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3,562,256

1,3-DIALKYL-5-(SUBSTITUTED ARYLSULFONYL)-TETRAHYDRO-1,3,5-TRIAZINE-4-THIONES

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U.S. Cl. 260—239.7 1 Claim

ABSTRACT OF THE DISCLOSURE

Disclosed herein is a class of novel compounds; namely, 1,3-dialkyl-5-(substituted arylsulfonyl)-tetrahydro - 1,3,5-triazine-4-ones and thiones. These compounds are particularly useful for the control of hyperglycemia and consequently exhibit exceptional hypoglycemic activity. In addition, processes for the preparation of these hypoglycemic compounds are described along with pharmaceutical compositions and methods of lowering blood sugar in animals by the administration of such compounds.

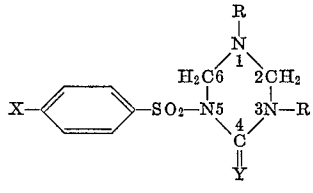
This invention relates to novel 1,3-dialkyl-5-(substituted arylsulfonyl)-tetrahydro-1,3,5-triazine-4-ones and thiones; processes for their preparation; pharmaceutical compositions thereof; and a method of lowering blood sugar in animals.

Generally, hyperglycemia has been treated by the regular parenteral administration of insulin. However, due to the necessity of frequent injections, patient discomfort, and related general difficulties, there has been a continual search to uncover new and improved means for controlling hyperglycemia.

As a result thereof, various hypoglycemic agents have been discovered which can be administered orally. Typical examples of such materials are disclosed in the following United States Pats. 3,150,178; 3,242,174; 3,259,544 and 3,282,784. For the most part, hypoglycemic or antidiabetic agents, such as these, are wanting in sufficient activity over a prolonged period of time. Consequently, substantial or repeated dosing is necessitated.

The present invention overcomes these problems by providing hypoglycemic agents of high activity and lower toxicity. Thus, this invention provides hypoglycemic agents which are readily utilized in the treatment of hyperglycemia. Because of such valuable properties, the present invention must be considered a substantial advance in the state of the art.

The novel compounds of this invention which may be referred to generically at times throughout this disclosure as "triazines" can be represented by the formula



(I)

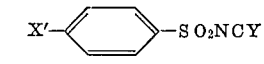
wherein:

X is methyl, chlorine, nitro, amino, methoxy or acetyl;
Y is oxygen or sulfur; and
R is alkyl of 2 to 7 carbon atoms, provided that when X is chlorine or methoxy, R is alkyl of 3 to 6 carbon atoms.

As stated above, R in Formula I is an alkyl of 2 to 7 carbon atoms and as such can be branched, cyclic, or normal. Typical alkyls which fall within this classification include: ethyl, propyl, isopropyl, cyclopropyl, butyl, t-butyl, cyclobutyl, pentyl, isopentyl, hexyl, cyclohexyl, and heptyl. Generally and preferably, both R positions (1 and 3) in

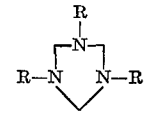
any particular compound will be substituted by the same alkyl group. However, this is not to be construed as a limitation of this invention since disparate alkyl groups in such positions are contemplated and within the scope thereof.

Preparation of the novel triazines represented by Formula I, excepting therefrom those compounds where X is amino, may be effected by reacting a substituted arylsulfonyl isocyanate or arylsulfonyl isothiocyanate of the formula



(II)

with an alkyl substituted trimethylene triamine of the formula



(III)

wherein Y and R represent the same substituents as defined for Formula I and X' is methyl, chlorine, nitro, methoxy or acetyl. The trimethylene triamine represented by Formula III is commonly referred to as an azomethine trimer.

This reaction proceeds on a molar basis of one mole substituted arylsulfonyl isocyanate or arylsulfonyl isothiocyanate to ⅔ mole of alkyl substituted azomethine trimer to produce one mole of triazine. While the reaction requires one mole of isocyanate or isothiocyanate for each ⅔ mole of azomethine trimer, it is advantageous to have a slight molar excess of isocyanate or isothiocyanate present. With this slight molar excess, the reaction proceeds much more readily.

It is advantageous and preferable to carry out the reaction in the presence of an inert solvent, such as for example, toluene, benzene, xylene, ethyl acetate, ethylene dichloride and the like.

Reaction temperature is not critical and under most circumstances the reaction will proceed at any temperature above 0° C. However, a temperature range of 25° to 110° C. is preferred and will insure a rapid completion of the reaction.

