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REARRANGEMENT OF 1-ACETYLINDOXYL OXIME TO 1-ACETYL-2-CHLORO-3-IMINOINDOLINE HYDROCHLORIDE

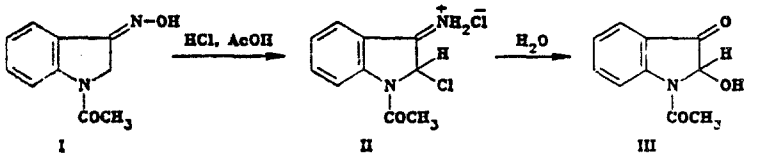
V. S. Velezheva and S. Yu. Ryabova

UDC 547.756:542.952

Rearrangement of 1-acetylindoxyl oxime upon treatment with hydrogen chloride in acetic acid results in the formation of 1-acetyl-2-chloro-3-iminoindoline hydrochloride. Hydrolysis and acylation of the latter have been studied, along with reaction of 1-acetyl-2-chloro-3-(ω-chloroacetyl)aminoindole with N- and S-nucleophiles.

We have previously demonstrated the conversion of 1-acetylindoxyl oxime (I) to 3-iminoindoline hydrogen sulfate involving simultaneous introduction of an acetoxy group in the 2-position [1].

In the present paper we propose a method for the synthesis of 2-chloro-3-iminoindoline, which is of interest for the preparation of 2-functional 3-aminoindole derivatives.



I II III

We have found that oxime I reacts with hydrogen chloride in acetic acid solution in the presence of acetic anhydride at a temperature of 13–25°C to give 1-acetyl-2-chloro-3-iminoindoline hydrochloride (II) [2]. The yield of hydrochloride II depends on the dilution factor and the amount of acetic anhydride present (Table 1).

S. Ordzhonikidze All-Union Scientific Research Chemical Pharmaceutical Institute, Moscow.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 617–621, May, 1990. Original article submitted October 31, 1988.

0009-3122/90/2605-0520$12.50

TABLE 1. Yield of Hydrochloride II and Its Dependence on Dilution and the Amount of Acetic Anhydride

Amount of oxime I, moles	Concentration of HCl, %	Amount of Ac_2O, moles	Yield of compound II, %	Amount of oxime I, moles	Concentration of HCl, %	Amount of Ac_2O moles	Yield of compound II, %
0,010	6,5	—	64	0,010	5,0	0,010	64
0,010	6,5	0,01	82	0,005	3,0	0,005	75
0,010	6,5	0,02	57	0,005	1,5	0,005	48
0,010	6,5	0,03	35	0,005	7,5	0,005	—
0,010	6,5	0,04	—	0,005	9,0	0,005	—
0,005	6,5	0,005	57				

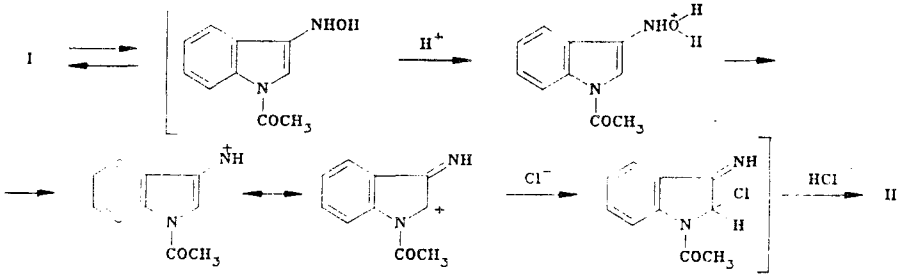
The highest yield of hydrochloride II (82%) is achieved at a ratio of oxime I to acetic anhydride equal to 1:1, and at a hydrogen chloride concentration of about 6.5%.

Formation of hydrochloride II is an exothermic process; at a temperature greater than 25°C a complex mixture of products is observed in addition to II, along with resin formation. One of the side reactions involves conversion of oxime I upon heating in a mixture of acetic acid and acetic anhydride to give 1-acetyl-2-acetoxy-3-acetylaminoindole [3].

Hydrochloride II is a labile material, which is stable without decomposition upon storage under vacuum with P_2O_5 for 5–7 days, but which darkens upon exposure to air.

