Oral Hypoglycemic Agents. Discovery and Structure–Activity Relationships of Phenacylimidazolium Halides

Samuel J. Dominianni* and Terence T. Yen

Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285. *Received March 28, 1988*

Blood glucose levels in viable, yellow, obese, diabetic mice are reduced following oral administration of phenacylimidazolium halides. Compounds **2** and **3** produced reductions of ca. 40% 2 h after doses of 100 mg/kg po. Since these mice do not respond to sulfonylureas, the glucose-lowering activity of phenacylimidazolium salts in this model suggests a mechanism other than that of stimulating insulin secretion. Only phenacylimidazolium halides with electron-donating groups were active; other azolium salts or variations in the phenacyl portion (alterations in the keto function; chain lengthening or extensive branching) produced inactive compounds.

Currently, diabetes mellitus is treated by diet restriction, insulin administration, sulfonylureas, or a combination of these. However limitations of these treatments require the continuous search for improved oral hypoglycemic agents.[1]

The present investigation was initiated by the discovery that 1-methyl-3-phenacylimidazolium chloride (**1**)[2] decreased blood glucose levels in mice that do not respond to sulfonylureas,[3] and since **1** produced a similar hypoglycemic response in alloxan diabetic rats, it is possible that an extrapancreatic mechanism is, at least in part, responsible for the reduction of blood glucose.

Earlier reports of hypoglycemic activity of quaternary salts include phenacylphosphoranes and phosphonium salts,[4] substituted 2-arylthiazolo[3,2-*a*]pyridinium salts,[5] isoxazolylpyridinium salts,[6] and 4-[3(5)-pyrazolyl]-pyridinium salts,[7] in which it was specifically noted that the phenacyl salt was devoid of hypoglycemic activity. Reports of biological activity of imidazolium salts have included antibacterial and antifungal (1-alkyl-3-(alkylthio)imidazolium chlorides[8]), thromboxane synthetase inhibition (1,3-disubstituted imidazolium halides[9]), antiinflamatory (enol betaines of phenacyl halides[10]), and antiarrhythmic (1,3-disubstituted imidazolium halides[11]) activity. Recently, phenacylimidazolium salts have been used as intermediates in a regiospecific synthesis of 3-substituted L-histidines.[12]

In an attempt to define the structural parameters necessary for hypoglycemic activity, we chose as synthetic targets compounds of general structure I:

Z–X–Ar(R)
I

in which the nature of the heterocycle Z, the presence or absence of charge, the length, branching, and nature of the intervening chain X, and the nature of the aryl (or alkyl) could be changed, as compared with those of **1**. The effect on hypoglycemic activity on each variation from **1** could then be assessed.

Chemistry

The compounds prepared in this study are listed in Table I. Azolium salts **2–12**, **15–46**, **48–50**, and **52–54** were prepared by treatment of the heterocycle with the appropriate α-halo ketone in acetonitrile or ethyl acetate (Figure 1).

Tertiary halides were of course very sluggish in this reaction; useful quantitites of, e.g., **53** were obtained only after several weeks at room temperature.

1-Methyl-4,5-dihydro-1*H*-imidazole was prepared by condensation of *N*-methylethylenediamine with DMF acetal. 3-(*n*-Propyloxy)acetophenone was obtained by alkylation of 3-hydroxyacetophenone, brominated with copper(II) bromide,[13] and used directly to prepare **33**. Procedure B (Figure 2) summarizes some standard synthetic transformations to manipulate functional groups.

Alkylation of imidazole with 3′-methoxy-1-bromoacetophenone[14] to produce **14** was accompanied by small amounts of the bis compound **60**. Formation of **60** could largely be suppressed by using a large excess of imidazole in DMF, followed by aqueous workup. Quaternization of **14** produced **47**; **51** was also prepared by quaternization.

Borohydride reduction of **14**, followed by quaternization produced **56**. Cleavage of the methoxyl group in **14** was effected with HBr/HOAc. Neutralization followed by quaternization provided **34**. Similar sequences of alkylation and transformation were used for **13** and **55**.

Procedure C (Figure 3), a Mannich exchange reaction,[15] was carried out in aqueous 1-propanol or toluene at reflux; quaternization of the product provided **59**.

Treatment of **46** with methoxide in methanol, followed by aqueous acid hydrolysis, cleanly produced **57**. Attempts to use aqueous bases always gave mixtures of **57** and **58**. Refluxing **46** in *N*-methylpyrrolidone gave **58** (Figure 4).

Pharmacology

The mice used in this study have been described previously.[16] Six mice were gavaged with the test compound, in saline–2% Emulphor, at 100 mg/kg. Six other mice were gavaged with vehicle. The mice were bled from the tail before dosing and 2 and 4 h after dosing. Blood glucose

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(2) Boekelheide, V.; Fedoruk, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 3830.
(3) Yen, T. T. *Life Sci.* **1987**, *41*, 2349.
(4) Blank, B.; DiTullio, N. W.; Deviney, L.; Roberts, J. T.; Saunders, H. L. *J. Med. Chem.* **1975**, *18*, 952.
(5) Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. *J. Med. Chem.* **1978**, *21*, 489.
(6) Bauer, V. J.; Fanshawe, W. J.; Dalalian, H. P.; Safir, S. R. *J. Med. Chem.* **1968**, *11*, 984.
(7) Bauer, V. J.; Dalalian, H. P.; Fanshawe, W. P.; Safir, S. R.; Tocus, E. C.; Boshart, C. R. *J. Med. Chem.* **1968**, *11*, 981.
(8) Pernak, J.; Skrzypzzak, A.; Kucharski, S.; Krysinski, J. *Arch. Pharm.* **1984**, *317*, 430.
(9) U.S. Patent 4,461,905, 1984.
(10) U.S. Patent 3,852,301, 1974.
(11) Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey, D. D.; Lumman, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.
(12) Chivikas, C. J.; Hodges, J. C. *J. Org. Chem.* **1987**, *52*, 3591.
(13) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.
(14) Nardi, D.; Tajana, A.; Leonardi, A.; Pennini, R.; Portioli, F.; Magistretti, M. J.; Subissi, A. *J. Med. Chem.* **1981**, *24*, 727.
(15) Tramontini, M. *Synthesis* **1973**, 703.
(16) Yen, T. T.; McKee, M. M.; Stamm, N. B. *Int. J. Obes.* **1984**, *8* (Suppl. 1), 65.

