REACTION OF D-6-METHYL-8-CHLOROMETHYLERGOLINE-I WITH SODIUM ALCOHOLATES AND WITH SODIUM ETHYL MALONATE*

V. ZIKÁN and M. SEMONSKÝ

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received July 3rd, 1973

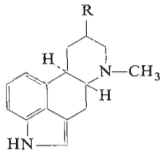
Reaction of D-6-methyl-8-chloromethylergoline-I (*I*) with excess sodium ethylate in dimethylsulfoxide at a raised temperature yielded D-6-methyl-8-methylenergoline-I (*II*); reaction of ergoline *I* with sodium butylate or with sodium ethylmalonate led to D-6-methyl-8-butoxymethylergoline-I (*III*) or to the diethyl ester of β(D-6-methyl-8-ergolin-I-yl)-α-carboxypropionic acid (*IV*). Saponification of *IV* resulted in the dicarboxy compound *V*.

In connection with preparing novel 8-substitution derivatives of D-6-methylergoline-I we took up the reaction of D-6-methyl-8-chloromethylergoline[1]-I (*I*) with some sodium alcoholates and with sodium ethylmalonate.

Reaction of ergoline-I with a large excess of sodium ethylate in ethanol, conducted in a boiling reaction mixture practically does not take place. On the other hand, the same reaction conducted at 125–130°C in dimethyl sulfoxide produced a high yield of D-6-methyl-8-methylenergoline-I (*II*). The reaction course is thus the same as with the reaction of D-6-methyl-8-chloromethylergolene with potassium carbonate, giving rise to D-6-methyl-8-methylenergolene (lysergene)[2]. In the IR region of the spectrum *II* shows a characteristic band at 897 cm^{-1}, indicating the presence of the $RR'C{=}CH_2$ grouping. The chirality of *II* followed on the basis of circular dichroism was studied by Bláha[3]. The reaction of ergoline-I with two molar equivalents of sodium butylate in butanol in a boiling reaction mixture yielded, on the contrary, besides *II*, also D-6-methyl-8-butoxymethylergoline-I (*III*), when a part of the starting compound *I* was recovered. The ratio of compounds *I* : *II* : *III* in the crude product was approximately 1·5 : 3 : 5 (followed by semiquantitative paper chromatography). Chromatography on a column of alumina yielded 44% of *III*. Reaction of other sodium alcoholates with chloromethyl ergoline-I conducted analogously in the corresponding alcohol (1-propanol, 1-pentanol, 1-dodecanol) in a boiling reaction mixture had also an inhomogeneous character and resulted invariably in greater or lesser amounts of *II* and another compound, assumed to be the corresponding D-6-methyl-8-alkoxymethylergoline-I. No detailed study of these crude products was taken up.

* Part XLI in the series Ergot Alkaloids; Part XL: This Journal *37*, 2600 (1972).

Condensation of ergoline-I with four molar equivalents of sodium ethyl malonate in dimethyl sulfoxide at 130–135°C led to the crude diethyl ester of β-(D-6-methyl-8-ergolin-I-yl)-α-carboxypropionic acid (*IV*) which was purified by column chromatography on alumina and then on silica gel. Saponification of the diethyl ester *IV* with aqueous–methanolic potassium hydroxide produced a fine yield of the corresponding acid *V* which was stable in an acid medium and did not decarboxylate.



II, R = $=CH_2$
III, R = $-CH_2OC_4H_9$-n
IV, R = $-CH_2CH(COOC_2H_5)_2$
V, R = $-CH_2CH(COOH)_2$

Results of a pharmacological evaluation of *II*–*V* as was carried out in connection with studying the relationships between chemical structure and biological effects in this group of compounds will be presented elsewhere.

EXPERIMENTAL

The melting points of the compounds were estimated in Kofler's block and are not corrected. Samples for analysis were dried in vacuo (0·1 Torr) at a temperature raidse in proportion to their melting point. The values of specific rotation refer to compounds free of the crystal solvent. Evaluation of the preparations by paper chromatography was done with *II*–*IV* using formamide–ammonium formate as the stationary phase and benzene–chloroform (3:7) as the mobile phase. In the case of *V*, the solvent system used was butanol–acetic acid–water (4 : 1 : 5). Compounds *II*–*V* were detected on the basis of their fluorescence in UV light after previous illumination with sunlight. Recording of the IR spectrum was done on a Unicam SP 200 G spectrophotometer.

