2-ACYLATED DERIVATIVES OF ERGOLINE*

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Reaction of ergoline derivatives *Ia—VIIa* with anhydrides of low-molecular-weight aliphatic acids, catalysed by boron trifluoride etherate, gave 2-acylated derivatives *Ib—Id*, *IIb—IId*, *IIIb—Vb*, or 1,2-diacylated derivatives *VIb* and *VIIb*. The compound *IIb* exhibited a hypotensive effect.

Substitution reactions of ergot alkaloids and their semi-synthetic derivatives at position 2 lead, in some cases, to essential changes in their biological activity[1]. Although halogenation was the reaction most frequently used[2] for this purpose, the high reactivity of position 2 in ergoline derivatives for an electrophilic aromatic substitution has so far been made use of for syntheses of other numerous compounds, of which many proved physiologically active. Thus ergoline derivatives were subjected to nitration[3], the Mannich reaction[4], an acid-catalysed dimerization[5], and to the reaction with carbonyl compounds[6]. However, none of these derivatives is convenient for chemical modification of the substituent at position 2, and thus for modification of the biological activity. The reactive formyl group was attached to position 2 by a two-step synthesis, consisting in the Friedel–Crafts dithiolanization[7], followed by dethioketalization[8]. However, a direct acylation or the Vilsmayer–Haack reaction of an ergoline derivative has not yet been effected, and other common acylation procedures have also ended in failure[7].

The present paper describes our attempts to attach higher acyls to the 2-position, *i.e.* to synthetize compounds having not only an electron-deficient carbonyl carbon (a^1 reactivity according to Seebach[9]), but also d^2 reactivity that could be made use of for further synthesis.

We tried the Friedel–Crafts acylation with the use of lower aliphatic acids, their halides and anhydrides with the usual combinations of catalysts ($AlCl_3$, $AlBr_3$, $TiCl_4$, boron trifluoride etherate) and solvents (carbon disulphide, nitrated or chlorinated hydrocarbons, both aromatic and aliphatic) and have found that only anhydrides of the lower aliphatic acids in the presence of boron trifluoride etherate give good yield of the 2-acyl derivatives required. We assume that the acylation proceeds by a two-

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TABLE I
Derivatives of 2-acylergoline

Compound Yield, %	M.p., °C solvent	$[\alpha]_D^{20}$ [a]	Formula (mol. mass)	Calculated/Found		
				% C	% H	% N
Ib [b]	220—221	−172·8	$C_{19}H_{22}N_2O_3$	69·92	6·79	8·58
58	ethyl acetate		(326·4)	69·65	6·79	8·57
Ic [c]	209—211	−165·9	$C_{20}H_{24}N_2O_3$	70·56	7·11	8·23
64	methanol		(340·4)	70·85	7·35	8·12
Id [d]	195—200	−148·0	$C_{22}H_{28}N_2O_3$	71·71	7·66	7·60
41	methanol		(368·5)	71·54	7·90	7·60
IIb [e]	271—273	−158·0	$C_{19}H_{21}N_3O$	74·24	6·89	13·68
68	methanol		(307·4)	74·24	7·07	13·63
IIc [f]	225—227	−147·5	$C_{20}H_{23}N_3O$	74·74	7·21	13·07
72	methanol		(321·4)	74·84	7·51	12·81
IId [g]	206—210	−134·0	$C_{22}H_{27}N_3O$	75·61	7·78	12·02
49	ethyl acetate–hexane		(349·5)	75·52	7·95	11·81
IIIb [h]	190—191	−164·1	$C_{20}H_{24}N_2O_3$	70·56	7·11	8·23
80	methanol		(340·4)	70·49	7·31	8·29
IVb [i]	260—261	−138·9	$C_{22}H_{24}N_4O$	73·31	6·71	15·54
63	ethanol–dichloromethane		(360·5)	73·06	6·86	15·69
Vb [j]	[k]	−105·8	$C_{19}H_{23}N_3O_2$	70·13	7·12	12·91
46	chloroform		(325·4)	69·85	7·32	12·56
VIb [l]	175—176	— 66·6	$C_{21}H_{24}N_2O_4$	68·46	6·57	7·60
50	benzene–hexane		(368·4)	68·18	6·68	7·78
VIIb [m]	80—84	31·0	$C_{24}H_{33}N_4O_{3,5}$	66·49	7·67	12·92
38	ethanol–water		(433·5)	66·38	7·76	12·79

