Synthesis and Pharmacological Activity of 1-(Arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones

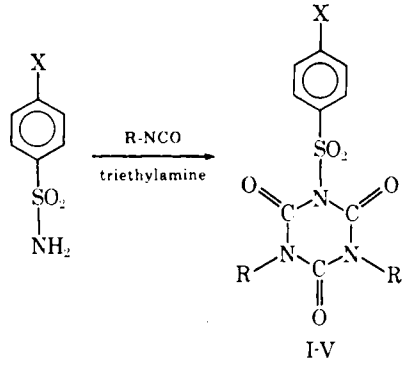
GEORGE N. HOLCOMB*▲, LORRAINE A. KLEMM*, THOMAS J. SILHAVY*‡, and RAYMOND E. COUNSELL†

Abstract □ A series of five 1-(arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones was synthesized by the base-catalyzed reaction of arylsulfonamides with alkyl isocyanates. The compounds were tested for apomorphine antagonism in mice, diuretic activity in fasted rats, antiviral activity in mice, antiviral activity in infected cell cultures, CNS stimulant activity in mice, and hypoglycemic activity in rats. The only biological activity exhibited by these compounds was a slight tendency to lower blood sugar levels in glucose-primed, fasted rats. This activity may be attributable to their structural similarity to the sulfonylurea hypoglycemics.

Keyphrases □ 1-(Arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones—synthesized and screened as potential hypoglycemic agents □ Triazine derivatives—synthesis as potential hypoglycemic agents and screening of 1-(arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones □ Hypoglycemic agents, potential—synthesis and screening of 1-(arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones

Recently it was reported that 1-(*p*-iodobenzenesulfonyl)-3,5-di-*n*-propyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (I) is formed when *p*-iodobenzenesulfonamide reacts with an excess of *n*-propyl isocyanate in the presence of triethylamine (1). This represents the first example of a 1-(arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione; however, this compound has certain structural features in common with a number of sulfonamides with known biological activity. Of particular interest in this regard is the structural similarity between I and the sulfonylurea hypoglycemics. In fact, I actually contains a sulfonylurea moiety within its structure.

The sulfonylureas are known to exert a wide variety of extrapancreatic effects (2). However, most investigators currently feel that the primary mode of action of these compounds is the stimulation of insulin release from pancreatic β-cells (3). Because of the structural similarities between I and the sulfonylureas, it seemed quite possible that I could interact with β-cell receptors in much the same way as the sulfonylureas and, thereby, it could be an active hypoglycemic.



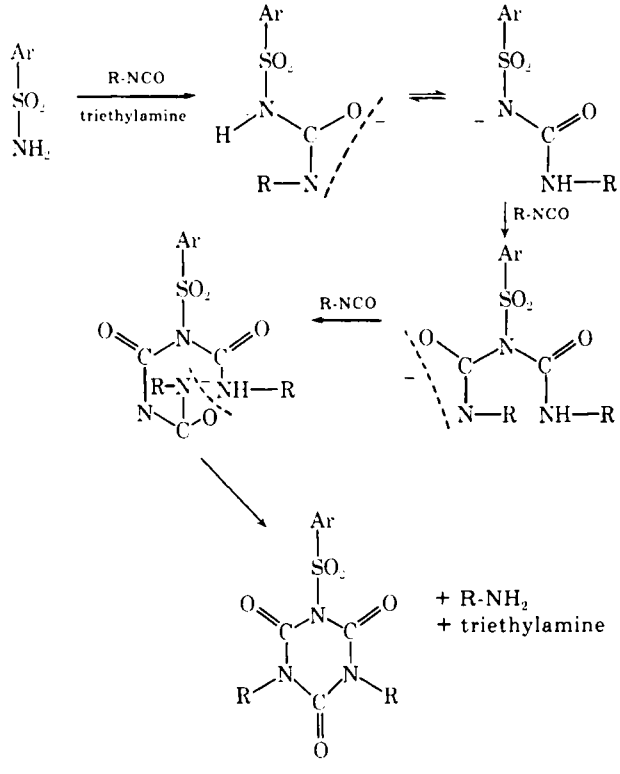
Scheme I

In addition to their hypoglycemic effects, sulfonamides are known to have various other pharmacological activities (4, 5). Some biological effects that have been attributed to sulfonamides are bacteriostatic (6), diuretic (7), hypotensive (8), anti-inflammatory (9), and CNS depressant effects (10).

The present studies were designed to determine if I and certain of its analogs possess sulfonylurea-like hypoglycemic activity and also to ascertain whether these compounds exert other significant biological effects.

The arylsulfonamides were prepared by treating the appropriate sulfonyl chloride with ammonium hydroxide as described in the *Experimental* section. The arylsulfonyl-*s*-triazine derivatives (I–V) were synthesized (Scheme I) by treating the arylsulfonamides with an excess of the appropriate alkyl isocyanate, with triethylamine as the catalyst.