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Table I. Physical and Activity Data for 1–59

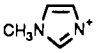
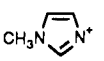
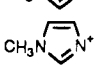
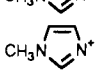
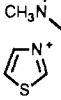
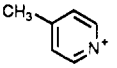
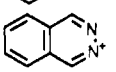
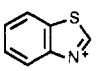
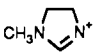
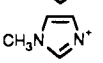
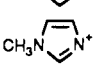
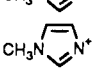
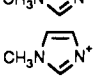
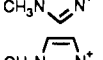
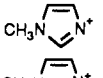
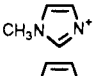
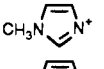
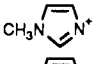
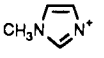
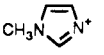
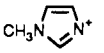
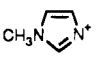
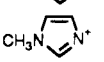
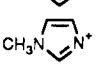
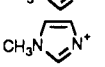
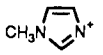
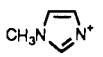
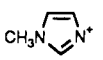
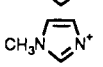
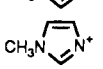
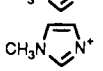
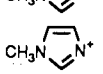
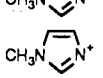
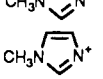
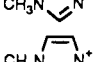
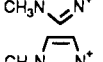
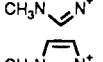
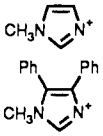
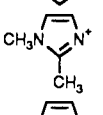
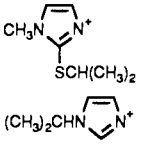
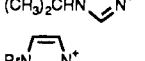
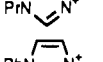
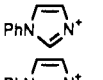
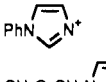
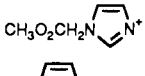
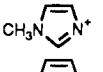
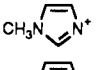
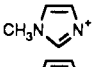
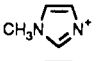
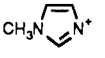
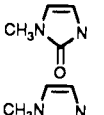
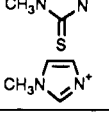
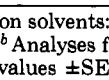
compd (proced)	X–Y–Ar(R) X	Y	Ar(R)	mp, °C solvent[a]	formula anal.[b]	blood glucose[c] 2 h	blood glucose[c] 4 h
1[g] (A)		CH_2CO	Ph	152–154[f] A	$C_{12}H_{13}BrN_2O$ C, H, N	74 ± 4[d]	71 ± 7[d]
2[g] (A)		CH_2CO	$C_6H_4CH_3$-4	148–151 M/EA	$C_{13}H_{15}BrN_2O$ C, H, N, Br	57 ± 4[d]	53 ± 5[d]
3[g] (A)		CH_2CO	$C_6H_4OCH_3$-3	171–173 A/EA	$C_{13}H_{15}BrN_2O_2$ C, H, N	58 ± 4[d]	72 ± 4[d]
