SYNTHESIS OF SOME SULPHONAMIDE DERIVATIVES OF THIADIAZINES AS POSSIBLE HYPOGLYCAEMIC AGENTS

R. N. GOYAL and SANDHYA BHARGAVA
Department of Chemistry, University of Roorkee, Roorkee 247 667, India.

ABSTRACT

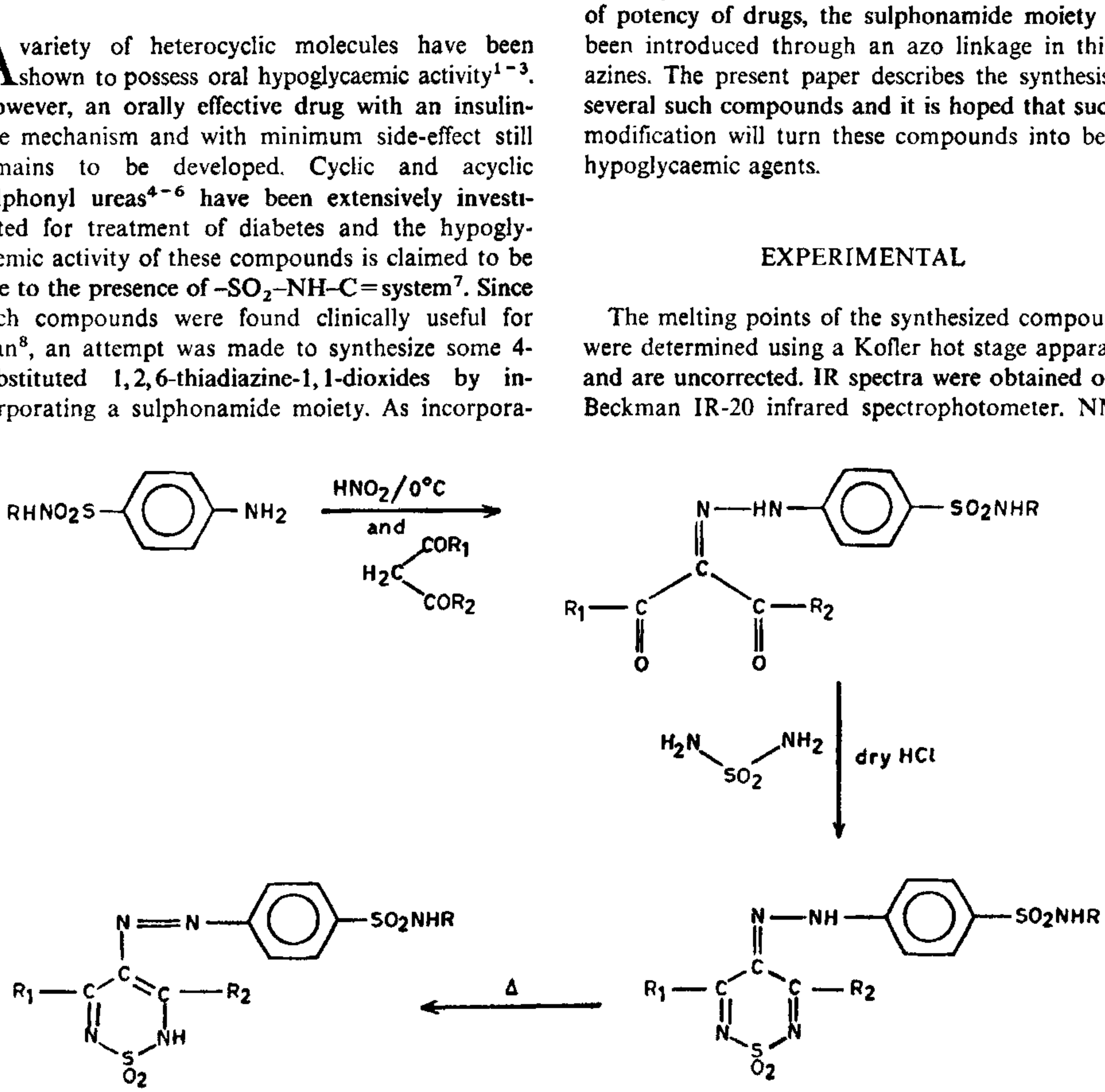
A wide range of thiadiazines 1, 1-dioxides properly substituted with sulphonamide moiety were prepared as possible hypoglycaemic agents. Their structures have been confirmed on the basis of elemental analysis, IR and NMR data.