Attempts to synthesize *s*-triazine derivatives from several isocyanates (*tert*-butyl, cyclohexyl, isopropyl, and isobutyl isocyanates) were unsuccessful, thus suggesting that the reaction is subject to steric hindrance. This is in agreement with a previous proposal that the *s*-triazines are formed by the base-catalyzed reaction of the arylsulfonamide with a threefold excess of the alkyl



Scheme II

Table I—Physical Data

Compound	R	X	Melting Point	Formula	Analysis, % Calc.	Found	Yield, %
I	n-C_3H_7	I	186–187°	$C_{15}H_{18}IN_3O_5S$	C 37.59 H 3.79 N 8.77	37.75 3.83 8.83	44
II	n-C_3H_7	Cl	223–224°	$C_{15}H_{18}ClN_3O_5S$	C 46.45 H 4.65 N 11.68	46.49 4.68 11.53	33
III	n-C_3H_7	Br	212–213°	$C_{15}H_{18}BrN_3O_5S$	C 41.67 H 4.17 N 9.72	41.40 4.14 9.88	14
IV	C_2H_5	Cl	215–217°	$C_{13}H_{14}ClN_3O_5S$	C 43.39 H 3.89 N 11.68	43.23 3.81 11.61	26
V	n-C_4H_9	Cl	176–177°	$C_{17}H_{22}ClN_3O_5S$	C 49.10 H 5.29 N 10.11	49.02 5.46 10.14	13

isocyanate, with the subsequent elimination of an alkyl amine (1). These observations are consistent with the mechanism proposed in Scheme II. The transient existence of the anionic intermediates can be justified by the delocalization of the developing charge as proposed by Ulrich (11) for similar reactions.

EXPERIMENTAL[1]

Arylsulfonamides—The appropriate arylsulfonyl chloride (0.085 mole) was dissolved in ether (300 ml.), and ammonium hydroxide (100 ml.) was added to the reaction dropwise over 20 min. The mixture was stirred for 30 min., and 1 *N* NaOH (250 ml.) was added. The aqueous layer was filtered, and the pH of the filtrate was adjusted to 6 with 1 *N* HCl. The arylsulfonamide precipitated on cooling and was isolated by suction filtration. Yields and melting points were as follows: *p*-iodobenzenesulfonamide, 91.4%, 191–192° [lit. (12) m.p. 190–191°]; and *p*-bromobenzenesulfonamide: 92.4%, 169–170° [lit. (12) m.p. 165°].

*1-(p-Iodobenzenesulfonyl)-3,5-di-*n*-propyl-*s*-triazine-2,4,6-(1H,3H,5H)-trione (I)*—This compound was prepared as described previously (1).

*1-(Arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1H,3H,5H)-triones (II-V)*—A mixture of the appropriate arylsulfonamide (0.02 mole), the corresponding alkyl isocyanate (0.20 mole), and triethylamine (1 ml.) was heated at 70° with stirring for 120 hr., and the excess alkyl isocyanate was removed under vacuum. The residual solid was washed with ether (25 ml.) and 1 *N* NaOH (20 ml.) and then recrystallized from ethanol–water. Yields and physical constants are reported in Table I.

Biological—The animals used for hypoglycemic testing were glucose-primed, fasted, pathogen-free, male rats[2]. The test compounds were administered orally in 0.5 ml. of carboxymethylcellulose vehicle. Immediately prior to administration of the test compound, the animals were injected subcutaneously with 100 mg. of glucose. The rats were bled *via* the jugular vein 2 hr. after the injection of the test compound. Blood glucose concentrations were determined[3] by a modification of the method of Hoffman (13).

RESULTS AND DISCUSSION

Although significant hypoglycemic activity was detected in some compounds, they were not as potent as tolbutamide (Table II). Compound I (X = I, R = n-C_3H_7) exhibited the greatest degree of hypoglycemic activity. However, this compound only depressed blood glucose levels by 10.1% when it was administered at a dose of 100 mg./kg., whereas tolbutamide produced a 34.0% decrease in blood sugar when administered at a dose of only 25 mg./kg. Compounds II (X = Cl, R = n-C_3H_7) and IV (X = Cl, R = C_2H_5) exhibited a slight tendency to lower blood sugar levels in glucose-primed, fasted rats. Compounds III (X = Br, R = n-C_3H_7) and V (X = Cl, R = n-C_4H_9) did not exhibit any significant hypoglycemic activity in this test system.

Table II—Hypoglycemic Activities of 1-(Arylsulfonyl)-3,5-dialkyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones

Treatment	Dose, mg./kg.	Number of Animals	Blood Glucose, mg. %, 2 hr. ±*SE*[a]	Percent Change
Control		8	71.6 ± 1.5	
Tolbutamide	25	4	47.3 ± 0.8	−34.0
I	100	4	64.4 ± 1.6	−10.1
Control		7	70.4 ± 0.8	
Tolbutamide	25	4	49.0 ± 1.0	−30.4
II	100	4	65.8 ± 2.3	−6.6
Control		8	72.1 ± 1.7	
Tolbutamide	25	4	45.3 ± 2.5	−37.1
III	100	4	72.9 ± 2.9	1.2
Control		7	70.4 ± 0.8	
Tolbutamide	25	4	49.0 ± 1.0	−30.4
IV	100	4	65.2 ± 1.5	−7.4
Control		7	74.0 ± 1.5	
Tolbutamide	25	4	49.1 ± 3.3	−33.6
V	100	4	72.4 ± 2.1	−2.2

[a] Standard error of the mean.