D-6-Methyl-8-methylenergoline-I (*II*)

A mixture of 2·0 g (7·3 mmol) D-6-methyl-8-chloromethyl ergoline[1]-I, 4·9 g (73 mmol) sodium ethylate and 70 ml dimethyl sulfoxide was heated under a KOH seal in a 125–130°C bath for 11 h. After distilling off the excess dimethyl sulfoxide *in vacuo* of a water pump the residue was dried for 2 h at 85°C, stirred with 80 ml water and the mixture left to stand overnight at 3°C. The precipitated product was filtered, washed with water and dried at 50°C/3 Torr. The crude product (1·67 g, 96%) was purified by chromatography on a column of silica gel (20 g, grain size 0·06–0·1 mm) using chloroform, or chloroform with 5% ethanol, as the elution agent. Combination of the corresponding fraction yielded 1·13 g (65%) of a homogeneous product which separated from ethanol in the form of a gel and, during filtration, formed prisms melting at 240–244°C; $[\alpha]_D^{20}$ −118° (*c* 0·5, pyridine). For $C_{16}H_{18}N_2$ (238·3) calculated: 80·63% C, 7·61% H, 11·75% N; found: 80·44% C, 7·79% H, 11·57% N.

D-6-Methyl-8-butoxymethylergoline-I (*III*)

D-6-Methyl-8-chloromethylergoline-I (1·1 g, 4 mmol) (ref.[1]) was added to a solution of 0·2 g (8·7 mmol) sodium in 40 ml butanol and the mixture was refluxed for 9 h with a KOH seal. After distilling off the butanol *in vacuo* of an oil pump, the residue was dried for 1 h at 60°C/4 Torr, triturated with 10 ml water, filtered and washed with water. A total of 1·18 g product was obtained, according to a semiquantitative evaluation by paper chromatography representing a mixture of D-6-methyl-8-methylenergoline-I, D-6-methyl-8-chloromethylergoline-I and D-6-methyl-8-butoxymethylergoline-I at a ratio of about 3 : 1·5 : 5. The mixture was separated on a column of alumina (100 g, activity IV) using chloroform, or chloroform with 5% ethanol for elution. Pooling of the individual fractions led to 0·55 g (44%) *III* which forms leaflets melting at 174 to 175°C (ethanol); $[\alpha]_D^{20}$ −80° (*c* 0·5, pyridine). For $C_{20}H_{28}N_2O$ (312·4) calculated: 76·88% C, 9·03% H, 8·96% N; found: 76·91% C, 9·07% H, 8·63% N.

Diethyl Ester of β(D-6-Methyl-8-ergolin-I-yl)-α-carboxypropionic Acid (*IV*)

Ethylmalonate (11·65 g, 73 mmol) was added to a solution of 1·68 g (73 mmol) sodium in 37 ml ethanol, the ethanol was distilled off at reduced pressure and the residue was combined with 5·0 g (18 mmol) D-6-methyl-8-chloromethylergoline-I and 180 ml dimethyl sulfoxide. The mixture was stirred under a KOH seal in a 130—135°C bath for 10 h. The dimethylsulfoxide was distilled off in a water-pump vacuum, the residue was dried *in vacuo* for 1 h at 80°C, mixed with 90 ml water and the precipitated product was filtered and washed with water. The crude product (6·78 g, 93%) was purified chromatographically on a column of alumina (90 g, activity IV) using chloroform for elution. The fast fractions (4·91 g) were pooled and further purified by chromatography on a column of silica gel (30 g, grain size 0·05—0·1 mm) using a mixture of chloroform with benzene (7 : 3) or the same mixture containing 10% ethanol, for elution. Pooling of the corresponding fractions yielded 4·31 g (59%) of a homogeneous product forming leaflets melting at 183—184°C (ethanol); $[\alpha]_D^{20}$ −78° (*c* 0·5, pyridine). For $C_{23}H_{30}N_2O_4$ (398·4) calculated: 69·32% C, 7·59% H, 7·03% N; found: 69·86% C, 7·70% H, 7·11% N.

β-(D-6-Methyl-8-ergolin-I-yl)-α-carboxypropionic Acid (*V*)

An aqueous–methanolic (1 : 1) 1M-KOH solution (25 ml) was added dropwise under stirring to a solution of 2·66 g (6·7 mmol) diethyl ester of acid *IV* in 20 ml methanol and the mixture was left to stand at 20°C overnight, then for 5 h at 0°C. The filtered product was dissolved in 20 ml hot water, the solution was filtered with charcoal and acidified with acetic acid to pH 5. The separated gel was filtered, washed with water and ethanol. Drying *in vacuo* over P_2O_5 yielded an amorphous, chromatographically homogeneous compound (1·94 g, 85%) which decomposes slowly on heating above 270°C. For $C_{19}H_{22}N_2O_4$ (342·4) calculated: 66·65% C, 6·47% H, 8·18% N; found: 66·21% C, 6·33% H, 8·28% N.

The analyses were caried out by Mr K. Havel and Mrs J. Komancová under the direction of Dr J. Körbl of the analytical department of this Institute. The paper chromatography was done by Mrs M. Jelinková, the IR spectrum was intrepreted by Dr E. Svátek, both of this institute.

REFERENCES

1. Semonský M., Kucharczyk N.: This Journal *33*, 577 (1968).
2. Beran M., Semonský M., Řežábek K.: This Journal *34*, 2819 (1969).
3. Bláha K.: This Journal *37*, 2473 (1972).

Translated by A. Kotyk.