SOME 6-ALKYL DERIVATIVES OF D-8-CYANOMETHYL AND D-8-METHYL ERGOLINE-I*

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Alkylation of D-8-cyanomethylergoline-I(*XV*) or of D-6-norfestuclavine (*XXVI*) with alkyl halogenides in dimethylformamide yielded 8-substituted D-6-alkylergolines-I *III*–*XIII*. Compounds *III*, *IV* and *VI* were also obtained by a reaction of sodium cyanide with D-6-alkyl-8-chloromethylergolines-I *XXIII*–*XXV* which were prepared from the methyl esters of D-6-nor-6-alkyl-9,10-dihydrolysergic acids *XVII*–*XIX via* the 8-hydroxymethyl derivatives *XX*–*XXII*. Compounds *III*–*XIII* displayed an antilactation and an antinidation effect in rats.

In an earlier paper[1] we described the synthesis of D-6-methyl-8-cyanomethylergoline-I (*I*) which showed a distinct prolactin-inhibiting effect in rats reflected in suppressed lactation and nidation[2]. It was of interest to see in what way the biological properties of *I* and of festuclavine (D-1,6-dimethylergoline-I) (*II*) (ref.[3]) would be affected by introducing another alkyl into position 6. In this context we prepared D-6-alkyl-8-cyanomethylergolines-I *III*–*VII* and D-6-alkyl-8-methylergolines-I (6-nor-6-alkylfestuclavines) *VIII*–*XIII*. Some analogous 2-chloro-6-alkyl-8-cyanomethylergolines-I were recently described[4].

Compounds *III*–*VII* were synthesized in two ways. In the first, compound *I* was demethylated with cyanogen bromide in dichloromethane at room temperature to obtain D-6-cyano-8-cyanomethylergoline-I (*XIV*) which underwent a selective reduction of the cyano group in position 6 of the ergoline ring with zinc in acetic acid (method in[4,5]) to yield the 6-nor derivative *XV*. Other ways of removing the 6-CN group, such as hydrogenation in the presence of Raney nickel[5] or action of sodium borohydride[6], were less useful from the point of view of yields. Alkylation of *XV* with alkyl halogenides in dimethylformamide at 20–100°C in the presence of potassium carbonate or triethylamine as a compound binding the hydrogen halide formed, yielded the 6-alkyl derivatives *III*–*VII*. In the second way we alkylated the methyl ester of 6-nor-9,10-dihydrolysergic acid[5] (*XVI*), the 6-alkyl derivatives obtained (*XVII*–*XIX*) were reduced with lithium aluminium hydride in ether to D-6-alkyl-8-hydroxymethylergolines-I *XX*–*XXII* which reacted with phosphorus

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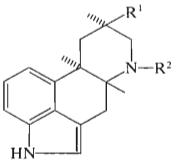
oxychloride at the boiling point of the mixture and were converted to D-6-alkyl--8-chloromethylergolines-I *XXIII*–*XV*. The last-named compounds reacted with sodium cyanide in dimethyl sulfoxide at a raised temperature to yield *III*, *IV* and *VI*.

Compounds *VIII*–*XIII* were synthesized analogously by alkylation of 6-norfestuclavine (*XXVI*) using alkyl halogenides in dimethylformamide in the presence of potassium carbonate. The nor derivative *XXVI* required here was prepared by the action of potassium on a solution of *XIV* or of D-6-nor-6-cyanofestuclavine (*XXVII*) in hexamethyltriamide of phosphoric acid at 20–40°C. In the first case the reaction is accompanied by a reduction of both nitrile groups in *XIV* and compound *XXVI* is formed in a 88·5% yield; in the second case a reductive decyanization results in the same yield. Compound *XXVII* was prepared in analogy to *XIV* by the action of cyanogen bromide on a solution of festuclavine in dichloromethane at room temperature. The yields and some physico-chemical properties of the 6-alkylergoline prepared (*III*–*XIII* and *XVIII*–*XXV*) are shown in Table I.



