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BENZOTHIAZOLYL GUANIDINES AS ANTIBACTERIALS

IN view of the significant biological activities associated with the diguanides and guanidines as antitubercular[1,2], antibacterial[1,3], algaecidal[4], etc, it was thought worthwhile to extend the research in this line. In the present communication several N-ethyl-N'-(substituted)-benzothiazolyl-N"-alkyl guanidines have been synthesised by desulphurisation of corresponding thiocarbamides with yellow lead oxide in presence of alkyl amines.

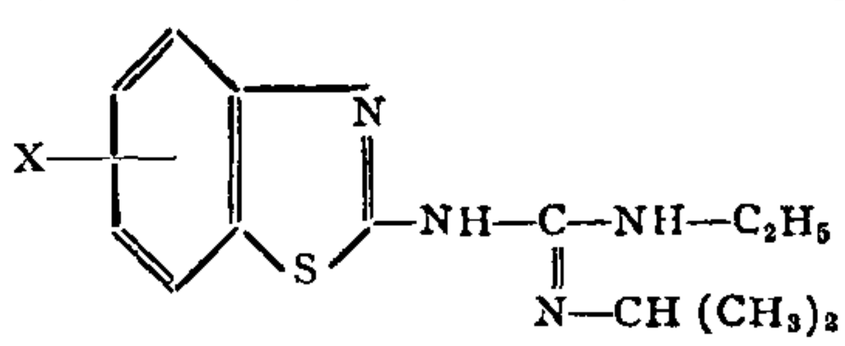
N-Ethyl-N'-2-(substituted)-benzothiazolyl thiocarbamides.—These were prepared by condensation of 2-amino-(substituted) benzothiazoles and ethyl isothiocyanate in the presence of dry benzene. The resulting product was washed with ether and dilute hydrochloric acid to remove unchanged reactants.

N-Ethyl-N'-2-(4-chloro)-benzothiazolyl-N"-isopropyl guanidines.—A mixture of N-ethyl-N'-2-(4-chloro)-benzothiazolyl thiocarbamide (2·7 g), yellow lead oxide (4·5 g), isopropyl amine (0·6 ml) in ethanol (20 ml) was heated in a sealed glass tube on a water-bath for 4 hours. After completion of the reaction the glass tube was opened carefully and the crude product filtered hot. The filtrate on cooling gave beautiful crystals. It was recrystallised from ethanol. Yield 60%, m.p. 202° C. Found: N, 18·62; S, 10·56 $C_{13}H_{17}ClN_4S$ requires N, 18·89; S, 10·79%).

Similarly, other N-ethyl-N'-2-(substituted)-benzothiazolyl-N"-isopropyl guanidines have

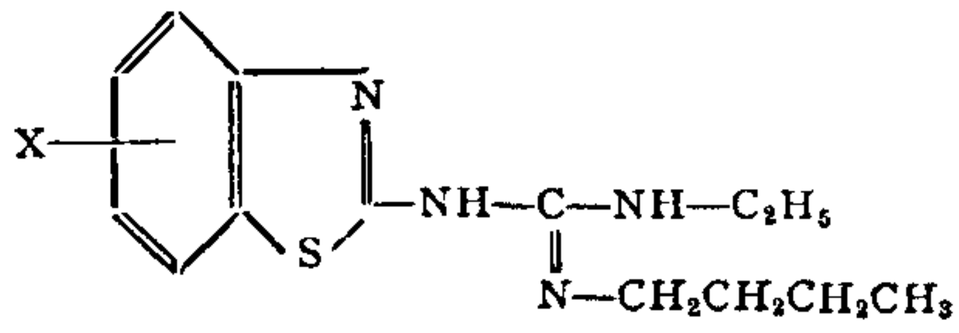
TABLE I

N-ethyl-N'-2-(substituted)-benzothiazolyl-N"-isopropyl guanidines



S. No.	Substituent	Yield %	M.P. °C.	Molecular formula	Nitrogen, %		Sulphur, %	
					Found	Calcd.	Found	Calcd.
1	4-Chloro ..	60	202	$C_{13}H_{17}SN_4Cl$	18·62	18·89	10·56	10·79
2	5-Chloro ..	65	186	$C_{13}H_{17}SN_4Cl$	19·19	18·89	10·42	10·79
3	4-Methyl ..	75	120	$C_{14}H_{20}N_4S$	20·00	20·29	11·32	11·60
4	5-Methyl ..	80	160	$C_{14}H_{20}N_4S$	20·52	20·29	11·38	11·60
5	6-Methyl ..	72	138	$C_{14}H_{20}N_4S$	20·49	20·29	11·41	11·60
6	4-Ethoxy ..	69	158	$C_{15}H_{22}N_4OS$	18·03	18·30	10·10	10·46