INTRODUCTION

A variety of heterocyclic molecules have been shown to possess oral hypoglycaemic activity[1-3]. However, an orally effective drug with an insulin-like mechanism and with minimum side-effect still remains to be developed. Cyclic and acyclic sulphonyl ureas[4-6] have been extensively investigated for treatment of diabetes and the hypoglycaemic activity of these compounds is claimed to be due to the presence of $-SO_2-NH-C=$ system[7]. Since such compounds were found clinically useful for man[8], an attempt was made to synthesize some 4-substituted 1,2,6-thiadiazine-1,1-dioxides by incorporating a sulphonamide moiety. As incorporation of an arylazo moiety results in the enhancement[9] of potency of drugs, the sulphonamide moiety has been introduced through an azo linkage in thiadiazines. The present paper describes the synthesis of several such compounds and it is hoped that such a modification will turn these compounds into better hypoglycaemic agents.

EXPERIMENTAL

The melting points of the synthesized compounds were determined using a Kofler hot stage apparatus and are uncorrected. IR spectra were obtained on a Beckman IR-20 infrared spectrophotometer. NMR

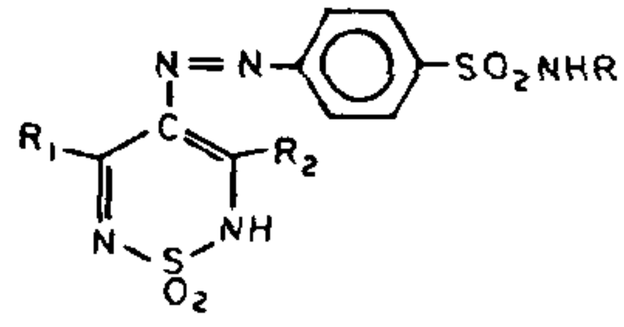


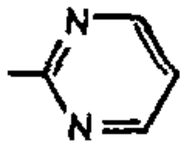
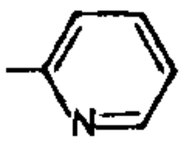
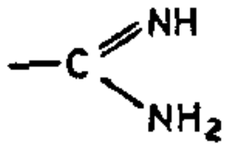
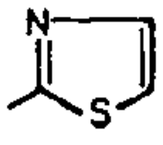
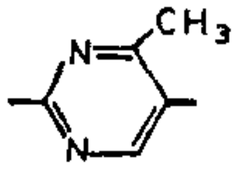
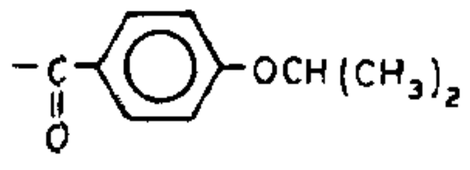
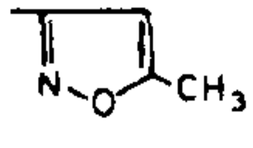
Scheme 1.

spectra were recorded on an IBM NR-80 spectrometer.