I, $R^1 = CH_2CN$, $R^2 = CH_3$
II, $R^1 = R^2 = CH_3$
III–*XIII* see Table I
XIV, $R^1 = CH_2CN$, $R^2 = CN$
XV, $R^1 = CH_2CN$, $R^2 = H$

XVI, $R^1 = COOCH_3$, $R^2 = H$
XVII, $R^1 = COOCH_3$, $R^2 = C_2H_5$
XVIII–*XXV* see Table I
XXVI, $R^1 = CH_3$, $R^2 = H$
XXVII, $R^1 = CH_3$, $R^2 = CN$

The antilactation and antinidation effects of *III*–*XIII* in rats were evaluated by Drs K. Řežábek and M. Aušková of this institute (for method see[7–9]). It was found that the introduction of the ethyl and of the n-propyl group into position 6 of the ergoline cycle of the compounds (*III*, *IV*, *VIII* and *IX*) brings about an increase of efficiency by an order of magnitude as compared with the 6-methyl derivatives *I* and *II*. On the other hand, the analogous 6-n-butyl compounds *VI* and *XI* and the n-heptyl compound *XIII* were little effective in these tests. Some of the compounds prepared (*e.g. III* and *IV*) showed a significant brief hypotensive effect on rats in urethane narcosis (for testing method see[9]). Details on the biological properties of *II*–*XIII* will be reported elsewhere.

TABLE I

8-Substituted 6-Alkylergolines-I

Compound R^2	Method (yield, %)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*)	Formula (mol. wt.)	Calculated/Found % C	% H	% N
			$R^1 = CH_2CN$				
III	*A*[a] *B*	253—255	−95	$C_{18}H_{21}N_3$	77·38	7·58	15·04
C_2H_5	(86) (65)	(ethanol)	(0·4)	(279·4)	77·54	7·82	14·76
IV[b]	*A*[c] *B*	264—266	−82·5	$C_{19}H_{23}N_3$	77·78	7·90	14·32
n-C_3H_7	(95) (57)	(95% ethanol)	(0·4)	(293·4)	77·67	7·94	14·12
V	*A*[d]	256—258	−99·5	$C_{19}H_{23}N_3$	77·78	7·90	14·32
i-C_3H_7	(80)	(ethanol)	(0·41)	(293·4)	77·76	7·84	14·25
VI	*A*[e] *B*	186—188	−79·1	$C_{20}H_{25}N_3$	78·13	8·20	13·67
n-C_4H_9	(94) (78)	(ethanol)	(0·37)	(307·4)	78·46	8·14	13·83
VII	*A*[f]	237—239	−93·1	$C_{20}H_{25}N_3$	78·13	8·20	13·67
i-C_4H_9	(75)	(ethanol)	(0·38)	(307·4)	78·23	8·28	13·55
			$R^1 = CH_3$				
VIII	*A*[g]	257—258	−107·7	$C_{17}H_{22}N_2$	80·27	8·72	11·01
C_2H_5	(87)	(chloroform–methanol)	(0·34)	(254·4)	79·93	8·77	11·00
IX	*A*[h]	188—190	−76·1	$C_{18}H_{24}N_2$	80·55	9·01	10·44
n-C_3H_7	(87)	(methanol–benzene)	(0·40)	(268·4)	80·65	9·04	10·69
X	*A*[i]	249—251	−95·6	$C_{18}H_{24}N_2$	80·55	9·01	10·44
i-C_3H_7	(39)	(benzene)	(0·37)	(268·4)	80·44	8·93	10·36
XI	*A*[j]	173—175	−78·2	$C_{19}H_{26}N_2$	80·81	9·28	9·92
n-C_4H_9	(90)	(methanol)	(0·37)	(282·4)	80·79	9·23	9·86
XII	*A*[k]	145—147	−85·2	$C_{19}H_{26}N_2$	80·81	9·28	9·92
i-C_4H_9	(71)	(methanol–chloroform)	(0·34)	(282·4)	80·67	9·48	9·63
XIII	*A*[l]	148—150	−55·7	$C_{22}H_{32}N_2$	81·43	9·94	8·63
n-C_7H_{15}	(54)	(methanol–chloroform)	(0·40)	(324·5)	81·34	9·63	8·51
			$R^1 = COOCH_3$				
XVIII	*A*[m]	212—214	−63·0[n]	$C_{19}H_{24}N_2O_2$	73·04	7·74	8·97
n-C_3H_7	(56)	(ethyl acetate)	(0·42)	(312·4)	73·12	7·85	8·84
XIX	*A*[o]	169—171	−62·8[p]	$C_{20}H_{26}N_2O_2$	73·58	8·03	8·58
n-C_4H_9	(61)	(methanol)	(0·47)	(326·4)	73·26	8·07	8·45

