SYNTHESIS OF N-(INDOL-3-YL)-N',N'-DIALKYLAMIDINES BY THE VILSMEIER REACTION WITH 3-AMINOINDOLES

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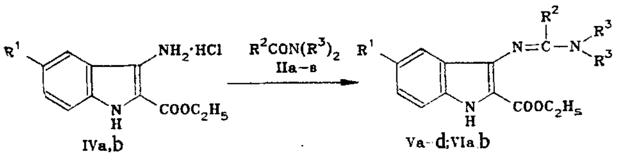
3-Aminoindoles substituted at C-2 and C-5 of the indole ring are converted by the action of Vilsmeier complexes into N-(indol-3-yl)-N',N'-dialkylamidines. When C-2 is unsubstituted, the formylation proceeds but not the acetylation of this position. N-(Indol-3-yl)-N',N'-dimethylacetamidine reacts with the complex obtained from DMF and $POCl_3$ to give 2-dimethylamino-3-formyl-δ-carboline. The optimal conditions were found for the conversion of amidines to amides.

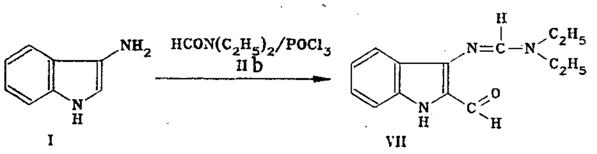
In our previous work [1], 3-aminoindole (I) and the Vilsmeier complex obtained from DMF and $POCl_3$ (IIa) gave N-(2-formylindol-3-yl)-N',N'-dimethylformamidine (III), which is a valuable synthetic precursor in the preparation of pyrimido[5,4-b]indoles. The present work was undertaken to continue the study of the Vilsmeier reaction of 3-aminoindoles for the preparation of N-(indol-3-yl)-N',N'-dialkylamidines with substituents on the side chain and indole ring.

The hydrochloride salts of 2-carboethoxy-3-aminoindoles IVa and IVb react with the Vilsmeier complexes obtained from DMF, diethylformamide and $POCl_3$ IIa-c to give amidines Va-d, VIa and VIb in yields from 63% to 83%. Formamidines Va-c are formed in higher yields than acetamidines VIa and VIb and at lower temperature. The highest yields among formamidines Va-d were achieved by the action of the DMF + $POCl_3$ complex (Table 1).



II, IV, Va $R^1=R^2=H$, $R^3=CH_3$; IIb, IVa, Vb $R^1=R^2=H$, $R^3=C_2H_5$; IIa, IVb, Vc $R^1=CH_3O$, $R^2=H$, $R^3=CH_3$; IIb, IVb, Vd $R^1=CH_3O$, $R^2=H$, $R^3=C_2H_5$; IIc, IVa, VIa $R^1=H$, $R^2=R^3=CH_3$; IIc, IVb, VIb $R^1=CH_3O$, $R^2=R^3=CH_3$

The complex obtained from diethylformamide IIb acts on 3-aminoindole I similarly to the complex obtained from the DMF complex IIa: The formyl and amidine moieties are introduced at C-2 and C-3 of the indole ring concurrently although the yield of amidine VII is only 48% while the yield of amidine III is 72%.



3-Aminoindole I reacts entirely differently with the Vilsmeier complex obtained from dimethylacetamide IIc. This reaction proceeds only at the amino group with the formation of acetamidine VIII. This result is unchanged upon increasing the temperatre from 20° to 100°C and increasing the amount of complex relative to amine to a fourfold excess.

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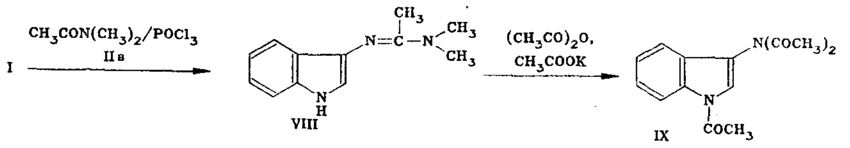
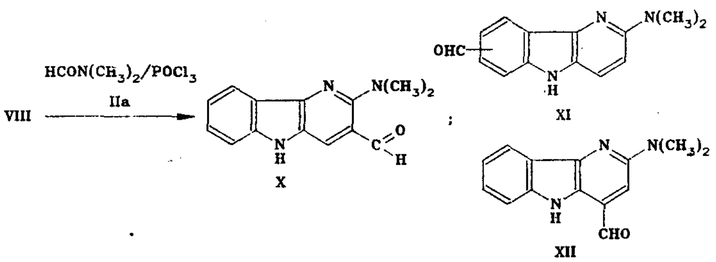


