication and, as a measure of enzyme inhibition, homogenates of their livers were examined for their ability to block codeine demethylation.[25] The results are tabulated in Table VI.

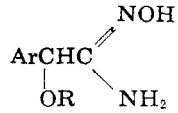
Surprisingly, **32** at a dose of 50 mg/kg po was found to be as powerful an inhibitor of the demethylation of codeine as SKF 525-A at 80 mg/kg ip. We did not investigate the many drug-metabolizing enzymes of the liver to determine the scope of inhibition by **32** and can only speculate as to the relationship of this finding to the wide species variation in toxicity (*vide supra*).

Summary

The introduction of an α-alkoxy group into a variety of benzyl-substituted bases predictably lowered their basicity. Although a resulting series of tetrahydropyrimidines

‡For comparison, 2-benzyl-2-imidazoline is reported to decrease blood glucose levels in alloxanized dogs[19] and unfasted rabbits[20] as well as in normal[20] and diabetic[20,21] man. It has further been observed to produce an antidiuretic effect in rats[22] and a marked decrease in urine flow in normal dogs and man.[23] There are no reports of hypoglycemic or natriuretic activities for 2-benzyl-1,4,5,6-tetrahydropyrimidine; the present studies showed the compound to be devoid of both activities.

Table III. 2-Alkoxy-2-arylacetamidoximes



Compd	Ar	R	Mp, °C (solv)[a]	% yield	Analyses[b]	Hypoglycemic response[c]	Natriuretic effect CD_{50},[d] Max[e] mg/kg	24-hr ALD_{50} po, mg/kg (species)[f]
83	C_6H_5	C_2H_5	128–130[h] (D)	61	C, H, N	0	Inactive	>1000 (M)
84	p-ClC_6H_4	C_2H_5	156–157[h] (B)	77	N, S	0	Inactive	500 (M)
85	o-ClC_6H_4	C_2H_5	100–102 (E)	55	N, Cl	20	*g*	300 (M)
86	3,4-$Cl_2C_6H_3$	C_2H_5	79–81 (F)	79	N, Cl	0	Inactive	350 (M)
87	2,6-$Cl_2C_6H_3$	C_2H_5	174–176 (C)	76	N, Cl	0	Inactive	310 (M)
88	p-$CH_3C_6H_4$	C_2H_5	149–151 (D)	40	C, H, N	0	*g*	625 (M)
89	p-$(CH_3O)C_6H_4$	C_2H_5	130–132 (D)	78	C, H, N	0	*g*	>1000 (M)
90	α-$C_{10}H_7$[i]	C_2H_5	147–149 (A)	85	C, H, N	45	*g*	*g*
91	β-$C_{10}H_7$[i]	C_2H_5	140–144 (D)	84	C, H, N	20	*g*	*g*
92	C_6H_5	n-C_3H_7	98–100 (G)	70	C, H, N	22	Inactive	250 (M)

[a] A, PhH; B, MeCN; C, EtOAc; D, *i*-PrOAc; E, *i*-PrOH; F, cyclohexane; G, Et_2O. [b–g] See footnotes in Table II. [h] *p*-Toluenesulfonate salt. [i] Naphthalene.

possessed new and interesting biological activities relative to the unsubstituted analog, a poor separation of activity and toxicity precluded studies in man. One of these compounds (**32**) may be a more potent inhibitor of liver enzymes than SKF 525-A but the mechanism of this inhibition is unknown.

Experimental Section**

Screening Procedure. A. Glucose-Primed Rats. Male rats of the Charles River CD strain weighing 90–100 g were used in the study. Food was removed from the cages at 4:00 P.M. At 8:00 A.M. the following morning 20 μl of blood was withdrawn from the tail vein and assayed for blood glucose concentration by the method of Reinicke.[26] The animals were divided into groups of five rats each on the basis of their fasting blood glucose levels. All rats were then given 100 mg of glucose subcutaneously in 0.5 ml of 0.85% saline. This was immediately followed by a single oral administration of the test compound in water. One group received vehicle only and served as the control. Postmedication blood samples were taken at 1, 2, 3, and 5 hr and assayed for glucose.

The deviation in blood glucose levels was determined as per cent of control at corresponding time intervals. Under the conditions of this screen, tolbutamide at a po dose of 50 mg/kg produced a 63% drop in blood glucose levels at 2 hr postmedication. Potencies relative to tolbutamide were based on cumulative changes in blood glucose over the 5-hr test period.

