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Synthesis and Hypoglycemic Activity of Some Substituted 2-Arylthiazolo[3,2-*a*]pyridinium Salts

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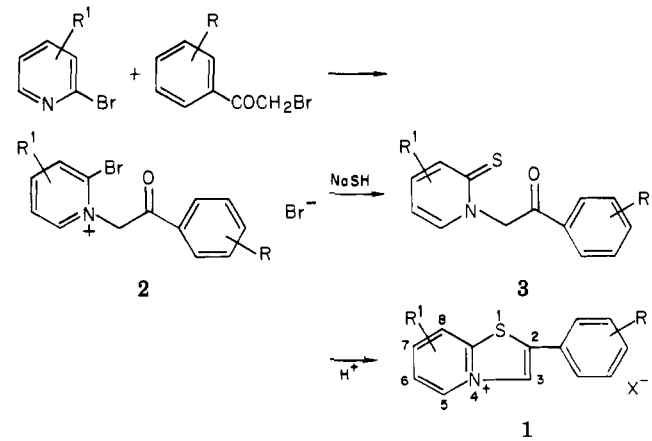
A series of substituted 2-arylthiazolo[3,2-*a*]pyridinium salts (**1a–q**) was prepared by known methods and tested for hypoglycemic activity in 48-h fasted rats. Two compounds, 2-phenylthiazolo- and 8-methyl-2-phenylthiazolo[3,2-*a*]pyridinium perchlorate (**1a** and **1q**), showed consistent hypoglycemic activity in this screen, demonstrating that a high degree of structural specificity was required for hypoglycemic activity. At higher doses the hypoglycemic activity of **1a** and **1q** was associated with elevated levels of hepatic triglycerides.

As part of a continuing program of screening novel structures, particularly pyridines, for hypoglycemic activity in the 48-h fasted rat, it was noted that 2-phenyloxazolo- and thiazolo[3,2-*a*]pyridinium salts had significant activity. These and several similar compounds have been described by Bradsher and co-workers.[1-5] Since the thiazolo compound seemed more potent, this system was chosen for further development. The 2-phenylthiazolo[3,2-*a*]-pyridinium compound **1a** was tested originally as the perchlorate. To obviate any problem that might have been attendant with this salt, three other salts (chloride, bisulfate, and trifluoroacetate) were prepared by modification of the ring closure procedure or by ion-exchange techniques and tested.

As a first approach to the selection of compounds for synthesis, use was made of a "best set of substituents" list authored by Dr. Richard Cramer of our laboratories. This list was based on proposals of Wootton et al.[6] The purpose of such choices was to search for a structure–activity trend (in terms of partition coefficients π, electronic effects σ, and steric factors) with the minimum number of compounds. The compounds prepared are listed in Table I. Their method of preparation paralleled that used by Bradsher and Boliek[5] (Scheme I).

Scheme I



2-Bromopyridines were quaternized in sulfolane (tetramethylene sulfone) with an arylacyl halide to produce the 2-bromopyridinium salts **2** (Table II). The salts were converted to pyridine-2-thiones **3** (Table III) by treatment

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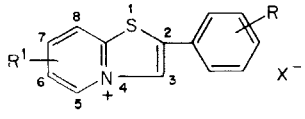
Table I. 2-Arylthiazolo[3,2-*a*]pyridinium Salts



