1,2-FUSED DERIVATIVES OF ERGOLINE*

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2-Formylergoline derivatives *I* and *II* were condensed with methyl isonitrilacetate in the presence of a base. Depending on the nature of this base, the main products of the reaction were either derivatives of pyrimido[1,6-a]ergoline, *III* and *IV*, or derivatives of 2-formylamino-3 oxo-3*H*-pyrrolo[1,2-*a*]ergoline, *V* and *VI*.

The high physiological efficacy of ergoline derivatives motivated synthesis of a number of compounds of this group. Nevertheless, not even one derivative containing another aromatic ring fused to the indole one has thus far been known. Our recent synthesis[1] of 2-formylergoline derivatives and the methods[2,3] for this type of ring fusion have enabled us to synthetize compounds with new heterocyclic ring systems.

The aldehydes *I* and *II* were allowed to react with methyl isonitrilacetate in tetrahydrofuran or a mixture of tetrahydrofuran and hexamethylphosphorictriamide. The α-anion of the isonitril compound was generated by 1,5-diazabicyclo[5,4,0]undec-4-ene. Reaction of the anion with the electrophilic aldehyde group was assumed[3] to be followed by elimination of a molecule of water. The N-anion produced by abstraction of the proton from the N_{Indole}—H bond, effected by the base employed, reacted with the isonitrile group, thus forming the expected products *III* and *IV*.

In addition to the compounds *III* and *IV*, very small amounts of unidentified by-products *V* and *VI* were also isolated from the reaction mixture. However, these compounds became the main products if sodium hydride was the base employed. High-resolution mass spectra assigned a formula $C_{21}H_{21}N_3O_4$ to compound *V* and $C_{21}H_{20}N_4O_2$ to *VI*. The compounds *V* and *VI* have a common difference in molecular formula from the original ergoline skeleton (without substitutents at positions 1 and 2) of the aldehydes *I* and *II* respectively, *viz.* C_4HNO_2. The IR spectrum of compound *VI* shows the presence of two C=O bonds (1 730 and 1 700 cm^{-1}), an N—H bond (3 300 cm^{-1}) and of the unchanged nitrile group (2 260 cm^{-1}). The IR spectrum of compound *V* contains absorption bands characteristic of the carbonyl group stretching vibration (1 725 and 1 690 cm^{-1}), and suggests the presence of an N—H bond (3 280 cm^{-1}). The ^1H NMR spectra of compounds *V* and *VI* have some common

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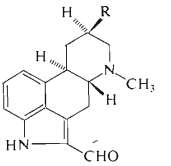
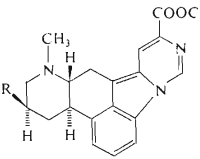
features, *viz.* the presence of an isolated olefinic proton ($\delta = 7{\cdot}20-7{\cdot}21$ ppm), another isolated C—H bond ($\delta = 8{\cdot}21-8{\cdot}24$ ppm), three aromatic hydrogens, as well as the preservation of the N—CH_3 bonds and the methyl ester group in compound *V*.



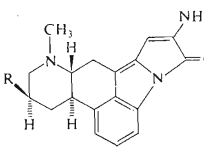
I: R = $COOCH_3$

II: R = CH_2CN



III: R = $COOCH_3$

IV: R = CH_2CN



V: R = $COOCH_3$

VI: R = CH_2CN

The above-given facts suggest that the reaction products *V* and *VI* probably retain the structure of the ergoline skeleton. If so, the bond N—H cannot be the bond N_{indole}–H since the fragment $C_4H_2NO_2$ bound to position 2 of the ergoline nucleus cannot be so formulated as to be compatible with the spectral data and acceptable from the viewpoint of the reaction mechanism. Both these criteria are met by derivatives of 2-formylamino-3-oxo-3*H*-pyrrolo[1,2-*a*]ergoline. In their synthesis the strong base employed deprotonizes the indole nitrogen of the starting aldehydes *I* and *II* with the formation of the corresponding anions[1], whose reaction with the electrondeficient carbonyl carbon of the ester group leads to the formation of a lactam. The formylamino group can be produced either by hydrolysis of the isonitril group in the working-up of the reaction mixture, or by opening of the 2-oxazoline ring, as the reaction intermediate[4]. The formation of compounds *V* and *VI* thus demonstrates ambident reactivity of esters of isonitrilacetic acid, governed by the nature of the base employed.