B. Rat Natriuretic Screen. Male albino rats, 160–200 g, were fasted overnight and water was removed from the cages 1 hr prior to the start of the experiment. The drugs were administered orally in 0.5% gum tragacanth in 0.85% NaCl at a volume of 2.5 ml/100 g of body weight. Emptying of the urinary bladder was accomplished at the start and the finish of each experiment by gentle suprapubic pressure or stimulation of vesicular reflexes by pulling or twisting the base of the tail. After drug loading, the animals were placed in metabolism cages, two animals per cage. Each drug was administered to six animals at each dose level. Twelve control (no drug) animals and six animals treated with 8 μmol/kg (2.38 mg/kg) of HCT were run in each experiment. A fixed molar dose schedule for drugs was used. The highest dose used was 50 μmol/kg. Succeeding doses were 40% of each preceding dose.

Data from each experiment were analyzed by means of Duncan's multiple range test based upon an analysis of variance utilizing a completely random design. The 0.05 level of probability was taken as the criterion of significance. Testing of a compound was completed when it no longer produced a natriuretic response which was significantly greater than that of the nondrug-treated groups. A minimal effective dose of a drug was defined as that dose which produced a response equal to 0.50 times that of the reference dose of HCT. This dose was determined graphically by plotting the lowest administered significant dose and the dose which produced the nonsignificant response. The dose of drug which produces a response 0.50 times that of HCT was reported as the CD_{50}. The efficacy (maximal natriuretic effect) of the test agent relative to HCT was recorded as greater, lesser, or not different.

2-Alkoxy-2-arylacetonitriles (Table I). The benzaldehyde dialkylacetals were prepared according to the procedure of Claisen[27] using excess trialkyl orthoformates and HCl as catalyst. The reactions were monitored by ir. The crude product was freed of solvent and unreacted orthoformate under reduced pressure and was used directly in the next step. Using slight modification of the procedure of Straus and Heinze,[6] the acetal was converted to the chloro ether by adding it (0.5 mol) dropwise to a stirred solution of 1.1 mol of AcCl and 1 ml of $SOCl_2$. The temperature was maintained below 25° by occassional external cooling. After standing at ambient temperatures overnight, the solution was concentrated under reduced pressure using a 40° water bath and the residual oil (usually >100% yield based on starting aldehyde) was added dropwise to a stirred suspension of 0.75 g-atom of NaCN in 200 ml of DMF. The addition usually took 1 hr and was followed by a further period of stirring (1–18 hr) at the end of which time the mixture contained a fine suspension of NaCl. The mixture was optimally diluted with an equal volume of PhH and 100 ml (dry volume) of filter cel was stirred in. The solids were removed by suction filtration through a pad of filter cel which was then washed with PhH. The combined filtrates were concentrated under reduced pressure and the residue was dissolved in PhH and H_2O. The organic solution was washed with H_2O, dried (Na_2SO_4), and concentrated and the residual material was distilled under reduced pressure or crystallized from an appropriate solvent.

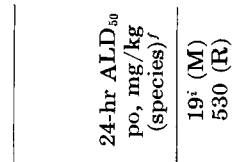
2-Ethoxy-2-phenylbutyronitrile. A solution of *t*-BuOK (27 g, 0.24 mol) in 270 ml of dry THF was added dropwise (30 min) under N_2 to a stirred, cooled (5–10°) solution of 2-ethoxy-2-phenylacetonitrile **2** (32.2 g, 0.2 mol) in 100 ml of THF. After an additional 15 min, 39 g (0.25 mol) of EtI was added over 15 min. The temperature was allowed to warm to 15–20° during the addition of the halide and for 45 min longer. The mixture was filtered and the filtrate was distilled finally under vacuum to give 23.8 g (63% yield) of oil, bp 113–114° (12 Torr). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

Similarly, starting with **7**, there was obtained a 51% yield of 2-(*p*-chlorophenyl)-2-ethoxybutyronitrile, bp 128–129° (9 Torr). *Anal.* ($C_{12}H_{14}ClNO$) C, H.

