- (7) B. R. Baker and R. R. Bramhall, J. Med. Chem., 15, 937 (1972).
- (8) M. Yoshimoto and C. Hansch, J. Med. Chem., 19, 71 (1976).
- (9) J. Van Dijk, J. Hartog, and T. A. C. Boschman, J. Med. Chem., 19, 982 (1976).
 (10) F. H. Frank, S. M. Bingel, J. T. Martin, B. J. Staring, J.
- (10) F. J. Turner, S. M. Ringel, J. T. Martin, P. J. Storino, J. M. Daley, and B. S. Schwartz, Antimicrob. Agents Chemother., 475 (1968).
- (11) S. Minami, T. Shono, and J. Matsumoto, Chem. Pharm. Bull., 19, 1482 (1971).
- (12) H. Nakao, M. Fukushima, H. Yanagisawa, and S. Sugawara, Chem. Pharm. Bull., 22, 1864 (1974).
- (13) H. Agui, T. Mitani, A. Izawa, T. Komatsu, and T. Nakagome, J. Med. Chem., 20, 791 (1977).
- (14) A. A. Santilli, A. C. Scotese, and J. A. Yurchenco, J. Med. Chem., 18, 1038 (1975).
- (15) R. Albrecht, Chim. Ther., 8, 45 (1973).
- (16) H. Yanagisawa, H. Nakao, and A. Ando, Chem. Pharm. Bull., 21, 1080 (1973).
- (17) H. Agui, T. Mitani, M. Nakashita, T. Nakagome, T. Komatsu, A. Izawa, and Y. Eda, Japanese Patent 97879 (1973); *Chem. Abstr.*, 80, 82714 (1974).
- (18) Y. Nagano and M. Murakami, Japanese Patent 88882 (1974); Chem. Abstr., 82, 43 195c (1975).
- (19) H. Agui, T. Mitani, M. Nakashita, T. Nakagome, T. Komatsu, Y. Eda, Japanese Patent 97 880 (1973); *Chem. Abstr.*, 80, 95 764r (1974).
- (20) L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles*, 3, 913 (1975).

- (21) L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles*, 5, 565 (1976).
- (22) G. M. Coppola, G. E. Hardtmann, and O. R. Pfister, J. Org. Chem., 41, 825 (1976).
- (23) R. P. Staiger and E. B. Miller, J. Org. Chem., 24, 1214 (1959).
- (24) S. Biniecki, Z. Kabzinska, and M. Szypulska, Acta Pol. Pharm., 20, 243 (1963); Chem. Abstr., 62, 466c (1965).
- (25) E. C. Wagner and M. F. Fegley, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1975, p 488.
- (26) W. Deuchel, Helv. Chim. Acta, 35, 1587 (1952).
- (27) H. Agui, T. Mitani, M. Nakashita, and T. Nakagome, J. Heterocycl. Chem., 8, 357 (1971).
- (28) H. Agui, T. Komatsu, and T. Nakagome, J. Heterocycl. Chem., 12, 557 (1975).
- (29) H. J. Hess, T. H. Cronin, and A. Scriabine, J. Med. Chem., 11, 130 (1968).
- (30) N. Barton, A. F. Crowther, W. Hepworth, D. N. Richardson, and G. W. Driver, British Patent 830 832 (1960); Chem. Abstr., 55, 7442e (1961).
- (31) L. A. Mitscher, R.-P. Leu, M. S. Bathala, W. Wu, J. L. Beal, and R. White, *Lloydia*, 35, 157 (1972).
- (32) D. G. O'Sullivan and P. W. Sadler, J. Chem. Soc., 2916 (1957).
- (33) G. E. Hardtmann, G. Koletar, and O. R. Pfister, J. Heterocycl. Chem., 12, 565 (1977).
- (34) Although Chemical Abstracts uses "2H-3,1-benzoxazine-2,4(1H)-dione", the authors prefer to use the more common trivial name of "N-substituted isatoic anhydride". We have adopted the anhydride numbering system as well.

