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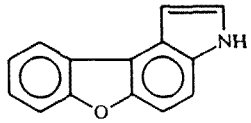
ACETYLATION OF INDOLOBENZO[*b*]FURANS, PYRROLOCARBAZOLE, PYRROLOPHENOTHIAZINE DIOXIDE AND PYRROLOACRIDINE UNDER VILSMEIER REACTION CONDITIONS

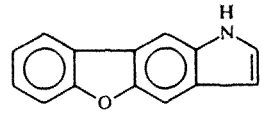
T. E. Khoshtariya, L. N. Kurkovskaya, and N. N. Suvorov

The course of the Vilsmeier acetylation of new heterocyclic systems, namely, indolo[4,5-d]-, indolo[6,5-d]-, indolo[5,6-d]-, indolo[5,4-d]benzo[b]furans, 3H-pyrrolo[2,3-c]carbazole, 3H-pyrrolo[2,3-c]pheno-thiazine 11,11-dioxide, and 3H-pyrrolo[2,3-c]acridine depends on the type of fusion of the pyrrole ring. Angular heterocycles are acetylated at the β-position of the pyrrole ring, while linear heterocycles under analogous conditions give dimerization products with a substituent at the nitrogen atom of the hydrogenated part of the dimer molecule. 3H-Pyrrolo[2,3-c]phenothiazine 11,11-dioxide and 3H-pyrrolo[2,3-c]acridine are not acetylated under Vilsmeier reaction conditions.

One of the most important problems in organic chemistry is establishing the interrelationship between molecular structure and properties, especially reactivity. The general method of Vilsmeier acylation has been used along with other methods [1-6] for this purpose. Complexes of N,N-dimethylacetamide and N,N-diethylchloracetamide with $POCl_3$ have been used as acylating agents and indolobenzo[*b*]furans I-IV, pyrrolocarbazole V, pyrrolophenothiazine dioxide VI, and pyrroloacridine VII synthesized in our previous work [7-10] were studied as substrates.



I



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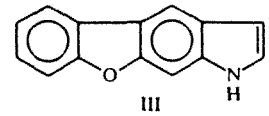

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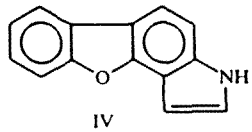

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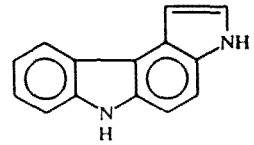

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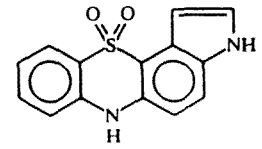
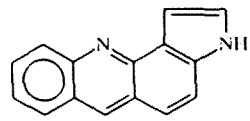


VI



VII

The Vilsmeier acetylation of 3H-pyrrolo[2,3-*c*]phenothiazine 11,11-dioxide (VI) and 3H-pyrrolo[2,3-*c*]acridine (VII) at the β-carbon atom of the pyrrole ring could not be accomplished with either N,N-dimethylacetamide or N,N-diethylchloracetamide regardless of the conditions. This failure is probably related to the insufficient electrophilicity of these

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Vilsmeier complexes and the diminished charge at the β-position of the pyrrole ring in pyrroloacridine VII. These results are in good accord with literature findings [11]. The electron density at the α-position of the pyrrole ring in VI and, especially, VII is probably insufficient for accomplishing the Vilsmeier reaction.

The reaction of 3H-pyrrolo[2,3-*c*]carbazole (V) with the N,N-diethylchloracetamide complex yielded 1-chloroacetyl derivative XII in 40% yield. The reaction proceeded with much greater difficulty in the case of N,N-dimethylacetamide, which gave 1-acetyl-3H-pyrrolo[2,3-*c*]carbazole (XIII) in only 10% yield, probably due to the reduced electrophilicity of the attacking complex as in the case of benzindole [12].

