1-ACETYL-2-CHLORO-3-IMINOINDOLINE HYDROCHLORIDE AND ITS N-ACETYL DERIVATIVES IN NUCLEOPHILIC SUBSTITUTION REACTIONS

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It is shown that the chlorine atom in position 2 of 1-acetyl-2-chloro-3-iminoindoline hydrochloride is readily substituted on treatment with secondary amines and thiophenol. The products of nucleophilic reaction are isolated as 2-substituted 3-aminoindoles or 3-acetylaminoindoles, and as 2-substituted 1-acetyl-3-indolinones. The latter are also formed from 1-acetyl-3-indolinone by successive bromination and treatment with secondary amines.

In previous works we used 1-acetylindoxyl oxime (I) as the starting reagent to formulate a method of synthesizing 1-acetyl-2-chloro-3-iminoindoline hydrochloride (II) and demonstrated that in the presence of acetic anhydride the latter is converted into 1-acetyl-2-chloro-3-aminoindole (VIII) [1, 2].

In the present work it is shown that the chlorine atom in position 2 of hydrochloride II can be replaced by nucleophilic reagents; this opens the way to obtaining 3-aminoindoles with heteroatoms and carbon substituents in position 2, which are compounds not readily synthesized by other means. We simplified the procedure for obtaining hydrochloride II from oxime I and hydrogen chloride in a mixture of acetic acid and acetic anhydride by replacing the latter mixture with the aprotonic solvents dioxane and tetrahydrofuran. The duration of the reaction then decreased from 6-7 h to 10-15 min, while the shelf life of the labile hydrochloride II increased from 5-6 h to 2-3 weeks.

The structure of hydrochloride II is confirmed by NMR spectral data. Thus, in the PMR spectrum of a solution of hydrochloride II in CF_3COOH a signal is observed at 7.14 ppm, which can be attributed to the methine 2-H proton. This is also borne out by the ^{13}C NMR spectrum of a solution of hydrochloride II in CF_3COOH—CD_2Cl_2, in which the doublet signal (J_{CH} = 179.2 Hz) of the carbon methine atom has a chemical shift of 69.29 ppm. It is worth noting that in PMR spectra of hydrochloride II recorded in CF_3COOD solution the 2-H signal is absent due to deuterium exchange.

In a weak base medium, such as a mixture of aprotonic solvent and triethylamine, the iminoindoline structure of hydrochloride II is retained. This is suggested by the insignificant change in chemical shift of the 2-H methine proton in a spectrum of hydrochloride II taken in a CD_3CN—Et_3N mixture against that recorded in pure acetonitrile (see Table 1).

However, the spectral data for hydrochloride II in protonic solvents such as CD_3OD and D_2O suggest that a mixture of solvolysis products are formed under these conditions. In D_2O a separate compound, 1-acetyl-2-hydroxy-3-indolinone [3] is formed in this case. It might be expected from the data that hydrochloride II or its base would react by nucleophilic substitution at the saturated $C_{(2)}$ atom and display appreciable reactivity.

In practice the chlorine atom in position 2 of hydrochloride II is readily substituted in the presence of S- and N-nucleophiles such as secondary amines and thiophenol. The reaction of hydrochloride II with these nucleophiles at 0-20°C proceeds for 5-10 min, ether, benzene, and acetonitrile being the most suitable solvents. Under these conditions the imino group is not affected

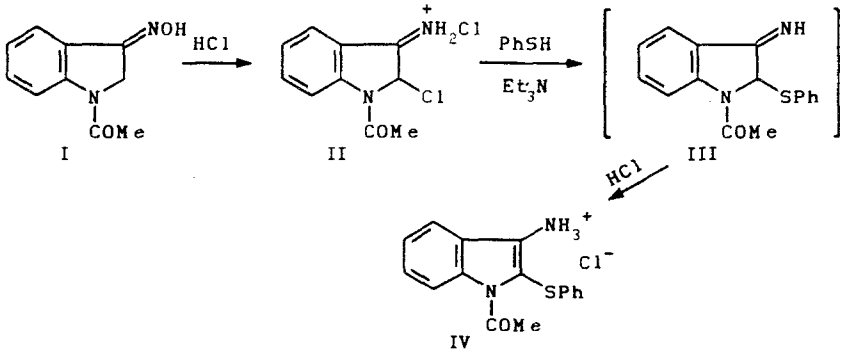

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TABLE 1. PMR Spectra of Compounds II, IV-VIII, and XV

