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Studies in Possible Oral Hypoglycaemic Agents: Part V—Synthesis of Carbamoylindoles, Carbamoylisoindolines, 3-Indolylethyl Urea (or Thiourea) & 2-Isoindolinylpropyl Urea (or Thiourea) Derivatives & Their Biological Activity

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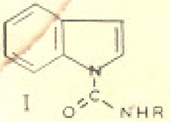
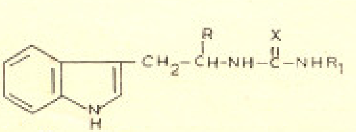
The synthesis of a number of carbamoylindoles and carbamoylisoindolines as well as 3-indolylethylurea or thiourea derivatives and 2-isoindolinylpropyl ureas and thioureas is described. Some of the indole derivatives synthesized exhibit moderate hypoglycaemic activity; the isoindolines prepared are mostly inactive.

MIRSKY'S observation that liver tissues contained a factor capable of inhibiting insulinase[1] led to a search for compounds with similar properties. A systematic examination of a wide variety of compounds has revealed that auxin and auxin-like substances such as indole-3-acetic, propionic and butyric acids[2-7], nicotinic and anthranilic acids[8,9] and tryptophane and its metabolites[3,10-12] are insulinase inhibitors *in vitro* and hypoglycaemic *in vivo*. Further, hypoglycaemic and auxin-like activities appear to have somewhat common structural requirements: most hypoglycaemic compounds possess a urea, thiourea or guanidino moiety, while some ureas as well as amides have also been noted as potent plant-growth regulators[10-14]. It, therefore, appeared interesting to synthesize some indole derivatives containing a urea moiety as possible antidiabetic compounds.

Structural resemblance with indole and its proven pharmacodynamic potentialities in other fields[15,16] prompted us to include the compounds with isoindoline nucleus also in the present study. Compounds of the series illustrated by formulae I to IV (X=O or S; R and R_1 as given in Tables 1-4) were thus synthesized.


I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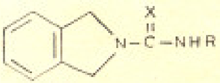
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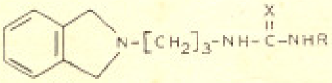
IV

Indole, prepared according to the method of Tyson[17], was condensed with appropriate isocyanates in the presence of a few drops of pyridine to give the desired alkyl- or aryl-substituted ureas.

Similarly, compounds of the type (II) were prepared by condensing tryptamine in petroleum ether with appropriate isocyanates or isothiocyanates to yield the corresponding urea or thiourea derivatives. The corresponding sulphonylurea derivative was obtained either by pyrolysing the salt of ethyl N-(*p*-toluenesulphonyl)carbamate with tryptamine or by refluxing the mixture of both in toluene solution[18].

Similarly, compound (Sl No. 8, Table 2) was prepared by converting tryptophane to its methyl ester and reacting the free base with ethyl N-(*p*-toluenesulphonyl)carbamate as described for tryptamine.

Of the several methods available for the preparation of isoindoline[19-24], Neumeyer's procedure[24], involving the synthesis of N-benzylisoindoline and its subsequent hydrogenolysis, was found to be the method of choice.

Isoindoline in petroleum ether solution reacted readily with isocyanates and isothiocyanates to give substituted ureas and thioureas. The corresponding urea or thiourea derivatives of 2-(3-aminopropyl)isoindoline[25] were easily obtained either by reacting it with an appropriate isocyanate or isothiocyanate in petroleum ether solution or by the action of appropriate amines on ethyl N-(γ-isoindolinyl propyl)carbamate. The latter was obtained according to the procedure of Marshall and Sigal[26] by refluxing the 2-(3-aminopropyl)isoindoline and ethyl chloroformate in acetone solution in presence of potassium carbonate.

Biological Activity

Selected compounds of each series were screened for their effect on blood sugar at a dose level of 250 mg./kg. body weight by administering orally to male albino rats. Prior to testing, the rats weighing 100-125 g., were starved for 18-24 hr. Blood was drawn from the tail at 2 and 4 hr intervals and sugar estimated using Nelson-Somogyi method. Carbutamide was chosen as a reference standard for direct comparison.

