ALKYLATION OF ERGOLINE DERIVATIVES AT POSITION $N_{(1)}$*

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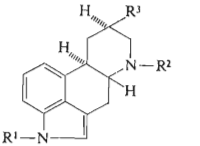
$N_{(1)}$-Alkyl-8β-ergolines *I*—*XII* were prepared by alkylation of 8β-ergoline derivatives *XIII* to *XVIII* with alkyl halides in dimethyl sulphoxide in the presence of potassium hydroxide. The compounds *I*—*XII* exhibited weak inhibition effects on the secretion of prolactin.

$N_{(1)}$-Alkylation of ergoline derivatives has so far been effected by exposure of an $N_{(1)}$ non-substituted derivative to the action of alkyl halide in liquid ammonia containing potassium amide[1]. This paper describes syntheses of $N_{(1)}$-alkyl derivatives of 8β-ergolines, *I*—*XII* (Table I), from compounds *XIII*—*XVIII* by a procedure analogous to that used for alkylation of indole[2]. The reaction conditions were modified to obtain maximum yields. The alkylation was carried out by the action of alkyl halides in dimethyl sulphoxide in the presence of a base (KOH, NaOH, NaH). The alkyl halide was added to a cooled reaction mixture gradually. In the use of dimethylformamide, hexamethylphosphorictriamide or tetramethylurea, instead of dimethyl sulphoxide, the yields were lower.



I—*XII* See Table I

XIII, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_3$ (ref.[7])
XIV, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2CN$ (ref.[8])
XV, $R^1 = H$, $R^2 = n\text{-}C_3H_7$, $R^3 = CH_2CN$ (ref.[3])
XVI, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2OH$ (ref.[5,8])
XVII, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2CONH_2$ (ref.[9])
XVIII, $R^1 = H$, $R^2 = CH_3$, $R^3 = COOH$ (ref.[1])

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TABLE I

Derivatives of 1-alkyl-substituted 8β-ergolines

Compound	R^2	Procedure	Formula	M.p., °C	$(\alpha)_D^{20}$(°, *c* 0·5)	Calculated/Found		
R^1	R^3	yield, %	(m.w.)	(solvent)	(solvent)	% C	% H	% N
I	CH_3	*A*	$C_{17}H_{22}N_2$	121—123	−107	80·26	8·72	11·02
CH_3	CH_3	46	(254·4)	(CH_3OH)	(pyridine)	80·07	8·98	10·98
II[a]	CH_3	*A*	$C_{18}H_{21}N_3$	171—173	−103	77·38	7·58	15·04
CH_3	CH_2CN	62	(279·4)	(C_2H_5OH)	(pyridine)	77·62	7·68	14·82
III	CH_3	*A*	$C_{19}H_{23}N_3$	161—162	−114	77·78	7·90	14·32
C_2H_5	CH_2CN	55	(293·4)	(C_2H_5OH)	(pyridine)	77·55	8·09	14·10
IV	CH_3	*A*	$C_{20}H_{25}N_3$	137—138	−108	78·13	8·20	13·67
n-C_3H_7	CH_2CN	48	(307·4)	(C_2H_5OH)	(pyridine)	77·85	8·46	13·82
V	n-C_3H_7	*A*	$C_{20}H_{25}N_3$	127—128	— 88	78·13	8·20	13·67
CH_3	CH_2CN	58	(307·4)	(C_2H_5OH)	(pyridine)	78·06	8·49	13·97
VI[b]	CH_3	*B*	$C_{17}H_{22}N_2O$	250—252	— 93	75·51	8·20	10·36
CH_3	CH_2OH	82	(270·4)	(C_2H_5OH)	(pyridine)	75·67	8·27	10·18
VII	CH_3	*B*	$C_{18}H_{23}N_3O$	261—263	— 85	72·69	7·79	14·13
CH_3	CH_2CONH_2	64	(297·4)	(CH_3OH)	(pyridine)	72·73	7·74	14·10
VIII	CH_3	*B*	$C_{20}H_{27}N_3O$	142—144	— 86	73·80	8·36	12·91
n-C_3H_7	CH_2CONH_2	42	(325·4)	(CH_3OH)	(pyridine)	73·73	8·37	12·99
IX[c]	CH_3	*C*	$C_{17}H_{20}N_2O_2$	over 360	— 76	71·80	7·09	9·85
CH_3	COOH	88	(284·4)	(H_2O)	(0·1M-NaOH)	71·64	7·26	9·67
X	CH_3	*C*	$C_{18}H_{22}N_2O_2$	298—301	— 84	72·45	7·43	9·39
C_2H_5	COOH	47	(298·4)	(H_2O)	(0·1M-NaOH)	72·36	7·54	9·37
XI	CH_3	*C*	$C_{19}H_{24}N_2O_2$	260—262	— 84	73·04	7·74	8·97
n-C_3H_7	COOH	35	(312·4)	(H_2O)	(0·1M-NaOH)	72·97	7·90	8·82
XII[d]	CH_3	*C*	$C_{23}H_{24}N_2O_2$	223—225	— 98	76·64	6·71	7·77
$C_6H_5CH_2$	COOH	52	(362·5)	(H_2O)	(0·1M-NaOH)	76·59	6·84	7·57

