9,10-DIHYDROERGOPEPTINES MODIFIED IN POSITION 6*

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9,10-Dihydroergopeptines modified in position 6 (*VII*—*XXIII*) were prepared from 9,10-dihydroergotamine (*I*) and 9,10-dihydroergocristine (*II*) which were converted via corresponding 6-demethyl-6-cyano compounds *III* and *IV* to 6-demethyl-9,10-dihydroergotamine (*V*) or 6-demethyl-9,10-dihydroergocristine (*VI*), respectively, which were then alkylated or acylated in position 6. Methylation of 6-demethyl-6-propyl compounds *VIII* and *IX* on N^1 gave 1-methyl-6--demethyl-6-propyl-9,10-dihydroergotamine (*XXIV*) and 1-methyl-6-demethyl-6-propyl-9,10--dihydroergocristine (*XXV*). In the majority of the compounds their antinidation properties, affinity to α_1 adrenergic receptors and D_2 receptors of dopamine were studied, and in some of them the protective effect against adrenaline and noradrenaline and dopaminergic activity in vivo were also tested.

Over the last two decades the majority of the investigations from the field of ergot alkaloids dealt with the preparation of simple ergoline derivatives and the study of their pharmacological properties. Although active compounds were found among them, the natural peptidic ergot alkaloids (fittingly named ergopeptines[1]) or their 9,10-dihydro derivatives retained their therapeutic importance owing to their important effects on smooth muscles and the vegetative symphatetic system. Since the sixties, when some total syntheses of peptidic parts of ergopeptines were mastered some of their analogues have been prepared in which the methyl group in position 6 of the ergoline part of the molecule was substituted by other alkyl groups[2,3]. The preparation of these analogues consisted in partial synthesis of reactive substituted derivatives of 6-demethyl-6-alkyl-9,10-dihydrolysergic acids and in their reaction with aminocyclols, i.e. cyclic peptides prepared by total synthesis, representing the peptidic part of ergopeptines. Thus, obtaining the mentioned analogues of ergopeptines is limited by the demanding, more than twenty-step synthesis of aminocyclols (cf. ref.[4]).

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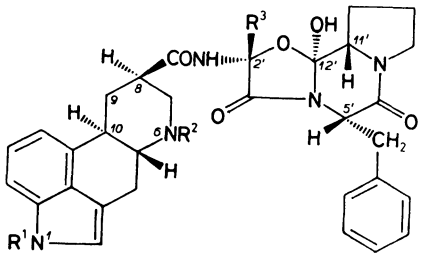
In our paper we report on the preparation of some dihydroergopeptine analogues by synthetic modifications carried out on the whole molecule of 9,10-dihydroergopeptine. As starting compounds we used 9,10-dihydroergotamine (*I*) and 9,10-dihydroergocristine (*II*) which we converted to 6-demethyl-9,10-dihydroergotamine (*V*) and 6-demethyl-9,10-dihydroergocristine (*VI*) via 6-demethyl-6-cyano compounds *III* and *IV*. For N^6-demethylation we used the classic Braun demethylation of tertiary amines with cyanogen bromide, modified by Fehr[5] for lysergic acid derivatives. Fehr and co-workers split off the cyano group from the derivatives of 6-demethyl-6-cyano-9,10-dihydrolysergic acid by hydrogenation in the presence of Raney nickel in dimethylformamide. The splitting off of the 6-cyano group from compounds *III* or *IV* with zinc in acetic acid (according to ref.[5]) is accompanied by the degradation of the starting compounds. We found that the splitting off of the cyano group from our 6-demethyl-6-cyano compounds *III* and *IV* proceeded smoothly on hydrogenolysis in the presence of Raney nickel in aqueous dioxane. From the reaction mixture after hydrogenolysis of 6-demethyl-6-cyano-9,10-dihydroergotamine (*III*) we isolated in small amount a compound, identified as 6-demethyl-6-formyl-9,10-dihydroergotamine (*XXVI*), in addition to 6-demethyl-9,10-dihydroergotamine (*V*). The compound *XXVI* is formed from an intermediary imino compound by hydrolysis. The formation of the corresponding 6-formyl compounds has also been described during the hydrogenolysis of 1-((5*R*,8*S*,10*R*)-6-cyano-8-ergolinyl)-3,3-diethylurea[6]. An analogous by-product is also formed during the hydrogenolysis of 6-demethyl-6-cyano-9,10-dihydroergocristine (*IV*). 6-Demethyl derivatives *V* or *VI* were alkylated or acylated under mild conditions, using conventional methods. We prepared in this way 6-demethyl-6-alkyl- or 6-demethyl-6-acyl derivatives of 9,10-dihydroergotamine *VII*, *VIII*, *X*, *XII*, *XIV*, *XVI*, *XVIII*, *XX* and *XXII* and 6-demethyl-6-alkyl- and 6-demethyl-6-acyl derivatives of 9,10-dihydroergocristine *IX*, *XI*, *XIII*, *XV*, *XVII*, *XIX*, *XXI* and *XXIII* (see Table I). Using the methylation on N^1 according to Troxler and Hofmann[7] we prepared from 6-demethyl-6-propyl-9,10-dihydroergotamine (*VIII*) and 6-demethyl-6-propyl-9,10-dihydroergocristine (*IX*) corresponding 1-methyl compounds *XXIV* and *XXV* (see Table I).