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-phenyloxazoloand 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 Boliek⁵ (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

	: act. in 48-h fasted rats ^b	3h 4h 5h	$-21^{d,f}$ $-39^{d,f}$ $-30^{d,f}$	$17^{d,e}$ $-33^{d,f}$ $-28^{d,f}$	$-31^{d,f}$ $-39^{d,f}$ $-39^{d,f}$	$-15^{d,i}$ $-18^{d,f}$ $-24^{d,e}$	$^{-1}$ $^{-5}$ 1	-12 13 3	13^e 2 4	9 9	8	3 9 4	-1 -1 22	-20 -7 -14	-4 9^{i} -10	-14 -6 -2	62	-13 13 0	-5 -6 6		-26 -27^{t} -16	-28 -29^{t} -22	-50' $-59'$ $50''$	-28' - 12' - 19'	-15^{t} -13^{t} -12	nts were determined in a Thomas- e are expressed as the percent differ-	s otherwise specified (i.e., 1a).	.1–162 °C. <i>h</i> Contains 1 mol of ² Contains 0.75 mol of H,O. ^o Lit. ⁵	r.		
	ypoglycemic	2 h	$-16^{d,f}$	$-8^{d,f}$	$-13^{d,f}$	6	4	-12	co C	-7^{e}	-16^{e}	8	0		-1 	-11,	-87	-2	5		-30	-4	42	-16''	20^{e}	Melting poi p). ^b Result: weight unless g Lit. ⁵ mp 16 ol of H,O. ⁿ	ıp 280-283°(202 002 d			
	I	1 h	$-6^{d,e}$	$-4^{d,f}$	$-\bar{4}^{d,e}$	L-	6	L	ი	-10^{e}	-10^{i}	12		8-	4	6	co	1	9^{-}		19	14	-17	12	-14^{e}	rise noted.	m of body	< 0.001. ins 0.25 m	^t Lit. ⁴ m		
		Formula ^a	C. H. NO.S.C	C. H. CINO.S	C, H, CINS	C_{i} , H, F, NO, S ^h	$C_{1,3}H_{1,0}BrNO_{4}S_{2}^{h}$	C ₁ ,H ₁ ,CINS ^c	C, H, NO,S,	$C_{1,H_{0}}N,O_{1}S_{1}^{k}$	C, H, CIN, O, S	C, H, CIN, O, S	C, H, CIN, O, S ^m	$C_{1}H_{1}CIN_{2}O_{4}S^{n}$	C ₁ ,H ₁ ,CINO,S	$C_{1,A_{1}}$, $CINO_{4}S_{2}$	C ₁₄ H ₁₂ CINO ₆ S ₂	$C_1, H_s CINS, \vec{k}$	C_1 H ₂ NO ₃ S ₃		$C_{14}H_{12}CINO_{4}S$	$C_{14}H_{12}CINO_{4}S$	$C_{14}H_{12}CINO_{4}S_{m}$	$C_{1,3}H_{1,6}CINO_4S^{r}$	$C_{H_{c}}CINO_{4}S$	al values unless otherw ned using a metal block of free base per kilogran ght. $^{e}p < 0.01$. $^{f}p <$ omposition. m Conta Lit. ⁴ mp 200–201 $^{\circ}$ C.	Lit. ⁴ mp 200-201 °C.				
	%	yield	88	0			61	06	75	57	57	62	25	32	78	16	92	92	83		62	77	52	10	31	theoretics	uetermin 02 mg of	ody weig with decc	of 1a. ^s		
	Rocustn	solvent	MeOH-FtOH	MeOH	i-PrOH	EtOH	MeOH	EtOH	TFA	MeCN-MeOH	MeOH	MeCN	EtOH	DMF	EtOH	H_2O	MeOH	EtOH	$40\% H_2 SO_4^{-}$	H_2O	MeOH	MeOH	MeOH	MeOH	MeOH	iis table were within $\pm 0.4\%$ of the the Melting points over 280 ° C were of a groups after a dose equivalent to 1 8 mg of free base per kilogram of b the ClO ₄ . ^k Hemihydrate. ¹ Melts y p 189–190 ° C. ^r 3-Phenyl isomer of the second seco	3-Phenyl isomer				
		$M_{p, \circ}C$	184-187	$164 - 167^{g}$	189-191	122 - 124	$238-241^{j}$	$261 - 263^{l}$	>485	222-224	173-175	236-238	188-190	222 - 224	187 - 190	298 - 301	262 - 264	135 - 137	>500		$204 - 207^{o}$	$169 - 171^{p}$	$193 - 195^{q}$	$190-192^{\circ}$	$283-284^{l}$		p 189-190 °C.				
		Х	USH		000	CF.CO.	HSO_{a}	ס		HSO,	CIO,	CIO,	CIO,	CIO	CIO	CIO,	CIO	CI			CIO₄	CI0⁴	CIO₁	CI04	CIO	i listed in th	and treated	valent to 6 71 °C for th	^q Lit. ⁵ m	[↓_5 <u>↓</u> so ₃ '
		R'	Н	H	H	H	H	Н	Н	Н	Η	Н	Н	Н	Н	Н	Н	Н	Η		6-Me	7-Me	8-Me	Н		compounds	is and are un in control	a dose equi mn 269-27	76-177°C.	$\chi^{\rm R}$ w	
		Я	п	пн	Η	H	<i>p</i> -Br	$p-C_{k}H_{c}$	p-C, H, SO,	m-NO,	m-NH,	m-NHÂc	m-N=CHNMe,	p-NH,	m-0-i-C,H,	<i>p</i> -SMe	p-SO,Me	, n	т		Н	Н	Η	r	п	ies (C, H, and N) for	etting point apparation to the mean change	$\frac{d}{i} \frac{d}{p} < 0.05 = \frac{j}{i} \frac{1}{1.45}$	03 °C. ^p Lit. ⁵ mp 1	X ^R . U H for	
		No.	1,	та			1b	lc	1d	1e	lf	10	1h	11	1i	1ĸ	11	1^{m}	1 n		10	1p	1q	1r	1s	^a Analys	ence betw	^c Hydrate. CF_CO_H	mp 202-2	, []	=