Recovery of the product, namely, the triazine from the reaction solution, is accomplished by any suitable means available to one skilled in the art. Typically, this would include filtration, crystallization, distillation, or any combination thereof and the like.

The isocyanate reactants represented by Formula II when Y is oxygen are known in the art and may be prepared by reacting a substituted arylsulfonamide and phosgene in the presence of a catalyst such as an alkyl isocyanate. Such preparations are reported in the Journal of Organic Chemistry, vol. 31, pages 2658–2661 (1966).

The arylsulfonyl isothiocyanate reactants, that is, the compounds represented by Formula II when Y is sulfur, are likewise known in the art. They may be obtained by the reaction of phosgene on N-substituted iminodithiocarbonates as reported in Chem. Ber., vol. 99, pages 2885–2899 (1966).

Substituted trimethylene triamines are similarly well known and readily available. They may be prepared by reacting a primary amine with formaldehyde and purified by drying with potassium hydroxide.

Preparation of the compounds of Formula I where X is amino involves the catalytic reduction of a Formula I compound where X is nitro. Typically, the reduction is carried out with platinum oxide under about 30 to 40 pounds of pressure per square inch at a temperature in the range of 25° to 30° C. and in an inert solvent, such as benzene, toluene, alcohol and the like. Saparation of the amino substituted triazine may be accomplished by con-

ventional procedures, such as for example, filtration, crystallization, distillation or any combination thereof.

This invention is further illustrated by the following examples, which are not to be construed as limitations thereof. On the contrary, resort may be had to various other embodiments, modifications and equivalents which readily suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or scope of the appended claims.

EXAMPLE 1

Preparation of 1,3-di-n-butyl-5-(p-tolylsulfonyl)-tetrahydro-1,3,5-triazine-4-one

In a 500 ml. three-neck, round bottom flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer, there was placed 300 ml. of toluene and 34 g. (0.126 mol.) of tri-N-butyl-trimethylene triamine. To this solution there was added 25 g. (0.126 mol.) p-toluenesulfonyl isocyanate and heated to reflux, with stirring for 2 hours. At the end of this time, the toluene was removed by evaporation under a vacuum of 15–20 mm. on the steam bath. The residue (a thick oil) crystallized on cooling (yield 59.2 g.). Recrystallization from a mixture of aqueous ethyl alcohol gave 1,3-di-n-butyl-5-(p-tolylsulfonyl)-tetrahydro-1,3,5-triazine-4-one having a M.P. of 78°–80° C. Yield: 21.1 g. (45.7% of theoretical).

Analysis.—Calculated for $C_{18}H_{29}N_3O_3S$ (percent): C, 58.82; H, 7.98; N, 11.43; S, 8.72. Found (percent): C, 58.86; H, 8.11; N, 11.51; S, 8.86.

EXAMPLE 2

Preparation of 1,3-di-n-propyl-5-(p-tolylsulfonyl)-tetrahydro-1,3,5-triazine-4-one

In a 500 ml. three-neck, round bottom flask equipped with a mechanical stirrer, a reflux condenser and a thermometer, there was placed 26.7 g. (0.126 mol.) of tri-N-propyl-trimethylene triamine and 300 ml. toluene. This

solution was stirred and 25 g. (0.126 mol.) p-toluene sulfonyl isocyanate was added slowly over a 30-minute period (reaction was slightly exothermic). The mixture was then heated to reflux (115° C.) for 2 hours. At the end of this time, the toluene was evaporated on the steam bath under a vacuum of 15–20 mm. The residue, a thick oil, was triturated until it crystallized. The crude product was recrystallized from isopropanol to give 1,3-di-n-propyl - 5 - (p - tolylsulfonyl)-tetrahydro-1,3,5-triazine-4-one having a M.P. of 102°–103° C. Yield: 25 g. (58% of theoretical).

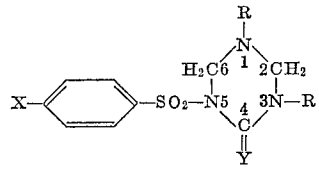
Analysis.—Calculated for $C_{16}H_{25}N_3O_3S$ (percent): C, 56.61; H, 7.42; N, 12.38; S, 9.45. Found (percent): C, 56.84; H, 7.56; N, 12.42; S, 9.44.

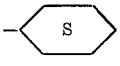
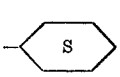
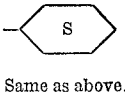
EXAMPLES 3 TO 14

Table I enumerates the variable substituents of Examples 3 to 14 along with their melting point (M.P.) and analysis. All of these examples were prepared by the general procedure hereinafter set forth.