In the preparation of 9,10-dihydroergopeptines modified at position 6 we applied mild methods used in the chemistry of ergot alkaloids, which, it may be assumed, cannot affect the absolute configuration of ergopeptines. It is the absolute configuration of the four centres of asymmetry in the peptidic tricyclic system, in positions 2′,5′,11′, and 12′, and the absolute configuration in the rest of the 9,10-dihydrolysergic acid in positions 5, 8, and 10. The configuration on the asymmetric centres in the 9,10-dihydrolysergic acid residue is perfectly stabilized by the saturation of the double bond in position 9, 10 of natural ergot alkaloids[8]. From the experiments of cyclol synthesis[4] it follows that the tricyclic oxazolopyrrolopyrazine cycle is relatively stable, especially from the point of view of the configuration in positions 5′,11′ and 12′. The procedures used by us, i.e. 6-demethylation with cyanogen

bromide in dichloromethane or in chloroform at room temperature, hydrogenolytic splitting off of the 6-cyano group in aqueous dioxane at 40°C and 6-alkylation or 6-acylation of the 6-demethyl derivatives obtained in this way using very mild conditions, practically exclude the configurations on the mentioned asymmetric centres being affected. The isomerizations taking place in the position 2′ of the cyclol, under formation of the so-called aci-isomers (see refs[9,10]), which are formed under the effect of acids on 9,10-dihydroalkaloids, do not come into consideration in our case, because the 9,10-dihydroergopeptines prepared by us were not exposed to the direct effect of acids.



I–XXVI

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
I	H	CH_3	CH_3	*XIV*	H	$CH_2CO_2C_2H_5$	CH_3
II	H	CH_3	$CH(CH_3)_2$	*XV*	H	$CH_2CO_2C_2H_5$	$CH(CH_3)_2$
III	H	CN	CH_3	*XVI*	H	$CH_2C_6H_5$	CH_3
IV	H	CN	$CH(CH_3)_2$	*XVII*	H	$CH_2C_6H_5$	$CH(CH_3)_2$
V	H	H	CH_3	*XVIII*	H	$COCH_3$	CH_3
VI	H	H	$CH(CH_3)_2$	*XIX*	H	$COCH_3$	$CH(CH_3)_2$
VII	H	CH_2CH_3	CH_3	*XX*	H	SO_2CH_3	CH_3
VIII	H	$CH_2CH_2CH_3$	CH_3	*XXI*	H	SO_2CH_3	$CH(CH_3)_2$
IX	H	$CH_2CH_2CH_3$	$CH(CH_3)_2$	*XXII*	H	$CO_2CH_2C_6H_5$	CH_3
X	H	$CH_2CH{=}CH_2$	CH_3	*XXIII*	H	$CO_2CH_2C_6H_5$	$CH(CH_3)_2$
XI	H	$CH_2CH{=}CH_2$	$CH(CH_3)_2$	*XXIV*	CH_3	$CH_2CH_2CH_3$	CH_3
XII	H	$CH_2C{\equiv}CH$	CH_3	*XXV*	CH_3	$CH_2CH_2CH_3$	$CH(CH_3)_2$
XIII	H	$CH_2C{\equiv}CH$	$CH(CH_3)_2$	*XXVI*	H	CHO	CH_3

These assumptions were confirmed by comparison of the properties (m.p., $[\alpha]_{20}^{D}$) of dihydroergopeptines prepared by us with those with a known absolute configuration, previously prepared semisynthetically (see refs[2,3]): 6-demethyl-9,10-dihydroergotamine (*V*) 181–183°C (acetone), −10·2° (*c* 0·2, methanol), lit. 184°C and −12·3° (*c* 0·88, methanol); 6-demethyl-9,10-dihydroergocristine (*VI*) 182–184°C

TABLE I

6-Substituted 9,10-dihydroergopeptines

Compound	Yield, % (Method)	M.p., °C (Solvent)	$[\alpha]_D^{20}$ (c)[a]	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
III	72	223—225 (methanol)	−7·3 (0·7)	$C_{33}H_{34}N_6O_5$ (594·6)	66·65 66·68	5·76 5·91	14·13 14·04
IV	90	189—194 (methanol)	+1·7 (0·5)	$C_{35}H_{38}N_6O_5$ (622·7)	67·50 67·19	6·15 6·19	13·50 14·34
V	59	181—183 (acetone)	−39·4 (0·5)	$C_{32}H_{35}N_5O_5.0{\cdot}5\ H_2O$ (578·6)	66·41 66·49	6·27 6·00	12·10 12·24
VI	69	182—184 (benzene)	−33·7 (0·2)	$C_{34}H_{39}N_5O_5.0{\cdot}5\ H_2O$ (606·7)	67·30 67·32	6·64 6·36	11·54 12·02
VII	50 (*A*)	223—226 (acetone)	−72·6 (0·2)	$C_{34}H_{39}N_5O_5.H_2O$ (615·7)	66·32 66·47	6·71 6·41	11·37 11·36
VIII	71 (*A*)	178—180 (benzene)	−64·2 (0·5)	$C_{35}H_{41}N_5O_5.0{\cdot}25\ H_2O$ (616·2)	68·21 68·28	6·78 6·72	11·36 11·35
IX	55 (*A*)	210—215 (methanol)	−47·1 (0·2)	$C_{37}H_{45}N_5O_5$ (639·8)	69·46 69·04	7·09 6·92	10·95 10·91
X	29 (*B*)	178—182 (acetone)	−68·1 (0·2)	$C_{35}H_{39}N_5O_5.0{\cdot}5\ H_2O$ (618·7)	67·94 67·75	6·51 6·49	11·32 11·25
XI	33 (*B*)	192—195 (methanol)	−61·2 (0·2)	$C_{37}H_{43}N_5O_5$ (637·8)	69·68 69·40	6·80 6·80	10·98 10·89