An attempt to introduce an acetyl group at C-2 in VIII by the action of acetic anhydride in the presence of perchloric acid or boron trifluoride etherate was unsuccessful. The reaction virtually does not proceed at 25°C, while there is heavy tar formation at 60°C. Heating VIII with acetic anhydride in the presence of potassium acetate gives triacetate IX. It was impossible to introduce an acetyl group at C-2 in amidine VIII, apparently as a consequence of steric hindrance related to the bulky substituent at C-3 of the indole ring.

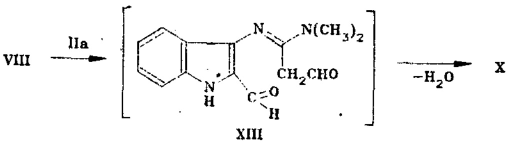
Complex IIa was used to introduce a formyl group at C-2 in amidine VIII. However, δ-carboline X was formed instead of the desired amidine.



Structures XI and XII which are isomeric to carboline X were rejected on the basis of the PMR and mass spectral data. The presence of a multiplet of four aromatic protons at 7.11-8.27 ppm in the PMR spectrum of δ-carboline X in $CDCl_3$ excludes structure XI. The chemical shifts of the protons at C-3 and C-4 in XII and X calculated by the additivity scheme on the basis of the data of Zhdanov [2] are 7.05 and 8.00 ppm, respectively. The experimental chemical shift is 8.02 ppm, which supports structure X.

The largest peak in the mass spectrum of X is the molecular ion M^+ 239. The peak with the second greatest intensity is the fragment ion with m/z 182 (73) due to the consecutive elimination of CO and NCH_3 units from the molecular ion. The loss of NCH_3 is possible only from C-2 of δ-carboline X, while the loss of $N(CH_3)_2$ is favored from another position [3]. The presence of the fragment ion with m/z 222 (46) which corresponds to the loss of an OH group from the molecular ion confirms the ortho arrangement of the $N(CH_3)_2$ and CHO groups.

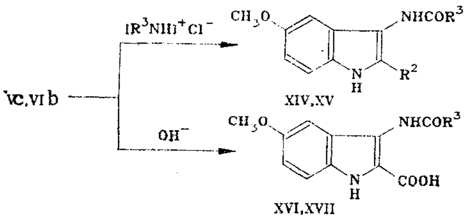
The formation of carboline X may be explained by a scheme, in which amidine VIII is diformylated at the methyl group in the side chain and at C-2 and then intermediate XIII undergoes dehydration.



Thus, the decisive factor for the introduction of an acyl group at C-2 of the indole ring in addition to the formation of the amidine group is the bulk of this group. Such a possibility is apparently realized only for the introduction of a formyl group.

The IR spectra of amidines Va-d, VIa, VIb, VII, and VIII have a C=N group b and at 1610-1630 cm^{-1}, indole NH group band at 3300-3350 cm^{-1}, and CO group band (for Va-d, VIa, and VIb) at 1665-1680 cm^{-1}.

In contrast to arylamidines [4], amidines Vc and VIb are very stable in solutions of acids and bases. Thus, formamidine Vc is converted to amide XIV only after prolonged heating in aqueous ethanol with an equivalent amount of acetic acid or KOH. In the case of KOH, the ester group is also hydrolyzed. Acetamidine VIb is converted to amide XV upon heating in ethanol in the presence of sodium ethylate. Amidines Vc and VIb are most readily hydrolyzed in aqueous ethanol in the presence of hydrochloride salts of amines such as triethylamine, benzylamine, and tert-butylamine.