TABLE I
(*Continued*)

Compound R^2	Method (yield, %)	M.p., °C (solvent)	$[\alpha]_D^{20}$ (*c*)	Formula (mol. wt.)	Calculated/Found % C	% H	% N
			$R^1 = CH_2OH$				
XX	*C*	252–254[q]	−91·0	$C_{17}H_{22}N_2O$	75·51	8·20	10·36
C_2H_5	(92)		(0·5)	(270·4)	75·08	8·21	10·33
XXI	*C*	181–182	−66·0	$C_{18}H_{24}N_2O$	76·01	8·51	9·85
n-C_3H_7	(86)	(water–ethanol)	(0·5)	(284·4)	75·74	8·23	9·68
XXII	*C*	152–154[r]	−68·2	$C_{19}H_{26}N_2O$	76·46	8·78	9·39
n-C_4H_9	(78)	(water–ethanol)	(0·5)	(298·4)	76·16	8·53	9·38
			$R^1 = CH_2Cl$				
XXIII[s]	*D*	239–241	−87·0	$C_{17}H_{21}ClN_2$	70·69	7·33	9·70
C_2H_5	(58)	(ethanol–hexane)	(0·2)	(288·8)	71·23	7·42	9·70
XXIV[t]	*D*	232–234[q]	−67·5	$C_{18}H_{23}ClN_2$	71·38	7·65	9·25
n-C_3H_7	(57)		(0·4)	(302·9)	71·13	7·74	9·14
XXV[u]	*D*	186–188	−62·0	$C_{19}H_{25}ClN_2$	72·01	7·95	8·84
n-C_4H_9	(63)	(ethanol–hexane)	(0·4)	(316·9)	71·62	8·21	8·78

[a] 0·25 g (1·6 mmol) ethyl iodide, 0·22 g (1·6 mmol) K_2CO_3, 8 h at 20°C; [b] UV spectrum (in methanol): λ_{max} 224 (4·05), 270 (3·81), 275 (3·83), 291 (3·75) nm (log ε); [c] 0·37 g (3·0 mmol) n-propyl bromide, 0·415 g (3·0 mmol) K_2CO_3, 24 h at 60°C, or 0·37 g (3·0 mmol) n-propyl bromide, 0·30 g (3·0 mmol) triethylamine, 20 h at 80°C; [d] 3·08 g (25 mmol) isopropyl bromide, 0·885 g (6·4 mmol) K_2CO_3, 50 h at 95°C; [e] 0·552 g (3·0 mmol) n-butyl iodide, 0·21 g (1·5 mmol) K_2CO_3, 16 h at 60°C; [f] 3·42 g (25 mmol) isobutyl bromide, 0·21 g (1·5 mmol) K_2CO_3, 23 h at 95°C; [g] 0·312 g (2 mmol) ethyl iodide, 0·22 g (1·6 mmol) K_2CO_3, 7 h at 20–25°C; [h] 0·339 g (2 mmol) n-propyl iodide, 0·276 g (2 mmol) K_2CO_3, 14 h at 20–25°C and 2 h at 50°C; [i] 0·246 g (2 mmol) isopropyl bromide, 0·22 g (1·6 mmol) K_2CO_3, 16 h at 80°C; [j] 0·368 g (2 mmol) n-butyl iodide, 0·276 g (2 mmol) K_2CO_3, 14 h at 20–25°C and 2 h at 50°C; [k] 0·274 g (2 mmol) isobutyl bromide, 0·22 g (1·6 mmol) K_2CO_3, 16 h at 80°C; [l] 0·358 g (2 mmol) n-heptyl bromide, 0·276 g (2 mmol) K_2CO_3, 8 h at 80°C; [m] 0·425 g (2·5 mmol) n-propyl iodide, 0·22 g (1·6 mmol) K_2CO_3, 35 h at 20°C; [n] in dichloro methane; [o] 0·30 g (2·2 mmol) n-butyl bromide, 0·22 g (1·6 mmol) K_2CO_3, 32 h at 20°C; [p] in methanol; [q] crystallized from a mixture of ethanol and chloroform and cyclohexane; [r] from the solvent mixture shown it crystallizes as monohydrate; for $C_{19}H_{26}N_2O.H_2O$ (316·4) calculated: 72·11% C, 8·92% H, 8·86% N, 5·70% H_2O; found: 72·08% C, 8·70% H, 8·84% N, 5·87% H_2O (loss on drying at 117°C/0·2 Torr); [s] calculated: 12·28% Cl, found: 12·71% Cl; [t] calculated: 11·71% Cl, found: 11·97% Cl; [u] calculated: 11·19% Cl, found: 11·15% Cl.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected. Samples of compounds for analysis were dried *in vacuo* (0·2 Torr) at a temperature raised in proportion to their melting point. Specific rotations were determined in pyridine (unless stated otherwise) using a Perkin-Elmer 141 polarimeter and they refer to compounds free of crystal solvent. UV spectra were recorded in an Optica Milano CF 4R spectrophotometer, IR spectra in an Infrascan Hilger and Watts spectrophotometer. The homogeneity of compounds was checked by paper chromatography in benzene or chloroform using paper impregnated with formamide and ammonium formate, or in 1-butanol–acetic acid–water (4 : 1 : 5). In this case detection was done in UV light after previous illumination of the chromatogram with sunlight. An alternative method of chromatography was the use of reflexion silica gel plates containing a luminescence indicator (Silufol UV_{254} by Kavalier) in chloroform–ethanol–triethylamine (90 : 10 : 5) — in this case detection was done with UV light at 254 nm or with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane and hydrogen chloride vapour.