XII	31	236—237	−66·8	$C_{35}H_{37}N_5O_5.0{\cdot}5\ H_2O$	68·16	6·21	11·35
	(*B*)	(methanol)	(0·25)	(616·7)	68·21	6·24	11·42
XIII	32	214—218	−56·6	$C_{37}H_{41}N_5O_5.H_2O$	67·97	6·62	10·71
	(*B*)	(ethanol)	(0·2)	(653·7)	67·63	6·55	10·43
XIV	46	171—172	−45·4	$C_{36}H_{41}N_5O_7.0{\cdot}5\ H_2O$	65·04	6·37	10·53
	(*B*)	(acetone)	(0·5)	(664·7)	65·29	6·34	10·39
XV	45	158—161	−39·4	$C_{38}H_{45}N_5O_7.0{\cdot}5\ H_2O$	65·87	6·69	10·10
	(*B*)	(diethyl ether)	(0·5)	(692·8)	66·16	6·68	10·34
XVI	23	232—233	−91·2	$C_{39}H_{41}N_5O_5.0{\cdot}25\ H_2O$	70·51	6·45	10·54
	(*A*)	(acetone)	(0·2)	(664·3)	70·54	6·20	10·21
XVII	20	205—207	−72·5	$C_{41}H_{45}N_5O_5.0{\cdot}5\ H_2O$	70·66	6·65	10·05
	(*B*)	(acetone)	(0·2)	(696·8)	70·66	6·57	10·00
XVIII	83	198—200	−103·9	$C_{34}H_{37}N_5O_6.H_2O$	64·84	6·24	11·12
		(ethanol)	(0·5)	(629·7)	64·97	6·07	11·14
XIX	81	191—192	−96·1	$C_{36}H_{41}N_5O_6.0{\cdot}5\ H_2O$	66·64	6·45	10·79
		(ethanol)	(0·5)	(648·7)	66·30	6·53	10·72
XX[b]	10	231—233	−33·2	$C_{33}H_{37}N_5O_7S.0{\cdot}25\ H_2O$	60·76	5·80	10·73
		(acetone)	(0·2)	(652·2)	60·78	5·94	10·33
XXI[c]	23	210—212	−24·0	$C_{35}H_{41}N_5O_7S.0{\cdot}5\ H_2O$	61·38	6·18	10·22
		(acetone)	(0·2)	(684·8)	61·65	6·06	10·16
XXII	37	232—233	−45·3	$C_{40}H_{41}N_5O_7.0{\cdot}5\ H_2O$	67·39	5·94	9·82
		(acetone)	(0·2)	(712·8)	67·28	5·98	9·60
XXIII	41	155—160	−37·9	$C_{42}H_{45}N_5O_7.0{\cdot}5\ H_2O$	68·08	6·25	9·45
		(acetone–water)	(0·2)	(740·8)	67·93	6·31	9·64

TABLE I
(*Continued*)

Compound	Yield, % (Method)	M.p., °C (Solvent)	$[\alpha]_D^{20}$ (*c*)[a]	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
XXIV[d]	40	187–191 (ethanol–diethyl ether)	−6·6[e] (0·2)	$C_{36}H_{43}N_5O_5.C_4H_6O_6$ (775·8)	61·92 62·04	6·37 6·52	9·03 8·97
XXV[f]	49	190–192 (acetone)	−46·3 (0·2)	$C_{38}H_{47}N_5O_5.H_2O$ (671·8)	67·92 67·74	7·35 7·43	10·42 10·35
XXVI	11·5	222–223 (benzene–ethanol)	−3·3 (0·2)	$C_{33}H_{35}N_5O_6.0·5\ H_2O$ (606·7)	65·33 65·24	5·98 5·89	11·54 11·54

[a] The specific rotations were measured in pyridine, if not stated otherwise; [b] calculated 4·91% S, found 5·40% S; [c] calculated 4·68% S, found 5·46% S; [d] hydrogen tartarate; elemental analysis of the base: for $C_{36}H_{43}N_5O_5.0·5\ H_2O$ (634·75) calculated: 68·12% C, 6·82% H, 11·03% N; found: 68·25% C, 6·69% H, 10·78% N; [e] in 50% ethanol; [f] hydrogen tartarate; m.p. 168–172°C, for $C_{38}H_{47}N_5O_5.C_4H_6O_6.1·5\ H_2O$ (830·9) calculated: 60·70% C, 6·79% H, 8·42% N; found: 60·81% C, 6·74% H, 8·28% N.