XIV—XVII $R^2=COOC_2H_5$; XIV, XVI $R^3=H$; XV, XVII $R^3=CH_3$

The IR spectra and melting points of amides XIV and XV were identical to samples obtained by the acylation of aminoindole IVb by acetic anhydride in pyridine and the mixed anhydride of formic and acetic acids. The latter method gives higher yields of amides XIV and XV.

The results of the present study and of our previous investigation [1] indicate several conclusions concerning the Vilsmeier reaction of 3-aminoindoles: 1) the conversion of 3-aminoindoles by the action of the Vilsmeier complexes to give stable N-(indol-3-yl)-N',N'-dialkylamidines is general in nature, 2) the formylation but not the acetylation of C-2 of the indole ring occurs simultaneously with the formation of the amidine group when this position is free, and 3) the highest yields of the desired products are achieved using the Vilsmeier complexes obtained using DMF.

EXPERIMENTAL

The reaction course and purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates. The IR spectra were taken on a UR-10 spectrometer in vaseline oil and the UV spectra were taken on a Specord UV-VIS spectrometer in ethanol. The PMR spectra were taken on an CFT-20 spectrometer at 80 MHz with TMS as internal standard. The mass spectra were taken on an MKh-1303 mass spectrometer with direct sample inlet into the ionization chamber, 50 eV ionizing voltage, and 1.55 mA cathode emission current.

N-(2-R¹-5-R²-Indol-3-yl)-N',N'-dialkylamidines (Va-d, VIa, VIb, VII, and VIII). A solution of aminoindole IVa or IVb in the minimal amount of dialkylamide was added with rapid stirring to Vilsmeier reagent IIa-c prepared from DMF, diethylformamide, or dimethylacetamide and $POCl_3$ at 5-10°C. A 1:1.2:1.2 ratio of the amine, dialkylamide, and $POCl_3$ was used for amidines Va-d, VIa, VIb, and VIII, while a ratio of 1:2.1:2.1 was used for amidine VII. The reaction mass obtained from complexes IIa and IIb was stirred at 20-25°C for 12 h, while that from complex IIc was stirred at 60-65°C for 6 h and then poured into ice water. The insoluble impurities were filtered off and the filtrate was then treated with ice cooling and stirring with 40% aqueous NaOH to give pH 11.0-11.5. The precipitate formed was filtered off, washed with water and a small amount of 2-propanol, dried and recrystallized from 2-propanol. The yields, melting points, elemental analysis data, IR, UV, and PMR spectral data are given in Table 1.

2-Dimethylamino-3-formyl-δ-carboline (X). A sample of 1.0 g (5 mmoles) amidine VIII in 2 ml DMF was added to the Vilsmeier reagent prepared from 1.1 g (15 mmole) DMF and 2.3 g (15 mmole) $POCl_3$ at 5-10°C. The reaction mass was stirred for 2 h at 20-25°C for 2 h and then for an additional 3 h at 60-65°C and poured into a mixture of 20 g ice and 75 ml water. The insoluble impurities were filtered off and the filtrate was treated with ice cooling and stirring with 40% aqueous NaOH to pH 11.0-11.5. The precipitate formed was filtered off, washed with 200 ml water and dried. Chromatographic separation of the mixture obtained was carried out on a column with 15 mm diameter packed with a 400-mm layer of silica gel 100/250 using chloroform as the eluent to give 0.22 g (15%) δ-carboline X, mp 164-165°C (from 1:2 chloroform-petroleum ether). IR spectrum (4% in chloroform): 1630 (C=C, C=N), 1670 (C=O), 3475 cm^{-1} (indole NH). UV spectrum, λ_{max} (log ε): 214 (4.35), 233 (4.48), 263 (4.32), 343 (4.26), 424 nm (3.81). PMR spectrum ($CDCl_3$): 10.21 (s, CHO), 8.02 (s, 4-H), 8.37-7.21 (m, NH, 6-, 7-, 8-, 9-H), 3.11 [s, $N(CH_3)_2$]. Found: C 70.7; H 5.4; N 17.6%. M^+ 239. Calculated for $C_{14}H_{13}N_3O$: C 70.3; H 5.4; N 17.6%, M 239.

