WITTIG TYPE REACTIONS OF 2-FORMYLATED DERIVATIVES OF 6-METHYLERGOLINE - I*

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Using the Horner–Wittig reaction, aldehydes *I* and *II* were converted, with high *E*-selectivity, into ethyl esters of substituted acrylic acids, *VI* and *VII*. The N-anions generated by deprotonation of derivative *I—V* with sodium hydride in tetrahydrofuran reacted with vinyltriphenylphosphonium bromide with the formation of derivatives of pyrrolo[1,2-*a*]ergoline-I, *XI—XV*.

The preceding communication[1] describes a simple procedure for the synthesis of 2-formylergoline-I derivatives. The aldehyde group in these compounds has its usual high electrophilic reactivity. We have made use of it for the syntheses of new compounds, which were then subjected to preliminary pharmacological testing. The present paper deals with some Wittig reactions giving rise to ergoline-I derivatives having a double bond conjugated with the indole ring of ergoline, and to derivatives with a new five-membered heterocyclic ring system.

The Horner–Wittig reaction of the aldehydes *I* and *II* gave the corresponding ethyl esters of substituted acrylic acids, *VI* and *VII*. A phosphonioylide was prepared[2] by reaction of ethyldiethoxyphosphinyl acetate with sodium hydride in tetrahydrofuran. These conditions led to a mixture of the *E*- and *Z*-isomers, whose proportion was determined by ^{1}H NMR spectroscopy. In the *Z*-configuration the two vicinal hydrogen atoms of the double bond have the same chemical shift, and thus give a singlet at 7·1 ppm, whereas in the *E*-isomer the difference in chemical shift of the olefinic hydrogens, $\Delta\delta$, is 1·6 ppm and the interaction constant $^3J_{trans} = 16\cdot0$ Hz. The compounds *VI* and *VII* were found to have a common *E* : *Z* ratio, 94·5 : 5·5. This high *E*-selectivity is consistent with the described reactions of PO-ylides[3]. In preparing the derivatives *VI* and *VII* we observed that the strong base employed deprotonized the indole nitrogen of the aldehydes *I* and *II*. Suspensions of these derivatives in tetrahydrofuran as a poor solvent reacted with stoichiometric amounts of sodium hydride with an evolution of hydrogen and produced yellow solutions, from which the starting aldehydes could be recovered by addition of a suitable proton donor. In the same way it was possible to deprotonize compounds *III — V*. The anions thus formed reacted with electrophilic agents, such as acylation and alkylation agents,

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giving rise to complex reaction mixtures. By contrast, the reaction with the triphenyl phosphonium salt[4] proceeded quite smoothly as the Michael addition, and the ylide thus formed underwent an intramolecular Wittig reaction with the carbonyl group at position 2, leading to derivatives of pyrrolo[1,2-a]ergoline-I.
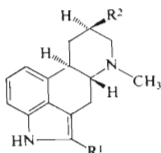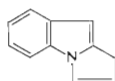

$I-IV$: R^1 = CHO
I: R^2 = CH$_3$
II: R^2 = CH$_2$CN
III: R^2 = COOCH$_3$
IV: R^2 = CH$_2$Cl
V: R^1 = COCH$_3$; R^2 = COOCH$_3$
VI, VII: R^1 = CH=CHCOOC$_2$H$_5$
VI: R^2 = CH$_3$
VII: R^2 = CH$_2$CN

VIII

IX

X

XVI
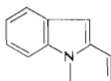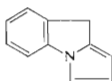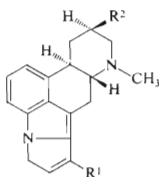
$XI-XIV$: R^1 = H
XI: R^2 = CH$_3$
XII: R^2 = CH$_2$CN
$XIII$: R^2 = COOCH$_3$
XIV: R^2 = CH$_2$Cl
XV: R^1 = CH$_3$; R^2 = COOCH$_3$
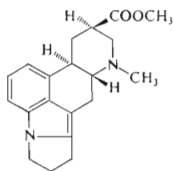
It is known from the literature[5] that the action of strong bases, instead of producing the expected 3H-pyrrolo[1,2-a]indole VIII, may result into the stabler[6] 9H-tautomer IX. The final alternative is the 1H-derivative X.