2-Alkoxy-2-arylimidazolines, 1,4,5,6-Tetrahydropyrimidines, and 4,5,6,7-Tetrahydro-1*H*-1,3-diazepines (Table II). The following is a general procedure. A mixture of 0.1 mol of 2-alkoxy-2-arylacetonitrile, 0.12 mol of diamine, and 3–5 drops of CS_2 was heated under N_2 on the steam bath for 6 hr. For more hindered

** All melting point and boiling point figures are uncorrected. Ir spectra were determined using a Perkin-Elmer Model 257 grating spectrophotometer. Nmr spectra were taken on a Varian Associates HA-100 spectrometer. Mass spectra were obtained on a Joelco JMC-01SC high-resolution double-focusing mass spectrometer. The pK_a measurements were taken using a Radiometer (Copenhagen, Denmark) type TTTlc automatic titrator coupled with a type SBR2c recording titrigraph. Raman spectra were run (at Rensselaer Polytechnic Institute) on a Jarrell-Ash Raman spectrometer using a helium–neon process. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Instranal Laboratories, Inc., Rensselaer, N. Y. The nmr and ir spectra of all compounds were compatible with proposed structures.

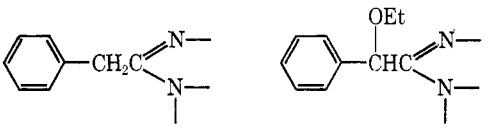
Table IV. 2-Alkoxy-2-arylacetamidines



Compd	Ar	R	R′	R″	R‴	Mp, °C of HCl salt (solv)[a] or bp, °C (Torr)	% yield	Analyses[b]	Hypoglycemic response[c]	Natriuretic effect CD_{50}[d]	Natriuretic effect Max[e]	24-hr ALD_{50} po, mg/kg (species)[f]
93	C_6H_5	C_2H_5	H	H		198–199 (A–C)	93	N, Cl	0	Inactive		19[i] (M)
94	C_6H_5	C_2H_5	H	*n*-C_3H_7		174 dec (A–C)	75	N, Cl	61	1.1	NSD	530 (R)
95	C_6H_5	C_2H_5	H	*i*-C_3H_7		190–191[j] (A–C)	81	N, Cl	45	0.7	(—)	375 (M)
96	C_6H_5	C_2H_5	H	*n*-C_4H_9		118–119 (A–C)	83	N, Cl	50	*g*		500 (M)
97	C_6H_5	C_2H_5	H	*i*-C_4H_9		179–181 (E–D)	52	C, H, N	L[h]	*g*		250 (M)
98	C_6H_5	C_2H_5	H	*n*-C_6H_{13}		108–109 (A–C)	78	N, Cl	L[h]	*g*		310 (M)
99	C_6H_5	C_2H_5	H	$(CH_2)_3OCH_3$		99–100 (A–C)	91	N, Cl	44	7.8	(—)	440 (M)
100	C_6H_5	C_2H_5	H	C_6H_{11}[k]		75–76[l]	72	C, H, N	L[h]	*g*		310 (M)
101	C_6H_4	C_2H_5	H	C_7H_7[m]		102 dec (B–C)	81	N, Cl	L[h]	*g*		190 (M)
102	C_6H_5	C_2H_5	H	C_8H_9[n]		195 dec (A–C)	73	N, Cl	20	*g*		375 (M)
103	C_6H_5	C_2H_5	H	$-(CH_2)_4-$		158–159 (A–C)	91	N, Cl	59	Inactive		500 (R)
104	C_6H_5	C_2H_5	H	$-(CH_2)_5-$		*o*	59	C, H, N	58	1.6	NSD	220 (M)
105	C_6H_5	C_2H_5	*n*-C_3H_7		H	94–95 (0.01)	43	C, H, N	L[h]	0.8	NSD	95 (R)
106	*p*-ClC_6H_4	C_2H_5	*n*-C_3H_7		H	115–117 (0.01)	52	N, Cl	L[h]	3.0	(+)	47 (R)
107	*p*-ClC_6H_4	C_2H_5	*n*-C_4H_9		H	125–127 (0.01)	35	C, H, N	L[h]	4.2	NSD	220 (R)
108	C_6H_5	CH_3	*n*-C_3H_7	$-(CH_2)_5-$		116–118 (0.05)	32	C, H, N	L[h]	2.0	(+)	55 (R)
109	C_6H_5	C_2H_5	*n*-C_3H_7	$-(CH_2)_5-$		116–118 (0.03)	55	C, H, N	*g*	1.2	(+)	220 (R)

[a] A, MeOH; B, EtOH; C, Et_2O; D, Me_2CO; E, H_2O. [b–k] See footnotes in Table II. [i] iv. [j] $MeOSO_4H$ salt. [k] Cyclohexane. [l] Free base. [m] Benzyl. [n] 2-Phenylethyl. [o] Undistillable oil.