[a] Reported[4] m.p. 173—175°C, $(\alpha)_D^{20}$ −105° (*c* 0·5, pyridine); [b] reported[5] m.p. 243—246°C, $(\alpha)_D^{20}$ −98° (*c* 0·5, pyridine); [c] reported[6] $(\alpha)_D^{20}$ −76° (*c* 0·5, 0·1M-NaOH); [d] reported[1] m.p. 217—222°C, $(\alpha)_D^{20}$ −106° (*c* 0·5, pyridine).

The effect of the compounds *I*–*XII* on the secretion of adenohypophyseal prolactin was determined with the aid of the antinidation and antilactation effects. We have found that alkylation at position $N_{(1)}$ leads to a lower activity compared to the non-alkylated compounds[3–9]. These tests were performed in the Research Institute for Pharmacy and Biochemistry under the direction of Dr K. Řežábek.

EXPERIMENTAL

The melting points, determined on the Boetius block, are not corrected. Analytical samples were dried *in vacuo* (30 Pa) at temperatures corresponding to their melting points. Specific rotations, determined in a polarimeter Perkin–Elmer 141, refer to compounds free of the crystallization solvent. Purity of the compounds was checked by thin-layer-chromatography on silica gel with a luminiscent indicator (Silufol UV_{254}, Kavalier), UV light of the wave length 254 nm being used as detector.

Alkylation of 8β-Ergolines

To a mixture of pulverized potassium hydroxide (5·6 g, 0·1 mol) in dimethyl sulphoxide (50 ml), which had been stirred for 10 min, was added a derivative of 8β-ergoline (0·02 mol) at room temperature and the mixture was stirred for 30 min, then cooled down to 17°C. At this temperature an alkyl halide (0·024 mol) was added dropwise under stirring in the course of 5 min (alkyl iodides in the syntheses of compounds *I*—*III*, *V*—*VII*, *IX* and *X*, bromides for compounds *IV*, *VIII* and *XI*, and benzyl chloride for *XII*). After another 5 min the solution was poured into 500 ml of water and *A*) extracted with chloroform, the extract was washed with water, dried with $MgSO_4$, taken to dryness and the residue was crystallized from the solvent given in Table I; *B*) the precipitate was collected on a filter, washed with water and recrystallized from the solvent given in Table I; *C*) the solution was discoloured with active carbon, brought to pH 6 with acetic acid, the precipitate was collected on a filter and dissolved in 2% aqueous ammonia. The solution was acidified with acetic acid to pH 6 and the separated product was collected on a filter, washed with water and dried *in vacuo*.

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