The structures of compounds $XI-XV$ were determined on the basis of their chemical reactivities and from their ^{1}H NMR spectra. The isomer containing 9H-pyrrolo-

TABLE I

Properties of compounds *VI, VII, XI—XVI*

Compound	Yield, % m.p., °C	Solvent	$(\alpha)_D^{20a}$	Formula (mol. mass)	Calculated/Found % C	% H	% N
VI[b]	71	water–pyridine	−141·9	$C_{21}H_{26}N_2O_2$	74·52	7·74	8·28
	87— 92	ethanol		(338·5)	74·47	7·98	7·97
VII[c]	70	water–pyridine	−148·8	$C_{22}H_{25}N_3O_2$	72·70	6·93	11·56
	195—202	ethanol		(363·5)	72·45	6·66	11·38
XI[d]	71	ethyl acetate–	−214·4	$C_{19}H_{22}N_2$	81·97	7·97	10·06
	163—166	light petroleum		(278·4)	81·62	7·98	9·82
XII[e]	60	dichloromethane	−108·8	$C_{20}H_{21}N_3$	79·17	6·98	13·85
	229—233	ethanol		(303·4)	78·84	6·91	13·86
XIII[f]	68	ethyl acetate	−113·4	$C_{20}H_{22}N_2O_2$	74·51	6·88	8·69
	207—210			(322·4)	74·48	7·09	8·73
XIV[g]	61	ethyl acetate	−91·6	$C_{19}H_{21}ClN_2$	72·95	6·77	8·95
	199—202			(312·9)	73·09	6·77	9·04
XV[h]	47	methanol	−132·5	$C_{21}H_{24}N_2O_2$	74·97	7·19	8·33
	175—177			(336·4)	74·61	7·22	8·23
XVI[i]	53	methanol	−118·3	$C_{20}H_{24}N_2O_2$	74·04	7·46	8·63
	163—165			(324·4)	73·75	7·23	8·46

[a] Concentration 0·5, pyridine. [b] UV spectrum: $\lambda_{max}(\log \varepsilon)$ 346 (4·47), 255 (3·95), 236 (3·8) nm; IR spectrum: 1 690 (ester), 1 625, 1 605, 1 540 (aromatic, C=C) cm^{-1}; ^{1}H NMR spectrum: δ 8·48 (bs, 1 H, NH), 7·70 (d, J = 16·0 Hz, olefinic H β to C=O, E-configuration), 7·10 (s, olefinic H, Z-configuration), 6·80—7·30 (m, 3 H, ArH), 6·10 (d, J = 16·0 Hz, olefinic H α to C=O, E-configuration), 4·20 (m, 2 H, OCH$_2$), 2·40 (s, 3 H, NCH$_3$), 1·21 (t, 3 H, OCH$_2$CH$_3$), 0·96 (d, 3 H, CH$_3$). [c] UV spectrum: $\lambda_{max}(\log \varepsilon)$ 347 (4·49), 255·5 (3·98), 236 (3·89) nm: IR spectrum: 2 330 (CN), 1 710 (ester), 1 625, 1 604, 1 550 (aromatic, C=C) cm^{-1}; ^{1}H NMR spectrum: δ 8·48 (bs, 1 H, NH), 7·70 (d, J = 16·0 Hz, olefinic H β to C=O, E-configuration), 7·10 (s, 2 H, olefinic H, Z-configuration), 6·80—7·30 (m, 3 H, ArH), 6·10 (d, J = 16·0 Hz, olefinic H, α to C=O, E-configuration), 4·20 (m, 2 H, OCH$_2$), 2·40 (s, 3 H, NCH$_3$), 1·31 (t, 3 H, OCH$_2$CH$_3$, E-configuration), 0·98 (t, 3 H, OCH$_2$CH$_3$, Z-configuration). [d] UV spectrum: λ_{max} (log ε) 346 (3·82), 330 (4·06), 316 (4·18), 332 (4·08) nm. IR spectrum: 3 080—3 010, 1 620, 1 590, 1 500 (aromatic), 2 820, 2 740, 1 440 (NCH$_3$) cm^{-1}; ^{1}H NMR spectrum: δ 6·60—7·10 (m, 4 H, ArH), 6·38 (bm, 1 H, NCH$_2$CH=C), 4·49 (bm, 2 H, NCH$_2$), 2·46 (s, 3 H, NCH$_3$), 0·98 (d, 3 H, CH$_3$). [e] UV spectrum: λ_{max}(log ε) 348 (3·797), 333 (4·043), 318 (4·147), 247 (3·911), 233 (3·996) nm; IR spectrum: 2230 (CN), 1 620, 1 600, 1 580 (C=C), 2 820 (NCH$_3$) cm^{-1}; mass spectrum: m/e 303 (M$^+$). [f] UV spectrum: λ_{max}(log ε) 348 (3·81), 333 (4·03), 3·18 (4·14), 244 (3·96), 233 (4·07) nm; IR spectrum: 2 760 (NCH$_3$), 1 730 (CO), 1 650, 1 615 (C=C) cm^{-1}; ^{1}H NMR spectrum: δ 6·20—7·30 (m, 5 H, ArH), 4·49 (m, 2 H, NCH$_2$CH=C), 3·75 (s, 3 H, OCH$_3$), 2·50 (s, 3 H, HCN$_3$). [g] UV spectrum: λ_{max}(log ε) 347 (3·81), 332 (4·04), 317 (4·15), 245 (3·93), 233 (4·02) nm; IR spectrun: 2 770 (NCH$_3$), 1 650 (C=C), 1 615, 1 605, 1 580 (aromatic)