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

R ¹											
No.	R	\mathbb{R}^1	х	Mp, °C	Recrystn solvent	% yield	Formula ^a				
2a	Н	Н	Br	176-178 ^b		60-75	C ₁₃ H ₁₁ Br ₂ NO				
2b	<i>p-</i> Br	н	Br	186–187°	EtOH	54	$C_{13}H_{10}Br_{3}NO$				
2 c	$p-C_{6}H_{5}$	н	\mathbf{Br}	174-176	<i>i</i> -PrOH	69	$C_{19}H_{15}Br_2NO$				
2 d	m-NO,	н	Br	171-173	EtOH	82	$C_{13}H_{10}Br_2N_2O_3$				
2e	p-NO,	н	Br	183-185	MeOH	50	$C_{13}H_{10}Br_{2}N_{2}O_{3}$				
2 f	<i>m</i> -NHAc	н	Br	208–209 ^d	MeOH	44	$C_{15}H_{14}Br_{2}N_{2}O_{2}$				
2g	m-O-i-C-H-	н	Br	132-136	i-PrOH	32	$C_{16}H_{17}Br_{2}NO_{2}e$				
2h	p-SMe	н	\mathbf{Br}	177	EtOH	53	$C_{14}H_{13}Br_{2}NOS$				
2 i	p-SO.Me	Н	\mathbf{Br}	179-181	MeOH-Et,O	72	C ₁₄ H ₁₃ Br ₂ NO ₃ S				
2i	f	н	Br	$183 - 184^d$	DMF-Et,Ô	10	$C_{11}H_{0}Br_{2}NOS$				
2k	́н	3-Me	Br	181 - 182	EtOH	35	$C_{14}H_{13}Br_{2}NO$				
21	H	4-Me	Cl	$172 - 174^{g}$	MeCN	63	$C_{14}H_{13}BrClNO^{h}$				
2m	Ĥ	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 H₂O. ⁱ Lit.⁵ mp 190-194 °C.

Table III. $1-(\beta-\operatorname{Aryl}-\beta-\operatorname{oxoethyl})$ pyridine-2-thiones