(benzene), +8·2° (*c* 0·2, dimethyl sulfoxide), lit. 192°C, +9·2° (*c* 0·978, dimethyl sulfoxide); 6-demethyl-6-ethyl-9,10-dihydroergotamine (*VII*) 223–226°C (acetone), −29·4° (*c* 0·2, dimethyl sulfoxide), lit. 208°C, −29·9° (*c* 0·473, dimethyl sulfoxide); 6-demethyl-6-propyl-9,10-dihydroergotamine (*VIII*) 178–180°C (benzene), −22·3° (*c* 0·2, dimethyl sulfoxide), lit. 194°C, −23·3° (*c* 0·476, dimethyl sulfoxide); (in the literature[2,3] the solvents used for crystallization are not mentioned). Hence, the 9,10-dihydroergopeptines prepared by us have the configuration indicated in the general formula; their structure has been confirmed by spectral analysis.

The compounds were submitted to some pharmacological tests. Their antinidation effects were studied, affinity to α_1-adrenoceptors and D_2 receptors of dopamine. In some substances the protective effect against adrenaline and noradrenaline and their dopaminergic activity were also tested.

The antinidation effect (an expression of the inhibition of prolactin secretion from adenohypophysis) was determined in 16 female Wistar rats of weights from 180 to 260 g. After copulation and subsequent detection of sperm in the vaginal smear eight females was administered the 5th day after copulation an oral dose of the tested substances in a 0·55 to 1·2 mg/5 ml H_2O/kg dose. Eight females remained without application and served as controls. The fifteenth day after copulation the rats were killed by breaking their necks and the number of embryos or resorptions was determined in their uteri. Of the compounds tested (*III*, *V*–*XXI*, *XXIII*–*XXVI*) compounds *XVII* and *XXI* had a limit activity (doses 0·55 or 0·9 mg/kg), compound *IX* had an 85·5% activity at a 1·2 mg/kg dose.

The protective effect of the compounds against adrenaline and noradrenaline in normal rats (males 160 to 180 g, fasting for 18 h, with the food given after administration of the tested compound) was determined so that 1 hour after adminitration of various doses of the tested substances adrenaline was injected intravenously in a 0·4 mg/kg dose or noradrenaline in a 1·0 mg/kg dose, which are approximately the lowest 100% active lethal doses. In compound *IX*, administered subcutaneously the PD_{50} (protective dose) against adrenaline was 0·34 mg/kg and against noradrenaline 3·4 mg/kg; for compound *X* PD_{50} against adrenaline was 3·5 mg/kg.

The affinity to α_1 adrenergic receptors was determined from the inhibition of the binding of 0·25 nM of ^{3}H-prazosine in the rat brain in vitro (ref.[11]). The compounds were tested in 1 000 nmol l^{-1} concentration. The values IC_{50} mean the concentration of the compound in the incubation medium inhibiting the binding of ^{3}H-prazosine to 50%. The affinity of the compounds to D_2 receptors of dopamine was determined from the inhibition of the binding of ^{3}H-spiperone (ref.[12]). IC_{50} (nM α_1--receptors; D_2-receptors): *IV* (>1 000; not determined), *V* (39·2; >200), *VI* (135; 218), *VIII* (44·4; 24·5), *IX* (35·2; 31·3), *X* (94·4; 52·5), *XI* (112·8; not determined), *XII* (347·3; not determined), *XIII* (853·7; not determined), *XIV* and *XVIII* (not determined; >200), *XV*, *XIX*–*XXI*, *XXIII* (>1 000; >1 000), *XVI* (<1 000; 112·4), *XVII* (243; <1 000), *XXIV* (184·0; 103·5), *XXV* (319; 93·5).

The effect on α_2-adrenergic receptors in vivo was determined only for compounds *XI*, *XIV*, *XV*, *XVIII* and *XIX*, in the test of the inhibition of clonidine hypothermy. The compounds were administered to rats in a 10 mg/kg dose p.o. Only after the administration of compound *XI* a weak inhibition of the effect of clonidine was observed.