N-ethyl-N'-2-(substituted)-benzothiazolyl-N"-butyl guanidines



7	4-Chloro ..	77	194	$C_{14}H_{19}SN_4Cl$	17·72	18·03	9·99	10·30
8	5-Chloro ..	64	182	$C_{14}H_{19}SN_4Cl$	18·30	18·03	10·59	10·30
9	4-Methyl ..	72	134	$C_{15}H_{22}N_4S$	19·20	19·52	11·30	11·04
10	5-Methyl ..	80	168	$C_{15}H_{22}N_4S$	19·80	19·52	11·79	11·04
11	6-Methyl ..	89	142	$C_{15}H_{22}N_4S$	19·28	19·52	11·58	11·04
12	4-Ethoxy ..	85	152	$C_{16}H_{24}N_4SO$	17·19	17·60	9·78	10·00

been synthesised by the reaction of N-ethyl-N'-2-(substituted)-benzothiazolyl-thiocarbamide and isopropyl amine (Table I).

N-ethyl-N'-2-(substituted)-benzothiazolyl-N"-alkyl guanidines.—These guanidines have been synthesised by treatment of the corresponding thiocarbamides with different alkyl amines, instead of isopropyl amine, as usual (Table I).

Hydrochloride of N-ethyl-N'-2-(5-chloro)-benzothiazolyl-N"-butyl guanidine.—To the solution of N-ethyl-N'-2-(5-chloro)-benzothiazolyl-N"-butyl guanidine prepared in dry benzene, dry HCl gas was passed. The product was filtered and washed with dry ether thrice. It was crystallized from absolute ethanol. Yield 60%, m.p. 254° C.

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EFFECT OF ESTROGEN ON TUBAL TRANSPORT OF OVA IN RATS FITTED WITH INTRAUTERINE CONTRACEPTIVE SUTURE

TRANSPORT of ova through the Fallopian tube of rats takes 4 days before they enter the uterus. Estrogens are known to interrupt pregnancy in this species when administered on day 1, 2 or 3 *post-coitum*[1-3]. Presence of a suture (IUCD) in the rat uterus has been reported to mimic or synergize some of the effects of estrogen[4-7]. Although it is now satisfactorily established that an IUCD does not normally influence the tubal transport of ova in rats[8], it has been considered worthwhile to explore if a sub-optimal dose of estrogen could synergize the effect of the device and accelerate ova passage in rats.

Colony-bred young adult rats (130–150 gm) of the Institute were fitted with a nylon suture in one uterine horn as described previously[4]; the contralateral horn served as the sham-operated control. The animals received post-operative antibiotic therapy for 3 days. Forty-five days after insertion of the suture the rats were mated to coeval males of proven fertility. The day on which the vaginal smears showed the presence of spermatozoa was considered day 1 of pregnancy.

In pilot tests with normal pregnant rats it was found that a single intramuscular injection of estrone (20 μg/rat) on day 1 of pregnancy caused cent per cent expulsion of ova from the tubes; 10 μg estrone was found to be ineffective. On this basis, groups of rats fitted with IUCD received either 10 or 20 μg estrone on day 1 of pregnancy and sacrificed 24 or 48 hr later; the ova collected from the Fallopian tube were examined under a phase contrast microscope.

It will be seen from the results presented in Table I that the presence of an IUCD had no effect on the tubal transport of ova. A single injection of estrone (10 μg/rat) on day 1 pregnancy also gave similar results. However, there was an acceleration of ova transport when the dose of estrogen was raised to 20 μg. This was evident only on day 3 of pregnancy, which was in contrast to the report of Banik and Pincus[1] who observed that this dose given on day 1 completely eliminated tubal ova within 24 hr. A strain difference in rats in response to estrogen was probably indicated. Microscopic examination of ova did not show any interference with fertilization or their development.

TABLE I

Effect of IUCD and estrogen on tubal transport of ova in rats

Treatment	Day of ova collection	
	Day 2	Day 3
No estrogen		
Control side ..	10 (3-4) *3*	11 (2-5) *4*
IUCD side ..	11 (2-5) *3*	10 (1-4) *4*
10 μg estrone		
Control side ..	11 (1-5) *4*	13 (1-4) *5*
IUCD side ..	12 (1-4) *4*	17 (2-4) *5*
20 μg estrone		
Control side ..	12 (1-4) *4*	0 (0-0) *6*
IUCD side ..	14 (1-5) *4*	0 (0-0) *6*

* Total No. of ova collected with range in parenthesis; Number of animals in italics.

It thus appears that IUCD has no effect on tubal transport, fertilization and development of ova in rats. Similarly, a sub-optimal or optimal dose of estrogen does not hasten the tubal passage of ova. Apparently, in this species an IUCD mimics only the uterine effects of estrogen and not those on the Follopian tube.

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