Linear heterocycles II and III react with the N,N-diethylchloracetamide complex under Vilsmeier reaction conditions to give chloroacetylated dimers. This substitution proceeds at the nitrogen atom of the pyrrole ring in the hydrogenated part of the dimer molecule. Angular heterocycles I and IV, similar to pyrrolocarbazole V, mainly give products of the substitution of a chloroacetyl group at the β-carbon atom of the pyrrole ring (X and XI). Thus, the acetylation of indolo[5,6-*d*]benzo[*b*]furan (III) with the complex of N,N-diethylchloracetamide gave dimer VIII. Indolo[5,4-*d*]benzo[*b*]furan (IV), which is an angular heterocycle, gave 1-chloroacetylindolo[5,4-*d*]benzo[*b*]furan (X). The Vilsmeier acetylation of a mixture of indolo[4,5-*d*]- (I) and indolo[6,5-*d*]benzo[*b*]furans (II) took place analogously.

Unfortunately, the product of the reaction of linear isomer II with the complex of N,N-diethylchloracetamide could not be isolated since this reaction was studied in the case of indolo[4,5-*d*]- (I) and indolo[6,5-*d*]benzo[*b*]furans (II) for mixtures of heterocycles I and II due to the difficulty in separating the angular and linear cyclic ethers simultaneously formed in the cyclization of the corresponding hydrazone, which are the starting compounds in the synthesis of unsubstituted heterocycles I and II. Naturally, the reaction products, which are also difficult to separate, could not be isolated as pure compounds in this case. Product IX was observed chromatographically and characterized in a mixture only by PMR spectroscopy. This compound will not be examined further due to the lack of analytical data.

The general scheme for the synthesis of the acetyl derivatives of the heterocyclic systems noted is given below.

The lack of a signal for proton **c** in the PMR spectra of X, XI, and XII and the appearance of singlets characteristic for the CH_2 group at 5.0 ppm indicate substitution of the hydrogen atom at $C_{(1)}$ in indolo[5,4-*d*]- (IV), indolo[4,5-*d*]benzo[*b*]furans (I), and 3H-pyrrolo[2,3-*c*]carbazole (V) by a chloroacetyl group. The large difference in the chemical shifts of proton **f** and its upfield shift in XI and XII compared to the analogous proton **h** in the corresponding formyl derivatives (by 0.7 and 0.8 ppm, respectively) described in our previous work [1, 3] indicate hindered rotation of the large $COCH_2Cl$ group. The conformation excluding approximation of proton **f** and the C=O group (the anisotropy of this group is not very evident) is favored. In other words, there should be strong steric interaction of protons **c** and **f** in the starting heterocycles from the outset. The presence of the $COCH_2Cl$ group in X accounts for the downfield shift of the signals for protons **a** and **b** in comparison with the unaltered ring IV [7].

The characteristic C=O group IR bands for X at 1655 cm^{-1}, for XI at 1640 cm^{-1}, and for XII at 1660 cm^{-1} indicate conjugation of the carbonyl group with the pyrrole ring. The molecular masses found for X-XII found by mass spectrometry were in accord with the calculated values.