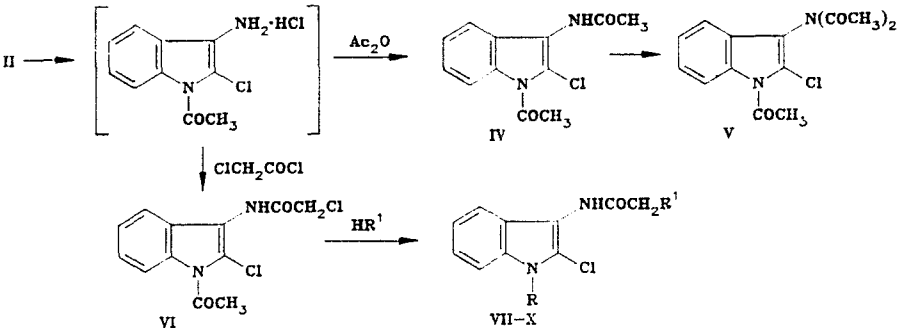
The indoline structure of hydrochloride II was confirmed based on its PMR spectral data, which contained a singlet signal for the 2-H proton at 7.15 ppm. The $=NH_2^+$ group is represented in the IR spectrum by a system of bands in the 2500–2800 cm^{-1} region.

We assume that oxime I is converted to hydrochloride II via a Bamberger-type rearrangement, during the course of which a chloride anion is inserted into the 2-position of the iminoindoline ring.



Upon dissolution in water hydrochloride II is hydrolyzed to 1-acetyl-2-hydroxyindolinone (III), which has been described previously in [4]; the identity of the substance was established based on its IR, UV, and PMR spectra.

Treatment of hydrochloride II with acetic anhydride and chloroacetyl chloride results in isomerization of the iminoindoline ring to an aminoindole ring with simultaneous acylation of the amino group.



VII R=$COCH_3$, R^1=SPh; VIII R=$COCH_3$, R^1= morpholino IX R=H, R^1= piperidino
X R=$COCH_3$, R^1=N- phenylpiperazino

Upon heating in acetic anhydride to 70°C hydrochloride II is converted to 1-acetyl-2-chloro-3-acetylaminoindole (IV), while at higher temperatures diacetylaminoindole V is formed; use of chloroacetyl chloride leads to the monoacylation product VI (Table 2).

TABLE 2. Physical Chemical Properties of Compounds II–XI

Compound	Mass spectrum			IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum	
	M^+	molecular formula	M			solvent	chemical shifts, ppm
II	208	$C_{10}H_{10}Cl_2N_2O$	208 pri	1670 (C=N), 1712 (C=O), 2800...2500 ($=NH_2$)	236 (4,33), 260 (3,86), 342 (3,34)	CF_3COOD	2,76 (3H, s, $COCH_3$), 7,15 (1H, s, 2-H), 7,62, 8,15 (1H, t, 5-H, 1H, t, 6-H, J=8 Hz), 8,45 (1H, d, 4-H; J=8 Hz), 8,52 (1H, br.s, 7-H)
III	191	$C_{10}H_9NO_3$	191	1670, 1730 (C=O), 3260 (OH)	205 (3,88), 240 (4,42), 263 (4,02), 345 (3,49)	$CDCl_3$	2,45 (3H, s, $COCH_3$), 5,30 (1H, s, 2-H), 6,38 (1H, br.s, OH), 8,44 (1H, br.d, 7-H, J=8 Hz), 7,20...7,70 (3H, m, arom. protons)
IV	250	$C_{12}H_{11}ClN_2O_2$	250	1660, 1710 (C=O), 3240 (NH)	207 (4,27), 242 (4,12), 278 (3,95), 294 (3,80), sh, 302 (3,77)) sh	DMSO-D6	2,12 (3H, s, $COCH_3$), 2,7 (3H, s, $COCH_3$), 9,74 (1H, s, $NHCOCH_3$), 8,56 (1H, m, 7-H), 7,28...7,44 (3H, m, arom. protons)
V	—	$C_{14}H_{13}ClN_2O_3$	—	1720, 1735 (C=O)	—	—	—
VI	284	$C_{12}H_{10}Cl_2N_2O_2$	285	1670, 1710 (C=O), 3260 (NH)	—	DMSO-D6	2,79 (3H, s, $COCH_3$), 4,39 (2H, s, $COCH_2Cl$), 8,29 (1H, d, 7-H), 10,15 (1H, s, $NHCOCH_2Cl$), 7,03...7,43 (3H, m, arom. protons)
VII	358	$C_{18}H_{15}ClN_2O_2$	358	1660, 1710 (C=O), 3240 (NH)	—	$CDCl_3$	2,76 (3H, s, $COCH_3$), 3,91 (2H, s, $COCH_2SPh$), 8,38 (1H, d, 7-H, 1H, br.s, NH), 7,15...7,50 (8H, m, arom. protons)
VIII	—	$C_{19}H_{18}ClN_3O_3$	335	1670, 1700, (C=O), 3200 (NH)	—	—	—
VIIIa	335	$C_{16}H_{19}Cl_2N_3O_3$	335 pri	1700, 1730 (C=O), 3140 (NH)	—	—	—
IX	—	$C_{15}H_{18}ClN_3O$	291	1670 (C=O), 3180, 3280 (NH)	219 (4,58), 246 (3,75), 252 (3,79), 259 (3,88), 272 (4,01), 281 (4,00) sh, 289 (3,92)	$CDCl_3$	1,51 (2H, m, 4-piperidino), 1,67 (4H, m, 3,5-piperidino), 2,64 (4H, t, 2,6-piperidino), 3,21 (2H, s, $NHCOCH_2R_1$), 8,88 (1H, s, $NHCOCH_2R_1$), 9,11 (1H, s, NH), 7,45...7,00 (4H, m, arom. protons)
IXa	291	$C_{15}H_{21}Cl_2N_3O_2$	291 pri	—	—	—	—
Xa	411	$C_{22}H_{24}Cl_2N_4O_2$	441	1690, 1720 (C=O), 3150...2480	—	—	—
XI	425	$C_{18}H_{22}Cl_2N_6O_2$	425	NH_2^+ band system —	—	—	—