[a] Concentration 0·2, pyridine; [b] UV spectrum: λ_{max} (log ε) 312 (4·413), 240 (4·064) nm; IR spectrum: 3 240 (NH), 1 725 (ester), 1 635 (ketone) cm^{-1}; ^1H NMR spectrum: δ 9·10 (bs, 1 H, NH), 6·90—7·50 (m, 3 H, ArH), 3·78 (s, 3 H, $COOCH_3$), 2·60 (s, 3 H, $COCH_3$), 2·55 (s, 3 H, NCH_3); [c] UV spectrum: λ_{max} (log ε) 311 (4·330), 240 (4·198) nm; IR spectrum: 3 300 (NH), 2 760 (NCH_3), 1 730 (ester), 1 645 (ketone) cm^{-1}; ^1H NMR spectrum: δ 9·12 (bs, 1 H, NH), 6·80—7·50 (m, 3 H, ArH), 3·82 (s, 3 H, $COOCH_3$), 2·90 (q, 2 H, $COCH_2$), 2·52 (s, 3 H, NCH_3), 1·30 (t, 3 H, $COCH_2.CH_3$); [d] UV spectrum: λ_{max} (log ε) 313 (4·288), 239 (4·188) nm; IR spectrum: 3 340 (NH), 2 780 (NCH_3), 1 722 (ester), 1 675 (ketone) cm^{-1}; ^1H NMR spectrum: δ 8·90 (bs, 1 H, NH), 6·80—7·40 (m, 3 H, ArH), 3·71 (s, 3 H, $COOCH_3$), 2·50 (s, 3 H, NCH_3), 1·40 (s, 9 H, $C(CH_3)_3$); [e] UV spectrum: λ_{max} (log ε) 313 (4·354), 241 (4·196) nm; IR spectrum: 3 380 (NH), 2 775 (NCH_3), 2 240 (CN), 1 660 (ketone) cm^{-1}; ^1H NMR spectrum: δ 6·80—7·30 (m, 3 H, ArH), 2·51 (s, 3 H, $COCH_3$), 2·40 (s, 3 H, NCH_3); [f] UV spectrum: λ_{max} (log ε) 312 (4·267), 240 (4·114) cm; IR

-step mechanism, starting with an attack by an electrophilic particle on position 3, after which the 3-acylated intermediate thus formed rearrange into 2-acyl derivatives, by the mechanism generally accepted for electrophilic reactions of 3-substituted indoles[10]. Best results were obtained in the use of a large excess of the anhydrides, which were also the solvent, and at least three equivalents of boron trifluoride etherate. Under these conditions the reaction was compatible with the presence of the common functional groups, as can be seen from Table I. In this way, it was also possible to prepare the derivatives *Id* and *IId*, carrying at position 2 the very bulky pivaloyl group. We also tried to apply this reaction to the preparation of 2-formyl derivatives, using mixed anhydride of formic and acetic acids, but the 2-acetyl derivative was invariably the only product to be isolated. The reaction proceeded smoothly with the 1-substituted derivatives *IIIa* and *IVa*. Since the reversed order of the reactions, *i.e.* acylation followed by substitution at position 1, is difficult to bring about[11], the direct acylation of 1-substituted derivatives is a good method for the synthesis of 1,2-disubstituted derivatives of ergoline. What has proved important for the course of the reaction is the configuration on the carbon atom in position 8. The 8α-derivaves *VIa* and *VIIa* gave the 1,2-diacyl compound *VIb* and *VIIb*, whereas all the 8β-derivatives with an equatorial substituent at position 8 gave the 2-acyl derivatives only.