The hypoglycemic activity exhibited by some compounds may be attributable to their structural similarity to the sulfonylurea hypoglycemics. No definite reason can be stated for their low order of potency, although it could be due to the presence or absence of certain structural features which interfere with their ability to interact with pancreatic β-cell receptors and stimulate insulin release. Alternatively, the diminished activity of these compounds could be a result of altered absorption and/or distribution characteristics arising from their extremely low aqueous solubility. The limited aqueous solubility observed in these compounds may be attributable to the fact that, unlike most other sulfonamides with demonstrated biological activity, they do not contain an acidic hydrogen.

All five compounds were also tested for apomorphine antagonism in mice, diuretic activity in fasted rats, antiviral activity (Influenza A_2 virus) in mice, antiviral activity in infected cell cultures, CNS stimulant activity in mice, and CNS depressant activity in mice. They did not exhibit significant activity in any of these tests.

[1] All melting points were determined on a Fisher-Johns melting-point apparatus and are corrected. The structures of all compounds were supported by IR and NMR spectra. IR spectra were taken on a Perkin-Elmer 337 spectrophotometer using KBr pellets. NMR spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ at a concentration of 10%, with trimethylsilane as an internal reference. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Chromatogram strips (K301R) were used for TLC, and the spots were detected with UV light.

[2] Upjohn Sprague-Dawley.

[3] By Auto-Analyzer.

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‡ Present address: Department of Biological Chemistry, Harvard Medical School, Boston, MA 02115

▲ To whom inquiries should be directed.

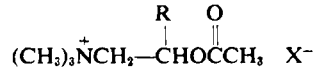
Ketoxime Acetates: Substrates for Cholinesterases

GEORGE M. STEINBERG▲, NORMAN C. THOMAS, MORTON L. MEDNICK, and VERNON BALTHIS

Abstract □ Ketoxime acetates function as typical substrates for acetylcholinesterase. Several 3-pyridinium ketoxime esters have potential utility for spectrophotometric studies with the enzyme. Each is highly water soluble and gives a large change in absorbance upon hydrolysis. With each, the acylation step is rate limiting. They bind to the enzyme strongly; the lowest $K_{m(app)}$ observed is 1.5×10^{-5} *M*. The substrates are hydrolyzed by butyrylcholinesterase. Several show great selectivity for butyrylcholinesterase over acetylcholinesterase.

Keyphrases □ Ketoxime acetates—as cholinesterase (acetyl and butyryl) substrates, binding constants, hydrolysis, absorbance changes, selectivity □ Cholinesterase substrates, acetyl and butyryl —ketoxime acetates, binding constants, hydrolysis, absorbance changes, selectivity □ Acetylcholinesterase—1-alkyl 3-pyridinium ketoxime halide esters as substrates □ Butyrylcholinesterase—1-alkyl 3-pyridinium ketoxime halide esters as substrates

A recent publication (1) reported the activity of aldoxime acetates as substrates for acetylcholinesterase (acetylcholine hydrolase, E.C. 3.1.1.7). The two principal purposes of that study were: (*a*) to gain information on the kinetic specificity and selectivity of the enzyme, and (*b*) to widen the range of spectrophotometrically useful substrates for studying enzyme properties. This note extends the work to ketoxime esters.

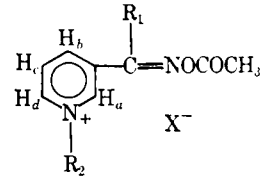


I: R = H
II: R = CH_3

Acetylcholinesterase is generally insensitive to bulking on the alcohol portion of the ester molecule. For example, methacholine (II) is hydrolyzed nearly as rapidly as acetylcholine (I) (2). The reverse pattern is observed with butyrylcholinesterase (acylcholine arylhydrolase, E.C. 3.1.1.8), where bulking near the ester linkage in a test substrate may markedly reduce or even completely abolish response to the enzyme (2). This study was initiated to learn if these characteristics extend to the oxime esters and to determine whether appreciable changes in K_m could be provided by the simple expedient of changing the size (bulk) of the alkyl group attached to the pyridine nitrogen atom.

EXPERIMENTAL

The oxime acetates (III–VII) were prepared in conventional manner by oximation of the corresponding aldehydes or ketones, acetylation with acetic anhydride, and finally alkylation of the pyridine nitrogen atom with methyl iodide or benzyl bromide (3–7).



	R_1	R_2
III:	CH_3	CH_3
IV:	CH_3	$C_6H_5CH_2$
V:	C_2H_5	CH_3
VI:	H	$C_6H_5CH_2$
VII:	acetophenone oxime acetate	