A solution of 0.134 mol. of the substituted benzene sulfonyl isocyanate or isothiocyanate in 200 ml. of dry toluene was placed in a 500 ml. round bottom flask equipped with a mechanical stirrer, a thermometer, a reflux condenser, and a dropping funnel. A solution of 0.1 mol. of the azomethine trimer dissolved in 100 ml. of dry toluene was added, dropwise, to the solution in the flask by means of the dropping funnel. This addition was carried out slowly (over a 30–45 minute period) so that the exothermic reaction did not exceed 50° C. After the addition of this second solution was completed, the mixture was stirred for 2 hours at 50°–60° C. At the end of this time, the mixture was cooled and filtered through a layer of dry aluminum oxide (Al_2O_3) one to two inches thick. The filtrate was then evaporated to ½ volume and diluted with hexane where upon the product precipitated as a solid. The product was removed by filtration, dried and recrystallized from a suitable solvent.

TABLE I.—EXAMPLES 3-14



	X	Y	R	M.P., ° C.	Analysis [1] Percent C	Percent H	Percent N	Percent Cl	Percent S
Example No.:									
3	CH_3	O	$-C_4H_9$-iso	94.5–95.5	58.76 (58.82)	8.05 (7.95)	11.43 (11.43)	----------	8.34 (8.72)
4	Cl	O	$-C_3H_7$-n	72–73.5	50.04 (50.06)	6.28 (6.16)	11.70 (11.67)	9.81 (9.85)	8.88 (8.91)
5	Cl	O	$-C_4H_9$-iso	102.5–104	52.48) (52.63)	6.83 (6.75)	10.76 (10.83)	9.06 (9.13)	8.33 (8.26)
6	CH_3	O	$-C_2H_5$	112–113.5	53.89 (53.99)	6.71 (6.79)	13.47 (13.49)	----------	10.11 (10.23)
7	CH_3	O		163–165	63.21 (62.97)	7.95 (7.92)	9.93 (10.01)	----------	7.74 (7.64)
8	Cl	O	Same as above	165–167	57.35 (57.32)	6.95 (6.87)	9.57 (9.55)	8.60 (8.05)	7.56 (7.28)
9	CH_3	O	$-C_7H_{15}$-n	57–59	64.25 (6.384)	9.60 (9.15)	9.36 (9.30)	----------	6.92 (7.09)
10	CH_3O	O	$-C_4H_9$-n	83–85	56.43 (56.37)	7.69 (7.62)	10.86 (10.95)	----------	8.28 (8.36)
11	CH_3O	O		184–185.5	60.90 (60.66)	7.56 (7.63)	9.46 (9.64)	----------	7.17 (7.36)
12	NO_2	O	$-C_4H_9$-n	125–126.5	51.16 (51.24)	6.34 (6.52)	14.04 (14.06)	----------	7.98 (8.04)
13	CH_3CO			147–150	61.56 (61.71)	7.22 (7.43)	9.20 (9.38)	----------	7.24 (7.16)
14	CH_3	S	Same as above	140–142	61.51 (60.65)	7.93 (7.63)	9.73 (9.64)	----------	14.10 (14.71)

[1] The number parenthesized represents the theoretical value, as calculated, using the empirical formula of each compound.

EXAMPLES 15 TO 28

The following triazines are prepared in a manner similar to that described for Examples 3 to 14:

(15) 1,3-di-ethyl - 5 - (p-acetylphenylsulfonyl)tetrahydro-1,3,5-triazine-4-one.

(16) 1,3 - di-t-butyl - 5 - (p-acetylphenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(17) 1,3 - di - isopropyl - 5-(p-acetylphenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(18) 1,3 - di-n-pentyl - 5 - (p-acetylphenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(19) 1,3 - di-isopentyl - 5 - (p-acetylphenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(20) 1,3 - di-n-propyl - 5 - (p-chlorobenzenesulfonyl)-tetrahydro-1,3,5-triazine-4-thione.

(21) 1,3 - di-n-butyl - 5 - (p-chlorobenzenesulfonyl)-tetrahydro-1,3,5-triazine-4-thione.

(22) 1,3 - di-n-butyl - 5 - (p-tolysulfonyl)-tetrahydro-1,3,5-triazine-4-thione.

(23) 1,3 - di - ethyl - 5-(p-nitrophenylsulfonyl)tetrahydro-1,3,5-triazine-4-one.