D-6-Cyano-8-cyanomethylergoline-I (*XIV*)

Cyanogen bromide (0·7 g, 6·5 mmol) was added to a solution of 1·33 g (5 mmol) *I* in 175 ml dichloromethane and the mixture was stirred for 7 days at room temperature. The small amount of precipitate was filtered, the filtrate was shaken with 10% tartaric acid and the solvent was distilled from the organic fraction at reduced pressure. The residue (1·30 g) was crystallized from 95% aqueous ethanol to yield neutral *XIV* (0·8 g), m.p. 276—278°C (under decomposition), $[\alpha]_D^{20}$ + 46·2° (*c* 0·4); IR (KBr): *v* 3400 (NH), 2245 (—CH_2CN), 2210 (NCN) cm^{-1}. For $C_{17}H_{16}N_4$ (276·4) calculated: 73·89% C, 5·84% H, 20·27% N; found: 73·86% C, 5·87% H, 20·52% N.

6-Nor-6-cyanofestuclavine (*XXVII*)

The compound was prepared from festuclavine (*II*) (240 mg, 1·1 mmol) and cyanogen bromide (159 mg, 1·5 mmol) in dichloromethane (40 ml) in the same way as *XIV*; the yield was 87·7%. M.p. 279—281°C (ethanol), $[\alpha]_D^{20}$ + 78·8° (*c* 0·34). For $C_{16}H_{17}N_3$ (251·3) calculated: 76·46% C, 6·82% H, 16·72% N; found: 76·59% C, 6·94% H, 16·81% N.

D-8-Cyanomethylergoline-I (*XV*)

Solution of 0·60 g *XIV* in a mixture of 120 ml acetic acid with 2·4 ml water was combined with 3·4 g zinc powder. The mixture was refluxed under stirring in an atmosphere of nitrogen for 7 h and filtered while hot, the filtrate was evaporated at reduced pressure, the residue was divided between 25 ml water and 25 ml chloroform, the aqueous fraction was shaken with 3 × 25 ml chloroform and alkalified with ammonia to pH 8. The precipitate was filtered, dried (0·46 g) and purified by chromatography on a column of silica gel (7 g) using a mixture of chloroform and ethanol (9 : 1) for elution. After crystallization from 90% ethanol, *XV* was obtained, melting at 273—275°C (under decomposition), $[\alpha]_D^{20}$ — 49·5° (*c* 0·4); p*K* (in 80% aqueous methyl cellosolve) 6·70; IR spectrum (KBr): 3425 (indole NH), 3300 (NH), 2240 (—CH_2—CN) cm^{-1}. For $C_{16}H_{17}N_3$ (251·3) calculated: 76·46% C, 6·82% H, 16·72% N; found: 76·42% C, 7·03% H, 17·00% N. Hydrogen tartrate of the base was prepared by using equimolar amounts of both components in ethanol: m.p. 205—207°C (under decomposition; 90% ethanol). $[\alpha]_D^{20}$ — 16·0° (*c* 0·4, water). For $C_{20}H_{23}N_3O_6$ (401·4) calculated: 59·84% C, 5·78% H, 10·47% N; found: 59·59% C, 5·74% H, 10·74% N.