The dopaminergic effect of the compounds in CNS was investigated in vivo on rats using the test of rotation after unilateral lesion of nigrostriatal neuronal pathways[13]. The compounds were applied in doses 5 to 10 mg/kg, i.p.; the compounds, during the application of which the animals died, were administered in a 20 mg/kg dose p.o. Contralateral rotation (with respect to the side of the lesion) was also observed. For compounds with which an effect could not be detected, potentiation or inhibition of the rotation elicited with apomorphine (0·25 mg/kg s.c.) was also determined. Of the compounds tested (*IV*–*XV*, *XVIII*–*XX*, *XXVI*) compound *XI* was weakly active in the rotation test. Compound *IX* inhibited the effect of apomorphine, similarly as compound *V* in which toxicity manifested itself, the same as in compounds *VIII* and *X*. For compounds *IV*–*VI* and *IX* the effect on catalepsy produced by perphenazine was also determined. The compounds were administered in doses of 10 to 20 mg/kg s.c. or p.o. Only in compound *V* an increase in the cataleptic effect of perphenazine was found, but the compound produced toxic symptoms. The effect on body temperature was tested in compounds *XI*, *XIV*, *XV*, *XVIII*, and *XIX*, which were without effect in a 10 mg/kg dose.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Analytical samples were dried in vacuo at approx. 20 Pa and 100°C to constant weight. The specific rotations of the compounds were determined with a Perkin–Elmer 141 polarimeter. The UV spectra were measured on a Pye Unicam SP 8000 spectrophotometer in concentrations $1 \cdot 10^{-5}$ mol l^{-1} in methanol. The IR spectra were recorded in KBr pellets using IR435-Shimadzu and Perkin–Elmer 577 instruments. The ^{1}H NMR spectra were measured using a Tesla BSC 487 (80 MHz) instrument, at about 10% concentration in deuterated dimethyl sulfoxide, with tetramethylsilane as internal reference; the δ values are expressed in ppm. The purity of the compounds and the reaction course were checked by thin-layer chromatography on silica gel with a luminescent indicator (Silufol UV 254, Kavalier) in a benzene–dioxane–ethanol–triethylamine 50 : 40 : 10 : 5 mixture; the spots were detected under UV light at 254 nm and by spraying the plate first with a 10% *p*-toluenesulfonic acid solution in methanol and, after drying, with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane. Column chromatography was carried out on silica gel (Merck Kieselgel 60). The solvents were evaporated on a vacuum rotatory evaporator, using a water pump and a 40°C warm water bath.

6-Demethyl-6-cyano-9,10-dihydroergopeptines *III* and *IV*

A solution of cyanogen bromide (6·27 g, 0·059 mol or 5·96 g, 0·056 mol) in 30 ml of chloroform prepared according to ref.[14] was added to a solution of base *I* (20·0 g, 0·0343 mol) or *II* (20·0 g,

0·0327 mol), respectively, and the mixture was stirred at room temperature for 30 h, filtered and evaporated. The residue was chromatographed on a silica gel column (200 g) using chloroform with 5—10% of ethanol as eluent. Corresponding fractions were combined and the products crystallized (Tables I and II).

6-Demethyl-9,10-dihydroergopeptines *V* and *VI*

A suspension of Raney nickel (50 ml) in dioxane (71 ml) was added to a solution of the base *III* (14·74 g, 0·0248 mol) or *IV* (13·65 g, 0·022 mol), respectively, in a mixture of dioxane (180 ml) and water (25 ml), and the mixture was hydrogenated at 40°C and atmospheric pressure and under stirring for 4 h. The catalyst was filtered off under suction, the solvent evaporated and the residue chromatographed on a silica gel column (500 g). Elution with chloroform–5% ethanol separated a substance which was identified as 6-demethyl-6-formyl-9,10-dihydroergotamine (*XXVI*, see Table I). The bases *V* and *VI* were eluted with chloroform containing 10 to 20% ethanol. The dry residues of the corresponding fractions were purified by crystallization (Tables I and II).

6-Demethyl-6-alkyl-9,10-dihydroergopeptines *VII*—*XVII*

Method A (ref.[15]): Corresponding aldehyde (8·8 mmol) and sodium cyanoborohydride (0·50 g, 8 mmol) were added to a solution of base *V* (2·28 g, 4 mmol) or *VI* (2·39 g, 4 mmol), respectively, in a mixture of methanol (40 ml) and chloroform (12 ml), and the pH of the mixture was adjusted to 5·2 with acetic acid. After 4 h stirring at room temperature the reaction mixture was diluted with chloroform (100 ml) and extracted with dilute ammonia (80 ml, 1 : 9) and water (40 ml). The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by column chromatography on silica gel (80 g). Using this method compounds *VII*—*IX* and *XVI* were prepared (Tables I and II).

Method B: Alkylating reagent (4 mmol of allyl bromide or propargyl bromide, or ethyl bromoacetate, or 2 mmol of benzyl bromide) and anhydrous sodium hydrogen carbonate (0·67 g, 8 mmol) was added to a solution of base *V* (1·14 g, 2 mmol) in 40 ml of dioxane, or *VI* (1·20 g, 2 mmol) in 80 ml of dioxane, respectively, and the mixture was heated under argon and stirring at 50°C. The reaction course was monitored by thin-layer chromatography and the reaction time was chosen accordingly. After the termination of the reaction the mixture was evaporated to dryness. The residue was partitioned between chloroform and water. After drying over sodium sulfate the chloroform layer was evaporated to dryness and the residue chromatographed on a silica gel column (60 g). Compounds *X*—*XV* and *XVII* (Tables I and II) were prepared in this manner.

6-Demethyl-6-acetyl-9,10-dihydroergopeptines *XVIII* and *XIX*

Acetic anhydride (0·75 ml, 8 mmol) was added dropwise to a solution of base *V* (0·57 g, 1 mmol) or *VI* (0·598 g, 1 mmol), respectively, in 10 ml of pyridine and the mixture was stirred at room temperature for 1 h. After pouring it into water (125 ml) the separated substance was filtered off under suction. Compound *XVIII* was purified by crystallization (see Table I), while compound *XIX* was purified by chromatography on silica gel (20 g) using chloroform with 5% ethanol as eluent, and crystallization (see Tables I and II).