The compounds *III* – *VI* were tested for antinidation and antilactation activity. In a dose of 0·1 mg/kg administered to rats Wistar (Konárovice) secretion of hypophyseal prolactin was not much inhibited.

EXPERIMENTAL

The melting points were determined on the Kofler block and are not corrected. Analytical samples were dried over phosphorus pentoxide at a pressure of about 60 Pa and temperatures below their melting points. UV spectra of methanolic solutions were recorded with an apparatus Unicam SP 8000, IR spectra in KBr pellets with a spectrophotometer Unican SP 200 G, ^{1}H NMR spectra in deuteriochloroform with an apparatus Tesla BS 487 C (80 Hz), the internal standard being tetramethylsilane, unless otherwise stated. Optical rotations were measured with a polarimeter Perkin–Elmer 141 and mass spectra with a spectrometer MCH 1320. Homogeneity of the compounds prepared was checked by TLC in systems chloroform–ethanol–triethylamine (92 : 6 : 2) and benzene–dioxan–ethanol–ammonia (48 : 38 : 10 : 5). The spots were detected under UV light (254 and 366 nm), and by a spray with 20% *p*-toluenesulphonic acid in methanol, followed by a brief heating.

(8b*R*, 10*R*, 12a*R*)-2,10-Dimethoxycarbonyl-12-methylpyrimido[1,6-*a*]ergoline (*III*)

To a stirred solution of 1,5-diazabicyclo[5,4,0]undec-4-ene (0·167 g, 1·1 mol) in tetrahydrofuran (5 ml) was added, at 40°C in the course of 5 min, a solution of methyl isonitril acetate[5] (0·109 g, 1·1 mmol) and aldehyde *I* (0·313 g, 1 mmol) in tetrahydrofuran (5 ml). The stirring was continued at this temperature for 30 min; the mixture was then cooled down to 0°C, 0·3 ml of acetic acid was added and the solvent was removed at 40°C *in vacuo* (water-jet pump). The residue was shaken between a saturated aqueous solution of $NaHCO_3$ and chloroform; the organic extract was dried ($MgSO_4$), taken to dryness and the residue was repeatedly chromatographed on Pre-coated PLC Plates Silika Gel F-254 (Merck) in a system chloroform–methanol (95 : 5). Crystallization from a mixture methanol–dichloromethane gave a yellow product melting at 260—266°C, $[\alpha]_D^{20} = -127{\cdot}35°$ (*c* 0·2, pyridine), yield 122 mg (31%). For $C_{22}H_{23}N_3O_4$ (393·4) calculated: 67·14% C, 5·89% H, 10·67% N; found: 66·88% C, 5·86% H, 10·40% N. UV spectrum: λ_{max} (log ε) 426 (3·717), 344 (3·764), 328 (3·764), 284 (4·526), 250 (4·182), 230 (4·046) nm IR spectrum: 1 720, 1 710 (CO), 1 430 (NHC_3) cm^{-1}. ^{1}H NMR spectrum: δ 9·02 (d, J = 1·0 Hz, 1 H, C(4)—H), 8·15 (d, J = 1·0 Hz, 1 H, C(1)—H, 7·20—7·60 (m, 3 H, ArH), 4·00 (s, 3 H, $COOCH_3$), 3·75 (s, 3 H, $COOCH_3$), 2·52 (s, 3 H, NCH_3). Mass spectrum: *m/e* 393·44 (M^+).