(24) 1,3 - di-n-propyl - 5 - (p-nitrophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(25) 1,3 - di-isopropyl - 5 - (p-nitrophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(26) 1,3 - di - n-hexyl - 5 - (p-nitrophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

EXAMPLES 27 TO 30

Compounds of Examples 23, 24, 25 and 26 are reduced with platinum oxide in benzene at a pressure in the range of 30 to 40 p.s.i. In accordance therewith, the following triazines are thus obtained.

(27) 1,3 - di - ethyl - 5 - (p-aminophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(28) 1,3 - di-n-propyl - 5 - (p-aminophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(29) 1,3 - di-isopropyl - 5 - (p-aminophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

(30) 1,3 - di-n-hexyl - 5 - (p-aminophenylsulfonyl)-tetrahydro-1,3,5-triazine-4-one.

A relative determination of hypoglycemic activity of these novel triazines was obtained by the procedure hereinafter set forth.

Male Sprague-Dawley rats were fasted for 18 hours prior to extracting a control blood sample. Immediately after taking blood sample, the rats are administered intragastrically the compound under evaluation in a 0.25% suspension of methyl cellulose. After such administration, subsequent blood samples are obtained from the rat at 1, 2, 3 and 5 hours. Each of these blood samples along with the control sample is analyzed for its blood glucose content.

By utilizing the blood glucose values so obtained, the hypoglycemic score is determined as follows: The blood glucose value for an individual rat at each of the post dose sampling intervals, namely, 1, 2, 3 and 5 hours, is substracted from that rat's control blood glucose value. Thus, a decrease in blood glucose would be expressed as a positive number and an increase in blood glucose as a negative number. The sum of these differences for the individual rat is designated as that rat's hypoglycemic score.

The compounds of Examples 1 to 11 were evaluated by the above procedure at varying dose levels and the results thereof are given in Table II. Since for statistical purposes more than one rat is tested at each dose level, the hypoglycemic score is reported as the mean thereof.

TABLE II.—HYPOGLYCEMIC ACTIVITY OF TRIAZINE

	Dose, mg./kg. of body weight	Number of rats	Mean hypoglycemic score
Compound of Example No.:			
1	25	21	28
	100	21	106
	400	21	98
2	25	4	−19
	100	4	72
	400	4	102
3	25	4	9
	100	4	63
	400	4	125
4	25	8	1
	100	8	91
	400	8	144
5	25	4	18
	100	4	44
	400	4	136
6	25	3	−44
	50	4	16
	100	4	29
7	25	3	12
	50	4	95
	100	4	42
8	25	3	−33
	50	4	13
	100	4	−12
9	25	3	18
	50	3	−3
	100	4	−45
10	25	3	−13.4
	50	3	7.1
	100	3	65.4
11	25	3	−13.3
	50	3	−17.5
	100	3	9.3

In addition to the hypoglycemic properties demonstrated above, the novel triazines disclosed herein have also exhibited DBI (Phenformin) activity, that is, the ability to lower blood glucose levels where diabetes has been induced by alloxan. This characteristic DBI hypoglycemic activity is described by Ungar, Freedman and Shapiro in Proc. Soc. Exper. Biol. and Med., vol. 95, pages 190–192 (1957).

In several experiments using rats which are made diabetic by means of alloxan, an 11.7% decrease in blood glucose level was observed 5 hours after the oral administration of 1,3 - di - n - butyl - 5 - (p - tolylsulfonyl)-tetrahydro - 1,3,5 - triazine - 4 - one. By way of comparison, several commercially available sulfonylurea hypoglycemic agents which were similarly evaluated failed to exhibit any such activity.

The triazines are especially important and useful because of their minimal toxicity. For example, in a toxicity evaluation, both 1,3 - di - n - butyl - 5 - (p - tolylsulfonyl)-tetrahydro - 1,3,5 - triazine - 4 - one and 1,3 - di - n - propyl - 5 - (p - tolylsulfonyl) - tetrahydro - 1,3,5 - triazine - 4 - one exhibited and LD_{50} greater than 2000 mg./kg. By way of contrast, tolbutamide and chlorpropamide, both commercially available oral hypoglycemics, had an LD_{50} of 1600 mg./kg. and 1000 mg./kg. respectively. Furthermore, the triazines are not only substantially less toxic than other oral hypoglycemic agents, but lower effective dosages are necessitated to achieve a desired level of hypoglycemic activity. Consequently, the compounds of this invention prove to be a particularly valuable group of hypoglycemic agents.

