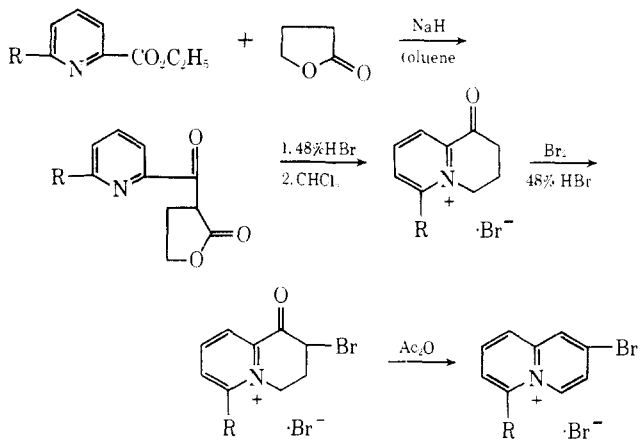
SCHEME I



2, R = H
3, R = CH_3

pared by a combination of two published procedures[5,6] as shown in Scheme I.

The reaction of **2** or **3** with an appropriately substituted amine in *i*-PrOH provided the corresponding 2-(substituted amino)quinolizinium bromides (**4**–**40**) shown in Table I.

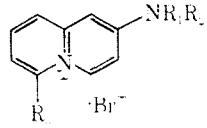
Biological Method. *A. suum.*—Drug administration was peroral to mice twice a day for 5 days. The infection was accomplished with embryonated eggs administered by gavage, halfway between the doses on the second day of medication. The mice were sacrificed and their lungs digested in buffered saline with added trypsin. Larvae were counted with the aid of a microscope. This method is a modification of the procedure outlined by Sprent.[7] Compound effectiveness was calculated as a percentage reduction based on the following formula.

$$\% \text{ reduction} = 100 - \left(\frac{\text{mean of medicated group counts} \times 100}{\text{mean of unmedicated control group counts}}\right)$$

The *A. suum* larvae counts were analyzed statistically by means of the Student "t" test.

Structure–Activity Relationships.—The anthelmintic activity of the compounds prepared in this work and a comparison drug, dithiazanine iodide,[8] are shown in Table I. In general, the compounds most active against *A. suum* contained a substituted anilino group in the 2 position of the quinolizinium ring. The presence of the Me group in the 6 position did not appear to cause a significant change in activity.

The substitution of alkylamino groups (**5**, **32**, and **33**) or hydrazino groups (**4** and **34**) on the quinolizinium ring resulted in somewhat lower activity when compared to compounds with anilino substituents. Substitution on the anilino ring with alkoxy or dialkylamino groups (**6** and **10**) resulted in increased activity over the unsubstituted anilino derivative (**14**). Substitution of halogens (**20**, **22**, and **30**), alkyl groups (**12**, **18**, **21**, and **23**), OH (**31**), or MeS (**38**) on the anilino ring resulted in diminished activity. Alkoxy groups in



5–34, R = H
35–41, R = Me

either the 2 or 4 position of the anilino ring resulted in high activity (**7**, **8**, **9**, **11**, **19**, **24**, **26**, **28**, **29**, **35**, and **40**), but two alkoxy groups in the 2 and 4 positions (**13** and **36**), the 3 and 4 positions (**25** and **39**), or the 2 and 5 positions (**27**) caused a reduction in anthelmintic activity. Three alkoxy groups in the 2, 4, and 6 positions (**15**) on the anilino ring resulted in significantly diminished activity. Extension of the alkoxy chain in the 4 position maintained activity at about the same high degree from Me through Pr and *i*-Pr (**8**, **19**, **24**, **35**, and **40**) but fell off slightly with *i*-Bu (**29**) and cyclopentyl (**28**), and markedly with *n*-Bu (**17**) and Ph (**16**).

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected.

2-(*o*-Anisidino)quinolizinium Bromide (7).—To a solution of 2-bromoquinolizinium bromide[5,6] (30 g, 0.1 mol) in *i*-PrOH (500 ml) was added *o*-anisidine (24 g, 0.2 mol). The stirred mixture was refluxed for 4.5 hr. After chilling the reaction mixture in an ice bath, the product was removed by filtration and washed thoroughly with Et_2O. After drying at 60° for several hours the product weighed 28 g (82%). Recrystallization from *i*-PrOH–Et_2O provided an analytical sample as tan needles.