TABLE II

Spectral data of compounds *III*—*XXVI*

Compound	UV, λ_{max}, nm (log ε)	IR, $\tilde{\nu}$, cm^{-1}	^1H NMR, δ
III	288 sh (3·75) 279 (3·83) 219 (4·55) 205 (4·56)	3 300, 3 400, 3 450 (NH, OH), 2 200 (CN) 1 720, 1 660 (CO) 1 630, 1 539 (NHCO)	10·80 bs, 1 H (indole H) 9·45 bs (NHCO) 6·50—7·50 m, 9 H (ArH) 4·55 t, 1 H (5′-H) 1·55 s, 3 H (2′-CH_3)
IV	289 sh (3·76) 280 (3·84) 220 (4·56) 205 (4·58)	3 380 (NH, OH) 2 200 (CN) 1 720, 1 660 (CO) 1 620, 1 530 (NHCO)	10·80 bs, 1 H (indole H) 9·45 bs (NHCO) 6·80—7·50 m, 9 H (ArH) 4·60 bt, 1 H (5′-H) 1·09 d, 3 H, 0·92 d, 3 H ($CH(CH_3)_2$)
V	289 sh (3·72) 280 (3·81) 220 (4·53) 204 (4·55)	3 500, 3 280 (NH, OH) 1 730, 1 660 (CO) 1 630, 1 540 (NHCO)	10·80 bs, 1 H (indole H) 9·45 bs (NHCO) 6·90—7·50 m, 9 H (ArH) 4·60 bt, 1 H (5′-H) 1·55 s, 3 H (2′-CH_3)
VI	289 sh (3·72) 279 (3·81) 220 (4·53) 204 (4·56)	3 400, 3 600 (NH, OH) 1 710, 1 660 (CO) 1 630, 1 530 (NHCO)	10·80 bs, 1 H (indole H) 9·45 bs (NHCO) 6·60—7·50 m, 9 H (ArH) 4·55 bt, 1 H (5′-H) 1·03 d, 3 H, 0·90 d, 3 H ($CH(CH_3)_3$)
VII	289 sh (3·77) 280 (3·86) 220 (4·57) 205 (4·59)	3 280, 3 220 (NH, OH) 1 720, 1 655 (CO) 1 640, 1 545 (CONH)	10·62 bs, 1 H (indole H) 9·25 bs, 1 H (NHCO) 7·00 m, 9 H (ArH) 4·48 bt, 1 H (J = 5·0 Hz, 5′-H) 1·50 s, 3 H (2′-CH_3) 0·98 bt, 3 H (NCH_2CH_3)
VIII	290 sh (3·73) 280 (3·82) 220 (4·55) 206 (4·58)	3 300, 3 220 (NH, OH) 1 720, 1 655 (CO) 1 640, 1 550 (NHCO)	10·65 bs, 1 H (indole H) 9·30 bs (CONH) 6·60—7·50 bm, 9 H (ArH) 4·52 t, 1 H (5′-H) 1·52 s, 3 H (2′-CH_3) 0·82 t, 3 H ($NCH_2CH_2CH_3$)
IX	290 sh (3·72) 280 (3·82) 220 (4·56) 206 (4·58)	3 300, 3 140 (NH, OH) 1 720, 1 640 (CO) 1 625, 1 540 (NHCO)	8·98 bs, 1 H (indole H) 6·60—7·50 m, 9 H (ArH) 4·52 bt, 1 H (5′-H) 0·80—1·30 m (unresolved CH_3)
X	289 sh (3·87) 282 (3·95) 243 sh (4·31)	3 260, 3 220 (NH, OH) 1 720, 1 655 (CO) 1 635, 1 535 (NHCO)	10·65 bs, 1 H (indole H) 6·60—7·50 m, 9 H (ArH) 5·95 m, 1 H (allyl H)

TABLE II
(*Continued*)