4[g] (A)		CH_2CO	C_6H_4CN-4	211–213 dec M/EA	$C_{13}H_{12}BrN_3O$ C, H, N, Br	105 ± 4	106 ± 5
5[g] (A)		CH_2CO	$C_6H_4OCH_3$-3	215–219 dec M/EA	$C_{12}H_{12}BrNO_2S$ C, H, N, S	105 ± 9	123 ± 10
6[g] (A)		CH_2CO	$C_6H_3(OCH_3)_2$-3,5	207 dec M/EA	$C_{13}H_{14}BrNO_4$ C, H, N	95 ± 5	97 ± 7
7[g] (A)		CH_2CO	$C_6H_4CH_3$-4	215–217 dec M/THF	$C_{13}H_{15}BrN_2O$ C, H, N, Br	83 ± 9	82 ± 8
8[e] (A)		CH_2CO	Ph	290–294 dec M/EA	$C_{14}H_{14}ClNO$ C, H, N	105 ± 7	103 ± 5
9[g] (A)		CH_2CO	$C_6H_4CH_3$-4	245–247 dec M/EA	$C_{13}H_{13}BrN_2O$ C, H, N, Br	105 ± 4	111 ± 3
10[g] (A)		CH_2CO	$C_6H_4CH_3$-4	201–202 dec M/EA	$C_{13}H_{13}BrN_2O$ C, H, N, Br	122 ± 7[d]	112 ± 9
11[g,l] (A)		CH_2CO	$C_6H_4CH_3$-4	167–171 dec M/EA	$C_{17}H_{15}BrN_2O$ C, H, N, Br	115 ± 11	108 ± 11
12[g] (A)		CH_2CO	$C_6H_4CH_3$-4	256–257 dec M/THF	$C_{16}H_{14}BrNOS$ C, H, N, S	106 ± 5	108 ± 6
13[h] (B)		CH_2CO	Ph	168–170[g] M/THF	$C_{11}H_{10}N_2O$·HBr C, H, N	103 ± 5	90 ± 10
14 (B)		CH_2CO	$C_6H_4OCH_3$-3	106–108 THF/H	$C_{12}H_{12}N_2O_2$	110 ± 5	121 ± 6
15[g] (A)		CH_2CO	$C_6H_4(OCH_3)$-3	156–159 A/THF	$C_{13}H_{17}BrN_2O_2$ C, H, N	81 ± 9	97 ± 7
16[g] (A)		CH_2CO	C_6H_4Cl-4	147–150 M/EA	$C_{12}H_{12}BrClN_2O$ C, H, N	94 ± 8	93 ± 5
17[g] (A)		CH_2CO	C_6H_4Cl-3	175–177 A/ET	$C_{12}H_{12}BrClN_2O$ C, H, N, Br	107 ± 8	112 ± 8
18[g] (A)		CH_2CO	$C_6H_3(Cl)_2$-3,4	182–185 dec M/EA	$C_{12}H_{11}Cl_2BrN_2O$ C, H, N, Cl	94 ± 11	79 ± 9
19[g] (A)		CH_2CO	C_6H_4F-2	178–180 dec I/ET	$C_{12}H_{12}BrFN_2O$ C, H, N	91 ± 8	99 ± 7
20[g] (A)		CH_2CO	$C_6H_4CONH_2$-4	233–236 dec M/EA	$C_{13}H_{14}BrN_3O_2$ C, H, N	100 ± 5	95 ± 5
21[j] (A)		CH_2CO	$C_6H_4CF_3$-3	184–186 dec M/THF	$C_{13}H_{12}F_3IN_2O$ C, H, N	95 ± 6	97 ± 4
22[g] (A)		CH_2CO	1-naphthyl	229–232 dec M/EA	$C_{16}H_{15}BrN_2O$ C, H, N, Br	90 ± 5	110 ± 17
23[g] (A)		CH_2CO	2-naphthyl	237–240 dec M/ET	$C_{16}H_{15}BrN_2O$ C, H, N, Br	89 ± 5	99 ± 8
24[g] (A)		CH_2CO	2-furyl	146–148 A/THF	$C_{10}H_{11}BrN_2O_2$ C, H, N	72 ± 7[d]	92 ± 9
25[g] (A)		CH_2CO	$C_6H_4OCH_3$-2	165–167 M/EA	$C_{13}H_{15}BrN_2O_2$ C, H, N, Br	90 ± 9	97 ± 13
26[g] (A)		CH_2CO	$C_6H_4OCH_3$-4	156–159 M/ET	$C_{13}H_{15}BrN_2O_2$ C, H, N, Br	70 ± 4[d]	77 ± 5[d]
27[g] (A)		CH_2CO	$C_6H_3(OCH_3)_2$-3,5	239–241 dec M/EA	$C_{14}H_{17}BrN_2O_3$ C, H, N, Br	83 ± 5	69 ± 5
28[g] (A)		CH_2CO	$C_6H_3(OCH_3)_2$-3,4	230–233 dec M/THF	$C_{14}H_{17}BrN_2O_3$ C, H, N	86 ± 7	81 ± 4
29[g] (A)		CH_2CO	$C_6H_3(OCH_3)_2$-2,3	215–217 dec A/EA	$C_{14}H_{17}BrN_2O_3$ C, H, N	83 ± 9	88 ± 10
30[g] (A)		CH_2CO	$C_6H_3(OCH_3)_2$-2,5	207–210 dec A/EA	$C_{14}H_{17}BrN_2O_3$ C, H, N, Br	78 ± 5[d]	86 ± 7
31[g] (A)		CH_2CO	C_6H_4OEt-4	143–146 dec M/EA	$C_{14}H_{17}BrN_2O_2$ C, H, N, Br	103 ± 15	104 ± 5