The remaining compounds in Table I were prepared in a similar manner from **2** or **3** and the appropriately substituted amine or hydrazine.

Acknowledgment.—The authors are grateful to Miss Yvonne Miller, Mr. James Sheffer, and Mr. R. Charles Finch for the preparation of chemical intermediates, and to Mr. Merville Jones and Mr. Stephen Ashton for their assistance in the biological testing. Microanalyses were performed by Mr. Marvin Tefft and Mr. Grant Gustin.

Hypoglycemic Activity of 1-Alkenyl- and 1-Alkenoyl-3-arylsulfonylureas

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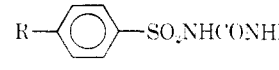
As part of our studies on new arylsulfonylureas,[1,2] we have prepared for hypoglycemic testing a number of compounds having the general formula I, in which R



I

was Cl, Me, or MeO, and R′ was an alkenyl or alkenoyl group. The new substances (Table I) were obtained

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(6) A. Fozard and G. Jones, *J. Chem. Soc.*, 2203 (1963).
(7) J. F. A. Sprent, *J. Infect. Diseases*, **90**, 165 (1952).
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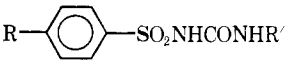
(1) G. Pala, A. Mantegani, and G. Coppi, *J. Med. Chem.*, **10**, 508 (1967).
(2) G. Pala, G. Coppi, A. Mantegani, and C. Bianchi, *J. Pharm. Pharmacol.*, **20**, 559 (1968).

TABLE I

1-ALKENYL- AND 1-ALKENOYL-3-ARYLSULFONYLUREAS



Compd	R	R′	Yield, %	Mp, °C	Formula[a]	Relative potency
1	CH_3	$(CH_3)_2C{=}CHCH_2$	93	137–138	$C_{13}H_{18}N_2O_3S$	0.85
2	CH_3	$(CH_3)_2C{=}CHCH_2CH_2$	79	94–95.5	$C_{14}H_{20}N_2O_3S$	0.00
3	CH_3O	$(CH_3)_2C{=}CHCH_2$	81	118–119.5	$C_{13}H_{18}N_2O_4S$	0.18
4	CH_3O	$(CH_3)_2C{=}CHCH_2CH_2$	69	98–99	$C_{14}H_{20}N_2O_4S$	0.14
5	Cl	$(CH_3)_2C{=}CHCH_2$	73	121–122	$C_{12}H_{15}ClN_2O_3S$	0.30
6	Cl	$(CH_3)_2C{=}CHCH_2CH_2$	78	114–115	$C_{13}H_{17}ClN_2O_3S$	0.09
7	CH_3	$(CH_3)_2C{=}CHCO$	43	173–175	$C_{13}H_{16}N_2O_4S$	0.17
8	CH_3	$(CH_3)_2C{=}CHCH_2CO$	22	120–122	$C_{14}H_{18}N_2O_4S$	0.16
9	CH_3	$(CH_3)_2C{=}CHCH_2CH_2CO$	37	108–109	$C_{15}H_{20}N_2O_4S$	0.27
10	CH_3O	$(CH_3)_2C{=}CHCO$	36	167–168	$C_{13}H_{16}N_2O_5S$	0.26
11	CH_3O	$(CH_3)_2C{=}CHCH_2CO$	29	131–132	$C_{14}H_{18}N_2O_5S$	0.00
12	CH_3O	$(CH_3)_2C{=}CHCH_2CH_2CO$	28	123–124	$C_{15}H_{20}N_2O_5S$	0.29
13	Cl	$(CH_3)_2C{=}CHCO$	40	161–163	$C_{12}H_{13}ClN_2O_4S$	0.16
14	Cl	$(CH_3)_2C{=}CHCH_2CO$	36	166–167	$C_{13}H_{15}ClN_2O_4S$	0.13
15	Cl	$(CH_3)_2C{=}CHCH_2CH_2CO$	37	156–157	$C_{14}H_{17}ClN_2O_4S$	0.00
Tolbutamide						1.00

[a] All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical values.

by condensing *N*-arylsulfonylcarbamates with amines or amides in boiling PhMe.

The drugs were tested orally in normal fasting rats. The results are listed in Table I in terms of relative potency, which was calculated as previously described[2] and expressed in relation to the hypoglycemic activity of tolbutamide, which has been assigned the potency of 1.0.