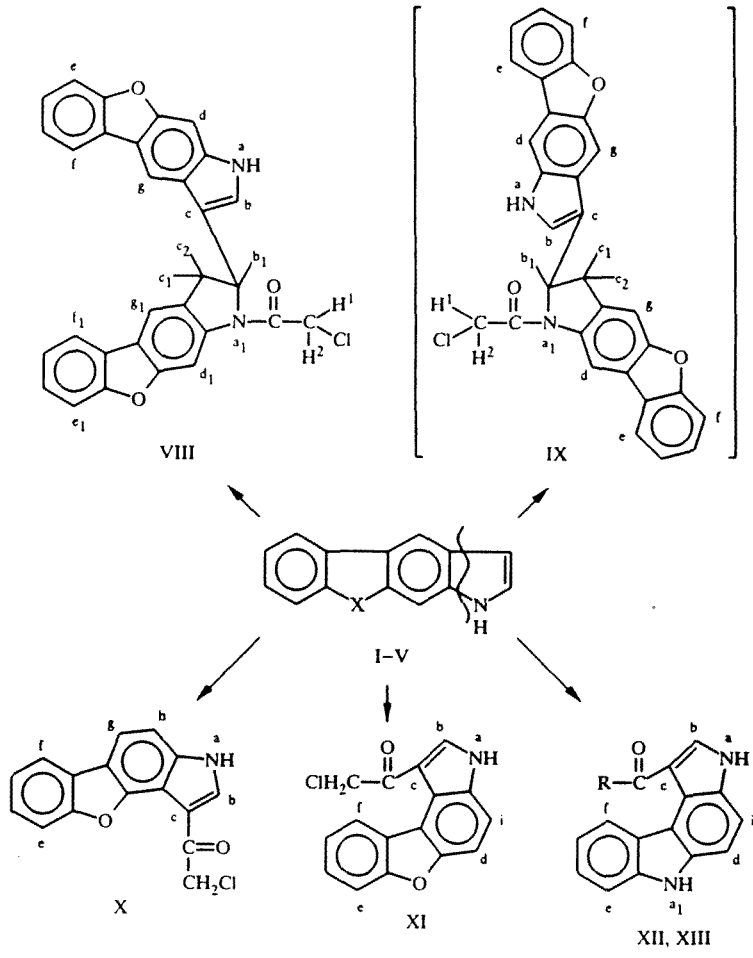
The lack of a signal for proton $\mathbf{a_1}$ in the PMR spectrum of VIII and the appearance of separate signals for the CH_2 group protons at 4.2 and 4.7 ppm with geminal coupling constant of 14.0 Hz indicate the presence of a chloroacetyl group in dimer VIII. The downfield shift of about 0.9 ppm of the signal for proton $\mathbf{d_1}$ in dimer VIII in comparison with the signal in starting ring III [7] due to the anisotropic effect of the carbonyl group and the finding of the signals for protons $\mathbf{b_1}$, $\mathbf{c_1}$, and $\mathbf{c_2}$ at 6.4, 4.1, and 3.4 ppm, respectively, indicate the presence of the chloroacetyl group precisely at the nitrogen atom of the hydrogenated pyrrole ring in this compound. Almost the same changes in the PMR spectrum were observed for dimer IX. The presence of a chloroacetyl group in dimer VIII leads to flattening of the molecule or greater steric strain, as indicated by the change in the angles in the hydrogenated pyrrole part (see the changes in the coupling constants in Table 1) and the downfield shift of the signal for proton **b**.

The increase in the intensity of the UV bands of VIII in comparison with starting III along with a hypsochromic shift indicates formation of a new conjugation system due to the presence of the electron-withdrawing chloroacetyl group in dimer VIII.

The molecular ion corresponds to the calculated molecular mass, while the nature of the subsequent fragmentation of the molecular ion is in accord with the proposed structure.

Of course, we cannot make exhaustive conclusions concerning the behavior of a particular heterocycle in the reaction studied limiting ourselves to scanty spectral data. However, the characteristic changes of the protons giving rise to the structure

Scheme



I–IV X = O; V X = NH; XII R = CH_2Cl; XIII R = Me

of the dimer and the presence of a chloroacetyl group in this compound permit us to make the following general conclusions using the PMR, UV, and IR spectral data.

1. The course of the acetylation reaction depends on the type of fusion of the pyrrole ring relative to the central heterocycle. The angular heterocycles, namely, indolo[4,5-*d*]- (I), indolo[5,4-*d*]-benzo[*b*]furans (IV), and 3H-pyrrolo-[2,3-*c*]carbazole (V) are acetylated in the Vilsmeier reaction by the N,N-diethylchloracetamide complex largely at the β-position of the pyrrole ring. The linear heterocycles, namely, indolo[6,5-*d*]- (II) and indolo[5,6-*d*]benzo[*b*]furans (III) give dimerization products VIII and IX under analogous conditions with the substituent at the nitrogen atom of the hydrogenated part of the dimer molecule.

2. The departure of tetracyclic systems, 3H-pyrrolo[2,3-*c*]phenothiazine 11,11-dioxide (VI) and 3H-pyrrolo-[2,3-*c*]acridine (VII) synthesized in our laboratory from the behavior of heterocycles I and V with an analogously fused pyrrole ring relative to the central heterocycle may be attributed to the decrease in reactivity toward electrophiles in the pyrroloacridine and pyrrolophenothiazine dioxide.

