DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS AND PROPERTIES OF 2-DIMETHYLAMINOVINYL DERIVATIVES OF THE 2-PYRROLIN-4-ONE SERIES AND THEIR CYCLIZATION TO PYRROLO[3,2-c]PYRIDINES

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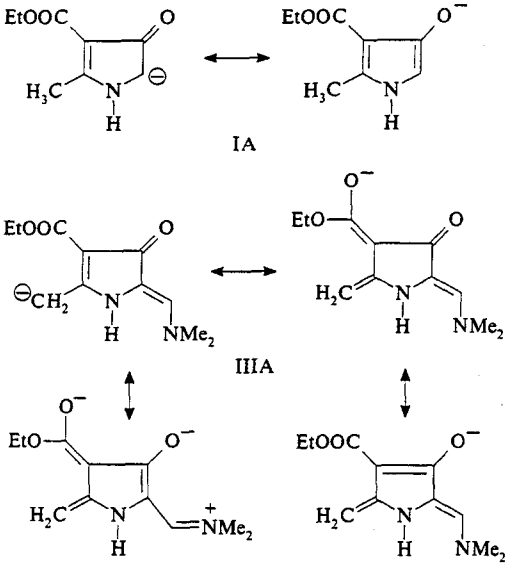
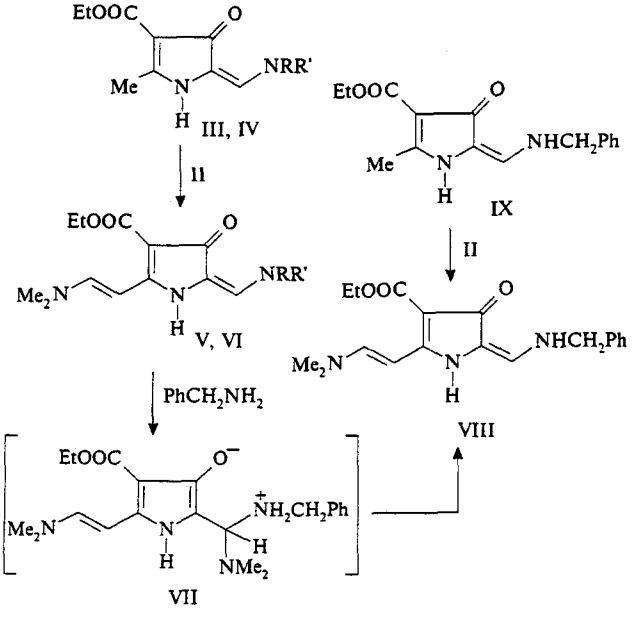
Earlier we have established that 2-methyl-3-ethoxycarbonyl-2-pyrrolin-4-one (I) readily reacts with dimethylformamide diethylacetal (II) with the formation of 2-methyl-3-ethoxycarbonyl-5-dimethylaminomethylene-2-pyrrolin-4-one (III) [1]. It was also of interest to obtain enamines with participation of the 2-methyl group of compound III and study the possibility of heterocyclization in systems of this type.



The attack of compound III with acetal must be sterically ordered. Indeed, an analysis of the structures of the corresponding anions (IA, IIIA), which serve as the main intermediates during interaction with amideacetals, shows that IA is considerably stabilized by aromatization, while the electron-acceptor influence of the carbonyl group in position 4 of IIIA is markedly reduced by the presence of the enamine fragment.



III, V: R = R′ = Me; IV, VI: R = H, R′ = 4-MeOC$_6$H$_4$.