The sulpha drugs used in these studies were sulphanilamide, sulphacetamide, sulphadiazine, sulphapyridine, sulphaguanidine, sulphamerazine, sulphaproxyline and these were obtained from the Sigma Chemical Company, USA. Sulphamethazole was a gift from Roche Products Ltd., Bombay. The reactive methylene compounds pentane-2,4-dione, 1-phenyl-1,3-butanedione and 1,3-diphenylpropane-1,

Table 1 *Characteristics of 4-(p-sulphamoylphenylazo)-3, 5-disubstituted (2H)-1,2,6-thiadiazine-1,1-dioxides*



R	R_1	R_2	Mol. formula	Colour	Yield (%)	M P. (°C)
H	CH_3	CH_3	$C_{11}H_{13}O_4N_5S_2$	DY	58	210
	CH_3	C_6H_5	$C_{16}H_{15}O_4N_5S_2$	DY	55	228
	C_6H_5	C_6H_5	$C_{21}H_{17}O_4N_5S_2$	DB	55	218
$-CH_2-C(=O)-NH_2$	CH_3	CH_3	$C_{13}H_{16}O_5N_6S_2$	Y	60	216
	CH_3	C_6H_5	$C_{18}H_{18}O_5N_6S_2$	Y	60	235
	C_6H_5	C_6H_5	$C_{23}H_{20}O_5N_6S_2$	DY	65	165
	CH_3	CH_3	$C_{15}H_{15}O_4N_7S_2$	Y	62	203
	CH_3	C_6H_5	$C_{20}H_{17}O_4N_7S_2$	O	60	186
	C_6H_5	C_6H_5	$C_{25}H_{19}O_4N_7S_2$	B	60	215
	CH_3	CH_3	$C_{16}H_{16}O_4N_6S_2$	Y	65	215
	CH_3	C_6H_5	$C_{21}H_{18}O_4N_6S_2$	O	63	268
	CH_3	C_6H_5	$C_{17}H_{17}O_4N_7S_2$	Y	65	187
	C_6H_5	C_6H_5	$C_{22}H_{19}O_4N_7S_2$	Y	60	202
	CH_3	CH_3	$C_{14}H_{14}O_4N_6S_3$	DY	66	236
	CH_3	C_6H_5	$C_{19}H_{16}O_4N_6S_3$	DY	65	210
	C_6H_5	C_6H_5	$C_{24}H_{18}O_4N_6S_3$	DB	60	120
	CH_3	CH_3	$C_{16}H_{17}O_4N_7S_2$	O	68	146
	CH_3	C_6H_5	$C_{21}H_{19}O_4N_7S_2$	RB	65	130
	C_6H_5	C_6H_5	$C_{26}H_{21}O_4N_7S_2$	O	65	172
	CH_3	CH_3	$C_{21}H_{23}O_6N_5S_2$	LY	66	180
	CH_3	CH_3	$C_{15}H_{16}O_5N_6S_2$	Y	50	218
	CH_3	C_6H_5	$C_{20}H_{18}O_5N_6S_2$	DY	55	240
	C_6H_5	C_6H_5	$C_{25}H_{20}O_5N_6S_2$	B	50	237

Colour: DY, Dark yellow; DB, Dark brown; B, Brown, Y, Yellow, O, Orange, RB, Red brown.

3-dione were BDH products and sulphamide was from E. Merck.

The diazotization of the appropriate sulphonamide and their coupling with reactive methylene compounds were carried out by the usual method[10] and gave different hydrazones. The hydrazones on treatment with sulphamide and subsequent cyclization gave 4-(*p*-sulphamoylphenylazo)-3, 5-disubstituted (2H)-1, 2, 6-thiadiazine-1, 1-dioxides as shown in scheme 1.

Synthesis of 3-(p-sulphamoylphenylhydrazone)-2, 4-pentanedione

Sulphanilamide (0.02 mol) was dissolved in a mixture of 6N HCl (12.5 ml) and water (12.5 ml) and was diazotized with a solution of $NaNO_2$ (0.02 mol) in H_2O (20 ml) at 0°C. It was then filtered into the ice-cold mixture of pentane-2, 4-dione (0.02 mol) containing sodium acetate (5.0 g) in ethanol (50 ml). A yellow-coloured precipitate began to separate almost immediately. This was allowed to stand overnight at room temperature, filtered, dried and recrystallized from ethanol. m.p. 224°C [Found C = 46.28% H = 4.60%, N = 14.71%, calculated for $C_{11}H_{13}O_4N_3S$, C = 46.64%, H = 4.59%, N = 14.84%].