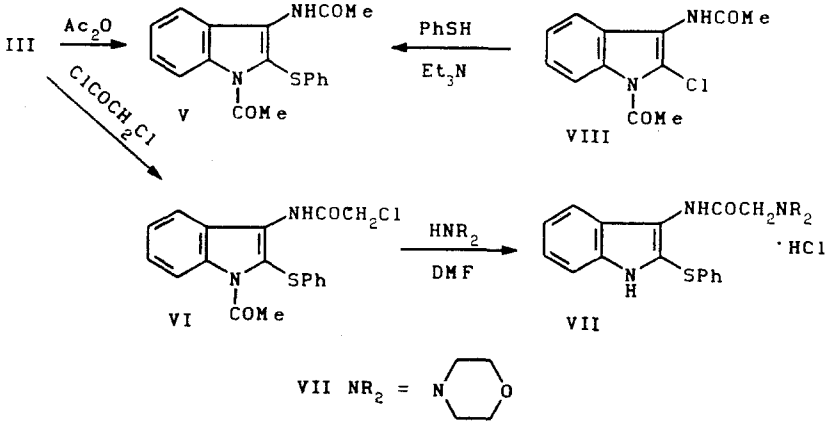
Compound	Solvent	δ, ppm						
		2-H, s	4-H, d	5-H, t	6-H, t	7-H, d	$COCH_3$	other signals
II	CF_3COOH	7,14	8,44	7,62	8,14	8,54	2,76	—
	CF_3COOD	—	8,47	7,63	8,16	8,57	2,76	—
	CD_3CN	6,16	7,81	7,35	7,79	8,36	2,46	—
	CD_3CN, Et_3N	6,13	7,81	7,34	7,79	8,36	2,46	—
IV	CD_3COOD	—	8,01	7,32	7,87	8,29	2,92	~ 7,30 (Ph)
	DMF*	—	8,12	7,24	7,53	8,52	2,71	11,6 (NH_3^+)
	CD_3OD	—	8,13	7,74	7,78	8,45	2,70	7,05...7,45 (Ph)
	CD_3OD, Et_3N	—	7,72	7,34	7,42	8,46	—	7,04...7,30 (Ph)
V	$CDCl_3$	—	7,71	—	7,45	8,43	2,78	7,05...7,40 (Ph); 2,19 ($COCH_3$)
VI	DMSO	—	7,51	7,33	7,44	8,26	2,75	7,10...7,30 (Ph); 4,32 (CH_2)
	$CDCl_3$	—	7,51	7,33	7,46	8,43	2,81	7,05...7,30 (Ph); 4,18 (CH_2);
VII	DMSO	—	7,68	7,28	7,46	8,31	2,76	7,08...7,37 (Ph); 2,76 (CH_2); 9,72 (NH)
VIII	$CDCl_3$	—	7,46	7,28	7,36	8,37	2,79	~ 6,3 (NH); 3,81 (OCH_3)
XV	$CDCl_3$	5,31	7,78	7,36	7,94	7,82	2,68	1,7, 2,2, 3,2...3.6 (piperidine)

*Spectrum measured at −30°C.

by the nucleophiles and, in particular, it is not solvolyzed, which is typical of hydrochloride II in protonic solvents. The labile free bases which form when the chlorine atom is replaced by nucleophiles were isolated as hydrochlorides and amides.

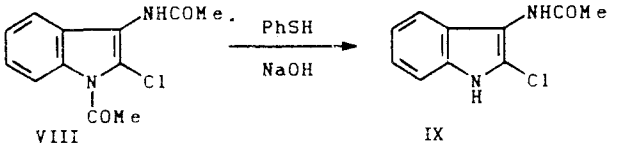
The reaction of hydrochloride II with thiophenol must be carried out in the presence of a base such as triethylamine. On treatment with hydrogen chloride the intermediate imine III changes quantitatively into hydrochloride IV, which has an aminoindole structure. This is confirmed by PMR spectral data. Signals that could be attributed to the 2-H methine proton are absent from the spectra of hydrochloride IV recorded in both protonic and aprotonic solvents (see Table 1).