The above considerations are fully confirmed by experimental results: the condensation of acetal II at the methylene unit of 2-pyrrolin-4-one (I) proceeds smoothly even at room temperature, while interaction of I with III or its 4-methoxyphenyl analog (IV) [1] (with the formation of *bis*-

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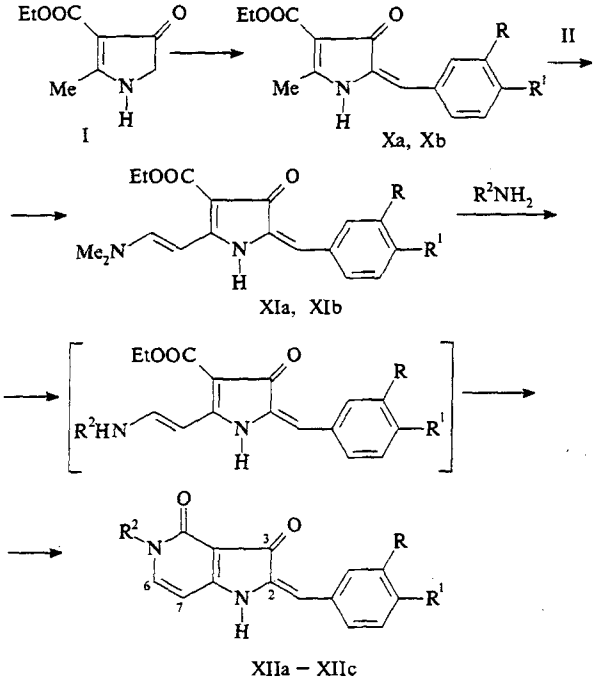
enamine derivatives) requires considerably more severe conditions (see the experimental part below). The same trend is retained with respect to the transamination of bis-enamines, as confirmed by the results of investigation of compound V using benzylamine as the transaminating agent. Here, the dominating process is the benzylamine attack of the enamine fragment in position 5 with the formation of compound VIII (the proposed structure of VIII was confirmed by direct synthesis via the condensation of enamine IX [1] with acetal II). In other words, stabilization of the intermediates also plays a decisive role in this system: the intermediate VII formed with participation of the 5-dimethylaminomethylene group is stabilized by aromatization.

Therefore, the 2-dimethylaminovinyl fragment is not subject to transamination under the conditions selected.

We have attempted to remove the influence of the enamine fragment in position 5 of the molecule on the dimethylaminovinyl group in position 2. To this end, the 5-dimethylaminomethylene group was replaced by an arylidene residue. The initial compounds were represented by 5-arylidene derivatives (Xa, Xb) [2], that is, by the compounds having no electron-donor groups in position 5 of the pyrrolinone cycle. Condensation of these derivatives with acetal II allowed us to synthesize enamines XIa, XIb).



Xa, XIa: R = H, R^1 = OMe;
Xb, XIb: R = R^1 = OMe;
XIIa: R = H, R^1 = OMe, R^2 = H;
XIIb: R = H, R^1 = OMe, R^2 = $PhCH_2$;
XIIc: R = R^1 = OMe, R^2 = $PhCH_2$.

An increase in the electron-acceptor effect of 4-oxo-group in compounds XIa and XIb must increase the partial positive charge on the α-carbon atom of the Me_2NCH=CH group and, accordingly, facilitate transamination of the dimethylaminovinyl group. Taking into account the presence of an ethoxycarbonyl group in position 3, this would favor heterocyclization at positions 2 and 3 of the pyrrole fragment.

In accordance with these considerations, compounds XIa and XIb were used in the reaction with ammonia and benzylamine. The process was not terminated at the stage of transamination and was followed by cyclocondensation with the formation of derivatives of pyrrolo[2, 3-c]pyridine (XIIa – XIIc).

The proposed structures of synthesized condensed compounds were confirmed by ^{1}H NMR data. The ^{1}H NMR spectrum of XIIa in DMSO-d_6 has the following signals (δ, ppm): 3.81 (s, 3H, OMe), 6.59 (s, 1H, α-CH), 7.03 and 7.66 (A_2B_2, 4H, C_6H_4), 6.15 (d, 1H, 7-CH, $J_{6,7}$ 6.8 Hz), 7.45 (t, 1H, 6-CH), 10.35 (bs, 1H, 1-NH), 11.08 (bs, 1H, 5-NH). The spectra of XIIb and XIIc are similar (see the experimental part below).

Thus, the passage from *bis*-enamines V, VI to derivatives with a single enamine fragment (XIa, XIb) allowed us perform a transamination accompanied by pyridone cyclization with the formation of new pyrrolo[2,3-c]pyridine-3,4-dione derivatives (XIIa – XIIc).

