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SOME N-(D-6-METHYL-8-ISOERGOLIN-I-YL)- AND N-(D-6-METHYL-8-ISOERGOLIN-II-YL)-N'-SUBSTITUTED UREAS

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N-(D-6-Methyl-8-isoergolin-I-yl) and N-(D-6-Methyl-8-isoergolin-II-yl) ureas (*I*, *Ia*) and analogous N'-substituted ureas (*II*—*VII* and *IIa*—*VIIa*) were prepared by stereospecific synthesis *via* the corresponding isocyanates. Ureas *III*, *IIIa*, *IV* and *IVa* were also prepared by a catalytic hydrogenation of the corresponding N-(D-6-methyl-8-isoergolenyl)-N'-substituted ureas. Of the compounds prepared, the most powerful antiferility and antilactation effect in experimental animals was displayed by urea *III*.

The present work proceeds from previous studies in the series of optically active N-(6-methyl-8-ergolenyl) and N-(6-methyl-8-isoergolenyl)-N'-substituted ureas[1] and analogous 8-ergolinylureas[1,2]. The pronounced dependence of the biological effects of the compounds on the steric condition of the molecule was demonstrated in the group of optically active N-(6-methyl-8-ergolenyl)- and N-(6-methyl-8-isoergolenyl)-N',N'-diethylureas and similarly, in the group of their $N_{(1)}$-methyl derivatives[1,3]. Of these compounds, pronounced antiserotonine activity was displayed by both isoergolenyl compounds belonging to the series of D-isolysergic acid.** In the present work we were interested in the effect of saturation of the double bond in position 9,10 of the N-(D-6-methyl-8-isoergolenyl)-N'-substituted ureas on their antiserotonine effect and in testing the dihydro compounds as to their antifertility and antilactation effects.

The two last-named effects were displayed in rats by amides of D-6-methyl-8-ergolin-I-ylacetic acid, particularly the unsubstituted amide, diethyl and cyclopentyl amides[4]. The N-(D-6-methyl-8-isoergolin-I-yl) ureas studied here (see below) differ from the above amides in the configuration at $C_{(8)}$ and in the presence of an isosteric —NH-group in the substituent at $C_{(8)}$. In view of the fact that N-(D-methyl-8-isoergolenyl) ureas were in their biological effects more effective than the isomeric ergolenyl ureas[1,3] it could have been expected that the difference in the configuration at $C_{(8)}$ of the above amides and isoergolin-I-yl ureas will not play a major role in their antifertility and antilactation effects. The saturation of the double bond of N-(D-6-methyl-8-isoergolenyl)

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** The N-(D-6-methyl-8-isoergolenyl)-N,N'-diethylurea with antiserotonine activity, was introduced in the form of hydrogen maleate into medical practice under the name of Lysenyl.

ureas in position 9,10 results (with the formation of a new asymmetry centre at $C_{(10)}$) in two diastereoisomers, of which the compounds with 5,10 *trans* configuration correspond sterically to D-dihydroisolysergic acid-I, those with a *cis* configuration to D-dihydroisolysergic acid-*I*[5].

N-(D-6-Methyl-8-isoergolin-I-yl)- and N-(D-6-methyl-8-isoergolin-II-yl)-ureas (*I* and *Ia*) and the analogous N'-substituted ureas *II* – *VII* and *IIa* – *VIIa* (Table I) were prepared by a stereospecific synthesis using the hydrazides of D-dihydroisolysergic acid-I (*VIII*) and D-dihydroisolysergic acid-II (*VIIIa*) as starting compounds.