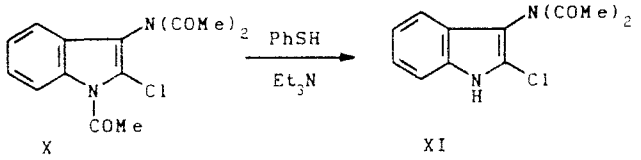
The acylation products obtained from free base III or its hydrochloride II also have an indole structure. On treatment with acetic anhydride and chloroacetylchloride, base III is converted into amides V and VI, respectively. In the reaction of amide IV with morpholine the chlorine atom is substituted, yielding amide VII, which is isolated as the hydrochloride.



In the PMR spectra of compounds V-VIII signals are observed for the side-chain substituents in position 3 of the indole ring, i.e., the $COCH_3$, $COCH_2$, and NH groups (see Table 1). No methine proton signal is found in any of these cases, which means that the compounds cannot exist in isomeric iminoindoline form.

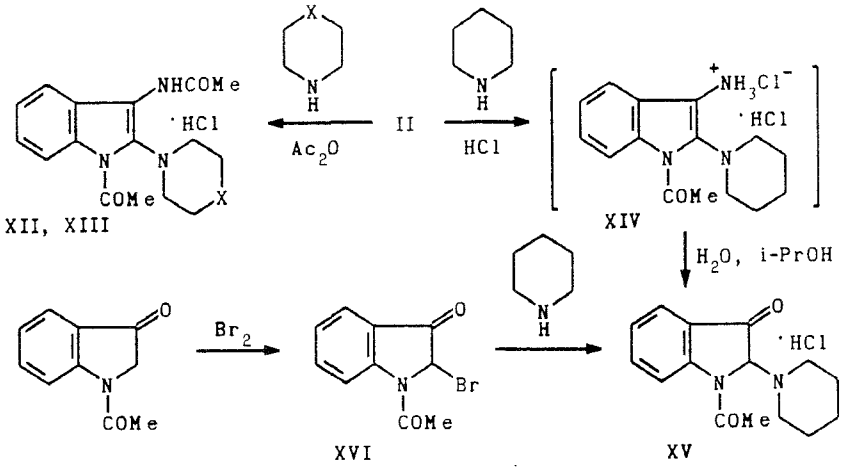
Unlike hydrochloride II, 1-acetyl-2-chloro-3-acetylaminoindole (VIII) does not readily react by nucleophilic substitution. Hence, an insignificant yield of compound V is produced when VIII reacts with thiophenol in the presence of triethylamine. Using a stronger base such as sodium hydroxide merely causes the acetyl group to be removed from the nitrogen heteroatom, yielding amide IX.





Diacetylaminoindole X is even more readily deacylated on treatment with thiophenol and triethylamine, the chlorine atom not being substituted in this instance.

Thus, effective substitution of the chlorine atom in hydrochloride II and its type VIII aminoacetyl derivatives requires the presence of the iminoindoline structure and an acetyl group on the nitrogen heteroatom.



XII X=O, XIII X=CH_2

In the presence of morpholine and piperidine, hydrochloride II is converted into labile bases which, on treatment with acetic anhydride, produce the 3-acetylaminoindoles XII and XIII. As in the previous case, this process involves substitution, N-acylation, and indolization stages.

The free base obtained in situ from hydrochloride II and piperidine is converted, on treatment with hydrogen chloride, into the highly labile dihydrochloride XIV. One way in which the latter can further transform is by hydrolysis of the amino(imino) group. Hence when dihydrochloride IV was dissolved in aqueous isopropanol, 2-piperidinoindoxyl XV was isolated in very low yield. Moreover, it is advisable to synthesize the 2-alkylaminoindoxyls, including compound XV, by a different route, namely by successive bromination and amination of the 1-acetylindoxyl. The intermediate 2-bromindoxyl XVI [4] can be reacted with the amine as a solution prepared in situ. The yield of 2-piperidinoindoxyl XV is then 71%.