Table V. Comparative pK_a Values



Compd	pK_a	Compd	pK_a[a]
2-Benzyl-2-imidazoline[b]	10.37[c] 10.58[d]	**22**	9.1
2-Benzyl-1,4,5,6-tetrahydropyrimidine[e]	11.5	**32**	8.4
2-Phenylacetamidoxime[f]	5.40[g]	**83**	4.9
2-Phenylacetamidine[h]	11.57[d]	**93**	~7

[a] All measurements in 1:1 MeOH–H_2O. [b] S. R. Aspinwall, *J. Amer. Chem. Soc.*, **61,** 3195 (1939). [c] J. Elguero, E. Gonzalez, J. L. Imbach, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 4075 (1969). [d] L. Villa, V. Ferri, and E. Grana, *Farmaco, Ed. Sci.*, **22,** 491 (1967). [e] P. Oxley and W. F. Short, *J. Chem. Soc.*, 859 (1950). [f] M. Kuraš and E. Ružička, *Chem. Listy*, **46,** 482 (1952). [g] S. Desivarte, A. Pezzoli, and J. Armand, *C. R. Acad. Sci., Ser. C*, **270,** 2062 (1970). [h] C. A. Rouiller, *Amer. Chem. J.*, **47,** 475 (1912).

Table VI. Inhibition of Demethylase Activity of Rat Liver Microsomes by SKF 525-A, **32,** and Combination Treatment

Treatment	Codeine demethylation[a]	Change from controls (% inhibition)
Group A (saline controls)	4.29 ± 0.29	
Group B, SKF 525-A (80 mg/kg ip)	3.13 ± 0.24	27% ($p < 0.01$)
Group C, SKF 525-A (80 mg/kg ip) + **32** (50 mg/kg po)	2.93 ± 0.25	31.5% ($p < 0.01$)
Group D, **32** (50 mg/kg po)	3.12 ± 0.54	27% ($p < 0.01$)

[a] μmol of HCHO formed per gram of liver per 30 min (mean ± S.E.), $N = 8$.

nitriles or for N-substituted amines, an oil bath at 140° was used and the progress of the reaction was followed by tlc. At the end of the reaction period, excess amine was removed under vacuum and the residue was dissolved in PhH and H_2O. The organic layer was washed once with H_2O and extracted with three 100-ml portions of 2 *N* HCl. Addition of solid K_2CO_3 to the acid solution reprecipitated the base which was distilled under reduced pressure or was crystallized from PhH–hexane or CH_2Cl_2–hexane.

2-Alkoxy-2-arylacetamidoximes (Table III). All of the entries of Table III were prepared as follows. To 1.5 l. of 95% EtOH was added in order 0.2 mol of $NH_2OH \cdot HCl$, 0.22 mol of anhydrous Na_2CO_3, and 0.1 mol of 2-alkoxy-2-arylacetonitrile. The mixture was stirred and refluxed under N_2 for 2 hr at which time tlc showed the complete disappearance of starting nitrile. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O and the organic layer was washed with H_2O. The dried (Na_2SO_4) organic solution was stripped and the residue was crystallized from an appropriate solvent or was converted to the *p*-toluenesulfonate salt using 1 equiv of the acid in a mixture of EtOH–PhH.

2-Alkoxy-2-arylacetamidines (Table IV). The procedure for the preparation of the imino ether L (R = Et) is similar to the one used by Faust, *et al.*[28] A solution of 17.0 g (0.105 mol) of α-ethoxy-α-phenylacetonitrile (**2**) and 7 ml (0.12 mol) of absolute EtOH in 600 ml of absolute Et_2O was placed in a three-necked 1-l. flask protected by a drying tube and equipped with a low-temperature thermometer. The mixture was stirred by a magnetic stirrer and cooled in a Dry Ice–*i*-PrOH bath to −15°. Dry HCl was bubbled sufficiently slowly so that the temperature kept below 10°; at the saturation point, the flow of HCl was stopped (the time required was *ca.* 1 hr). A large excess of HCl is probably sufficient even if saturation is not reached. The mixture was allowed to stand overnight at room temperature. The next day the solution was carefully stripped on the rotary evaporator until solid appeared, the bath being kept below 30°. The solid was collected, washed with 100 ml of dry Et_2O, and kept in a vacuum

desiccator to give 14.9 g of white solid, mp 107° dec. An aliquot was washed with ether by decantanation to give the analytical sample, mp 113° dec. *Anal.* ($C_{12}H_{17}NO_2$·HCl) C, H, N.