[1,2-*a*]indole as a structural unit can be ruled out on the basis of a ready hydrogenation of the derivative *XIII* to compound *XVI* and because compounds *XI*−*XIV* contain only five aromatic hydrogens. Distinguishing between the remaining two isomers is possible by comparing the chemical shifts of the methylene group hydrogens in the five-membered ring of indene ($\delta_{CH_2} = 3\cdot33$ ppm) and in compounds *XI*−*XV* ($\delta_{CH_2} = 4\cdot60 - 4\cdot70$ ppm). The shift to lower values of the field in comparison with indene is caused by the screening effect of the heteroatom N in α-position to the CH$_2$ group, which suggests the presence of structure *VIII*. This assumption is in accordance with the found values of chemical shift for olefinic hydrogens. In structure *X* the olefinic hydrogen in α-position to the heteroatom N would have to be screened more than the other aromatic hydrogens, with an assumed chemical shift $\delta \approx 8$ ppm. The final decision on the structures of compounds *XI*−*XV* is based on the spectrum of the methyl derivative *XV*, in which the methyl group on the double bond gave a doublet with an interaction constant $^4J = 1$ Hz.

Information assessment of the antinidation and antilactation efficacy of compounds *VI*−*VII* and *XI*−*XV* on Wistar rats (Konárovice) in a dose of 0·1 mg/kg showed no marked inhibition of secretion of hypophyseal prolactin. Compound *XIII* in a dose of 1 mg/kg had negative inotropic and negative chronotropic effects on isolated atrium of a rabbit heart.

EXPERIMENTAL

The melting points were determined on the Kofler block and are not corrected. Analytical samples were dried at a pressure of c. 60 Pa over phosphorus pentoxide at temperatures adequate to their melting points. UV spectra were recorded (in methanolic solution) with an apparatus Unicam SP 8000, IR spectra (in KBr pellets) with a spectrophotometer Unicam SP 200 G, ^{1}H NMR spectra (in deuteriochloroform solutions) with an apparatus Tesla BS 487 C (80 MHz), tetramethylsilane being used as internal standard; optical rotation was determined with a polarimeter Perkin–Elmer 141 and mass spectra with a spectrometer Varian MAT 44 S. The compounds prepared were tested for homogeneity by TLC chromatography on Silufol plates UV 254, using systems chloroform–ethanol–triethylamine (92 : 6 : 2) and benzene–dioxan–ethanol–ammonium hydroxide (48 : 38 : 10 : 5). The spots were detected with a spray of 20%, *p*-toluenesulphonic acid in methanol, followed by a brief heating to 50°C. Derivatives *VI* and *VII* gave a bluish green colouration, compounds *XI*−*XVI* a dark blue one.