EXPERIMENTAL

IR spectra were taken on a Perkin—Elmer instrument in Vaseline. PMR spectra were recorded on a Varian XL-200, internal standard TMS. Mass spectra were obtained on a Varian MAT-112 (Germany, 70 eV) mass spectrometer with direct sample insertion into the ion chamber. The purity of the substances isolated was monitored using TLC on a Silufol UV-254 plate in ethyl acetate. Development in UV light.

Elemental analysis data were in line with calculated values for the compounds synthesized.

1-Acetyl-2-chloro-3-iminoindoline Hydrochloride (II). To a suspension of 1.9 g (10 mmoles) of 1-acetylindoxyl oxime (I) in 50 ml of dry dioxane or tetrahydrofuran at 20°C and with vigorous stirring were added momentarily 20 ml of a 1 N solution of hydrogen chloride in ether. Stirring was continued for 15 min, then the yellow precipitate was filtered off and washed with ether. Mp 200°C (with decomposition); data in [1] give mp 200°C. Yield 2.2 g (90%).

1-Acetyl-2-phenylthio-3-aminoindole Hydrochloride (IV, $C_{16}H_{14}N_2OS \cdot HCl$). To a suspension of 0.72 g (3 mmoles) of hydrochloride II in 40 ml of ether at 10-15°C were added 0.43 ml (3 mmoles) of thiophenol and 1.26 ml (9 mmoles) of triethylamine, and the mixture stirred for 30 min. The triethylamine hydrochloride was filtered off and the mother liquor treated with an ethereal solution of hydrogen chloride. The precipitate obtained was filtered off, washed with ether, and recrystallized from isopropyl alcohol. Mp 153-155°C. IR spectra: 1710 (C=O); 3420-3480 cm^{-1} (NH_2). M^+ 282. Yield 0.28 g (28%).

1-Acetyl-2-phenylthio-3-acetyliminoindole (V, $C_{18}H_{16}N_2O_2S$). A. Synthesis was carried out as for the previous compound from 0.24 g (1 mmole) of hydrochloride II. After separation of triethylamine hydrochloride the mother liquor was evaporated and the residue mixed with 5 ml of acetic anhydride. The precipitate formed was filtered off and washed with acetic anhydride and ether. Mp 186-187°C (from isopropyl alcohol). IR spectra: 1660, 1700 (2 C=O), 3280 cm^{-1} (NH). M^+ 324. Yield 0.15 g (50%).

B. A suspension of 0.75 g (3 mmoles) of 1-acetyl-2-chloro-3-acetylaminoindole (VIII), 0.64 ml (4.5 mmoles) of thiophenol, and 1.26 ml (9 mmoles) of triethylamine in 24 ml of benzene was stirred for 30 h at 20°C. Triethylamine hydrochloride and unreacted starting compound were filtered off. The mother liquor was evaporated and the residue stirred with ether. Mp 186-187°C (from isopropyl alcohol). Yield 0.15 g (15%). From TLC and melting point the compound was found to be identical to a known sample.

1-Acetyl-2-phenylthio-3-(ω-chloroacetyl)-aminoindole (VI, $C_{18}H_{15}ClN_2O_2S$). This was obtained from 1.2 g (5 mmoles) of hydrochloride II in a similar manner to compound IV. After separation of triethylamine hydrochloride 1.68 g (15 mmoles) of chloroacetylchloride were added to the ethereal mother liquor with stirring at 10-15°C. The precipitate was filtered off and washed with water, alcohol, and ether. Mp 171-172°C (from isopropyl alcohol). IR spectra: 1670, 1710 (2 C=O), 3260 cm^{-1} (NH). M^+ 358. Yield 0.2 g (26%).

1-Acetyl-2-phenylthio-3-(ω-morpholinoacetyl)-aminoindole Hydrochloride (VII, $C_{22}H_{23}N_3O_3S \cdot HCl$). To a solution of 0.45 g (1.25 mmoles) of amide VI in 8 ml of dry DMF were added 0.52 ml (6 mmoles) of morpholine and the mixture left to stand for 2 h at 20°C. It was then poured into water, and the resulting precipitate was filtered off, washed with water, and dried. The base was next dissolved in an ether—acetone mixture (1:1) and treated with an ethereal hydrogen chloride solution. The resulting precipitate was filtered off and washed with ether. Mp 186-188°C (from isopropyl alcohol). IR spectra: 3140-2500 (N^+H); 1700 cm^{-1} (2 C=O). M^+ 409. Yield 0.4 g (71%).