Compound	UV, λ_{max}, nm (log ε)	IR, $\tilde{\nu}$, cm^{-1}	^1H NMR, δ
	224 (4·65)		5·24 bd, 1 H (H_E, J = 16·0 Hz)
	204 (4·68)		5·20 bd, 1 H (H_Z, J = 9·0 Hz)
			4·50 t, 1 H (5′-H, J = 5·0 Hz)
			1·48 s, 3 H (2′-CH_3)
XI	290 (3·75)	3 340, 3 240 (NH, OH)	10·68 bs, 1 H (indole H)
	280 (3·84)	1 730, 1 160 (CO)	9·05 bs, 1 H (NHCO)
	219 (4·57)	1 650, 1 550 (NHCO)	7·60–7·50 m, 9 H (ArH)
			5·95 m, 1 H (allyl CH)
			5·24 bd, 1 H (H_E, J = 16·0 Hz)
			3·20 bd, 1 H (H_Z, J = 9·0 Hz)
			4·55 t, 1 H (5′-H, J = 5·0 Hz)
			1·05 d, 3 H, 0·90 d, 3 H
			(2′-CH(CH_3)$_2$, J = 7·0 Hz)
XII	289 sh (3·75)	3 350, 3 120 (NH, OH)	10·68 bs, 1 H (indole H)
	280 (3·83)	3 200, 2 100 (C≡CH)	9·30 bs (NHCO)
	220 (4·57)	1 625, 1 555 (NHCO)	6·50–7·50 m, 9 H (ArH)
	204 (4·58)		4·50 t, 1 H (5′-H)
			1·50 s, 3 H (2′-CH_3)
	288 sh (3·73)	3 360, 3 180 (NH, OH)	10·60 bs, 1 H (indole H)
XIII	279 (3·82)	3 240, 2 200 (C≡CH)	9·00 bs, 1 H (NHCO)
	220 (4·55)	1 730, 1 660 (CO)	6·70–7·70 m, 9 H (ArH)
	204 (4·57)	1 630, 1 535 (NHCO)	4·50 bt, 1 H (5′-H)
			1·02 d, 6 H (2′-CH(CH_3)$_2$)
XIV	289 sh (3·76)	3 400, 3 280 (NH, OH)	10·70 bs, 1 H (indole H)
	220 (4·56)	1 721, 1 660 (CO)	9·45 bs, 1 H (NHCO)
	205 (4·58)	1 620, 1 540 (NHCO)	6·50–7·50 m, 9 H (ArH)
			4·58 bt, 1 H (5′-H)
			4·15 q, 2 H ($CO_2CH_2CH_3$)
			(J = 7·0 Hz)
			1·55 s, 3 H (2′-CH_3)
			1·25 t, 3 H ($CO_2CH_2CH_3$)
			(J = 7·0 Hz)
XV	289 sh (3·39)	3 340, 3 280 (NH, OH)	10·70 bs, 1 H (indole H)
	280 (3·87)	1 720, 1 655 (CO)	9·05 bs, 1 H (NHCO)
	219 (4·57)	1 630, 1 530 (NHCO)	6·60–7·50 m, 9 H (ArH)
	204 (4·61)		4·60 bt, 1 H (5′-H)
			4·13 q, 2 H ($CO_2CH_2CH_3$, J = 7·0 Hz)
			1·25 t, 3 H ($CO_2CH_2CH_3$,
			J = 7·0 Hz)
			1·10 d, 3 H, 0·95, 3 H
			(2′-CH(CH_3)$_2$, J = 7·0 Hz)

TABLE II
(*Continued*)

Compound	UV, λ_{max}, nm (log ε)	IR, $\tilde{\nu}$, cm^{-1}	^1H NMR, δ
XVI	290 sh (3·77) 281 (3·84) 274 sh (3·81) 205 (4·68)	3 360, 3 250 (NH, OH) 1 740, 1 660 (CO) 1 620, 1 535 (NHCO)	10·67 bs, 1 H (indole H) 9·24 bs, 1 H (NHCO) 6·55—7·50 bm, 14 H (ArH) 4·18 bs, 1 H (5′-H) 3·36 s, 2 H ($NCH_2C_6H_5$) 1·46 s, 3 H (2′-CH_3)
XVII	288 sh (3·74) 279 (3·82) 205 (4·69)	3 350, 3 280 (NH, OH) 1 730, 1 670 (CO) 1 640, 1 510 (NHCO)	(insoluble at 20°C, determined at 60°C) 10·55 bs, 1 H (indole H) 8·80 bs, 1 H (NHCO) 6·60—7·60 bm, 14 H (ArH) 4·55 bt, 1 H (5′-H, J = 5·0 Hz) 4·25 bd, 1 H, 3·50 bd, 1 H ($NCH_2C_6H_5$, J = 13·3 Hz) 0·95 bdd, 6 H (2′-$CH(CH_3)_2$, J = 7·0 Hz, J = 9·0 Hz)
XVIII	289 sh (3·75) 280 (3·81) 219 (4·57) 205 (4·60)	3 200, 3 310 (NH, OH) 1 725, 1 640, 1 650 (CO) 1 630, 1 550 (NHCO)	9·35 bs, 1 H (indole H) 6·60—7·50 m, 9 H (ArH) 6·48 bs, 1 H (NH) 4·55 t, 1 H (5′-H, J = 6·0 Hz) 2·10 s, 3 H (N–$COCH_3$) 1·54 s, 3 H (2′-CH_3)
XIX	288 sh (3·75) 279 (3·82) 219 (4·58) 204 (4·63)	3 320, 3 200 (NH, OH) 1 725, 1 660, 1 640 (CO) 1 630, 1 550 (NHCO)	9·05 bs, 1 H (indole H) 6·71—7·40 m, 10 H (ArH + CONH) 4·60 t, 1 H (5′-H, J = 6·0 Hz) 2·08 s, 3 H ($NCOCH_3$) 1·10 d, 3 H, 0·95 d, 3 H (2′-$CH(CH_3)_2$, J = 6·5 Hz)
XX	289 sh (3·68) 279 (3·75) 220 (4·49)	3 280, 3 190 (NH, OH) 1 720, 1 650 (CO) 1 615, 1 530 (NHCO) 1 310, 1 140 (NSO_2)	10·75 bs, 1 H (indole H) 9·45 bs, 1 H (NHCO) 6·55—7·45 bm, 9 H (ArH) 4·52 bt, 1 H (5′-H, J = 5·5 Hz) 3·12 bs, 3 H (NSO_2CH_3) 1·45 bs, 3 H (2′-CH_3)
XXI	289 sh (3·73) 280 (3·81) 220 (4·57) 206 (4·58)	3 300 (NH, OH) 1 730, 1 670 (CO) 1 640, 1 540 (NHCO) 1 320, 1 150 (NSO_2)	10·75 bs, 1 H (indole H) 9·15 bs, 1 H (CONH) 7·10 m, 9 H (ArH) 4·56 bt, 1 H (5′-H) 3·12 bs, 3 H (NSO_2CH_3) 1·1 bm, 6 H (2′-$CH(CH_3)_2$)