EXPERIMENTAL PART

The IR spectra of synthesized compounds were measured on a Perkin-Elmer Model 457 spectrophotometer using samples prepared as nujol mulls. The mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct introduction of samples into the ion source, operated at an ionizing electron energy of 70 eV. The NMR spectra were recorded on a Varian XL-200 instrument (USA) using DMSO-d_6 as the solvent and TMS as the internal standard. The course of reactions was monitored by thin-layer chromatography or Silufol UV-254 plates eluted in the isopropanol – aqueou ammonia – ethyl acetate system (3 : 1 : 5). The data of ele mental analyses coincided with the results of analytical calcu lations.

2-(β-Dimethylaminovinyl)-5-dimethylaminomethylene-3-ethoxycarbonyl-2-pyrrolin-4-one (V). A mixture o 1.75 g (7.8 mmole) of enaminoketone III [1] and 30 ml o diethylacetal II was boiled for 15 min and cooled. The pre cipitate was separated by filtering and washed with methanc to obtain 1.45 g of compound V. Physicochemical propertie and yields of all new compounds are given in Table 1.

2-(β-Dimethylaminovinyl)-5-(methoxyphenylaminomethylene)-3-ethoxycarbonyl-2-pyrrolin-4-one (VI Compound VI was obtained by a procedure similar to that de scribed above, using 1.5 g (5 mmole) of enaminoketone I [1] and 15 ml of diethylacetal II. Yield of compound V 0.83 g.

5-Benzylaminomethylene-2-(β-dimethylaminovinyl)-3-ethoxycarbonyl-2-pyrrolin-4-one (VIII).

Method 1. Compound VIII was obtained similarly i compound V using 0.3 g (1.04 mmole) of enaminoketone I

TABLE 1. Yields and Physicochemical Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C (solvent)	Mass spectrum (M^+)	Empirical formula	IR spectrum (ν_{max}, cm^{-1})
V	66	235 – 237 (methanol – DMF, 4 : 1)	279	$C_{14}H_{21}N_3O_3$	3120, 1690, 1670
VI	62	273 – 275 (dioxane – DMF, 4 : 1)	357	$C_{19}H_{23}N_3O_4$	3250, 3150, 1660, 1610
VIII	90	233 – 235 (dioxane – DMF, 4 : 1)	341	$C_{19}H_{23}N_3O_3$	3220, 3160, 1690, 1660, 1620
XIa	50	283 – 285 (methanol – dioxane, 4 : 1)	342	$C_{19}H_{22}N_2O_4$	3140, 1670, 1620
XIb	88	265 – 267 (methanol – dioxane, 4 : 1)	372	$C_{20}H_{24}N_2O_5$	3150, 1660, 1630
XIIa	80	385 – 387 (methanol – DMF, 1 : 5)	268	$C_{15}H_{12}N_2O_3$	3120, 1680, 1620
XIIb	78	277 – 279 (dioxane – DMF, 9 : 1)	358	$C_{22}H_{18}N_2O_3$	3260, 1690, 1650, 1560
XIIc	95	283 – 285 (DMF)	388	$C_{23}H_{20}N_2O_4$	3250, 1680, 1650, 1560

and 15 ml of diethylacetal II. Yield of compound VIII, 0.25 g.

Method 2. A mixture of 1 g (3.58 mmole) of *bis*-enaminoketone V and 0.5 g (7.16 mmole) of benzylamine in 40 ml of isopropanol was boiled for 1 h and cooled. The precipitate was separated by filtering and washed with isopropanol to obtain 1.1 g of compound VIII identical with the product obtained by Method 1.

2-Methyl-5-(4-methoxybenzylidene)-3-ethoxycarbonyl-2-pyrrolin-4-one (Xa) and 2-methyl-5-(3,4-dimethoxybenzylidene)-3-ethoxycarbonyl-2-pyrrolin-4-one (Xb). Compounds Xa and Xb were obtained as described in [2].