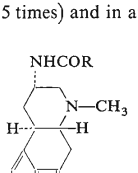
Hydrazides *VIII* and *VIIIa* were converted by treatment with nitrous acid to acid azides[6] and these underwent thermic degradation in benzene to D-6-methyl-8-isoergolin-I-yl, or D-6-methyl-8-isoergolin-II-yl isocyanate. Both isocyanates were then condensed, without isolation in benzene, with ammonia or with the corresponding amines. Ureas *III*, *IIIa*, *IV* and *IVa* were also prepared by catalytic hydrogenation of the corresponding N-(D-6-methyl-8-isoergolenyl)-N'-substituted ureas[1,7]. Detailed attention was devoted to the preparation of compounds *III* and *IIIa*. Using palladium black as catalyst in a medium of acetic acid, at a hydrogen pressure of 35 atm and at 20°C, a mixture of ureas *III* and *IIIa* in a ratio of about 2 : 3 was obtained (estimated semiquantitatively by paper chromatography). On the other hand, hydrogenation in dioxane, using Raney nickel as catalyst, at a pressure of 35 atm and 70°C, yielded a mixture of *III* and *IIIa* in a ratio of about 4 : 1. Hydrogenation of N-(D-6-methyl-8-isoergolenyl)-N',N'-di-n-propylurea carried out under the same conditions, resulted in a mixture in which compounds *IV* and *IVa* were represented also in a 4 : 1 ratio. Crude mixture of the bases was separated by chromatography on a column of alumina, using chloroform and its mixture with ethanol as the elution agent, purifying the obtained bases by crystallization (Table I).

For informative biological testing we used aqueous solutions of tartrates of the bases. When testing the antifertility effect, the compounds were applied to adult female rats, in 24-h intervals, *per os*, either 5 times during the first 5—7 days after mating, or in a single dose during that period. The animals were killed after 20 days and dissected to establish the possible pregnancy and the state of the fetuses. When examining the antilactation effect the compounds were applied per os to lactating female rats in daily intervals for four days between the third and eighth day after giving birth to the young. The formation of milk was assessed from the daily increase in weight of the sucklings and from the degree of filling of their stomachs with milk.

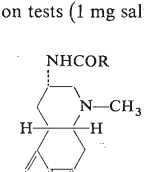
The highest antifertility effect was shown by *III*. It prevents completely nidation at a daily dose of 250 μg salt/kg (5 times), it is partly effective even at a dose of 50 μg/kg (5 times). Full activity was shown by *III* upon a single dose of 1·25 mg/kg, applied on the first or third day, partial activity was found on application on the seventh day after mating. Other compounds, such as *II*, *IV* and *VII*, were also active but at higher doses, up to 2·5 mg salt/kg (5 times).

An inhibitory effect on lactation of rats was displayed by *III* from a daily dose of 20 μg salt/kg, complete inhibition being reached at a daily dose of 1 mg/kg. The dose decreasing the lactation to one-half was about 100 μg/kg. An antilactation

effect was shown *e.g.* also by compounds *VI* and *VII*. The effect of *III* on rat lactation could be suppressed by prolactin. Compound *III* is interesting also because after blocking lactation it provokes oestrus and a resumption of the menstrual cycles. In bitches, *III* caused oestrus and made pregnancy possible. In lactating bitches, *III* stopped lactation and new oestrus set in within several days. In contrast with the biologically active ureas *I*—*VII* the isomeric ureas *Ia*—*VIIa*, belonging sterically to the series of D-dihydroisolysergic acid-II, were practically inactive both in antifertility test (2·5 mg salt/kg, 5 times) and in antilactation tests (1 mg salt/kg).



A = *I*—*VII*



B = *Ia*—*VIIa*

Compounds *III* and *IIIa* were examined in this institute by Prof. V. Trčka, Dr M. Vaněček and Mrs J. Muratová, using also a comparison with the effect of the hydrogen maleate of N-(D-6-methyl-8-isoergolenyl)-N′,N′-diethylurea (lysenyl). The effect of the compounds was tested on foot-pad edema of rats caused by a subplantar application of serotonine (1 μg as 1% solution). Compound *III* at a dose of 50 μg/kg *i.v.* had 50% of the effect of Lysenyl, urea *IIIa* was practically without effect at a dose of 100 μg/kg, with the same type of application. It follows that saturation of the double bond in position 9,10 results in a decrease of the antiserotonine effect (with *III*) or in its complete abolition (with *IIIa*).

EXPERIMENTAL

The melting points were measured in a capillary and are not corrected. For analysis, the compounds were dried *in vacuo* of 0·1 Torr at a temperature raised appropriately to their melting point. The values of specific rotation of the compounds (Table I) refer to compounds free of crystal solvent. Evaluation of the compounds by paper chromatography was done by using a system of formamide–ammonium formate as the stationary phase and chloroform as the mobile phase. The compounds were detected by fluorescence in UV light after previous illumination with sunlight.