TABLE II
(*Continued*)

Compound	UV, λ_{max}, nm (log ε)	IR, $\tilde{\nu}$, cm^{-1}	^1H NMR, δ
XXII	290 sh (3·77) 281 (3·84) 274 sh (3·81) 205 (4·68)	3 340, 3 220 (NH, OH) 1 720, 1 650 (CO) 1 660 (NCOO) 1 640, 1 540 (NHCO)	10·75 bs, 1 H (indole H) 9·35 bs, 1 H (NHCO) 6·40—7·50 bm, 14 H (ArH) 5·05 ABq, 2 H ($CO_2CH_2C_6H_5$, J = 12·5 Hz, J = 20·0 Hz) 4·50 bt, 1 H (5′-H, J = 5·0 Hz) 1·52 s, 3 H (2′-CH_3)
XXIII	288 sh (3·74) 279 (3·82) 205 (4·69)	3 320, 3 250 (NH, OH) 1 730, 1 670 (CO, NCO_2) 1 640, 1 540 (NHCO)	10·7 bs, 1 H (indole H) 9·05 bs, 1 H (CONH) 7·15 m, 14 H (ArH) 5·05 ABq, 2 H ($CO_2CH_2C_6H_5$, J = 12·5 Hz, J = 21·5 Hz) 4·55 bt, 1 H (5′-H, J = 5·0 Hz) 1·08 d, 3 H, 0·95 d, 3 H (2′-CH(CH_3)$_2$, J = 7·0 Hz)
XXIV	289 (3·83) 223 (4·56)	3 400 (NH, OH) 2 820 (NCH_3) 1 735, 1 660 (CO) 1 650, 1 560 (NHCO)	6·50—7·50 m, 9 H (ArH) 4·68 bt, 1 H (5′-H) 3·70 s, 3 H (N^1–CH_3) 1·50 s, 3 H (2′-CH_3) 0·85 bt, 3 H ($NCH_2CH_2CH_3$)
XXV	288 (3·82) 222 (4·55)	3 540, 3 210 (NH, OH) 1 720, 1 630 (CO) 1 650, 1 550 (NHCO)	6·50—7·50 m, 9 H (ArH) 4·68 t, 1 H (5′-H) 3·70 s, 3 H (N–CH_3) 1·09 d, 3 H, 0·91 d, 3 H (2′-CH(CH_3)$_2$) 0·89 t, 3 H ($NCH_2CH_2CH_3$)
XXVI	289 sh (3·78) 280 (3·86) 210 sh (4·61) 206 (4·67)	3 280, 3 220 (NH, OH) 1 730, 1 640 (CO) 1 630, 1 535 (NHCO)	10·75 bs, 1 H (indole H) 9·45 bs, 1 H (CONH) 8·40 s, 1 H (CHO) 6·60—7·50 m, 9 H (ArH) 4·50 t, 1 H (5′-H, J = 5·0 Hz) 1·50 s, 3 H (2′-CH_3)

6-Demethyl-6-acyl-9,10-dihydroergopeptines *XX* and *XXIII*

The acylating reagent (2·2 mmol of methanesulfonyl chloride or benzyloxycarbonyl chloride) and triethylamine (0·308 ml, 2·2 mmol) were added to a solution of base *V* (1·14 g, 2 mmol) or *VI* (1·20 g, 2 mmol), respectively, in 40 ml dioxane and the mixture was stirred at room temperature. After the termination of the reaction the residue of the evaporated reaction mixture was

partitioned between chloroform and water. The residue of the chloroform layer was chromatographed on a silicagel column (40 g), using chloroform with 5% ethanol for elution (Tables I and II).

1-Methyl-6-demethyl-6-propyl-9,10-dihydroergopeptines *XXIV* and *XXV* (procedure according to ref.[7])

Potassium metal (59 mg, 1·5 mmol) was dissolved in 270 ml of liquid ammonia and the persisting blue coloration of the complex was decolourized with a few crystals of iron(III) nitrate. Base *VIII* (0·612 g, 1 mmol) or *IX* (0·640 g, 1 mmol), respectively, was added to the above solution, followed by methyl iodide (0·094 ml, 1·5 mmol) in 5 ml of diethyl ether. After 2 h stirring and refluxing ammonia was eliminated with a stream of argon, under which the reaction was carried out. The residues were chromatographed on silica gel columns (20 g) with chloroform containing 10% of ethanol (for other data see Tables I and II).

The elemental analyses were carried out by Mrs J. Komancová and Dr M. Čech of the analytical department of this Institute (Dr J. Körbl head, and Dr J. Dohnal).

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