Table I (Continued)

compd (proced)	X	Y	Ar(R)	mp, °C solvent[a]	formula anal.[b]	blood glucose[c] 2 h	blood glucose[c] 4 h
32[g] (A)		CH_2CO	C_6H_4OEt-3	137–138 M/EA	$C_{14}H_{17}BrN_2O_2$ C, H, N, Br	63 ± 5[d]	64 ± 6
33[g] (A)		CH_2CO	C_6H_4OPr-3	84–86 M/EA	$C_{15}H_{19}BrN_2O_2$ C, H, N	63 ± 4[d]	72 ± 5
34[k] (A)		CH_2CO	C_6H_4OH-3	96–98 dec M/THF	$C_{19}H_{20}N_2O_5S$ C, H, N, S	93 ± 6	87 ± 8
35[e] (A)		CH_2CO	$C_6H_3(OH)_2$-3,4	251–254 dec M/THF	$C_{12}H_{13}ClN_2O_3$ C, H, N	108 ± 4	107 ± 8
36[g] (A)		CH_2CO	C_6H_4NHAc-3	202–204 M/THF	$C_{14}H_{16}BrN_3O_2$ C, H, N	100 ± 5	109 ± 5
37[g] (A)		CH_2CO	$C_6H_4CH_3$-2	152–154 A/ET	$C_{13}H_{15}BrN_2O$ C, H, N, Br	80 ± 8[d]	87 ± 8
38[g] (A)		CH_2CO	$C_6H_4CH_3$-3	185–187 A/ET	$C_{13}H_{15}BrN_2O$ C, H, N, Br	78 ± 5[d]	73 ± 7
39[g] (A)		CH_2CO	$C_6H_3(CH_3)_2$-2,4	179–181 A/EA	$C_{14}H_{17}BrN_2O$ C, H, N, Br	62 ± 7[d]	79 ± 10
40[g] (A)		CH_2CO	$C_6H_3(CH_3)_2$-3,4	163–165 M/EA	$C_{14}H_{17}BrN_2O$ C, H, N, Br	83 ± 4	95 ± 4
41[g] (A)		CH_2CO	$C_6H_2(CH_3)_3$-2,4,6	221–224 dec A/ET	$C_{15}H_{19}BrN_2O$ C, H, N, Br	94 ± 4	97 ± 6
42[g] (A)		CH_2CO	$C_6H_4CH_2CH_3$-4	177–179 A/EA	$C_{14}H_{17}BrN_2O$ C, H, N, Br	77 ± 5[d]	88 ± 6
43[g] (A)		CH_2CO	C_6H_4Ph-4	247–250 dec M/A	$C_{18}H_{17}BrN_2O$ C, H, N, Br	103 ± 7	103 ± 7
44[g] (A)		CH_2CO	$C_6H_4CH_3$-4	180–183 A/EA	$C_{25}H_{23}BrN_2O$ C, H, N, Br	102 ± 17	105 ± 21
45[e] (A)		CH_2CO	Ph	247–250 dec A/EA	$C_{13}H_{15}ClN_2O$ C, H, N, Cl	90 ± 8	81 ± 8
46[g] (A)		CH_2CO	$C_6H_4OCH_3$-3	157–158 dec A/THF	$C_{16}H_{21}BrN_2O_2S$ C, H, N	101 ± 7	121 ± 12
47[g] (B)		CH_2CO	$C_6H_4OCH_3$-3	177–179 dec M/THF	$C_{15}H_{19}BrN_2O_2$ C, H, N	79 ± 5[d]	83 ± 8
48[e] (A)		CH_2CO	Ph	148–150 A/THF	$C_{14}H_{17}ClN_2O$ C, H, N	79 ± 7[d]	79 ± 7[d]
49[g] (A)		CH_2CO	$C_6H_4OCH_3$-3	146–148 M/EA	$C_{18}H_{17}BrN_2O_2$ C, H, N, Br	96 ± 9	91 ± 11
50[e] (A)		CH_2CO	CH_3	171–173 M/EA	$C_{12}H_{13}ClN_2O$ C, H, N, Cl	105 ± 5	109 ± 4
51[g] (B)		CH_2CO	Ph	123–126 A/THF	$C_{14}H_{15}BrN_2O_3$ C, H, N, Br	89 ± 9	84 ± 9
52[g] (A)		$CH(CH_3)CO$[i]	Ph	167–170 M/ET	$C_{13}H_{15}BrN_2O$ C, H, N, Br	70 ± 6	61 ± 7
53[g] (A)		$C(CH_3)_2CO$	Ph	137–140 M/EA	$C_{14}H_{17}BrN_2O$ C, H, N, Br	104 ± 5	113 ± 4
54[e] (A)		$CH(Ph)CO$[i]	Ph	175–178 M/EA	$C_{18}H_{17}ClN_2O$ C, H, N, Cl	94 ± 12	83 ± 4
55[j] (B)		$CH_2C(=NOCH_3)$	$C_6H_4CH_3$-4	104–106 M/ET	$C_{14}H_{18}IN_3O$ C, H, N	86 ± 12	81 ± 8
56[j] (A)		CH_2CHOH[j]	$C_6H_4OCH_3$-3	162–165 M/EA	$C_{13}H_{17}IN_2O_2$ C, H, N	106 ± 3	103 ± 7
57 (D)		CH_2CO	$C_6H_4OCH_3$-3	98–100 EA/H	$C_{13}H_{14}N_2O_3$ C, H, N	101 ± 9	103 ± 12
58 (D)		CH_2CO	$C_6H_4OCH_3$-3	135–137 I/H	$C_{13}H_{14}N_2O_2S$ C, H, N, S	99 ± 17	80 ± 7
59[j] (C)		CH_2CH_2CO	$C_6H_4OCH_3$-3	120–122 M/ET	$C_{14}H_{17}IN_2O_2$ C, H, N	91 ± 5	94 ± 6

[a] Recrystallization solvents: A, acetonitrile; E, ethanol; EA, ethyl acetate; ET, diethyl ether; H, hexanes; I, 2-propanol; M, methanol; THF, tetrahydrofuran. [b] Analyses for the indicated elements were within 0.3% of the calculated values. [c] Values as percent of zero time (dose 100 mg/kg po; mean values ±SE of the mean for six mice. [d] Value significantly different ($p < 0.05$) from vehicle control over the same time period. [e] Quaternary chloride. [f] Literature[2] mp 153–155 °C. [g] Quaternary bromide. [h] Hydrobromide salt. [i] *d,l* mixture. [j] Quaternary iodide. [k] Quaternary *p*-toluenesulfonate. [l] Methanol solvate.

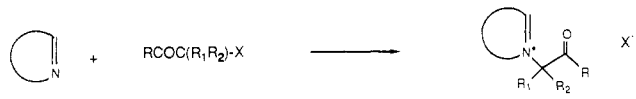


Figure 1. Procedure A.

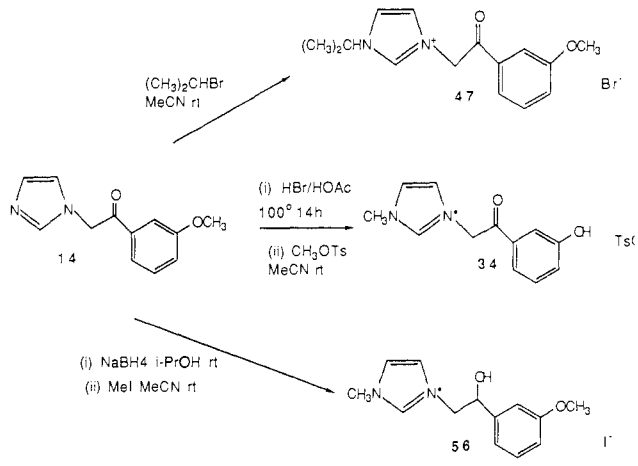


Figure 2. Procedure B.