TABLE 1. Characteristics of Va-d, VIa, VIb, VII and VIII

Compound	mp, °C	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm	Found, %			Chemical formula	Calculated, %			Yield, %
					C	H	N		C	H	N	
Va	132—133	1630 (C=N), 1660 (C=O), 3300 (NH)	208 (4,31), 235 (4,30), 310 (4,12), 369 (3,65)	1,34, 4,28 (t, q $COOC_2H_5$), 7,81 (s, =CH), 3,11 (s, CH_3), 6,79—7,36 (m CH arom.), 9,79 (s, NH)	65,3	6,9	16,4	$C_{14}H_{17}N_3O_2$	64,9	6,6	16,2	69
Vb	163—164	1630 (C=N), 1660 (C=O), 3330 (NH)	210 (4,19), 239 (4,41), 310 (3,98), 356 (3,59)	1,28, 4,12 (t, q $COOC_2H_5$), 7,76 (s, =CH), 1,28, 3,58 (t, q C_2H_5), 6,78—7,31 (m CH arom), 9,87 s (NH)	67,1	7,0	14,3	$C_{16}H_{21}N_3O_2$	66,9	7,3	14,6	65
Vc	158—159	1630 (C=N), 1665 (C=O), 3350 (NH)	219 (4,62), 306 (4,36)	1,35, 4,34 (t, q $COOC_2H_5$), 3,76 (s, CH_3O), 3,13 (s, CH_3), 7,78 (s, =CH), 6,93—7,47 (m CH arom.), 9,84 (s, NH)	62,6	6,9	14,6	$C_{15}H_{19}N_3O_3$	62,3	6,6	14,5	83
Vd	165—166	1630 (C=N), 1665 (C=O), 3320 (NH)	223 (4,83), 310 (4,39)	1,26, 4,28 (t, q $COOC_2H_5$), 3,73 (s, CH_3O), 1,26, 3,58 (t, q C_2H_5), 7,78 (s, =CH), 6,72—7,41 (m CH arom), 9,90 (s, NH)	64,4	7,4	13,3	$C_{17}H_{23}N_3O_3$	64,4	7,3	13,2	63
VIa	157—158	1625 (C=N), 1670 (C=O), 3320 (NH)	211 (4,18), 234 (4,30), 306 (4,04), 339 (3,67)	1,38, 4,28 (t, q $COOC_2H_5$), 1,89 (s, CH_3), 3,09 (s, CH_3), 6,83—7,29 (m CH arom), 9,89 (s, NH)	66,2	7,2	15,7	$C_{15}H_{19}N_3O_3$	65,9	7,0	15,4	63
VIb	188—189	1610 (C=N), 1665 (C=O), 3320 (NH)	220 (4,79), 308 (4,41)	1,34, 4,35 (t, q $COOC_2H_5$), 3,78 (s, CH_3O), 1,89 (s, CH_3), 3,07 (s, CH_3), 6,90—7,43 (m CH arom), 9,75 (s, NH)	63,7	7,2	14,1	$C_{16}H_{21}N_3O_3$	63,4	6,9	13,9	67
VII*	132—133	1620 (C=N), 1650 (C=O), 3250 (NH)	209 (4,29), 267 (4,31), 328 (4,38), 384 (3,95)	1,37, 3,36 (t, q C_2H_5), 7,83 (s, =CH), 9,83 (s, CHO), 7,19—7,72 (m CH arom.), 8,91 (s, NH)	68,9	7,1	17,4	$C_{14}H_{17}N_3O$	69,1	7,0	17,3	48
VIII*	139—140	1600 (C=N), 3150 (NH)	217 (4,48), 2,78 (3,84)	1,93 (s, CH_3), 3,03 (s, CH_3), 6,58 (d, 2-H), 6,83—7,34 (m CH arom.), 9,61 (s, NH)	71,6	7,4	20,9	$C_{12}H_{15}N_3$	71,6	7,5	20,9	53

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*The PMR spectra of VII and VIII were taken in $CDCl_3$, while the corresponding spectra of Va-d, VIa, and VIb were taken in acetone-d_6.