An examination of the relative hypoglycemic potencies revealed that, among all the tested substances, only **1** was found to display an activity of some interest. This compound was then tested also orally in fasting rabbits as well as in normally fed rats and rabbits; the values for relative potency were 0.63, 0.85, and 0.41, respectively. From these findings, the conclusion may be drawn that **1** [1-(3-methyl-2-butenyl)-3-*p*-tolylsulfonylurea] possesses hypoglycemic properties, which, however, are inferior to those of tolbutamide. Apart from this, the introduction of a branched alkenyl group in the 1 position of arylsulfonylureas does not seem to lead to interesting hypoglycemic agents.

Experimental Section[3]

3-Methyl-2-butenylamine.—1-Bromo-4-methyl-2-butene (111.75 g, 0.75 mol) in Et_2O (375 ml) was dropped for 3 hr into a solution of $NaNH_2$ [from Na (17.3 g, 0.75 g-atom) and liquid NH_3 (900 ml)]. The mixture was refluxed for 2 hr with stirring, NH_3 was allowed to evaporate, and the residue was cautiously taken up with 30% NaOH and Et_2O. The organic layer was separated and dried (NaOH). The solvent was evaporated and the residue was distilled at 110–112° (lit.[4] 110.5°) to give a colorless liquid (26 g, 40%).

4-Methyl-3-pentenylamine.—1-Bromo-4-methyl-2-butene (44.7 g, 0.3 mol) and 97% CuCN (27.7 g, 0.3 mol) were rapidly heated to 60° with stirring. After the exothermic reaction had started, the mixture was cautiously cooled, the temperature was kept at 50–60° for 30 min, and the suspension was taken up in MeCN and filtered. Evaporation of the solvent under reduced pressure and distillation of the residue at 58–60° (14 mm) gave 10.8 g (37.5%) of 4-methyl-2-pentenonitrile sufficiently pure for further work.

The nitrile (10.8 g, 0.113 mol) in Et_2O (100 ml) was dropped for 1 hr into a stirred suspension of LAH (8.6 g, 0.226 mol) in Et_2O (600 ml). After 30 min stirring, the reaction mixture was cooled and then cautiously decomposed with 30% NaOH (100 ml). The organic layer was separated, washed with H_2O, and dried (NaOH). The solvent was evaporated and the residue was distilled at 48–50° (30 mm) to give 4-methyl-3-pentenylamine[5] as a colorless liquid (4.96 g, 44%). *Anal.* ($C_6H_{13}N$) C, H, N.

1-Alkenyl-3-arylsulfonylureas.—A solution of alkenylamine (0.05 mol) and ethyl *N*-arylsulfonylcarbamate (0.056 mol) in anhydrous PhMe (120 ml) was refluxed for 5 hr. The hot solution was filtered and cooled to separation of a crystalline solid, which was filtered, washed with Et_2O, and dried. When concentrated, the mother liquor gave additional but less pure product.

3-Methyl-2-butenamide was prepared according to Pitrè.[6] The following amides were similarly obtained: **4-methyl-3-pentenamide,** 96%, mp 78–81°; *Anal.* ($C_6H_{11}NO$) C, H, N; **5-methyl-4-hexenamide,** 78%, mp 83–85; *Anal.* ($C_7H_{13}NO$) C, H, N.

1-Alkenoyl-3-arylsulfonylureas.—A solution of alkenylamide (0.05 mol) and ethyl *N*-arylsulfonylcarbamate (0.055 mol) in anhydrous PhMe (120 ml) was refluxed for 48 hr. During this time, the solvent was gradually distilled off and replaced with fresh solvent to remove the EtOH formed. The hot solution was filtered, evaporated to dryness, and the residue taken up in 5% NaOH (50 ml) and Et_2O (250 ml). A solid separated which was dissolved in H_2O. After filtering with charcoal, the solution was acidified with 10% HCl and the precipitate which formed was filtered, washed with Et_2O, and dried at room temperature under reduced pressure.

Acknowledgments.—The authors thank Dr. R. Perego for the microanalyses, Mr. E. Zugna for preparing the compounds, and Mr. E. Pavesi for the hypoglycemic tests.

(3) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(4) D. Semenow, Chin Hua Shin, and G. Young, *J. Amer. Chem. Soc.*, **80**, 5472 (1958).

(5) This compound was previously described in a mixture with 4-methyl-4-pentenylamine by A. C. Cope and W. D. Burrows, *J. Org. Chem.*, **31**, 3099 (1966).

(6) D. Pitrè, *Farmaco Ed. Sci.*, **4**, 657 (1949).