No.	R	R¹	X	Mp, °C	Recrystn solvent	% yield	Formula[a]	Hypoglycemic act. in 48-h fasted rats[b] 1 h	2 h	3 h	4 h	5 h
1a	H	H	HSO_4	184–187	MeOH–EtOH	88	$C_{13}H_{11}NO_4S_2$[c]	−6[d,e]	−16[d,f]	−21[d,f]	−39[d,f]	−30[d,f]
	H	H	ClO_4	164–167[g]	MeOH		$C_{13}H_{10}ClNO_4S$	−4[d,f]	−8[d,f]	−17[d,e]	−33[d,f]	−28[d,f]
	H	H	Cl	189–191	*i*-PrOH		$C_{13}H_{10}ClNS$[c]	−4[d,e]	−13[d,f]	−31[d,f]	−39[d,f]	−39[d,f]
	H	H	CF_3CO_2	122–124	EtOH		$C_{15}H_{10}F_3NO_2S$[h]	−7	−9	−15[d,i]	−18[d,f]	−24[d,e]
1b	*p*-Br	H	HSO_4	238–241[j]	MeOH	61	$C_{13}H_{10}BrNO_4S_2$[k]	9	−4	−1	−5	1
1c	*p*-C_6H_5	H	Cl	261–263[l]	EtOH	90	$C_{19}H_{14}ClNS$[c]	-7	−12	−12	13	3
1d	*p*-$C_6H_4SO_3$	H		>485	TFA	75	$C_{19}H_{13}NO_3S_2$	3	3	13[e]	2	4
1e	*m*-NO_2	H	HSO_4	222–224	MeCN–MeOH	57	$C_{13}H_9N_2O_6S_2$[k]	−10[e]	−7[e]	−6	−6	0
1f	*m*-NH_2	H	ClO_4	173–175	MeOH	57	$C_{13}H_{11}ClN_2O_4S$	−10[i]	−16[e]	−8	−7	−8
1g	*m*-NHAc	H	ClO_4	236–238	MeCN	62	$C_{15}H_{13}ClN_2O_5S$	12	8	3	9	4
1h	*m*-N=CHNMe$_2$	H	ClO_4	188–190	EtOH	25	$C_{16}H_{16}ClN_3O_4S$[m]	1	0	−1	−1	22
1i	*p*-NH_2	H	ClO_4	222–224	DMF	32	$C_{13}H_{11}ClN_2O_4S$[n]	−8	1	−20	−7	−14
1j	*m*-O-*i*-C_3H_7	H	ClO_4	187–190	EtOH	78	$C_{16}H_{16}ClNO_5S$	4	−1	−4	9[i]	−10
1k	*p*-SMe	H	ClO_4	298–301	H_2O	16	$C_{14}H_{12}ClNO_4S_2$[n]	−9	−11	−14	−6	−2
1l	*p*-SO_2Me	H	ClO_4	262–264	MeOH	92	$C_{14}H_{12}ClNO_6S_2$	3	−8[f]	6	−6	−2
1m	*u*	H	Cl	135–137	EtOH	92	$C_{11}H_8ClNS_2$[k]	1	−2	−13	13	0
1n	*w*	H		>500	40% H_2SO_4–H_2O	83	$C_{11}H_7NO_3S_3$	−6	5	−5	−6	6
1o	H	6-Me	ClO_4	204–207[o]	MeOH	62	$C_{14}H_{12}ClNO_4S$	19	−30[i]	−26	−27[i]	16
1p	H	7-Me	ClO_4	169–171[p]	MeOH	77	$C_{14}H_{12}ClNO_4S$	14	−4	−28	−29[i]	−22
1q	H	8-Me	ClO_4	193–195[q]	MeOH	52	$C_{14}H_{12}ClNO_4S$[m]	−17	−42[f]	−51[f]	−59[f]	−50[e]
1r	*r*	H	ClO_4	190–192[s]	MeOH	10	$C_{13}H_{10}ClNO_4S$[k]	−12	−16[e]	−28[i]	−12	−19[i]
1s	*v*		ClO_4	283–284[t]	MeOH	31	$C_7H_6ClNO_4S$	−14[e]	−20[e]	−15[i]	−13[i]	−12

[a] Analyses (C, H, and N) for compounds listed in this table were within ± 0.4% of the theoretical values unless otherwise noted. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. Melting points over 280 °C were determined using a metal block (Mel-temp). [b] Results are expressed as the percent difference between the mean change in control and treated groups after a dose equivalent to 102 mg of free base per kilogram of body weight unless otherwise specified (i.e., 1a). [c] Hydrate. [d] Administered at a dose equivalent to 68 mg of free base per kilogram of body weight. [e] $p < 0.01$. [f] $p < 0.001$. [g] Lit.[5] mp 161–162 °C. [h] Contains 1 mol of CF_3CO_2H. [i] $p < 0.05$. [j] Lit.[5] mp 269–271 °C for the ClO_4. [k] Hemihydrate. [l] Melts with decomposition. [m] Contains 0.25 mol of H_2O. [n] Contains 0.75 mol of H_2O. [o] Lit.[5] mp 202–203 °C. [p] Lit.[5] mp 176–177 °C. [q] Lit.[5] mp 189–190 °C. [r] 3-Phenyl isomer of 1a. [s] Lit.[4] mp 200–201 °C. [t] Lit.[4] mp 280–283 °C.