While the triazines of this invention may be administered alone, they are generally and preferably taken in the form of pharmaceutical compositions, that is, the triazine is administered as a therapeutically effective active agent in combination with a pharmaceutically acceptable carrier. In such a composition, the triazine usually constitutes by weight about 0.5 to 99.5% of the total composition. In any particular composition, the amount of active ingredient therein will vary depending upon the therapeutic form selected, i.e., capsules, tablets, emulsions, etc., along with the dose level of each unit and the like.

Included in the recitation "pharmaceutically acceptable carriers" is any substance which is pharmaceutically compatible with the triazines of this invention. Typi-

cal carriers include the following: diluents, such as lactose, sucrose and starch; binders, such as starch paste, gelatin solution, methylcellulose and ethylcellulose; disintegrators, such as dried corn or potato starch; lubricants, such as calcium stearate, magnesium stearate, talc and cocoa butter; coating materials, such as acacia, kaolin, shellac, and calcium carbonate; vehicles, such as water, alcohol, glycerin and citric acid; thickening agents, such as tragacanth, carrageenin and pectin; wetting agents, such as sodium lauryl sulfate and benzalkonium chloride; and preservatives, such as benzoic and sorbic acid. Clearly, the above enumeration is merely exemplary and is not to be construed as a limitation thereof. It should also be noted that while the majority of pharmaceutical carriers are inert, it may be advantageous and/or necessary on occasion to formulate compositions wherein therapeutic agents other than the triazines are also incorporated therein.

Pharmaceutical compositions are usually and preferably in suitable therapeutic or dosage form, such as for example, capsules, tablets, solutions, emulsions and the like. Coated or uncoated tablets and capsules are the preferable unit dosage forms. Depending upon the therapeutic form under consideration, the concentration of active agent; namely, triazine, selected for any individual unit thereof will be contingent upon numerous variables. Typical tablet, capsule and powder formulations may contain from 50 to 2000 mg. and preferably 250 to 1000 mg. of triazine per unit.

Illustrative pharmaceutical composition formulations are set forth below. In each such formulation, the designated materials are given in proportions by weight.

TABLETS

Ingredients:	Parts by Weight
1,3-di-n-butyl - 5 - (p-tolylsulfonyl)-tetrahydro-1,3,5 - triazine - 4 - one	500
Corn starch	100
Ethylcellulose	20
Calcium stearate	30

After thoroughly blending the above ingredients, tablets are formed by standard means so as to contain 500 mg. of triazine per tablet.

CAPSULES

Ingredients:	Parts by Weight
1,3-di-n-butyl - 5 - (p-tolylsulfonyl)-tetrahydro-1,3,5 - triazine - 4 - one	500
Corn starch	50
Talc	50

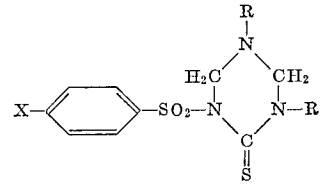
The above ingredients are agitated sufficiently to obtain a uniformily powdered product which is then utilized for the filling of gelatin capsules, both the hard-shelled and soft elastic types. Capsules should be chosen which are of such a size as to be capable of accommodating a sufficient quantity of material to provide 250 mg. of triazine per unit. Of course, larger or smaller capsules for different concentrations of active agent may be readily employed where desired or necessitated.

Lowering of blood sugar in animals is induced in accordance with this invention by orally administering to such animals at least one of the triazines described herein in an amount which is effective for such purpose. Where the animal is afflicted with hyperglycemia, the treatment thereof comprises the oral administration in a therapeutically effective amount of at least one triazine. The actual dosage to be administered at one time or over any extended period will, of course, vary with the particular animal being treated.

In the case of a human being, such factors as age, weight, extent of hyperglycemia, general health of the patient and the like must be considered in determining the dosage to be employed in any given situation. Generally speaking, a daily dose of 100 to 3000 mgs. of triazine will satisfactorily treat hyperglycemia in an adult human. Of course, this may be administered as a single daily dose, or more preferably, extended through multiple doses of 2 to 4 times daily. In most situations the triazine will be administered as the active agent in an orally ingestible pharmaceutical composition such as previously described.

We claim:

1. A compound of the formula



wherein X is methyl, chlorine, nitro, amino, methoxy or acetyl; and R is alkyl of 2 to 7 carbon atoms, provided that when X is chlorine or methoxy, R is alkyl of 3 to 6 carbon atoms.

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260—248; 424—229, 249