2-Chloro-3-acetylaminoindole (IX, $C_{10}H_9ClN_2O$). A mixture of 0.25 g (1 mmole) of compound VIII, 0.1 ml (1 mmole) of thiophenol and 0.04 g (1 mmole) of sodium hydroxide in 2 ml of DMF was left to stand for 10 h at 20°C and poured into water. The solution was extracted with ether; the ethereal layer was washed with water and dried with magnesium sulfate. The ether was evaporated off to give compound IX. Mp 150-153°C (from isopropyl alcohol). IR spectra: 1640 (C=O), 3240 cm^{-1} (NH). M^+ 208. PMR spectrum ($CDCl_3$): 2.28 (3H, s, CH_3), 7.10-7.50 (4H, m, arom), 8.26 (1H, s, NH), 8.44 ppm (1H, s, NH). Yield 0.11 g (52%).

2-Chloro-2-diacetylaminoindole (XI, $C_{12}H_{11}ClN_2O_2$). To a solution of 0.6 g (2 mmoles) of 1-acetyl-2-chloro-3-diacetylaminoindole in 25 ml of benzene were added 0.43 g (3 mmoles) of thiophenol and 0.5 ml (3.5 mmoles) of triethylamine and the mixture allowed to stand for 24 h at 20°C. The resultant precipitate was filtered off and washed with benzene. The mother liquor was evaporated and the residue stirred with ether; the precipitate was filtered off and washed with ether. Mp 176-177°C (from isopropyl alcohol). IR spectra: 1640, 1720 (2 C=O), 3250 cm^{-1} (NH). M^+ 250. Yield 0.25 g (50%).

1-Acetyl-2-morpholine-3-acetylaminoindole (XII, $C_{16}H_{19}N_3O_3$). To a suspension of 2.4 g (10 mmoles) of hydrochloride II in 125 ml of ether were added 3.5 ml (40 mmoles) of morpholine with stirring at 10-15°C. After 5-10 min the morpholine hydrochloride was filtered off. The mother liquor was evaporated and the residue stirred with 10 ml of acetic anhydride. The resultant precipitate was filtered off and washed with acetic anhydride and ether. Mp 271-273°C (with decomposition, from isopropyl alcohol). IR spectra: 1660, 1770 (2 C=O), 3240 cm^{-1} (NH). M^+ 301. Yield 0.55 g (18%).

1-Acetyl-2-piperidine-3-acetylaminoindole (XIII, $C_{17}H_{20}N_3O_2$) was obtained in a similar way to compound XII. Mp 263°C (with decomposition, from alcohol). IR spectra: 1660, 1770 (2 C=O), 3240 cm^{-1} (NH). M^+ 299. Yield 67%.

1-Acetyl-2-piperidine-3-indolinone Hydrochloride (XV, $C_{15}H_{18}N_2O_2 \cdot HCl$). A. A solution of 1.6 g (10 mmoles) of bromine in 50 ml of dioxane was added momentarily to a solution of 1.75 g (10 mmoles) of 1-acetylindoxyl in 50 ml of dioxane, followed by 2.55 g (30 mmoles) of piperidine. After 10 min the resultant precipitate was filtered off and 20 ml of 1 N hydrogen chloride in ether were added to the filtrate. The solvent was evaporated off and the residue triturated with ether. Mp 158°C

(with decomposition). IR spectra: 1690, 1720 (C=O, NC=O), 2300-2500 cm^{-1} (N^+H). M^+ 258. Yield 2.1 g (71%).

B. To a suspension of 0.5 g (2 mmoles) of hydrochloride II in 15 ml of ether were added 0.5 ml (5 mmoles) of piperidine with stirring at 10-15°C. After 10-15 min piperidine hydrochloride was filtered off and the mother liquor treated with an ethereal hydrogen chloride solution. The resultant dihydrochloride XIV was filtered off and then stirred with isopropyl alcohol. The newly-formed precipitate was filtered off and washed with isopropyl alcohol and ether. Yield 0.1 g (19%). From the IR spectrum the compound was found to be identical to a known sample.

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