The new compounds were used for informative pharmacological tests. It has been found that the compound *IIb*, administered to rats in urethane narcosis in a dose of 1 mg/kg, has a hypotensive effect.

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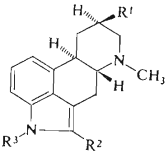
spectrum: 3 380 (NH), 2 240 (CN), 1 645 (ketone) cm^{-1}; ^1H NMR spectrum: (CD_3SOCD_3) δ 6·70—7·30 (m, 3 H, ArH), 2·90 (q, J = 7·0 Hz), 2 H, $COCH_2$), 2·39 (s, 3 H, NCH_3), 1·14 (t, J = 7·0 Hz, SH, $COCH_2CH_3$); [g] UV spectrum: λ_{max} (log ε) 314 (4·296), 239 (4·182 nm; IR spectrum: 3 335 (NH), 2 235 (CN), 1 655 (ketone) cm^{-1}; ^1H NMR spectrum:(CD_3SOCD_3) 11·00 (bs, 1 H, NH), 6·70—7·40 (m, 3 H, ArH), 2·40 (s, 3 H, NCH_3), 1·40 (s, 9 H, $C(CH_3)_3$); [h] UV spectrum: λ_{max} (log ε) 310 (4·332), 241 (4·233) nm; IR spectrum: 2 800, 2 780 (NCH_3), 1 740 (ester), 1 650 (ketone) cm^{-1}; ^1H NMR spectrum: δ 6·80—7·50 (m, 3 H, ArH), 4·00 (s, 3 H, $N_{(1)}CH_3$), 3·75 (s, 3 H, $COOCH_3$), 2·60 (s, 3 H, $COCH_3$), 2·54 (s, 3 H, NCH_3); [i] UV spectrum: λ_{max} (log ε) 309 (4·350), 241 (4·193) nm; IR spectrum: 2 760 (NCH_3), 2 240 (CN), 1 655 (ketone) cm^{-1}; ^1H NMR spectrum: (CD_3SOCD_3/DCl)δ 6·80—7·50 (m, 3 H, ArH), 4·68 (t, 2 H, NCH_2), 3·00 (s, 3 H, $COCH_3$), 2·85 (t, 2 H, CH_2CH_2CN), 2·70 (s, 3 H, NCH_3); [j] UV spectrum: λ_{max} (log ε) 308 (4·300), 238 (4·240) nm; IR spectrum: 3 300 NH), 3 180, 1 640 (prim. amide), 1 660 (ketone) cm^{-1}; ^1H NMR spectrum: (CD_3SOCD_3, 80°C) δ 8·80 (bs, 1 H, NH), 6·70—7·20 (m, 3 H, ArH), 2·52 (s, 3 H, $COCH_3$), 2·40 (s, 3 H, NCH_3); [k] does not melt up to 350°C; [l] UV spectrum: λ_{max} (log ε) 309 (4·220), 243 (4·168) nm; IR spectrum: 2 780 (NCH_3), 1 735 (ester), 1 715 ($NCOCH_3$), 1 655 (ketone) cm^{-1}; ^1H NMR spectrum: λ_{max} 6·90—7·60 (m, 3 H, ArH), 3·68 (s, 3 H, $COOCH_3$), 2·50 (s, 3 H, $COCH_3$), 2·40 (s, 3 H, $COCH_3$), 2·30 (s, 3 H, NCH_3); [m] hemihydrate, UV spectrum: λ_{max} (log ε) 309 (4·107), 244 (4·076) nm; IR spectrum: 3 440 (NH), 2 780 (NCH_3), 1 690 (ketone), 1 640 (subst. urea) cm^{-1}; ^1H NMR spectrum: δ 7·00—7·60 (m, 3 H, ArH), 5·45 (d, J = 7·0 Hz, 1 H, NH), 4·25 (bm, 1 H, $C_{(8)}H$), 3·18 (q, J = 7·0 Hz, 4 H, NCH_2CH_3), 2·62 (s, 3 H, $COCH_3$), 2·50 (s, 3 H, $COCH_3$), 2·40 (s, 3 H, NCH_3), 1·14 (t, J = 7·0 Hz, 6 H, NCH_2CH_3).