2-(β-Dimethylaminovinyl)-5-(4-methoxybenzylidene)-3-ethoxycarbonyl-2-pyrrolin-4-one (XIa). Compound XIa was obtained similarly to *bis*-enamine V using 3 g (10.4 mmole) of arylidene derivative Xa and 30 ml of diethylacetal II. Yield of compound XIa, 1.82 g; ^{1}H NMR spectrum (δ, ppm): 1.23 (t, 3H, $CH_2\underline{CH_3}$), 4.14 (q, 2H, $\underline{CH_2}CH_3$), 3.83 (s, 3H, OCH_3), 6.24 (d, 1H, 2-α-CH, J 13.3 Hz), 8.98 (d, 1H, 2-β-CH, J 13.3 Hz), 6.38 (s, 1H, 5-α-CH), 9.52 (bs, 1H, NH), 2.99 and 3.25 (2bs, 6H, $(CH_3)_2N$), 7.61 and 6.95 (A_2B_2, 4H, C_6H_4).

2-(β-Dimethylaminovinyl)-5-(3,4-dimethoxybenzylidene)-3-ethoxycarbonyl-2-pyrrolin-4-one (XIb). Compound XIa was obtained similarly to *bis*-enamine V using 3 g (9.5 mmole) of arylidene derivative Xb and 30 ml of diethylacetal II. Yield of compound XIb, 3.1 g; ^{1}H NMR spectrum (δ, ppm): 1.23 (t, 3H, $CH_2\underline{CH_3}$), 4.14 (q, 2H, $\underline{CH_2}CH_3$), 3.89 and 3.83 (2s, 6H, 2 × OCH_3), 6.26 (d, 1H, 2-α-CH, J 13.3 Hz), 8.28 (d, 1H, 2-β-CH, J 13.3 Hz), 6.37 (s, 1H, 5-α-CH), 9.57 (bs, 1H, NH), 3.01 and 3.25 (2bs, 6H, $(CH_3)_2N$), 6.74 – 7.24 (m, 3H, C_6H_3).

2-(4-Methoxybenzylidene)-2,3,4,5-tetrahydropyrrolo-[3,2-c]pyridine-3,4-dione (XIIa). A mixture of 2 g (5.8 mmole) of enaminoester XIa and 80 ml of a 20% ammonia solution in methanol was treated for 10 h in an autoclave at 100 – 110°C and cooled. The precipitate was separated by filtering and washed with methanol to obtain 1.25 g of compound XIIa.

5-Benzyl-2-(4-methoxybenzylidene)-2,3,4,5-tetrahydropyrrolo[3,2-c]pyridine-3,4-dione (XIIb). A mixture of 2 g (5.8 mmole) of enaminoester XIa and 2.5 g (23.4 mmole) of benzylamine in 60 ml of isopropanol was boiled for 10 h and cooled. The precipitate was separated by filtering and washed with methanol to obtain 1.85 g of compound XIIb; ^{1}H NMR spectrum (δ, ppm): 3.81 (s, 3H, OCH_3), 6.62 (s, 1H, α-CH), 7.02 and 7.66 (A_2B_2, 4H, C_6H_4), 6.23 (d, 1H, 7-CH, J 7.3 Hz), 7.94 (d, 1H, 6-CH, J 7.3 Hz), 10.20 (bs, 1H, 1-NH), 5.04 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ph).

5-Benzyl-2-(3,4-dimethoxybenzylidene)-2,3,4,5-tetrahydropyrrolo[3,2-c]pyridine-3,4-dione (XIIc). Compound XIIb was obtained similarly to bicycle XIIb using a mixture of 0.3 g (0.8 mmole) of enaminoester XIb and 0.34 g (3.2 mmole) of benzylamine in 20 ml of isopropanol. Yield of compound XIIc, 0.3 g; ^{1}H NMR spectrum (δ, ppm): 3.81 and 3.82 (2s, 6H, 2 × OCH_3), 6.63 (s, 1H, α-CH), 6.24 (d, 1H, 7-CH, J 7.2 Hz), 7.95 (d, 1H, 6-CH, J 7.2 Hz), 10.40 (bs, 1H, NH), 5.04 (s, 2H, CH_2Ph), 7.21 – 7.37 (m, 7H, Ph, 2′-CH, 6′-CH), 7.04 (d, 5′-H).

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