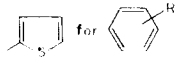
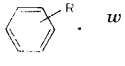
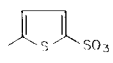
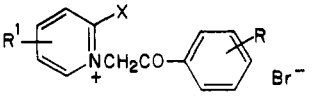
[u]  [v] H for  [w] 

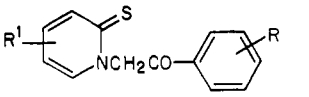
Table II. 1-(β-Aryl-β-oxoethyl)-2-halopyridinium Bromides



No.	R	R¹	X	Mp, °C	Recrystn solvent	% yield	Formula[a]
2a	H	H	Br	176–178[b]		60–75	$C_{13}H_{11}Br_2NO$
2b	*p*-Br	H	Br	186–187[c]	EtOH	54	$C_{13}H_{10}Br_3NO$
2c	*p*-C_6H_5	H	Br	174–176	*i*-PrOH	69	$C_{19}H_{15}Br_2NO$
2d	*m*-NO_2	H	Br	171–173	EtOH	82	$C_{13}H_{10}Br_2N_2O_3$
2e	*p*-NO_2	H	Br	183–185	MeOH	50	$C_{13}H_{10}Br_2N_2O_3$
2f	*m*-NHAc	H	Br	208–209[d]	MeOH	44	$C_{15}H_{14}Br_2N_2O_2$
2g	*m*-O-*i*-C_3H_7	H	Br	132–136	*i*-PrOH	32	$C_{16}H_{17}Br_2NO_2$[e]
2h	*p*-SMe	H	Br	177	EtOH	53	$C_{14}H_{13}Br_2NOS$
2i	*p*-SO_2Me	H	Br	179–181	MeOH-Et_2O	72	$C_{14}H_{13}Br_2NO_3S$
2j	*f*	H	Br	183–184[d]	DMF-Et_2O	10	$C_{11}H_9Br_2NOS$
2k	H	3-Me	Br	181–182	EtOH	35	$C_{14}H_{13}Br_2NO$
2l	H	4-Me	Cl	172–174[g]	MeCN	63	$C_{14}H_{13}BrClNO$[h]
2m	H	5-Me	Br	173–175[i]	EtOH	81	$C_{14}H_{13}Br_2NO$

[a] See footnote *a*, Table I. [b] Lit. mp 177–177.5 °C: C. Djerassi and G. R. Pettit, *J. Am. Chem. Soc.*, 76, 4470 (1954). [c] Lit.[5] mp 175–176 °C. [d] With decomposition. [e] Hydrate. [f] See footnote *u* in Table I. [g] Lit.[5] mp 181–182 °C for X = Br. [h] Contains 0.25 mol of H_2O. [i] Lit.[5] mp 190–194 °C.

Table III. 1-(β-Aryl-β-oxoethyl)pyridine-2-thiones



No.	R	R¹	Mp, °C	Recrystn solvent	% yield	Formula[a]
3a	H	H	187–190[b]	EtOH-MeOH	95	$C_{13}H_{11}NOS$
3b	*p*-Br	H	180–182[c]	EtOH	78	$C_{13}H_{10}BrNOS$
3c	*p*-C_6H_5	H	227–229	$MeNO_2$	58	$C_{19}H_{15}NOS$
3d	*m*-NO_2	H	177–179	MeCN	65	$C_{13}H_{10}N_2O_3S$[e]
3e	*m*-NHAc	H	167–169	EtOH-H_2O	75	$C_{15}H_{14}N_2O_2S$[d]
3f	*p*-NH_2	H	129–131	EtOH	54	$C_{13}H_{12}N_2OS$[d]
3g	*m*-O-*i*-C_3H_7	H	125–126	EtOH	52	$C_{16}H_{17}NO_2S$
3h	*p*-SMe	H	173–175	EtOH-MeOH	87	$C_{14}H_{13}NOS_2$
3i	*p*-SO_2Me	H	178–180	MeOH	64	$C_{14}H_{13}NO_3S_2$
3j	*f*	H	175–177	EtOH	98	$C_{11}H_9NOS_2$
3k	H	3-Me	195–197[g]	MeOH	98	$C_{14}H_{13}NOS$
3l	H	4-Me	176–178[h]	MeCN	79	$C_{14}H_{13}NOS$
3m	H	5-Me	177–179[i]	MeOH	92	$C_{14}H_{13}NOS$

[a] See footnote *a*, Table I. [b] Lit. mp 180.5–181.5 °C (reference in footnote *b*, Table II). [c] Lit.[5] mp 177–178 °C. [d] Contains 0.25 mol of H_2O. [e] Did not analyze satisfactorily. [f] See footnote *u* in Table I. [g] Lit.[5] mp 190–193.5 °C. [h] Lit.[5] mp 181–182 °C. [i] Lit.[5] mp 175–176.5 °C.

with aqueous sodium hydrosulfide. The *p*-nitro group in **2e** was reduced concomitantly to give the *p*-aminothione **3f**. In the case of the *m*-nitro compound **2d**, a mixture of nitro- and aminothiones was produced.