Isoindoline derivatives — The isoindoline derivatives except for compounds (Sl. Nos. 10, 18 and 20) were found to be devoid of any hypoglycaemic activity.

Indole derivatives — All the compounds of this series exhibited some hypoglycaemic activity and maximum activity in this class of compounds was observed in tryptophane and tryptamine derivatives.

TABLE 1 — 1-(ALKYL- OR ARYLCARBAMOYL) INDOLES (I) AND BIOLOGICAL DATA

Sl No.	R	m.p. °C.	Formula	N (%)		Av. fall in blood sugar in three animals
				Found	Reqd	
1	C_6H_5	135-6	—	—	—	++
2	p-$CH_3OC_6H_4$	221	$C_{16}H_{14}N_2O_2$	10·61	10·53	++
3	n-C_3H_7	199	$C_{12}H_{14}N_2O$	13·71	13·86	nil

(+) = up to 10 per cent; (++) = 11-30 per cent; carbutamide = +++ (above 30 per cent)

TABLE 2 — N-β-(3-INDOLYL)ETHYL, N′-ALKYL-, ARYL- OR ARYLSULPHONYL UREAS OR THIOUREAS (II) AND BIOLOGICAL DATA

Sl No.	R	R_1	X	m.p. °C.	Formula	N (%)		Av. fall in blood sugar in three animals
						Found	Reqd	
4	H	p-$CH_3OC_6H_4$	O	88-89	$C_{18}H_{19}N_3O_2$	13·67	13·59	Not tested
5	H	n-C_3H_7	O	106	$C_{14}H_{19}N_3O$	17·06	17·14	++
6	H	n-C_4H_9	S	96	$C_{15}H_{21}N_3S$	15·40	15·27	Not tested
7	H	p-$CH_3C_6H_4SO_2$	O	140	$C_{18}H_{19}N_3O_3S$	11·84	11·76	+
8	$COOCH_3$	p-$CH_3C_6H_4SO_2$	O	191	$C_{20}H_{21}N_3O_5S$	9·69	10·01	++

TABLE 3 — CARBAMOYL- AND THIOCARBAMOYLISOINDOLINES (III) AND BIOLOGICAL DATA

Sl No.	R	X	m.p. °C.	Formula	Nitrogen %		Av. fall in blood sugar in three animals
					Found	Reqd	
9	C_6H_5	O	231	$C_{15}H_{14}N_2O$	12·09	11·76	Not tested
10	p-$CH_3OC_6H_4$	O	178	$C_{16}H_{16}N_2O_2$	10·53	10·44	++
11	p-$NO_2C_6H_4$	O	241	$C_{15}H_{13}N_3O_3$	15·11	14·84	Not tested
12	n-C_3H_7	O	161	$C_{12}H_{16}N_2O$	13·59	13·72	do
13	n-C_4H_9	S	148	$C_{13}H_{18}N_2S$	12·01	11·96	+

TABLE 4 — ISOINDOLINYLPROPYL UREAS OR THIOUREAS (IV) AND BIOLOGICAL DATA

Sl No.	R	X	m.p. °C.	Formula	N (%)		Av. fall in blood sugar in three animals
					Found	Reqd	
14	C_6H_5	O	105-6	$C_{18}H_{21}N_3O$	14·13	14·23	+
15	C_6H_5	S	169	$C_{18}H_{21}N_3S$	13·22	13·50	+
16	n-C_4H_9	S	91	$C_{16}H_{25}N_3S$	14·72	14·43	+
17	Allyl	S	97	$C_{15}H_{21}N_3S$	15·50	15·28	0
18	p-$NO_2C_6H_4$	O	136-7	$C_{18}H_{20}N_4O_3$	16·54	16·47	++
19	p-$NH_2C_6H_4$	O	126-8	$C_{18}H_{22}N_4O$	17·92	18·06	Not tested
20	p-$CH_3OC_6H_4$	O	133-4	$C_{19}H_{23}N_3O_2$	13·00	12·92	++

The results are summarized in Tables 1-4.

