SYNTHESIS OF 1,1-DIETHYL-4-(D-6-METHYL-8-ERGOLIN-I-YL)SEMICARBAZIDE AND ITS ISOERGOLIN-I-YL AND ISOERGOLIN-II-YL ISOMERS

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1,1-Diethyl-4-(D-6-methyl-8-ergolin-I-yl)-, -4-(D-6-methyl-8-isoergolin-I-yl)- and -4-(D-6-methyl-8-isoergolin-II-yl)semicarbazides (*I*—*III*) were obtained in a reaction of the corresponding isocyanates with 1,1-diethylhydrazine. The semicarbazides *I*—*III* were informatively tested for antinidation activity and were found to be less potent than the corresponding derivatives of N',N'-diethylurea.

In previous work[1,2] we studied the biological effects of the stereoisomers of N-(D-6-methyl-8-isoergolenyl)-N',N'-diethylurea. From the point of view of antiserotonin activity the most interesting was the above-mentioned isoergolinyl derivative** which was catalytically hydrogenated to N-(D-6-methyl-8-isoergolin-I-yl)-N',N'-diethylurea and the diastereoisomeric isoergolin-II-yl derivative[3]. Both the parent compound[4] and the hydrogenation product with relative *trans* configuration at $C_{(5)}$ and $C_{(10)}$ of the molecule[3] displayed a pronounced antinidation and antilactation effect in rats which may be overcome by exogenous prolactin.

Some analogous derivatives of 1,1-diethylsemicarbazide were prepared here: 1,1-diethyl-4-(D-6-methyl-8-ergolin-I-yl)semicarbazide (*I*) and the stereoisomeric isoergolin-I-yl and isoergolin-II-yl compounds *II* and *III*. It was of particular interest to establish to what extent the 1,1-diethylsemicarbazide substituent in the molecule of *II* will be effective in comparison with the analogous derivative of urea, identical stereochemically at all the centres of chirality.

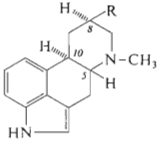
The semicarbazides *I*—*III* were prepared by stereospecific synthesis using hydrazide of D-dihydrolysergic-I acid or D-dihydroisolysergic-I acid or D-dihydroisolysergic-II acid as starting compounds[5]. The acid hydrazides were converted *via* the various azides[5] to the corresponding isocyanates which were condensed without isolation with 1,1-diethylhydrazine in benzene. The molecular weight of *I*—*III* was confirmed

* Part XLIII in the series Ergot Alkaloids; Part XLII: This Journal *39*, 1768 (1974).

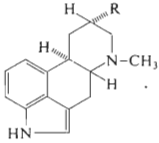
** The active component of Lysenyl-SPOFA.

by mass spectrometry. In the IR region, *I—III* displayed a split peak at 3240 to 3380 cm^{-1} (amide and indole NH-group), 1650 cm^{-1} and 1530 cm^{-1} (the NHCONH-grouping), 1615, 1510 (i) and 745 cm^{-1} (aromatic substituted rings).

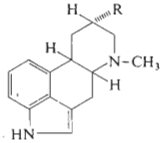
To test the effect of *I—III* on the nidation of fertilized ova in rats (K.Ř.) the compound was dissolved in the form of tartrate in 5 ml water per kg body weight and administered through a gastric tube for 5 days during the first week after mating. Experimental and control groups (these received only a corresponding volume of water) contained ten animals each. Compound *II* prevented nidation in all animals at daily doses of 5 mg/kg but had no effect at 0·5 mg/kg. On the other hand, compounds *I* and *III* were ineffective at doses of 5 mg/kg in preventing nidation. The data indicate that replacement of the N,N-diethylurea residue in the molecule of N-(D-6-methyl--8-isoergolin-I-yl)-N′,N′-diethylurea[4] with 1,1-diethylsemicarbazide results in rats in a marked depression of the antinidation effect. The effect of *II* is linked to the steric situation of the molecule, the diastereoisomeric compounds *I* and *III* being practically ineffective in equal doses.



I



II



III

R = $-NHCONHN(C_2H_5)_2$

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. The melting was accompanied by decomposition of the compounds. Samples for analysis were dried at 0,1 Torr at a suitable temperature. The values of specific rotation refer to compounds free of the crystal solvent. The purity of the compounds was checked by paper chromatography using formamide with 5% ammonium formate as the stationary phase and chloroform as the mobile phase. The compounds were detected with UV light after previous illumination with sunlight. The IR spectra were recorded in KBr pellets using a UR-20 (Zeiss-Jena) spectrophotometer.

Semicarbazides *I—III*

1·0 g (3·52 mmol) hydrazide of D-dihydrolysergic-I acid (for the synthesis of *I*) or D-dihydroisolysergic-I acid (for the synthesis of *II*) or D-dihydroisolysergic-II acid (for the synthesis of *III*) was converted to the azide of the corresponding acid[5] and this was extracted from the alkaline solution with benzene (600 ml). The benzene solution was dried with anhydrous potassium carbonate and the filtrate was refluxed for 10 min under nitrogen. The isocyanate solution[3] was combined with a solution of 2·0 g (22·5 mmol) 1,1-diethylhydrazine[6] in 20 ml benzene. The mixture

was then refluxed for 5 min. After standing for 20 h at room temperature it was evaporated in water-pump vacuum and the residue (c. 1·2 g, 95%) was further purified. In the case of *II* and *III* the crude products were purified by chromatography on a column of alumina (45 g, activity IV) using chloroform for elution. The appropriate fractions were pooled and crystallized. In the case of *I*, the crude product was crystallized from aqueous ethanol and ethyl acetate.

1,1-*Diethyl*-4-(D-6-*methyl*-8-*ergolin*-I-*yl*)*semicarbazide* (I): m.p. 124—126°C (ethyl acetate); $[\alpha]_D^{20}$ −74·6° (*c* 0·6, pyridine). For $C_{20}H_{29}N_5O$ (355·5) calculated: 67·57% C, 8·22% H, 19·70% N; found: 67·23% C, 8·51% H, 19·28% N.

1,1-*Diethyl*-4-(D-6-*methyl*-8-*isoergolin*-I-*yl*)*semicarbazide* (II): m.p. 195—198°C (ethanol–acetone–hexane); $[\alpha]_D^{20}$ +12·3° (*c* 0·3, pyridine). For $C_{20}H_{29}N_5O$ (355.5) calculated: 67·57% C, 8·22% H, 19·70% N; found: 67·86% C, 8·37% H, 19·50% N.

1,1-*Diethyl*-4-(D-6-*methyl*-8-*isoergolin*-II-*yl*)*semicarbazide* (III): m.p. 230—232°C (ethanol); $[\alpha]_D^{20}$ +103·2° (*c* 0·24, pyridine). For $C_{20}H_{29}N_5O$ (355·5) calculated: 67·57% C, 8·22% H, 19·70% N; found: 67·19% C, 8·35% H, 19·80% N.

The analyses shown here were done by Mrs J. Komancová from the analytical department of this Institute under the direction of Dr J. Körbl. Paper chromatography was done by Mrs M. Jelínková and the IR spectra were interpreted by Dr B. Kakáč, both of this Institute. The molecular weight determinations by mass spectrometry were kindly performed by Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague.

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