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cm^{-1}; mass spectrum: m/e 312 (M$^+$); ^{1}H NMR spectrum: δ 6·20−7·30 (M, 5 H, ArH), 4·48 (m, 2 H, NCH$_2$CH=C), 2·45 (s, 3 H, NCH$_3$). ^{h} UV spectrum: λ_{max}(log ε) 344 (3·94), 327 (4·15), 316 (4·22), 249 (4·06), 229 (4·42) nm; IR spectrum: 2 800 (NCH$_3$), 1 730 (CO), 1 620, 1 610, 1 580, 1 510 (aromatic, C=C) cm^{-1}; ^{1}H NMR spectrum: δ 6·80−7·20 (m, 3 H, ArH), 5·98 (bm, 1 H, olefinic H), 4·40 (bm, 2 H, NCH$_2$CH=C), 3·70 (s, 3 H, OCH$_3$), 2·48 (d, $J = 1$, 0Hz, 3 H, =CHCH$_3$). ^{i} UV spectrum: λ_{max}(log ε) 287 (3·90), 229 (4·57); IR spectrum: 1 620,*1 610, 1 580, 1 500, (aromatic), 2 780 (NCH$_3$), 1 740 (CO) cm^{-1}; ^{1}H NMR spectrum: δ 6·80−7·30 (m, 3 H, ArH), 3·71 (s, 3 H, OCH$_3$), 2·48 (s, 3 H, NCH$_3$).

Substituted Ethyl Acrylates *VI* and *VII*

To a solution of ethyldiethoxyphosphinyl acetate (675 mg, 3 mmol) in 10 ml of tetrahydrofuran was added sodium hydride (96 mg, 4 mmol) and the mixture was stirred at room temperature for 1·5 h. To the solution of the ylide thus prepared was slowly added a suspension of the aldehyde *I* or *II* (2 mmol) in tetrahydrofuran (10 ml), the mixture was stirred for 30 min and cooled down to 0°C. Acetic acid (240 mg, 4 mmol) was added, the solvent dsitilled off *in vacuo* and the residue was shaken between chloroform and a saturated aqueous solution of sodium hydrogen carbonate. The organic extract was taken to dryness and chromatographed on a column of silica gel with 3% methanol in chloroform as eluant. The qualitatively identical fractions were combined and taken to dryness. The residue was crystallized.

Derivatives of (7b*R*, 11a*R*)-11-Methyl-3*H*-pyrrolo[1,2-*a*]ergoline, *XI—XV*

To a stirred suspension of one of the 2-acyl derivatives *I— V* (2 mmol, ref.[1]) was added sodium hydride (85 mg, 3·5 mmol) at room temperature. After 5 min the solution was cooled down to −5°C and 1·01 g (2·7 mmol) of vinyltriphenylphosphonium bromide was added in one portion. The mixture was stirred at room temperature for 10 min, chilled to −5°C and 210 mg (3·5 mmol) of acetic acid was added. Tetrahydrofuran was distilled off *in vacuo*, a saturated aqueous solution of sodium hydrogen carbonate was added to the residue and the mixture was extracted with several portions of chloroform. The combined organic extracts were dried (MgSO₄), taken to dryness in *vacuo* and the residue was chromatographed on a colum of silica gel with 2% methanol in chloroform. The residue of the qualitatively identical fractions was crystallized from a suitable solvent (Table I) to a constant melting point.

(7b*R*, 9*R*, 11a*R*)-9-Methoxycarbonyl-11-methyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]ergoline, *XVI*

A solution of the derivative *XIII* (322 mg, 1 mmol) in 1,4-dioxan (50 ml) was hydrogenated on 5% Pd/C (300 mg) at room temperature and atmospheric pressure for 16 h. The mixture was filtered through diatomaceous earth, the filtrate was distilled *in vacuo* and the crystalline residue was chromatographed on a column of silica gel; the eluant was chloroform with an increasing content of methanol (up to 4%). The qualitatively identical fractions were combined, distilled *in vacuo* and the residue was crystallized from methanol.

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