Ring closure of **3** to **1** was effected usually in sulfuric acid. In two instances, **1c** and **1m**, sulfuric acid treatment led to sulfonation of the 2-aryl substituent. Concentrated hydrochloric acid proved a suitable alternative.

The known 3-phenyl isomer of **1a** (**1r**) and the parent compound, thiazolo[3,2-*a*]pyridinium perchlorate (**1s**),[4] were prepared for comparative purposes. The effect of pyridine ring substitution on hypoglycemic activity was determined by preparing and testing the known, isomeric 6-, 7-, and 8-methyl congeners of **1a** (**1o–q**).[5]

Discussion

Of the compounds prepared in this study only **1a** and **1q** had consistent hypoglycemic activity in the 48-h fasted rat at an oral dose of 102 mg of free base/kg (equivalent to 150 mg/kg of **1a** perchlorate). At this dose both compounds also caused a significant elevation in hepatic triglyceride levels (200–300% increase). At the lower dose of 34 mg of the free base/kg, **1a** still had hypoglycemic activity but did not cause a significant rise in hepatic triglycerides. **1a** also lowered blood glucose levels in streptozotocin-diabetic and normal fed rats. No increase in hepatic triglycerides was noted in the diabetic animals at doses up to 136 mg of free base/kg (equivalent to 200 mg/kg of the perchlorate). In in vitro kidney cortex preparations **1a**, at a concentration of 10^{-4} M, inhibited glucose production from lactate indicating that the compound acted, at least in part, by inhibiting gluconeogenesis.

Hypoglycemic activity in this series of compounds is very sensitive to small changes in structure. Any change to the 2-phenyl group had a deleterious effect on hypoglycemic activity. Even replacement of the 2-phenyl group with the isosteric thienyl group (compare **1a** with **1m**) caused a loss of hypoglycemic activity. Similarly, additional bulk on the pyridine ring at positions 6 and 7 (**1o** and **1p**) caused a loss of glucose-lowering activity, whereas **1q** with an 8-methyl substituent had activity comparable to **1a**. The lesser, though consistent activity seen with the unsubstituted thiazolopyridinium compound **1s** may indicate that hypoglycemic activity is a property of this ring system, and the enhanced activity noted with **1a** and **1q** results from better binding of these two analogues to the site of action because of the 2-phenyl substituent.

With the information currently available it is not possible to say why only **1a** and **1q** in this series exert the

effects shown, although steric factors seem to be involved.

Experimental Section

All melting points below 280 °C were taken in a Thomas-Hoover melting point apparatus and are uncorrected. Higher melting points were determined using an electrically heated metal block (Mel-temp) and are also uncorrected. Compounds for which formulas are given were analyzed for C, H, and N and often also for Br or S; analytical values were within ±0.4% of the calculated values unless otherwise noted. Analyses were performed by members of our Analytical and Physical Chemistry Section.

Phenacyl Bromides. These compounds were purchased (4-Br, 3-NO_2, and 4-NO_2) or prepared from the corresponding acetophenone by treatment with 2-pyrrolidinone hydrotribromide (3-NHAc, 3-O-*i*-C_3H_7, 4-SMe, 4-SO_2Me) (see example below). Exceptions were the 4-phenylphenacyl bromide which was obtained by treating biphenyl with bromoacetyl bromide under Friedel–Crafts conditions[7] and β-(2-thienyl)-β-oxoethyl bromide which was obtained from 2-acetylthiophene on treatment with Br_2 in CCl_4.[8]

3-Acetamidophenacyl Bromide. A mixture of 7 g (0.04 mol) of 3-acetamidoacetophenone,[9] 3.7 g (0.042 mol) of 2-pyrrolidinone, and 13.7 g (0.042 mol) of 2-pyrrolidinone hydrotribromide in 100 mL of THF was stirred under reflux for 2 h. An additional 2 g of tribromide was added and the mixture was stirred under reflux overnight. The mixture was cooled, the pyrrolidinone hydrobromide was removed, and the filtrate was concentrated. The oily residue was triturated with ice H_2O to precipitate a solid. The solid was collected and recrystallized from MeOH-H_2O: yield 7 g (68%); mp 67–72 °C.