I, $R^1 = COOCH_3$, $R^3 = H$

Ia, $R^2 = H$
Ib, $R^2 = COCH_3$
Ic, $R^2 = COCH_2CH_3$
Id, $R^2 = COC(CH_3)_3$

II, $R^1 = CH_2CN$, $R^3 = H$

IIa, $R^2 = H$
IIb, $R^2 = COCH_3$
IIc, $R^2 = COCH_2CH_3$
IId, $R^2 = COC(CH_3)_3$

III, $R^1 = COOCH_3$, $R^3 = H$

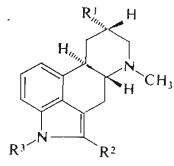
IIIa, $R^2 = H$
IIIb, $R^2 = COCH_3$

IV, $R^1 = CH_2CN$, $R^3 = CH_2CH_2CN$

IVa, $R^2 = H$
IVb, $R^2 = COCH_3$

V, $R^1 = CH_2CONH_2$, $R^3 = H$

Va, $R^2 = H$
Vb, $R^2 = COCH_3$



VI, $R^1 = COOCH_3$

VIa, $R^2 = R^3 = H$
VIb, $R^2 = R^3 = COCH_3$

VII, $R^1 = NHCON(C_2H_5)_2$

VIIa, $R^2 = R^3 = H$
VIIb, $R^2 = R^3 = COCH_3$

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. Samples for elemental analyses were dried at a pressure of about 30 Pa and temperatures adequate to the melting points. The optical rotations were determined in pyridine, a Perkin–Elmer polarimeter 141 being used. The ^1H NMR spectra were measured with a spectrometer Tesla BSC 487 (80 MHz) in deuteriochloroform and with tetramethylsilane as internal standard, unless otherwise specified; the values of δ are given in ppm. Purity of the compounds prepared was verified by TLC in systems chloroform–ethanol–triethylamine (92 : 6 : 2) and benzene–dioxan–ethanol–25% aqueous ammonia (48 : : 38 : 10 : 5). The spots were detected under ultraviolet light (254 and 366 nm), and with a spray of 20% *p*-toluenesulphonic acid in methanol, followed by a brief heating to approx. 80°C. Column chromatography was ran on silica gel Merck KG 60 (mesh 70—230). The eluant was chloroform with an increasing concentration of methanol (0·1—5%).

Preparation of 2-Acyl Ergoline Derivatives *Ib—Id, IIb—IId, IIIb—VIIb*

To a stirred solution or suspension of 10 mmol of an ergoline derivative (prepared according to the described procedures — *Ia*, *VIa* (ref.[12]), *IIa* (ref.[13]), *IIIa* (ref.[15]), *IVa* (ref.[16]), *VIIa* (ref.[17]) in 60 ml of the corresponding anhydride was added without cooling in the course of 5 min 7·1 g (50 mmol) of boron trifluoride etherate. The mixture was stirred for 20 min at room temperature (for 16 h in the preparation *Id* and *IId*) and poured into an excess of water and ice. pH was adjusted with an aqueous saturated solution of sodium hydrogen carbonate to approx. 8 and the product was extracted into dichloromethane (3 × 150 ml). The combined organic extracts were dried with magnesium sulphate, taken to dryness, and the residue was chromatographed. The qualitatively identical fractions were combined, taken to dryness and the residue was crystallized from a suitable solvent (Table I).

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