We have also found that reaction of 1-acetyl-2-chloro-3-(ω-chloroacetyl)aminoindole (VI) with S- and N-nucleophilic reagents leads to substitution only of the side chain chlorine atom. Thus, compounds VII–X were obtained upon treatment with thiophenol, morpholine, piperidine, and n-phenylpiperazine, respectively. Piperidine displaces not only the chlorine atom in compound VI, however, but also cleaves the N-acetyl group. Compound VI and urotropine readily yield the urotropinium salt XI. Compounds VIII–X are further converted to hydrochlorides VIIIa–Xa upon treatment with an ether solution of hydrogen chloride.

In the PMR spectra of compounds VII–X the signals due to the CH_2 group protons are shifted more upfield (3.9–3.2 ppm) than the signals for the same group of protons in the starting material, compound VI (4.39 ppm).

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer spectrophotometer using Vaseline mulls, UV spectra on a Perkin–Elmer 575 spectrophotometer using ethanol solutions. PMR spectra were obtained on a Varian XL-200 spectrometer versus TMS as internal standard. Mass spectra were measured on a Varian MAT-112 mass spectrometer (70 eV) using direct sample introduction into the ion source. Sample purity was assayed by TLC on Silufol UV-254 plates in ethyl acetate and were visualized in UV light.

The results of elemental analysis of the newly synthesized compounds agreed with calculations.

1-Acetyl-2-chloro-3-iminoindoline Hydrochloride (II). To 1.9 g (10 mmoles) oxime I was added with stirring a cooled (13–15°C) mixture of 15 ml glacial acetic acid saturated with hydrogen chloride (6.5%) and 1 ml (10 mmoles) acetic anhydride. The mixture was stirred 6–7 h at 13–25°C. The resulting precipitate was removed by filtration, washed with acetic anhydride and ether. Yield 2 g (82%), mp ~200°C (decomp.).

1-Acetyl-2-hydroxyindolin-3-one (III). Hydrochloride II (0.5 g, 2 mmoles) was dissolved with stirring in 30 ml water at 25–30°C and the reaction mixture was allowed to stand 24 h at 20°C. The resulting precipitate was removed by filtration, washed with water and isopropyl alcohol. Yield 0.08 g (20%), mp 155–156°C (from benzene).

1-Acetyl-2-chloro-3-acetylaminoindole (IV). A mixture of 4.15 g (17 mmoles) hydrochloride II and 25 ml acetic anhydride was heated with stirring to 70°C and maintained at this temperature for 30 min. The reaction mixture was cooled, the precipitate was removed by filtration, and washed with acetic anhydride and ether. Yield 3.25 g (77%), mp 203°C (decomp. from methanol–DMF, 4:1).