Ureas *I*—*VII* and *Ia*—*VIIa* Using the Azide Method

1·0 g (3·52 mmol) hydrazide of D-dihydroisolysergic acid-I[6] (for *I*—*VII*) or of D-dihydroisolysergic acid-II (for *Ia*—*VIIa*) was converted to the azide of the same acid[6] which was extracted from the alkaline aqueous medium with 600 ml or 200 ml benzene. The benzene solution of the azide was dried by passing through a short column of potasite (K 3A, Slovnaft, Bratislava) and refluxed for 10 min under exclusion of atmospheric humidity, in nitrogen. The isocyanate solution was mixed with a solution of 1·3 g (17·6 mmol) diethylamine in 20 ml benzene, the mixture was refluxed for 5 min under the above conditions and left to stand at 20°C for 20 h. The volatile components were distilled off *in vacuo* (water-pump) and the crude product (86—90%) was

TABLE I

N-(D-6-Methyl-8-isoergolin-I-yl)- and N-(D-6-Methyl-8-isoergolin-II-yl)urea

Compound	R	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*, pyridine)	Formula (M. w.)	Calc./Found		
					% C	% H	% N
I NH_2	A	275—277 (dimethyl-formamide)	+17° (0·23)	$C_{16}H_{20}N_4O$ (284·3)	67·58 67·06	7·09 7·25	19·70 19·67
Ia NH_2	B	259—262 (ethanol–chloroform)	+120° (0·30)	$C_{16}H_{20}N_4O$ (284·3)	67·58 67·59	7·09 7·47	19·70 19·33
II NHC_2H_5	A	228—230 (ethanol)	+10° (0·58)	$C_{18}H_{24}N_4O$ (312·4)	69·20 68·94	7·74 8·00	17·94 17·54
IIa NHC_2H_5	B	138—140 (benzene)	+100° (0·23)	$C_{18}H_{24}N_4O$ (312·4)	69·20 69·70	7·74 7·87	17·94 17·62
III[a] $NH(C_2H_5)_2$	B	202—204 (ethanol)	+29° (0·45)	$C_{20}H_{28}N_4O$ (340·5)	70·55 70·25	8·29 8·57	16·45 16·23
IIIa[b] $NH(C_2H_5)_2$	B	208—210 (aq. ethanol)	+80° (0·45)	$C_{20}H_{28}N_4O$ (340·5)	70·55 70·63	8·29 8·37	16·45 16·62
IV $N(C_3H_7\text{-n})_2$	A	207—208 (ethanol)	+28° (0·50)	$C_{22}H_{32}N_4O$ (368·5)	71·70 72·02	8·75 8·58	15·20 15·27
IVa $N(C_3H_7\text{-n})_2$	B	186—188 (methanol)	+98° (0·49)	$C_{22}H_{32}N_4O$ (368·5)	71·70 71·45	8·75 9·02	15·20 15·32
V N-C_5H_9-cyclo	A	260—262 (ethanol)	+7° (0·29)	$C_{21}H_{28}N_4O$ (352·4)	71·56 71·45	8·00 8·27	15·89 15·61
Va N-C_5H_9-cyclo	B	240—242 (ethanol)	+85° (0·38)	$C_{21}H_{28}N_4O$ (352·4)	71·56 71·77	8·00 8·30	15·89 15·23
VI $NCH_2(CH_2)_2CH_2$	A	163—166 (aq. ethanol)	+7° (0·28)	$C_{21}H_{28}N_4O$ (352·4)	71·56 71·94	8·00 8·13	15·89 15·61
VIa $NCH_2(CH_2)_3CH_2$	B	about 135 (aq. methanol)	+74° (0·33)	$C_{21}H_{28}N_4O$ (352·4)	71·56 71·69	8·00 8·29	15·89 15·73
VII $NCH_2CH_2OCH_2CH_2$	A	184—186 (ethanol)	+6° (0·34)	$C_{20}H_{26}N_4O_2$ (354·4)	67·77 67·94	7·33 7·65	15·80 15·69
VIIa $NCH_2CH_2OCH_2CH_2$	B	about 135 (aq. methanol)	+79° (0·44)	$C_{20}H_{26}N_4O_2$ (354·4)	67·77 67·12	7·33 7·62	15·80 15·68