R ¹ NCH ₂ CO											
No.	R	R¹	Mp, $^{\circ}$ C	Recrystn solvent	% yield	Formula ^a					
3a 3b 3c 3d 3e 3f 3g 3h 3i	H p-Br p-C ₆ H ₅ m-NO ₂ m-NHAc p-NH ₂ m-O- i -C ₃ H ₇ p-SMe p-SO ₄ Me	H H H H H H H H	187-190b 180-182c 227-229 177-179 167-169 129-131 125-126 173-175 178-180	EtOH-MeOH EtOH MeNO ₂ MeCN EtOH-H ₂ O EtOH EtOH EtOH MeOH	95 78 58 65 75 54 52 87 64	$C_{1_{3}}H_{1_{1}}NOSC_{1_{3}}H_{1_{0}}BrNOSC_{1_{9}}H_{1_{9}}NOSC_{1_{3}}H_{1_{0}}N_{2}O_{3}S^{e}C_{1_{3}}H_{1_{0}}N_{2}O_{3}S^{d}C_{1_{3}}H_{1_{2}}N_{2}OS^{d}C_{1_{6}}H_{1_{7}}NO_{2}SC_{1_{4}}H_{1_{3}}NOS_{2}C_{1_{4}}H_{1_{3}}NO_{3}S_{2}$					
3j 3k 3l 3m	Î H H H H	H 3-Me 4-Me 5-Me	175–177 195–197 ^g 176–178 ^h 177–179 ⁱ	EtOH MeOH MeCN MeOH	98 98 79 92	C ₁₁ H ₂ NOS C ₁₄ H ₁₃ NOS C ₁₄ H ₁₃ NOS C ₁₄ H ₁₃ NOS 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 H₂O. ^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 $\pm 0.4\%$ 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-NO₂, and 4-NO₂) or prepared from the corresponding acetophenone by treatment with 2-pyrrolidinone hydrotribromide (3-NHAc, 3-O-*i*-C₃H₇, 4-SMe, 4-SO₂Me) (see example below). Exceptions were the 4-phenylphenacyl bromide which was obtained by treating biphenyl with bromoacetyl bromide under Friedel–Crafts conditions⁷ and β -(2-thienyl)- β -oxoethyl bromide which was obtained from 2-acetylthiophene on treatment with Br₂ in CCl₄.⁸

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 H₂O to precipitate a solid. The solid was collected and recrystallized from MeOH-H₂O: 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 Et₂O. The resulting gum or solid was triturated with Et₂O and/or collected, washed, and recrystallized.

 $1-(\beta$ -Aryl- β -oxoethyl)pyridine-2-thiones 3a-m (Table III). A mixture of 2 and a 2 molar excess of NaSH in H₂O (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 H₂O, dried, and recrystallized.

Subjecting 2e to these conditions resulted in the concomitant reduction of the nitro group so that the isolated product was 1-(3-4-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-1,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% HClO₄ (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 azeo-troped 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 (ClO₄) 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 (ClO₄) 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/cm² of H₂. There was no uptake of H₂. The mixture was flushed with N₂, an additional 0.5 g of catalyst was added, and reduction was resumed as before. There was now a steady uptake of H₂ until the theoretical amount of H₂ 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 E_2O . A gum precipitated. It was triturated twice with fresh portions of Me₂CO 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 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 CHCl₃ fractions as described by van Handel and Zilversmit.¹⁴

References and Notes

- C. K. Bradsher and M. F. Zinn, J. Heterocycl. Chem., 1, 219 (1964).
- (2) C. K. Bradsher and M. F. Zinn, J. Heterocycl. Chem., 4, 66 (1967).
- (3) C. K. Bradsher, R. D. Brandau, J. E. Boliek, and T. L. Hough, J. Org. Chem., 31, 2129 (1969).
- (4) C. K. Bradsher and D. F. Lohr, Jr., J. Heterocycl. Chem., 3, 27 (1966).
- (5) C. K. Bradsher and J. E. Boliek, J. Org. Chem., 32, 2409 (1967).
- (6) R. Wootton, R. Cranfield, G. C. Sheppey, and P. J. Goodford, J. Med. Chem., 18, 607 (1975).
- (7) E. L. Anderson, J. E. Casey, Jr., E. E. Force, E. M. Jensen, R. S. Matz, and D. E. Rivard, J. Med. Chem., 9, 211 (1966).
- (8) F. Kipnis, H. Soloway, and J. Ornfelt, J. Am. Chem. Soc., 71, 10 (1949).
- (9) N. J. Leonard and S. N. Boyd, Jr., J. Org. Chem., 11, 405 (1946).
- (10) F. H. Case, J. Am. Chem. Soc., 68, 2574 (1946).
- (11) N. W. DiTullio, C. E. Berkoff, B. Blank, V. Kostos, E. J. Stack, and H. L. Saunders, *Biochem. J.*, 138, 387 (1974).
- (12) B. Blank, N. W. DiTullio, C. K. Miao, F. F. Owings, J. G. Gleason, S. T. Ross, H. L. Saunders, J. Delarge, and C. L. Lapiére, J. Med. Chem., 17, 1065 (1974).
- (13) J. Folch, M. Lees, and G. H. Sloane Stanley, J. Biol. Chem., 226, 497 (1957).
- (14) E. van Handel and D. B. Zilversmit, J. Lab. Clin. Med., 50, 152 (1957).