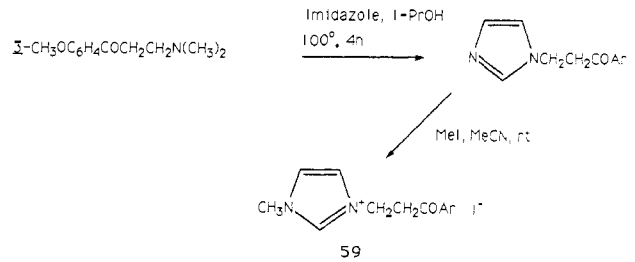


Figure 3. Procedure C.

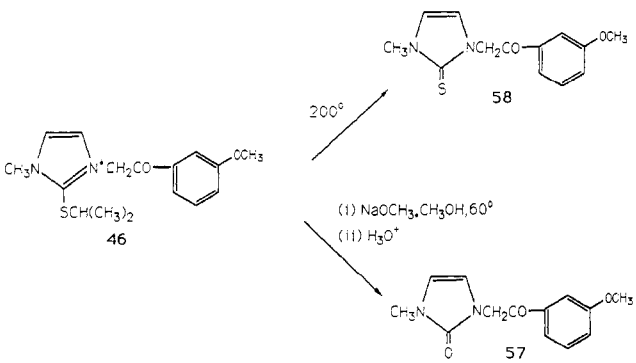


Figure 4. Procedure D.

was determined by the glucose oxidase method with a Technicon Autoanalyzer Model 12-60. The percent changes at 2 and 4 h of the treated mice were considered significant at $p < 0.05$ when compared with controls by using Student's t test.

Results and Discussion

Blood glucose values, reported as percentage of controls, are recorded in Table I. Of the compounds examined, only **1–3**, **26–27**, **30**, **32–33**, **38–40**, **42**, **47**, **48**, and **52** could be regarded as active, producing reductions of blood glucose of 20–40%. Phenacyltriphenylphosphonium bromide, which was active in 48-h fasted rats,[4] was inactive in the yellow, diabetic mice; conversely, our compounds did not show hypoglycemic activity in fasted rats. In short, of the heterocycles examined, hypoglycemic activity was confined to the imidazoles and even within the imidazoles our results place severe constraints on structure I. Only imidazolium salts were active; e.g., **3** was hypoglycemic but the corresponding unquaternized base (**14**) was not. Introduction of a 2-substituent produced an inactive imidazolium salt (**46** and **45**). The 1-substituent was limited to small unfunctionalized alkyls (**47** and **48**), as evidenced by the inactivity of e.g. **50**. The 4,5-dihydro- (**15**) and the 4,5-diphenyl- (**42**) imidazolium salts were inactive.

The intervening chain, X, was optimally two carbons in length; extension by an additional atom (**59**) abolished activity. Small α-substituents could be tolerated (**52**) but not larger ones (**54**). Di-α-substitution (**53**) abolished activity; it is not clear that this is only a substituent effect since α-disubstitution would also preclude ylide formation. Ylide formation is important in the chemistry of phenacylimidazolium halides;[2] whether is is important in the hypoglycemic activity of, e.g., **1** or **3** remains an open question since we have so far been unable to prepare and isolate a characterizable ylide in this series. Reduction of the keto group in X or conversion to an oxime produced inactive salts (**55** and **56**).

The Ar(R) moiety in I was also relatively inflexible. Electron-withdrawing substituents had a deleterious effect on activity (**4** and **16–21**). Electron-donating substituents do not present a wholly consistent picture. Thus, whereas the 3′-methoxy and 3′,5′-dimethoxy analogues (**3** and **27**) represented improvements over the parent **1**, other alkoxy substitution patterns were less active (e.g., **25**, **28**, and **29**). Small alkyl groups usually gave active compounds (**2**, **37–40**, and **44**) , but the 2′,4′,6′-trimethyl analogue **41** was inactive. Very narrow ranges of structural variation have been noted in other hypoglycemic series.[4,5,17]

Because we believe our animal model is indicative of efficacy in type II diabetes and because of the possibility that the phenacylimidazolium salts may be operating through a novel hypoglycemic mechanism, some examples of the series have been chosen for more detailed examination. Future publications will report our studies of pharmacology, absorption, and metabolic routes, together with studies designed to elucidate the mechanism of action.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated silica gel F254 plates (E. Merck). Analytical and spectral data (IR, NMR, and MS) were all in accord with the assigned structures.

Examples of Procedure A. 4,5-Dihydro-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-1*H*-imidazolium Bromide (15). A solution of 25 g of 1-methylethylenediamine in 20 mL of THF was added dropwise to a stirred solution of DMF dimethyl acetal in 50 mL of THF over 0.5 h. After the addition was complete, the solution was refluxed for 8 h and kept at room temperature for 8 h under a drying tube, and the solvent removed by distillation. The residue was purified by distillation; 1-methyl-4,5-dihydro-1*H*-imidazole was obtained as a clear, colorless liquid, bp 39–41 °C (6 mm) in 48% yield. A stirred solution of the dihydroimidazole (2.29 g) in 20 mL of MeCN was treated with 0.90 g of 1-bromo-3′-methoxyacetophenone. The solution was kept at room temperature for 24 h; TLC ($CHCl_3$) showed that the halide had been consumed. The solvent was removed in vacuo and the oily residue was triturated with THF. The resulting solid crystallized from MeCN/THF as fine, matted needles of **15**, mp 157–159 °C in 66% yield.