2-Carboethoxy-5-methoxy-3-formylaminoindole (XIV). A. A sample of 2.7 g (10 mmoles) hydrochloride salt IVb was added to a mixture of 1.4 g (30 mmoles) formic acid and 3.1 g (30 mmoles) acetic anhydride maintained for 2 h at 60°C. The reaction mass was stirred for 1 h at 20-25°C and poured into 100 ml water. The mixture obtained was heated at reflux with 1 g activated charcoal and filtered. The precipitate formed from the filtrate was filtered off and washed with water to give 2.3 g (88%) XIV, mp 214-215°C (from ethanol). IR spectrum: 1650 (amide $C=O$), 1710 ($CO_2C_2H_5$), 3060 (amide NH), 3240 (indole NH). Found: C 59.2; H 5.6; N 10.9%. Calculated for $C_{13}H_{14}N_2O_4$: C 59.6; H 5.3; N 10.7%.

B. A mixture of 1.4 g (5 mmoles) amidine Vc and 0.8 g (5 mmoles) benzylamine hydrochloride in 30 ml ethanol was heated at reflux for 2 h. The reaction mass was cooled to 20-25°C, diluted with 150 ml water and the resultant precipitate was filtered off, washed with water to give 0.8 g (63%) amide XIV, which was identical in its melting point and IR spectrum to the sample obtained by method A.

C. By analogy with experiment B, 1.4 g (5 mmoles) amidine Vc, 5 ml 50% acetic acid, and 40 ml ethanol gave 0.9 g (69%) amide XIV which was identical in its melting point and IR spectrum to the sample obtained by method A.

3-Acetylamino-2-carboethoxy-5-methoxyindole (XV). A. A sample of 1.2 g (12 mmoles) was added to a mixture of 2.7 g (10 mmoles) hydrochloride IVb and 20 ml pyridine. The reaction mass was maintained for 1 h at 20-25°C and then poured into 100 ml water. The resultant precipitate was filtered off and washed with 5% aq. HCl and water to give 1.7 g (78%) (XV, mp 229-230°C (from ethanol). IR spectrum: 1630 (amide $C=O$), 1700 ($CO_2C_2H_5$), 3050 (amide NH), 3240 cm^{-1} (indole NH). Found: C 59.9; H 5.9; N 10.3%. Calculated for $C_{14}H_{16}N_2O_4$: C 60.2, H 5.8; N 10.2%.

B. By analogy with method B for the preparation of XIV, 1.5 g (5 mmoles) amidine VIb and 0.8 g (5 mmoles) benzylamine hydrochloride in 60 ml ethanol to give 0.7 g amide XV which was identical in its melting point and IR spectrum to the compound obtained by method A.

5-Methoxy-3-formylaminoindole-2-carboxylic acid (XVI). A sample of 3.0 g (75 mmoles) NaOH was added to a solution of 2.9 g (10 mmoles) amidine Vc and 70 ml ethanol and the mixture was heated at reflux for 2 h. The reaction mixture was poured into 200 ml water and the insoluble impurities were filtered off. The filtrate was treated at 0-5°C with 0.1 N aqueous hydrochloric acid to pH 5.5-6.0. The resultant precipitate was filtered off and washed with water to give 1.7 g (73%) XVI, mp 222-223°C (from 4:1 DMF-water). IR spectrum: 1680 (amide $C=O$), 1700 (acid $C=O$), 2600-2750 (acid OH), 3200-3480 cm^{-1} (indole NH, amide NH). Found: C 56.6; H 4.5; N 11.9%. Calculated for $C_{11}H_{10}N_2O_4$: C 56.4; H 4.3; N 12.0%.

3-Acetylamino-5-methoxyindole-2-carboxylic acid (XVII). A sample of amidine VIb was added to a solution of sodium ethylate prepared from 0.12 g (5 mmoles) sodium and 50 ml absolute ethanol and the mixture was heated at reflux for 3 h. The subsequent treatment was as in the synthesis of acid XVI to yield 0.8 g (64%) acid XVII, mp 232-234°C (from acetone). IR spectrum: 1660 (amide $C=O$), 1690 (acid $C=O$), 2630-2750 (acid OH), 3200-3400 cm^{-1} (indole, NH, amide NH). Found: C 58.5; H 5.2; N 11.0% $[M - CO_2]^{+\bullet}$ 204. Calculated for $C_{12}H_{12}N_2O_4$: C 58.1; H 4.8; N 11.3%, M 248.

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