EXPERIMENTAL

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 silica gel plates. The UV absorption spectra were taken in ethanol on a Specord UV-VIS spectrometer using cells with 1-cm pathlength. Data are given for λ_{max}, nm and (log ε). The infrared spectra were taken for Vaseline mulls on a UP-20

TABLE 1. Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) in the PMR Spectra of I-XIII in DMSO-d_6

Compound	Protons																Coupling constant
	a	a_1	b	b_1	c	c_1	c_2	d	d_1	e	e_1	f	f_1	g	g_1	h	i	
I	11,3	–	7,4	–	7,0	–	–	7,7	–	8,0	–	8,8	–	–	–	–	7,5	J_{ab} = 2,0, J_{ac} = 1,7, J_{bc} = 2,9, J_{di} = 8,1
II	11,0	–	7,4	–	6,5	–	–	7,7	–	7,5	–	8,1	–	8,0	–	–	–	J_{ac} = 2,0, J_{bc} = 3,1
III*	10,3	–	7,4	–	6,6	–	–	7,6	–	7,5	–	8,0	–	8,2	–	–	–	J_{ab} = 2,2, J_{ac} = 2,0, J_{bc} =3,1, J_{dc} = J_{dg} =0,8
IV	11,4	–	7,4	–	6,7	–	–	–	–	7,6	–	8,0	–	7,4	–	7,3	–	J_{ac} = 2,2, J_{bc} = 3,3, J_{ch} = 0,4, J_{gh} = 8,7
V*	10,0	10,2	7,4	–	7,0	–	–	7,2	–	7,4	–	8,2	–	–	–	–	7,4	J_{ab} = 2,2, J_{ac} = 1,8, J_{bc} = 3,3, J_{ci} = 0,8, J_{di} =8,9
VI*	10,6	9,7	7,4	–	7,0	–	–	7,6	–	†	–	8,0	–	–	–	–	7,7	J_{ab} = 2,5, J_{ac} = 2,0, J_{bc} = 3,0, J_{di} = 8,7, $^5J_{ci}$ =0,9
VII	11,8	–	7,4	–	7,3	–	–	7,7	–	8,1	–	8,2	–	–	–	–	7,7	J_{ab} = 2,6, J_{ac} = 2,3, J_{hc} = 3,0, J_{di} = 8,9
VIII	11,3	–	7,2	6,4	–	4,1	3,4	7,5	8,5	7,7	7,4	8,0	7,8	8,0	8,0	–	–	J_{ab} = 2,1, J_{b1c1} =9,5, trans-oid · J_{b1c2} = 2,1, J_{c1c2} =15,6, cisoid · J_{H1H2} =14,0
X	12,3	–	8,4	–	–	–	–	–	–	7,7	–	8,1	–	8,0	–	7,8	–	J_{gh} = 8,4
XI	12,3	–	8,6	–	–	–	–	7,6	–	7,6	–	8,7	–	–	–	–	7,7	J_{di} = 8,7
XII*	11,4	10,5	8,4	–	–	–	–	7,5	–	7,1...7,4		8,6	–	–	–	–	7,6	J_{ab} = 3,5, J_{di} = 8,7
XIII	11,9	11,2	8,3	–	–	–	–	7,4	–	7,0...7,4		8,6	–	–	–	–	7,5	J_{ab} = 3,2, J_{di} = 8,8

*Spectrum taken in acetone-d_6.

†Found in the aromatic proton region. The chemical shift for the CH_3 group proton in XII is 2.6 ppm, while the shifts for H^1 and H^2 in VIII are 4.2 and 4.7 ppm, respectively. The chemical shifts for the CH_2 group protons in X-XII are all found at 5.0 ppm.

spectrophotometer using NaCl and LiF plates. The scan rate was 160 and the slit width was 4 cm. The PMR spectra were taken in deuterated solvents on a Bruker WP-200 SY spectrometer at 200 MHz. The chemical shifts were measured relative to tetramethylsilane as the internal standard to ±0.01 ppm. The error in the coupling constants was ±0.1 Hz. The mass spectrum was taken on an MKh-1303 mass spectrometer with direct sample inlet into the ion source. The cathode emission current was 1.5 μA and the ionizing voltage was 50 eV.