1-Methyl-3-[2-oxo-2-(3-propoxyphenyl)ethyl]-1*H*-imidazolium Bromide (33). 3-Hydroxyacetophenone was alkylated (PrBr, EtOH/H_2O, K_2CO_3, 12-h reflux) and freed from unconsumed starting material by extraction with 2 N NaOH. 3-Propoxyacetophenone was obtained as tan crystals, mp 23 °C from cold 30–60 petroleum ether. Bromination ($CuBr_2$,

(17) Shroff, J. R.; Bandurco, V.; Desai, R.; Kobrin, S.; Cervoni, P. *J. Med. Chem.* **1981**, *24*, 1521.

$CHCl_3$/EtOAc, reflux 6 h) produced the α-bromo ketone as nearly white crystals from cold MeOH, mp <20 °C.

A stirred solution of 0.02 M 1-bromo-3′-propoxyacetophenone in 20 mL of MeCN was treated with 1.0 mL of 1-methylimidazole. The initially slightly exothermic reaction was allowed to proceed for 12 h. The supernatant was decanted from the dark gum that had precipitated. Triituration of the gum with EtOAc produced a tan powder, which crystallized from warm MeCN/EtOAc as nearly white crystals of **33**, mp 83–86 °C.

Examples of Procedure B. 2-(1*H*-Imidazol-1-yl)-1-(3-methoxyphenyl)ethanone (14) and 1,3-Bis[2-(3-methoxyphenyl)-2-oxoethyl]-1*H*-imidazolium Bromide (60). A stirred solution of 20.0 g of 1-bromo-3′-methoxyacetophenone in 100 mL of DMF was treated with 16.3 g of imidazole and kept at ambient temperature for 12 h. The solution was treated with 400 mL of H_2O and 200 mL of EtOAc and filtered to remove the interfacial solid. The solid was washed with H_2O, EtOAc, and Et_2O and recrystallized from warm MeOH/EtOAc to provide 1.65 g of **60** as short, white needles, mp 215–217 °C dec. Anal. ($C_{21}H_{21}BrN_2O_4$) C, H, N, Br.

The filtrates were combined, and the EtOAc layer was washed with H_2O and brine, dried with Na_2SO_4, and evaporated in vacuo. The oily residue solidified on trituration with cold *i*-PrOH. Recrystallization from *i*-PrOH provided 6.17 g of 14 as glittering, tan flakes, mp 106–108 °C.

3-[2-(3-Methoxyphenyl)-2-oxoethyl]-1-(1-methylethyl)-1*H*-imidazolium Bromide (47). A stirred solution of 1.08 g of 14 in 20 mL of MeCN was treated with 2.6 mL of 2-bromopropane and kept at ambient temperature for 72 h. The solvent was removed in vacuo and the residual brown glass was triturated with THF. The resulting tan powder was recrystallized from MeOH/THF to provide 0.46 g of **47** as white crystals, mp 177–179 °C dec.

***d,l*-3-[2-Hydroxy-2-(3-methoxyphenyl)ethyl]-1-methyl-1*H*-imidazolium Iodide (56).** A stirred mixture of 2.20 g of 14 and 20 mL of *i*-PrOH was treated with 1.00 g of $NaBH_4$ and kept at room temperature for 12 h. The solvent was removed in vacuo and the residue was partitioned between EtOAc/H_2O. The EtOAc layer was washed with H_2O and brine, dried with Na_2SO_4, and evaporated.

A solution of 5.1 g of the residue in 20 mL of EtOAc was treated with 1 mL of MeI and kept at room temperature for 12 h. The precipitate which formed was collected, washed with EtOAc, and recrystallized from MeOH/EtOAc to provide 0.47 g of **56** as fine, white crystals, mp 162–165 °C.

3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-1-methyl-1*H*-imidazolium 4-Methylbenzenesulfonate (34). A stirred mixture of 3.01 g of 14, 10 mL of HOAc, and 10 mL of 48% HBr was refluxed for 36 h and cooled overnight and the resulting mixture was diluted with 20 mL of 1/1 *i*-PrOH/THF. The solid was filtered, washed with THF, and recrystallized from MeOH/THF to provide 1.24 g of the 3-hydroxy hydrobromide as a fine, white powder, mp 221–223 °C dec.

A solution of 1.4 g of the saalt and 3.0 g of K_2CO_3 in 40 mL of 1/1 H_2O/MeOH was stirred for 12 h, filtered, and evaporated in vacuo. The residue was washed with small portions of H_2O and dried to provide 0.60 g of the free base, mp 246–250 °C dec. A solution of the free base (0.2 g), 0.2 g of methyl *p*-toluenesulfonate and 5 mL of MeCN was refluxed for 6 h, kept overnight, and diluted with THF. The resulting precipitate was recrystallized from MeOH/THF to provide 0.19 g of **34** as glittering flakes, mp 96–98 °C dec.

Procedure C. 3-[3-(3-Methoxyphenyl)-3-oxopropyl]-1-methyl-1*H*-imidazolium Iodide (59). A stirred mixture of 2.53 g of the Mannich ketone from 3′-methoxyacetophenone, formaldehyde, and dimethylamine,[18] 0.92 g of imidazole, and 20 mL of 1/1 1-PrOH/H_2O was refluxed for 6 h, kept overnight, and diluted with hexanes. The precipitated oil was dissolved in 15 mL of EtOAc, treated with 2 mL of MeI and kept at room temperature for 12 h. The oil which precipitated solidified on trituration with Et_2O. Recrystallization from MeOH/Et_2O afforded fine, white needles of **59**, mp 120–122 °C.