(8b*R*, 10*R*, 12a*R*)-11-Cyanomethyl-2-methoxycarbonyl-13-methylpyrimido[1,6-*a*]ergoline (*IV*)

The procedure was analogous to the preparation of compound *III*, except that the poorly soluble aldehyde *II* was added to the solution of the base in the form of a solution in hexamethylphosphorictriamide. After evaporation of tetrahydrofuran the mixture was poured into water, the precipitate was collected on a filter and worked up in the same way as the residue of the organic extract in the preparation of compound *III*. Crystallization from a mixture of methanol and dichloromethane gave a yellow product (21%), m.p. > 320°C, $[\alpha]_D^{20} = -85{\cdot}4°$ (*c* 0·2, pyridine). For $C_{22}H_{22}N_4O_2$ (374·4) calculated: 70·57% C, 5·92% H, 14·96% N; found: 70·22% C, 5·96% H, 14·71% N. UV spectrum: λ_{max} (log ε) 426 (3·712), 344 (3·728), 328 (3·782), 284 (4·537), 250 (4·209), 230 (4·081) nm. IR spectrum: 2 260 (CN), 1 720 (CO), 1 430 (NCH_3) cm^{-1}. Mass spectrum: *m/e* 374·44 (M^+).

(7b*R*, 9*R*, 11a*R*)-2-Formylamino-9-methoxycarbonyl-11-methyl-3-oxo-3*H*-pyrrolo[1,2-*a*]ergoline (*V*)

To a stirred suspension of NaH (48 mg, 2 mmol) in tetrahydrofuran (5 ml) at room temperature was added a solution of methyl isonitrilacetate (0·109 g, 1·1 mmol) and aldehyde *I* (0·313 g, 1 mmol) in tetrahydrofuran (5 ml). The mixture was stirred for 30 min and cooled down to 0°C. After an addition of acetic acid (0·5 ml) the mixture was taken to dryness *in vacuo*. The residue was shaken between a saturated aqueous solution of sodium hydrogen carbonate and chloroform. The separated chloroform layer was washed with water, dried with $MgSO_4$ and taken to dryness *in vacuo*. The residue was chromatographed as was compound *III*. Crystallization from a dichloromethane–methanol mixture gave 68·3 mg (18%) of a red product, m.p. 301—302°C, $[\alpha]_D^{20} = -227{\cdot}10°$ (*c* 0·2, pyridine). For $C_{21}H_{21}N_3O_4$ (379·4) calculated: 66·48% C, 5·58% H, 11·07% N; found: 66·31% C, 5·57% H, 10·71% N. UV spectrum: λ_{max} (log ε) 381 (3·897, 366 (3·891), 287 (4·215), 247 (3·920), 221 (4·265) nm. IR spectrum: 3 280 (NH), 1 725, 1 690 (CO) cm^{-1}. ^1H NMR spectrum: (CD_3SOCD_3) δ 8·21 (s, 1 H, NCHO), 7·20 (s, 1 H, C(1)—H), 6·70—6·90 (m, 3 H, Ar—H), 3·56 (s, 3 H, OCH_3), 2·25 (s, 3 H, NCH_3). Mass spectrum: *m/e* 379·42 (M^+).

(7b*R*, 9*R*, 11a*R*)-(-2-Formylamino-9-cyanomethyl-11-methyl-3-oxo-3*H*-pyrrolo[1,2-*a*]ergoline (*VI*)

The procedure was analogous to the preparation of derivative *V*, except that the poorly soluble aldehyde *II* was added to the base as a suspension in tetrahydrofuran. Crystallization from a mixture of dichloromethane and ethanol gave a red product (22%), m.p. 273—275°C, $[\alpha]_D^{20} = -211{\cdot}10°$ (*c* 0·2, pyridine). For $C_{21}H_{20}N_4O_2$ (360·4) calculated: 69·98% C, 5·59% H, 15·54% N; found: 69·68% C, 5·65% H, 15·22% N. UV spectrum: λ_{max} (log ε) 380 (4·021), 364 (4·020), 287 (4·03), 278 (4·374), 247 (4·041), 222 (4·370) nm. IR spectrum: 3 300 (NH), 2 260 (CN), 1 730, 1 700 (CO) cm^{-1}. ^1H NMR spectrum: ($CD_3SO\,CD_3$) δ 8·24 (s, 1 H, NCHO), 7·21 (s, 1 H, C(1)—H), 6·70—6·95 (m, 3 H, Ar—H), 2·21 (s, 3 H, NCH_3). Mass spectrum: *m/e* 360·42 (M^+).

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