2-(Indolo[5,6-*d*]benzo[*b*]furan-3-yl)-1-chloroacetyl-2,3-dihydroindolo[5,6-*d*]benzo[*b*]furan (VIII). A mixture consisting of 0.3 g (0.002 mole) $POCl_3$ and 0.3 ml diethylchloracetamide was stirred at room temperature for 30 min. A solution of 0.2 g (0.001 mole) indolo[5,6-*d*]benzo[*b*]furan (III) and 3 ml diethylchloracetamide was added to the Vilsmeier complex obtained with cooling. The mixture was stirred for 1 h at 60°C, cooled, and poured into water. The precipitated oil was extracted with ethyl acetate and washed with aqueous sodium carbonate. Chromatography on a silica gel column using 1:4 ether—hexane as the eluent gave 0.19 g (40%) VIII, mp 264-266°C. IR spectrum: 3195 (NH), 1660 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 202 (5.02), 216 (5.06), 249 (5.16), 208 (4.72), 296 (4.82), 303 (4.81), 315 (4.88), 326 (4.87). Found: C, 73.7; H, 4.0; N, 6.0; Cl, 7.2%. Calculated for $C_{30}H_{19}ClN_2O_3$: C, 73.4; H, 3.9; N, 5.7; Cl, 7.2%.

1-Chloroacetylindolo[5,4-*d*]benzo[*b*]furan (X) was obtained in 50% yield from indolo[5,4-*d*]benzo[*b*]furan (IV) by analogy to VIII, mp 248-250°C. IR spectrum: 3200 (NH), 1655 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 203 (4.90), 247 (5.03), 2.86 (4.65), 316 nm (4.57). Found: C, 67.9; H, 3.8; N, 5.1; Cl, 12.1%. Calculated for $C_{16}H_{10}ClNO_2$: C, 67.7; H, 3.5; N, 4.9; Cl, 12.5%.

1-Chloroacetylindolo[4,5-*d*]benzo[*b*]furan (XI) was obtained in 25% yield from indolo[4,5-*d*]benzo[*b*]furan I by analogy to VIII, mp 240-242°C. IR spectrum: 3200 (NH), 1640 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 214 (5.57), 235 (4.36), 259 (4.16), 270 (4.33), 290 (4.39), 300 (4.40), 316 nm (4.39). Found: C, 67.5; H, 3.8; N, 5.2; Cl, 12.8%. Calculated for $C_{16}H_{10}ClNO_2$: C, 67.7; H, 3.5; N, 4.9; Cl, 12.5%.

1-Chloroacetyl-3H-pyrrolo[2,3-*c*]carbazole (XII) was obtained in 40% yield from 3H-indolo[2,3-*c*]carbazole (V) by analogy to VIII, mp 270-272°C. IR spectrum: 3400, 3430 (NH), 1660 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 220 (4.22), 256 (4.39), 267 (4.33), 302 nm (4.53). Found: C, 67.6; H, 3.8; N, 10.0; Cl, 12.4%. Calculated for $C_{16}H_{11}ClN_2O$: C, 67.9; H, 3.9; N, 9.9, 12.6%.

1-Acetyl-3H-pyrrolo[2,3-*c*]carbazole (XIII). A sample of 0.2 g (0.001 mole) 3H-pyrrolo[2,3-*c*]carbazole (V) dissolved in 2 ml dimethylacetamide was added to the Vilsmeier complex prepared from 0.2 ml dimethylacetamide and 0.13 ml $POCl_3$. On the following day, the reaction mixture was poured into ice water and made basic. Unreacted starting product V was eluted with benzene. The reaction product was purified on a silica gel column using 1:4 ether—hexane as the eluent to give 0.024 g (10%) XIII, mp 274-275°C. IR spectrum: 3390, 3435 (NH), 1630 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 229 (4.31), 256 (4.26), 267 (4.22), 297 (4.39), 350 nm (3.67). Found: C, 77.3; H, 4.6; N, 11.2%. Calculated for $C_{16}H_{12}N_2O$: C, 77.4; H, 4.8; N, 11.3%.

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