1-Acetyl-2-chloro-3-diacetylaminoindole (V). A mixture of 2.7 g (11 mmoles) hydrochloride II and 27 ml acetic anhydride was refluxed for 1 h. The solution was cooled, filtered, and poured into water. The resulting precipitate was removed by filtration and washed with water and alcohol. Yield 2.1 g (65%), mp 107–109°C (isopropyl alcohol).

1-Acetyl-2-chloro-3-(ω-chloroacetyl)aminoindole (VI). A mixture of 5.1 g (2 mmoles) hydrochloride II and 30 ml chloroacetyl chloride was heated with stirring (5 min) until solution occurred and a new precipitate appeared. The suspension was cooled, the precipitate was filtered and washed with chloroacetyl chloride. The precipitate was transferred with stirring into 100 ml water, filtered again after 30 min, then washed with water and alcohol. Yield 4.2 g (70%), mp 215–216°C (methanol–DMF, 4:1).

1-Acetyl-2-chloro-3-(ω-phenylthioacetyl)aminoindole (VII). To a suspension of 0.29 g (1 mmole) compound VI in 8 ml benzene was added 0.1 ml (1 mmole) thiophenol and 0.42 ml (3 mmoles) triethylamine and the mixture was stirred 4 h. The precipitate was removed by filtration and washed with water, isopropyl alcohol, and ether. Yield 0.2 g (55%), mp 160–161°C (from isopropyl alcohol).

1-Acetyl-2-chloro-3-(ω-morpholinoacetyl)aminoindole (VIII). To a solution of 1.43 g (5 mmoles) compound VI in 14 ml DMF was added 2.17 g (25 mmoles) morpholine and the mixture was allowed to stand for 3 h at 20°C. The DMF was removed and to the residue was added ether. Morpholine hydrochloride was then filtered off. The ether was evaporated and water was added to the residue. The precipitate was removed by filtration and washed with water and isopropyl alcohol. Yield 1.3 g (77%), mp 161–171°C (from isopropyl alcohol).

1-Acetyl-2-chloro-3-(ω-morpholinoacetyl)aminoindole Hydrochloride (VIIIa). Compound VIII was dissolved in 30 ml acetone upon heating. The solution was cooled to 15–20°C and treated with ethereal hydrogen chloride solution. Dry ether was then added (30 ml) and the resulting precipitate was removed by filtration and washed with ether. Yield 1.45 g (100%), mp 207°C (decomp., from isopropyl alcohol).

2-Chloro-3-(ω-piperidinoacetyl)aminoindole (IX). To a solution of 2.86 g (10 mmoles) compound VI in 28 ml DMF was added 4.25 g (50 mmoles) piperidine and the mixture was allowed to stand at 20°C for 3 h. The resulting precipitate of piperidinium hydrochloride was filtered off. Water was added to the mother liquor. The resulting precipitate was

removed by filtration and washed with water, isopropyl alcohol, and ether. Yield 2.2 g (66%), mp 144–145°C (from isopropyl alcohol).

2-Chloro-3-(ω-piperidinoacetyl)aminoindole Hydrochloride (IXa). A solution of 0.63 g (2 mmoles) compound IX in 5 ml acetone was treated with ethereal hydrogen chloride solution. The resulting precipitate was removed by filtration and washed with acetone and ether. Yield 0.65 g (93%), mp 245–247°C (from ethyl alcohol). The compound was characterized in the form of its hydrate.

1-Acetyl-2-chloro-3-(ω-N-phenylpiperazinoacetyl)aminoindole Hydrochloride (Xa). Compound VI (0.29 g, 1 mmole) was dissolved in 10 ml acetonitrile with stirring and heating for 30 min. The solution was cooled to 20°C and 0.33 ml (2 mmoles) N-phenylpiperazine was added; the mixture was allowed to stand for 24 h. The resulting precipitate of N-phenylpiperazine hydrochloride was filtered off, and the acetonitrile solvent evaporated. The oily residue was dissolved in ether and filtered. The filtrate was treated with a solution of hydrogen chloride in ether. The resulting precipitate was removed by filtration and washed with ether. Yield 0.38 g (91%), mp 226–227°C (decomp., from water).

1-Acetyl-3-chloro-3-(ω-chloroacetyl)aminoindole Urotropinium Salt (XI). Compound VI (0.29 g, 1 mmole) was dissolved upon heating in 25 ml acetone. The solution was filtered and 0.15 g (1 mmole) urotropine was added to the filtrate. The mixture was refluxed for 4 h. The resulting precipitate was removed by filtration and washed with hot acetone. Yield 0.25 g (55%), mp 178°C (decomp.).

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