Procedure D. 3-[2-(3-Methoxyphenyl)-2-oxoethyl]-1-methyl-2-[(1-methylethyl)thio]-1*H*-imidazolium Bromide (46). A stirred solution of 5.05 g of 1-bromo-3′-methoxyacetophenone in 40 mL of MeCN was treated with 3.39 g of 1-methyl-2-[(1-methylethyl)thio]-1*H*-imidazole[19] and kept for 12 h, during which time the mixture solidified. The mixture was diluted with THF and filtered. Recrystallization of the solid provided 8.41 g of **46** as white crystals, mp 154–156 °C dec.

1,3-Dihydro-1-[2-(3-methoxyphenyl)-2-oxoethyl]-3-methyl-2*H*-imidazol-2-one (57). A stirred solution of 3.75 g of **46** and 30 mL of MeOH was treated with 1.23 g of NaOMe and refluxed for 6 h. The cooled yellow orange mixture was treated with 100 mL of 1 N HCl, stirred for 1 h, and extracted with four 30-mL portions of EtOAc. The pooled extracts were washed with brine, dried ($MgSO_4$), and evaporated to a yellow oil which solidified. Recrystallization from *i*-PrOH/hexanes afforded 1.78 g of **57** as white crystals mp 95–98 °C.

2-(2,3-Dihydro-3-methyl-2-thioxo-1*H*-imidazol-1-yl)-1-(3-methoxyphenyl)ethanone (58). A stirred mixture of 3.57 g **46** and 10 mL of *N*-methylpyrrolidone was refluxed for 1.5 h. The resulting solution was cooled and poured into 200 mL of H_2O and the brown precipitate was collected. Recrystallization from *i*-PrOH provided 1.96 g of **58** as glittering, light tan flakes, mp 135–137 °C.

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Registry No. 1, 19748-13-1; 2, 59349-28-9; 3, 103793-22-2; 4, 121704-44-7; 5, 121704-45-8; 6, 121704-46-9; 7, 121704-47-0; 8, 105757-72-0; 9, 121704-48-1; 10, 121704-49-2; 11, 121704-50-5; 12, 121704-51-6; 13, 121704-52-7; 14, 80170-14-5; 15, 121704-53-8; 16, 59349-29-0; 17, 121704-54-9; 18, 121704-55-0; 19, 121730-23-2; 20, 121704-56-1; 21, 103793-38-0; 22, 121704-57-2; 23, 121704-58-3; 24, 121704-59-4; 25, 103793-32-4; 26, 39888-94-3; 27, 103793-33-5; 28, 121704-60-7; 29, 121704-61-8; 30, 103793-31-3; 31, 103793-34-6; 32, 103793-23-3; 33, 121704-62-9; 34, 103793-37-9; 35, 121704-63-0; 36, 103793-39-1; 37, 103793-26-6; 38, 103793-30-2; 39, 103793-29-9; 40, 103793-35-7; 41, 121704-64-1; 42, 103793-25-5; 43, 121704-65-2; 44, 121704-66-3; 45, 121704-67-4; 46, 121704-68-5; 47, 103815-49-2; 48, 103815-48-1; 49, 121730-24-3; 50, 121704-69-6; 51, 121730-25-4; 52, 103793-27-7; 53, 103793-24-4; 54, 121704-70-9; 55, 121704-71-0; 56, 121704-72-1; 57, 121704-73-2; 58, 121704-74-3; 59, 121704-75-4; 60, 121704-76-5; *p*-$BrCH_2COC_6H_4CONH_2$, 83070-12-6; *m*-$ICH_2COC_6H_4CF_3$, 121704-79-8; *m*-$BrCH_2COC_6H_4OEt$, 103793-40-4; *m*-$BrCH_2COC_6H_4NHAc$, 30095-56-8; *o*-$BrCH_2COC_6H_4Me$, 51012-65-8; *m*-$BrCH_2COC_6H_4Me$, 51012-64-7; *p*-$BrCH_2COC_6H_4Ph$, 135-73-9; $BrCH(CH_3)COPh$, 2114-00-3; $BrC(CH_3)_2COPh$, 10409-54-8; ClCH(Ph)COPh, 447-31-4; *m*-$MeOC_6H_4CO(CH_2)_2NMe_2$, 35076-32-5; *N*-methylethylenediamine, 109-81-9; dimethylformamide dimethyl acetal, 4637-24-5; 1-methyl-4,5-dihydro-1*H*-imidazole, 53517-93-4; 1-bromo-3′-methoxyacetophenone, 5000-65-7; 3-hydroxyacetophenone, 121-71-1; 1-bromopropane, 106-94-5; 3-propoxyacetophenone, 121704-77-6; 1-bromo-3′-propoxyacetophenone, 121704-78-7; 1-methylimidazole, 616-47-7; imidazole, 288-32-4; *p*-methylphenacyl bromide, 619-41-0; *p*-cyanophenacyl bromide, 20099-89-2; 3,5-dimethoxyphenacyl bromide, 50841-50-4; phenacyl chloride, 532-27-4; *p*-chlorophenacyl bromide, 536-38-9; *m*-chlorophenacyl bromide, 41011-01-2; 3,4-dichlorophenacyl bromide, 2632-10-2; *o*-fluorophenacyl bromide, 655-15-2; 1-(1-naphthyl)-2-bromoethanone, 13686-51-6; 1-(2-naphthyl)-2-bromoethanone, 613-54-7; 1-(2-furyl)-2-bromoethanone, 15109-94-1; *o*-methoxyphenacyl bromide, 31949-21-0; *p*-methoxyphenacyl bromide, 2632-13-5; 3,4-dimethoxyphenacyl bromide, 1835-02-5; 2,3-dimethoxyphenacyl bromide, 121704-80-1; 2,5-dimethoxyphenacyl bromide, 1204-21-3; *p*-ethoxyphenacyl bromide, 51012-63-6; 3,4-dihydroxyphenacyl chloride, 99-40-1; 2,4-dimethylphenacyl bromide, 26346-85-0; 3,4-dimethylphenacyl bromide, 2633-50-3; 2,4,6-trimethylphenacyl bromide, 4225-92-7; *p*-ethylphenacyl bromide, 2632-14-6; monochloroacetone, 78-95-5; thiazole, 288-47-1; oxazole, 288-42-6; 1-methylpyrazole, 930-36-9; 4-methylpyridine, 108-89-4; pyridazine, 289-80-5; pyrazine, 290-