[a] Hydrogen maleate of base *III*: m.p. 190—191°C (ethanol); for $C_{24}H_{32}N_4O_5$ (456·5) calculated: 63·14% C, 7·06% H, 12·27% N; found: 63·15% C, 7·17% H, 12·08% N. [b] Hydrogen maleate of base *IIIa*: m.p. 193°C (ethanol); for $C_{24}H_{32}N_4O_5$ (456·5) calculated: 63·14% C, 7·06% H, 12·27% N; found: 63·04% C, 7·10% H, 12·07% N.

purified by chromatography on a column of alumina (50 g, activity IV), using chloroform and its mixture with 2% ethanol for elution, and finally by crystallization from ethanol (Table I). In the case of *I*, *Ia*, or *II*, *IIa*, the benzene solution of isocyanate was cooled to 10°C, saturated with gaseous ammonia or else mixed with a solution of 0·79 g (17·6 mmol) ethylamine in 20 ml benzene, and the mixture was left to stand for 20 h at 20°C. In the case of *IIIa*—*VIIa* the crude products were purified by crystallization only. The hydrogen maleates of ureas *III* and *IIIa* were prepared from equimolar amounts of both components in ethanol (Table I).

Ureas *III* and *IIIa* Using Hydrogenation of N-(D-6-Methyl-8-isoergolenyl)-N′,N′-diethylurea

a) *On palladium*: A solution of 1·38 g starting urea in 50 ml glacial acetic acid was hydrogenated in the presence of 250 mg palladium black, at a pressure of 35 atm H_2 and 20°C for 4 h. After filtration of the catalyst, the volatile fractions were distilled *in vacuo* (water-pump), the residue was extracted with 50 ml chloroform, the chloroform extract was shaken with 1M-$NaHCO_3$ and with water and dried. The filtrate was evaporated at reduced pressure to dryness and dried further at 40°C/2 Torr (1·19 g, 86%). The chloroform solution of a mixture of crude bases was chromatographed on a column of alumina (45 g, activity IV) using the same solvent or its mixture with 2% ethanol for elution. The course of the chromatography was followed by a semiquantitative evaluation of the fractions by paper chromatography. The combined fractions containing the less polar urea *III* or the more polar urea *IIIa* (the ratio was about 2 : 3) were purified by crystallization from ethanol. By its composition and properties the compound *III* [m.p. 203–204°C, $[\alpha]_D^{20} + 30°$ (*c* 1·0, pyridine), R_F in paper] or *IIIa* [m.p. 208–210°C, $[\alpha]_D^{20} + 80°$ (*c* 0·65, pyridine), R_F in paper] correspond to the same compounds prepared from hydrazide *VIII* and *VIIIa*. Compounds *III* and *IIIa* were analyzed in the form of hydrogen maleates, prepared from equimolar amounts of the two components in ethanol (Table I).

b) *On Raney nickel*: 1·9 g of the starting urea dissolved in 120 ml dioxane was hydrogenated in the presence of 3·0 g Raney nickel, at 35 atm H_2 and 70°C for 14 h. The mixture after hydrogenation was processed as shown under *a*). A total of 1·70 g (90%) of a crude mixture of bases with ureas *III* and *IIIa* was obtained at a ratio of 4 : 1. The pure compounds corresponded in their properties (m.p., optical rotation, R_F on paper) to the same compounds prepared from hydrazide *VIII* or *VIIIa*.

Ureas *IV* and *IVa* Using Hydrogenation of N-(D-6-Methyl-8-isoergolenyl)-N′,N′-di-n-propylurea

1·0 g of the starting urea dissolved in 40 ml dioxane was hydrogenated in the presence of 1·0 g Raney nickel, at 35 atm and 70°C, for 14 h. The mixture was then processed to obtain *IV* and *IVa* in the same way as shown under *a*). A total of 0·9 g (90%) of a crude mixture of bases was obtained, in which compounds *IV* and *IVa* were represented at a ratio of about 4 : 1. Compounds *IV* and *IVa* recrystallized from ethanol and methanol, respectively, were identical (m.p., optical rotation, R_F on paper) with the corresponding compounds prepared from hydrazide *VIII* or *VIIIa* (Table I).

The analyses shown here were done by Mr K. Havel and Mrs J. Komancová (direction: Dr J. Körbl) of the analytical department of this Institute; Mrs M. Jelínková of this Institute has done the paper chromatography.

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