The following is illustrative of the preparation of the N-monosubstituted and N,N-disubstituted amidines of Table IV.

2-Ethoxy-2-phenyl-*N*-propylacetamidine Hydrochloride (94). This procedure follows that of Djerassi, *et al.*[29] In a three-necked 250-ml flask equipped with a magnetic stirrer, drying tube, and a dropping funnel was placed 7.3 g (0.030 mol) of ethyl 2-ethoxy-2-phenylacetimidate hydrochloride (L, R = Et). Absolute EtOH (40 ml) was added and the mixture stirred at ambient temperatures until complete solution occurred and then stirred in an ice bath. *n*-Propylamine previously dried over KOH (3.5 ml, 0.042 mol) was added dropwise with stirring. After the addition, the ice bath was removed and stirring was continued until the mixture warmed to room temperature and then stopped (the solution was homogeneous). After standing 43 hr the solvent was stripped below 30° on a rotary evaporator to give a yellow oily residue which was treated with 50 ml of cold 5% NaOH. This mixture was extracted with Et_2O (3 × 50 ml) and the extracts were treated with cold 1 *N* HCl (2 × 50 ml). The aqueous extract was washed once with $CHCl_3$, basified with 10% NaOH, and extracted into $CHCl_3$ (2 × 75 ml). The $CHCl_3$ extract was washed with H_2O (2 × 50 ml), dried over anhydrous K_2CO_3, charcoaled, and stripped on a rotary evaporator below 30° to give 6.7 g of yellow oil. A solution of this in 100 ml of absolute Et_2O was cooled and treated portionwise with 15 ml of 2 *N* HCl in Et_2O. The resulting suspension was cooled and the white solid collected and washed with ether to give 5.8 g (75% yield), mp 174° dec.

The following procedure was applied to the preparation of compounds **105–111.**

1-(2-Methoxy-2-phenyl-*N*-propylacetimidoyl)hexamethyleneimine (108). Methyl 2-methoxy-2-phenylacetate (10.7 g, 0.0595 mol) was converted to the *N*-propylamide by refluxing it with an excess of *n*-$PrNH_2$ overnight. The crude oil from this preparation (ir_{film} 1670 cm^{-1}) was dissolved in 100 ml of dry PhH and 12.5 g (0.06 g-atom) of PCl_5 was added all at once. The mixture was brought to reflux and boiled for 20 min at the end of which time the solid had dissolved and the solution was dark brown. The solvent and $POCl_3$ were stripped and 100 ml of PhMe was added and stripped. The stripping procedure with PhMe was repeated two more times and the residual crude imino chloride was poured with vigorous stirring into a solution of 15 ml of hexamethyleneimine and 50 ml of absolute EtOH. The mixture was kept for 2 hr at room temperature and then at reflux for 15 min. The volatile materials were removed under vacuum and the residue was taken up in 100 ml each of H_2O and Et_2O. The organic layer was extracted with two 50-ml portions of 2 *N* HCl and the combined aqueous solutions were back-washed with Et_2O. The base was liberated from the aqueous solution by the addition of 20% NaOH (ice) and was extracted into Et_2O. The dried (K_2CO_3) organic solution was concentrated and the residue was distilled under vacuum to give 5.5 g (32% yield from methyl 2-methoxy-2-phenylacetate) of a pale yellow oil: bp 116–118° (0.05 Torr); ir_{film} 1610 cm^{-1} (strong, N=C).

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Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms. 1

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In continuation of our work on hypoglycemic sulfonylaminopyrimidines [*e.g.*, glidanile (**4**)] compounds with chiral carbon atoms were synthesized (compounds **18–63**). The (*S*)-1-phenylethylamides of 4-[*N*-(2-pyrimidinyl)sulfamoyl]phenylacetic acid exhibit extraordinary activities, *e.g.*, compound (*S*)-**46**, causing blood glucose decrease at a dose of 0.05 mg/kg (rabbit). The dependency of pharmacological activity on the configuration of the asymmetric carbon atom and other structural features is discussed.

The well-known "classic" sulfonylureas, sulfonylsemicarbazides, and sulfonylaminopyrimidines [*e.g.*, glymidine (**1**), Table I] display blood glucose lowering activity in rabbits in a dose range of 15–30 mg/kg. In man, this corresponds to a daily dosage of 0.5–1 g. During the last few years compounds of much higher potency became known,