Experimental Procedure

Indole was prepared according to the method used by Tyson; b.p. 121°/5 mm.; m.p. 52-53°.

1-(Phenylcarbamoyl)indole was prepared according to Henry's procedure[27]; m.p. 135-6°C.

1-(p-Methoxyphenylcarbamoyl)indole — This was prepared by slight modification of the above procedure by reacting indole (1·17 g., 0·01 mole) and *p*-methoxyphenyl isocyanate (1·5 g., 0·01 mole), in petroleum ether solution in the presence of a few drops of pyridine. The product crystallized from aq. ethanol; yield 85 per cent.

1-(n-Propylcarbamoyl)indole was prepared similarly by the action of *n*-propylisocyanate on indole, crystallizing the product from aq. ethanol; yield 70 per cent.

The physical constants of these compounds are given in Table 1.

N-β-(3-Indolyl)ethyl-N′-(p-methoxyphenyl) urea — The following procedure illustrates in general the preparation of all the urea derivatives of tryptamine now prepared. These were crystallized from aq. ethanol; yield 70-80 per cent.

p-Methoxyphenylisocyanate (1·5 g., 0·01 mole) was added, with stirring, to a suspension of tryptamine (1·6 g., 0·01 mole) in ligroin and the mixture heated for 30 min. at 100°C. After cooling, the product was filtered and washed several times with boiling ligroin. It was finally crystallized from aq. ethanol.

N-β-(3-Indolyl)ethyl-N′-p-toluenesulphonyl urea — A mixture of tryptamine (1·6 g., 0·01 mole) and ethyl N-(*p*-toluenesulphonyl) carbamate (3·16 g., 0·012 mole) in dry benzene was refluxed till a homogeneous suspension was obtained. The solvent was removed, the residue heated at 120°/8 mm. for 8 hr and crystallized from aq. ethanol.

N-(γ-Carbomethoxy-β-3-indolyl)ethyl-N′-p-toluenesulphonyl urea was prepared similarly.

All these derivatives based on tryptamine are listed in Table 2.

Isoindoline was prepared according to the method of Neumeyer by hydrogenolysis of N-benzylisoindoline over Pd/C (5 per cent) at 50° under a pressure of 50 p.s.i. of hydrogen; b.p. 105°/20 mm.

Carbamoyl- or thiocarbamoylisoindolines, isoindolinylpropyl urea or isoindolinylpropyl thiourea — As a general preparatory procedure, a solution of isoindoline or 2-(3-aminopropyl)isoindoline (0·01 mole) in petroleum ether was treated gradually, with stirring, with the corresponding isocyanate or isothiocyanate (0·012 mole) in petroleum ether in cold. After standing for 2 hr at room temperature, the product was filtered, washed with petroleum ether and crystallized from aqueous ethanol.

The compounds prepared in both the series are listed in Tables 3 and 4 respectively.

N-p-Aminophenyl-N′-γ-(2-isoindolinyl)propyl urea — N-*p*-Nitrophenyl-N′-γ-(2-isoindolinyl)propyl urea (5·0 g.) prepared above was reduced over Raney nickel in tetrahydrofuran solution under an initial pressure of 30 p.s.i. of hydrogen. After the absorption of the theoretical quantity of hydrogen, the catalyst was filtered off and the solvent removed from the filtrate. The residue was dissolved in aq. ethanol and left overnight in cold. The resulting precipitate was crystallized from acetone-petrol mixture (charcoal).

Ethyl N-γ-(2-isoindolinyl)propyl carbamate hydrochloride — This was prepared according to the procedure of Marshall and Sigal[26] by refluxing 2-(3-aminopropyl)isoindoline and ethyl chloroformate in acetone solution for 12 hr in the presence of potassium carbonate. The product was isolated as the hydrochloride, m.p. 122-3° (Found: N, 9·57. $C_{14}H_{21}ClN_2O_2$ requires N, 9·84%).

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