6-Norfestuclavine (*XXVI*)

a) *From* XXVII: A solution of 503 mg (2 mmol) *XXVII* in 30 ml hexamethyltriamide of phosphoric acid was combined under stirring in an atmosphere of nitrogen with 780 mg (20 mmol) potassium added in parts and the mixture was stirred at 20—25°C for 3 h. After pouring the mixture into water (300 ml) the precipitate was filtered and washed with water. After recrystallization of the crude product (402 mg, 89%) from a mixture of chloroform with methanol (1 : 1) pure *XXVI* was obtained, m.p. 242—245°C, $[\alpha]_D^{20}$ — 35·9° (*c* 0·35). For $C_{15}H_{18}N_2$ (226·3) calculated: 79·61% C, 8·01% H, 12·38% N; found: 79·32% C, 8·02% H, 12·32% N.

b) *From* XIV: Compound *XIV* (276 mg, 1 mmol) in phosphoric acid hexamethyltriamide (10 ml) was treated at 40°C with 390 mg potassium (10 mmol) by the same procedure as used under (*a*) to obtain crude *XXVI* (200 mg, 88·5%) which was recrystallized from a mixture of chloroform and methanol to yield a product melting at 242—245°C, identical with the compound obtained under (*a*).

8-Substituted 6-Alkylergolines *III*—*XIII* and *XVIII*—*XXV*

Method A: A solution of 1 mmol 6-nor-derivative (251 mg, *XV*, 226 mg *XXVI*, 270 mg *XVI*) in 10 ml dimethylformamide was combined with 0·21—0·885 g (1·5—6·4 mmol) potassium carbonate or 0·151—0·303 g (1·5—3·0 mmol) triethylamine and 1·5—25 mmol alkyl halogenide. The mixture was stirred at 20—100°C (the reaction conditions for the individual compounds are seen in Table I), diluted with 100 ml water, or else most of the dimethylformamide was distilled at reduced pressure and the residue was stirred with 25 ml water, the pH of the mixture was adjusted with ammonia to 7—7·5, the precipitated compound was filtered and the crude product was purified by column chromatography on silica gel (eluted with chloroform and ethanol 9 : 1) and crystallization. The yields, melting points and solvents used for crystallization are shown in Table I.

Method B: A mixture of 1 mmol 8-chloromethyl derivative (289 mg *XXIII*, 303 mg *XXIV*, 317 mg *XXV*), 0·25 g (5 mmol) sodium cyanide and 6·5 ml dimethyl sulfoxide was heated for 3 h to 120°C and the solution was poured into 30 ml water. The precipitate was heated for 15 min to 65°C with 20 ml water, filtered, dried and crystallized. The yields, melting points and solvents used for crystallization are shown in Table I.

Method C: A solution of 7·32 mmol of the appropriate methyl ester (2·18 g *XVII* (ref.[5]), 2·28 g *XVIII*, 2·385 g *XIX*) in 640 ml ether was added dropwise to a suspension of 4·59 g (121 mmol) lithium aluminium hydride in 1 200 ml ether stirred under nitrogen. The mixture was then stirred for 3 h at room temperature and combined dropwise with a mixture of ethanol (27 ml) and water (9 ml). The inorganic fraction was filtered, extracted with 3 × 200 ml boiling mixture of chloroform with ethanol (4 : 1), the organic fractions were combined, dried with Na_2CO_3, the solvents were distilled at reduced pressure and the residue was crystallized. The yields, melting points, and solvents used for crystallization are shown in Table I.

Method D: A mixture of 1·78 mmol 8-hydroxymethylergoline (0·48 g *XX*, 0·505 g *XXI*, 0·563 g hydrate of *XXII*) and 30 ml phosphorus oxychloride was refluxed for 3 h. The volatile fractions were distilled at reduced pressure, the residue was heated for 15 min to 90—95°C with 5% sodium hydrogen carbonate and the precipitated product was filtered. The crude product was chromatographed on a column of silica gel using chloroform with 1% ethanol for elution. The yields of chromatographically purified products, their melting points and solvents used for crystallization are shown in Table I.

The analyses were done by Mrs J. Komancová at the analytical department (headed by Dr J. Körbl), paper chromatography by Mrs M. Jelínková under the direction of Dr V. Rábek. The UV and IR spectra were registered by Dr J. Vachek at the physico-chemical department of this institute.

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