2-Halopyridines. 2-Chloro-4-methylpyridine was purchased while 2-bromo-3- and -5-methylpyridines were prepared from the corresponding amino compounds by the method of Case.[10]

1-(β-Aryl-β-oxoethyl)-2-bromopyridinium Bromides 2a–m (Table II). Equimolar amounts of the appropriate pyridine and arylacyl bromide in sulfolane (75 mL/0.17 mol) were stirred and heated overnight on a steam bath. The resulting mixture or solution was cooled and diluted with several volumes of Et_2O. The resulting gum or solid was triturated with Et_2O and/or collected, washed, and recrystallized.

1-(β-Aryl-β-oxoethyl)pyridine-2-thiones 3a–m (Table III). A mixture of **2** and a 2 molar excess of NaSH in H_2O (120 mL/0.01 mol) was stirred and heated on a steam bath for 2–3 h. The mixture was cooled and filtered, and the solid was washed with H_2O, dried, and recrystallized.

Subjecting **2e** to these conditions resulted in the concomitant reduction of the nitro group so that the isolated product was 1-(β-4-aminophenyl-β-oxoethyl)pyridine-2-thione (**3f**). In the case of **2d** there was partial reduction of the nitro group leading to a mixture of reduced material and **3d**.

2-Arylthiazolo[3,2-*a*]pyridinium Salts 1a,b,d,e,g,i–l,n–q. A. A solution of 0.05 mol of **3** in 100 mL of concentrated H_2SO_4 was stirred initially with cooling and then overnight at room temperature. The reaction mixture was poured carefully over ice. In some cases the bisulfate salt (**1a** and **1e**) or betaine (**1d** and **1n**) precipitated. These were collected, washed with cold H_2O, and purified. In other instances the solution was treated with 70% $HClO_4$ (12 mL/0.05 mol of **3** used). The precipitated perchlorates were then treated as the bisulfates.

B. **1c and 1m.** A solution of 0.05 mol of **3c** or **3j** and 120 mL of concentrated HCl was stirred overnight at room temperature. The solution was concentrated in vacuo; the residue was azeotroped with EtOH and recrystallized.

C. **1a Trifluoroacetate.** A mixture of **3a** and TFA (10 mL/g of **3a**) was stirred under reflux for 5 h and left overnight at room temperature. The solution was filtered and the filtrate was concentrated. The residue was diluted with Et_2O and the solid was collected, washed with Et_2O, and recrystallized.

D. **1a Chloride.** A column containing ca. 450 mL of moist resin (IRA 400, Cl^-) was washed with MeOH until the washes were clear. A solution of 12.5 g (0.04 mol) of **1a** (ClO_4) in MeOH was passed through the column using additional MeOH. The progress of the elution was followed by TLC. The eluates were evaporated and the residue weighing 9.8 g was recrystallized.

2-(3-Aminophenyl)thiazolo[3,2-*a*]pyridinium Perchlorate (1f). A slurry of 3.6 g (0.01 mol) of **1e** (ClO_4) and 0.5 g of 10% Pd/C in 200 mL of HOAc was shaken for 2 h under an initial pressure of 3.5 kg/cm^2 of H_2. There was no uptake of H_2. The mixture was flushed with N_2, an additional 0.5 g of catalyst was added, and reduction was resumed as before. There was now a steady uptake of H_2 until the theoretical amount of H_2 was absorbed.

The mixture was filtered through a mat of Supercel and the filtrate was evaporated. The residue was azeotroped with C_6H_5Me and recrystallized.

2-(3-Dimethylaminomethyleneaminophenyl)thiazolo-[3,2-*a*]pyridinium Perchlorate (1h). A suspension of 2.9 g (8.9 mmol) of **1f** in 25 mL of dry DMF was treated with 7 mL of dimethylformamide dimethyl acetal to produce a dark green solution. The solution was stirred at 60 °C for 2 h, cooled, and diluted with Et_2O. A gum precipitated. It was triturated twice with fresh portions of Me_2CO and the resulting semisolid was collected. The semisolid (ca. 1.6 g) was dissolved in hot MeCN (charcoal) and the solution was filtered and cooled. A small amount of insoluble material was removed and the MeCN was evaporated. The residue was recrystallized from dry EtOH to give yellowish green solid.

Biochemistry. Hypoglycemic testing was carried out in 48-h fasted male rats. In vitro studies were carried out using rat kidney cortex slices. Both procedures have been described.[11,12] Hepatic triglycerides were determined by extracting livers according to the method of Folch et al.[13] and analyzing the material in the $CHCl_3$ fractions as described by van Handel and Zilversmit.[14]

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