During the preparation of 3-(*p*-sulphamoylphenylhydrazono)-2, 4-pentanedione the sulpha drugs used showed considerable variation in their behaviour. Sulphanilamide was diazotized easily and the coupling required less time as compared to sulphacetamide and sulphapyridine which required much longer time.

4-(p-sulphamoylphenylazo)-3, 5-dimethyl-(2H)-1, 2, 6-thiadiazine-1, 1-dioxide

A mixture of sulphamide (0.005 mol) and 3-(*p*-sulphamoylphenylhydrazono)-2, 4-pentanedione (0.005 mol) in 15 ml of ethanol (99%) was treated with HCl gas for 10–15 min. The mixture was refluxed for 7 h at 80°C, and evaporated to dryness in vacuum. The residue was triturated several times with ether and filtered after each treatment. The ether insoluble residue was then washed with water and on recrystallization with ethanol, mustard coloured shining crystals were obtained (m.p. 210 C).

Following the same procedure other thiadiazine-1, 1-dioxide were prepared by using different sulpha drugs and reactive methylene compounds and the characteristics of thiadiazines prepared are summarized in table 1.

CHARACTERIZATION

The synthesized compounds were characterized on the basis of their elemental analysis for C, H and N. Their melting points were determined and found to be sharp. The presence of characteristic absorption bands at 3130–3141 (N–H), 2970–2994 (C–H), 1599–1621 (N=N), 1615–1639 (=N), 1320–1333 (SO_2) cm^{-1} supported the proposed structure[11]. The NMR spectra of some selected compounds, for example compound 1 [table 1] exhibited δ value: 1.56 (6H, $2CH_3$), 2.52 (2H, NH_2), 2.63 (1H, NH) and 7.26 (4H, ArH). It is expected that all these compounds would exhibit considerable blood sugar lowering effect after oral administration than observed for 4-phenylazo-3, 5-dimethyl-1, 2, 6-thiadiazine-1, 1-dioxide by Wright and coworkers[12] because of the presence of sulphonamide moiety. Some selected samples have also been sent for evaluation of their hypoglycaemic activity and the results will be reported later.

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NEWS

'SIGNALS' FOR POLLUTION CHECKS

Industries have been classified into 'red', 'orange' and 'green' categories for inspection and enforcement of pollution control laws.

In all, 71 industries have been placed in the red category and 51 each in the orange and green categories under the new guidelines issued by the Ministry of Environment and Forests.

The guidelines have been issued following representation by small scale units to the Government that the number of inspections under various pollution control statutes should be reduced to ensure the least disturbance to the industry's working.

The guidelines pertain to reduction in the frequency of visits by Government officials keeping in view the requirement of pollution control on the one hand and least disturbance to the working of industries on the other by keeping inspections to the minimum.

Depending upon the category under which an industry is classified, the frequency of visits by the Pollution Control Board officials and other inspectorate staff concerned with pollution control and environmental safeguards should be determined. It may range between once in a month to once in two years.

Among the industries classified as 'red' are ceramics, rubber, large flour mills, oil extraction, steam generating plants, machine tools, industrial gases, petroleum, drugs, refrigeration units, photographic products, metal extraction, cement plants, synthetic fibres, sugar mills, caustic soda and explosives.

The 'orange' category consists of industries like electroplating, galvanizing, cotton spinning and weaving, automobile servicing, restaurants, steel furniture, light engineering, dyes, plastics, readymade garments and fish processing.

The list of industries under the 'green' category includes atta chakkies, rice millers, leather footwear, musical instruments manufacture, bamboo and cane products, assembly of domestic appliances, and electronic, medical and surgical equipment.

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