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Studies in Possible Oral Hypoglycaemic Agents: Part VI—Synthesis of Some 2- & 4-Pyridylethyl Ureas & Thioureas & Some Barbiturates & Their Biological Activity

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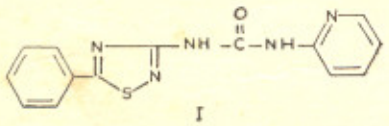
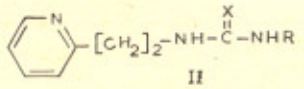
The synthesis of some 2- and 4-pyridylethyl ureas and thioureas described involves pyridylethylation of ammonia and the condensation of the resulting pyridylethyl amine with isocyanate or isothiocyanate respectively. In experimental animals none of the pyridylethyl ureas exhibit any blood-sugar lowering activity; N-phenyl-2-pyridylethyl thiourea causes moderate hyperglycaemia. Amongst the barbiturates prepared, 1-phenyl- and 1-*o*-methoxyphenylbarbituric acids show moderate blood-sugar lowering activity.

IN view of the encouraging results obtained during animal experiments on the hypoglycaemic activity of N-(2-pyridyl)-N'-[3-(5-phenyl-1,2,4-thiadiazolyl)] urea (I). (Mukerjee, S. K., unpublished data), it was considered desirable to assess the pharmacodynamic potentiality, if any, of the pyridine moiety in terms of hypoglycaemic action. Accordingly, the following types of simple urea and thiourea derivatives (II and III; X=O or S) were synthesized.



I



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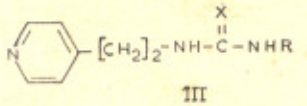

III

Two methods were tried for this purpose. The first method involves pyridylethylation of suitably substituted ureas with 2- or 4-vinylpyridine on the analogy of the reaction of the latter with acetamide or propionamide[1] or with succinimide[2]. This was, however, unsuccessful. The only products isolated were gums or unchanged ureas. The second procedure involved the pyridylethylation of ammonia[1] to yield pyridylethylamine which was then condensed with the appropriate isocyanate or isothiocyanate to give compound (II) or (III) respectively. This route was successful and the pyridylethyl ureas or thioureas reported in Table 1 were prepared by this method.

The study of some of the barbiturates was undertaken in view of the activity exhibited by the hydantoins previously[3]. The barbiturates may be regarded as homohydantoins and although the data in this field is of a conflicting nature[4-6], some of these do seem to possess hypoglycaemic activity[7,8]. The 1-substituted barbiturates were prepared by standard methods. Their analytical data and biological activity are reported in Table 2.

TABLE 1 — PYRIDYLETHYL UREAS AND THIOUREAS (II AND III) AND BIOLOGICAL DATA

Sl No.	R	X	m.p. °C.	Formula	N (%) Found	N (%) Reqd	Av. rise or fall in blood sugar in three animals
				4-ISOMER			
1	C_6H_5	O	156	$C_{14}H_{15}N_3O$	17·02	17·42	+ ↓
2	*p*-$CH_3OC_6H_4$	O	153	$C_{15}H_{17}N_3O_2$	15·68	15·50	Not tested
3	*n*-C_3H_7	O	54-57	$C_{11}H_{17}N_3O$	20·49	20·29	+ ↓
4	*n*-C_4H_9	S	66	$C_{12}H_{19}N_3S$	17·58	17·72	Not tested
				2-ISOMER			
5	C_6H_5	O	123-4	$C_{14}H_{15}N_3O$	17·60	17·42	do
6	*p*-$CH_3OC_6H_4$	O	128	$C_{15}H_{17}N_3O_2$	15·67	15·50	do
7	*n*-C_3H_7	O	Liquid at room temp.	$C_{11}H_{17}N_3O$	20·09	20·29	+ ↓
8	C_6H_5	S	110-11	$C_{14}H_{15}N_3S$	16·29	16·34	+ + ↑

(↑) rise; (↓) fall in blood sugar; (+) up to 15 per cent; (++) 16-30 per cent; and (+++) above 30 per cent. Carbutamide = +++.

TABLE 2 — 1-SUBSTITUTED BARBITURIC ACIDS AND BIOLOGICAL DATA

Sl No.	R	m.p. °C.	Formula	N (%)		Av. fall in blood sugar in three animals
				Found	Reqd	
9	C_6H_5	262	—	—	—	++
10	p-$CH_3C_6H_4$	243-4	—	—	—	+
11	Cyclo-C_6H_{11}	181	$C_{10}H_{14}N_2O_3$	13·68	13·34	Not tested
12	o-ClC_6H_4	232-3	$C_{10}H_7ClN_2O_3$	11·63	11·74	+
13	o-$CH_3OC_6H_4$	253	$C_{11}H_{10}N_2O_4$	11·70	11·96	++

Experimental Procedure

2- & 4-(2-Aminoethyl)pyridines were prepared according to the procedure of Magnus and Levine[1]. 2-(2-Aminoethyl)pyridine, b.p. 90-93°/9 mm. and 4-(2-aminoethyl)pyridine, b.p. 117-20°/15 mm. were obtained in 84 and 65 per cent yields respectively.

N-Alkyl (or aryl), N'-β-(2- or 4-pyridyl)ethyl ureas or thioureas — As a general preparatory procedure, the appropriate isocyanate or isothiocyanate in petroleum ether solution was added gradually to a stirred suspension of 2-, or 4-(2-aminoethyl)pyridine in petroleum ether. After stirring for 30 min. at room temperature, the product was filtered, washed with boiling petroleum ether and crystallized from aq. ethanol or ether-petroleum ether mixture.

These compounds are reported in Table 1.

1-Substituted barbituric acids — These were prepared according to the method described by Stein *et al.*[9] which involved the reaction of 1-substituted ureas with ethyl malonate in the presence of sodium ethoxide in absolute ethanol. The products were crystallized from aq. ethanol or water.

These have been described in Table 2.

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