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11β-Nitrate Estrane Analogues: Potent Estrogens

Richard H. Peters, David F. Crowe, Mitchell A. Avery, Wesley K. M. Chong, and Masato Tanabe*

Bio-Organic Chemistry Laboratory, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025.
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Various estrane derivatives 1 reacted with cerium ammonium nitrate (CAN) selectively and efficiently to provide 9α,11β-difunctionalized derivatives **2**, which were subsequently deoxygenated at C-9 with triethylsilane/boron trifluoride etherate to the desired target 11β-nitratoestranes **3a**, **3b**, and **5**. When examined for estrogenic and postcoital antifertility activity, 11β-nitrates **2c**, **2d**, and **3b** most notably displayed more potent oral activity than did ethynylestradiol.

It has long been recognized that estrogenic hormones are important pharmacological materials and consequently are found to have a wide range of beneficial applications in human and veterinary therapy: for example, they are supplements for the maintenance of estrogen levels in hypogonadic states and are routinely incorporated into oral contraceptives. In our ongoing efforts to provide estrogens with reduced side effects, we describe herein 11-nitratoestrogen analogues that are extremely potent as orally active estrogens in the absence of the classical 17β-hydroxyl-17α-ethynyl group for oral activity.

Inhoffen et al.[1] first reported in the late 1930s that ethynylestradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol, EE) was an orally active estrogen. Since then, EE has been widely employed with progestins (such as norethindrone and norethindrone acetate) in oral contraceptive formulations. However, these products have been blamed for various possible drawbacks, which are extremely serious for the large number of women who take oral contraceptives or estrogen supplements routinely on a long-term basis. These suspected problems can include enhancing the risk of endometrial carcinoma; induction of malignant carcinoma, especially of the cervix, breast, vagina, and liver; and promotion of gallbladder disease, thromboembolic and thrombotic diseases, myocardial infarction, hepatic adenoma, elevated blood pressure and hypercalcemia, and hypersensitized glucose tolerance.

These maladies apparently manifest themselves at the dosage levels needed to achieve the desired primary estrogenic and contraceptive effects. In the event that these side effects are dose-related and more potent orally active extrogens are available, they might in principle be used in lower amounts with a consequential lowering of the body's metabolic burden. Hypothetically, the side effects could, at least in part, then be avoided.

Within this context, we felt that estrogens that were selectively substituted at C-11 presented potentially useful orally active contraceptive agents.

Chemistry

We found that C-11 functionalized estrone derivatives are conveniently available from the process outlined in Scheme I, which reflects our efforts targeted for the production of 11β-nitrato compounds **3**. In the first step of Scheme I, ceric ammonium nitrate (CAN) effected oxidation of estrone 3-acetate (**1a**) and $\Delta^{9,11}$-estrone 3-acetate (**1b**) to selectively provide 9α,11β-difunctionalized estrones **2**, which were subsequently deoxygenated at the C-9-benzylic position with retention of configuration to the 11β-nitratoestrones **3**. The overall transformation **1** → **2** → **3** circumvents problems that we encountered with the generalization of an existing approach, which involved the aromatization by lithium biphenyl of the 17-ketal of 11β-hydroxyandrosta-1,4-diene-3,17-dione,[2] followed by deprotection to the 17-ketone, possible introduction of other functionality at C-17, and formation of the nitrate ester. We examined alternative methods within the context of Scheme I, and some of these efforts are discussed below. In summary, we found that the process shown in Scheme I was very efficient and stereoselective and allowed for a wide range of structural complexity in the substrate estrones **1**.

The selection of CAN as an oxidant stemmed from a report by Sykes et al.[3] on the isolation of a C-9 isomeric mixture of 9α-hydroxy-11β-nitratoestrone 3-acetates from the oxidation of estrone 3-acetate. In general, CAN has been reported[4] to introduce heteroatoms at a variety of other sites under similar conditions and in a manner highly dependent on the substrate estrone functionality. Despite the reported lack of selectivity, in our hands the use of 2 molar equiv of CAN in 90% acetic acid proved satisfactory. For example, 7α-methylestrone 3-acetate (**1b**) and $\Delta^{9,11}$-7α-methylestrone 3-acetate (**1c**), were each converted into isomerically pure 9α-hydroxy-7α-methyl-11β-nitratoestrone 3-acetate (**2b**, R_1 = =O, R_2 = CH_3) in high yield. Routine NMR examination of the derivatives **2b** confirmed the equatorial position of the 11α-hydrogen, and the 9α-hydroxyl orientation was tenatively assigned by analogy to prior chemical correlations made by Sykes.[3]

Sykes[3] also proposed a possible mechanism for the reaction with CAN, which is pictorially depicted in Scheme II. For estrone 3-acetate (**1a**, R_1 = =O, R_2 = H), initial dehydrogenation to 9,11-dehydroestrone 3-acetate was assumed on the basis of the identical results obtained with either compound as substrates with CAN. The styrene **1g** ($\Delta^{9,11}$, R_1 = =O, R_2 = H) presumably becomes a ligand for cerium(IV) via attachment from the α-underside to form

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