SYNTHESIS AND REACTIONS OF 2-AMINO-3-(ω-CHLOROAKLYL)INDOLES

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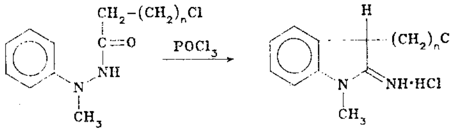
The reaction of N-methyl-N-phenyl-N'-(ω-chloro)acylhydrazines with $POCl_3$ yields derivatives of 2-amino-3-(ω-chloroalkyl)indoles. Hydrazides of β-chloropropionic acid were found to exist as the cyclic quaternary 3-oxopyrazolidinium salt. Several reactions involving the nucleophilic substitution of the chlorine atom in N-acylated derivatives of 2-aminoindole were studied.

The reactions of arylhydrazides of carboxylic acids with phosphorus halides is accompanied by the Kost rearrangement and formation of derivatives of 2-aminoindoles [1]. This reaction opened the way to the synthesis of 2-aminoindoles containing functional groups at the β-carbon atom, in particular, an amino group [2]. In the present work, we studied the applicability of the rearrangement of ω-haloalkylcarboxylic acids for the preparation of 2-amino-3-(ω-haloalkyl)indoles. The reactions of N-methyl-N-phenylhydrazides of ω-chloroalkylcarboxylic acids Ia-c with phosphoryl chloride features facile rearrangement and the formation of the hydrochloride salts of the corresponding 2-imino-3-(ω-chloroalkyl)indoles IIa-c.



I a-c

II a-c

I, II a n=0; b n=2; a n=3

Indoles II have UV spectra characteristic for salts of 2-aminoindoles [1,3] with bands at 125-217 nm (log ε 4.15-4.16) and 263-265 nm (log ε 3.86-3.88). The IR spectra of these compounds have broad bands in the region from 2500 to 3300 cm^{-1} corresponding to an amino group in the salt form and a band at 1690-1710 cm^{-1} corresponding to the C=N bond. Hence, the compounds obtained exist as 2-iminoindolines; this form is characteristic for 2-aminoindoles.

We might have expected that the introduction of the electron-withdrawing chlorine atom at the β-carbon atom of the indole system (IIa) would lead to stabilization of the 2-aminoindole form. However, the PMR spectrum of IIa (in CF_3CO_2H) shows singlets at 3.71 (3H, N—CH_3) and at 5.98 ppm (1H, β-H), an aromatic proton multiplet at 7.11-7.81 ppm (4H), and a broad signal from the two protons of the protonated imino group at 8.55 ppm, which indicates that this compound exists entirely in CF_3CO_2H solution as 3-chloro-2-iminoindoline.

It was impossible to study the reaction of the phenylhydrazide of β-chloropropionic acid with $POCl_3$ since an attempt to obtain this phenylhydrazide by the acylation of N-methyl-N-phenylhydrazine using β-chloropropionyl chloride under ordinary conditions (in the presence of triethylamine and in the absence of amine) gave a compound IIIa differing drastically in its physicochemical indices from the other hydrazides of ω-chloroalkylcarboxylic acids Ia-c. In contrast to the other hydrazides, this product is highly soluble in water and gives a positive test with silver nitrate for the presence of chloride ion. The IR spectrum of this product, in contrast to those of hydrazides Ia-c which have strong bands at 3250-3180 cm^{-1} corresponding to NH stretching vibrations and amide carbonyl bands at 1670-1660 cm^{-1}, has a broad band at 2540-2340 cm^{-1} characteristic for the stretching vibrations of the NH group in

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*Deceased.

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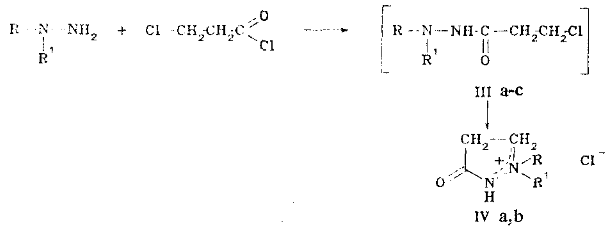
salt form. The carbonyl band is shifted toward higher frequencies and is found at 1725 cm^{-1}. These spectral data and the elemental analysis permit assignment of the structure of 3-oxo-1-methyl-1-phenylpyrazolidinium chloride (IVa). The proposed structure is supported by the PMR spectrum in CF_3CO_2H which has two complex multiplets for the methylene group protons at 3.10-3.51 (2H) and 4.54-5.10 ppm (2H), a singlet for the N–CH_3 group at 4.14 ppm (3H) and an aromatic proton singlet at 7.74 ppm (5H).



III, IV a $R=C_6H_5$, $R^1=CH_3$; b $R=CH_3$, $R^1=CH_3$; c $R=C_6H_5$, $R^1=C_6H_5$

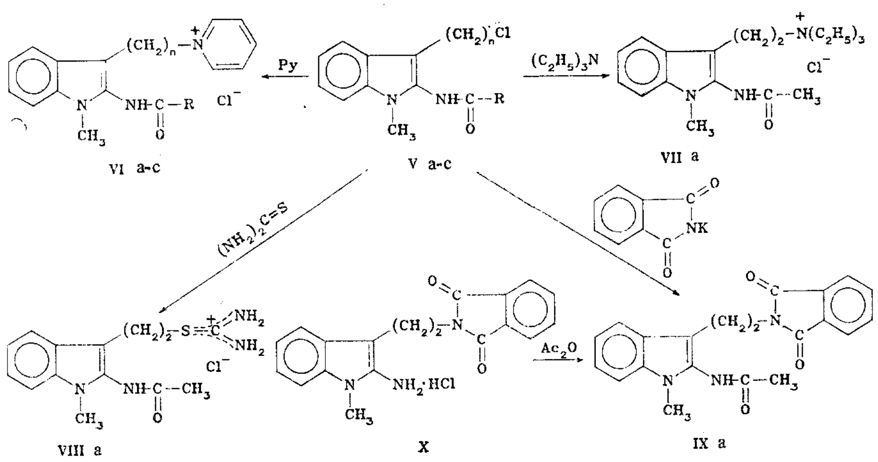
The formation of an ananlgous salt IVb occurs in the acylation of β-chloropropionyl chloride by unsymmetrical dimethylhydrazine. The IR spectrum of IVb also has a broad band for the NH group in salt form at 2400-2600 cm^{-1} and the carbonyl group band at 1730 cm^{-1}. The PMR spectrum of this compound in D_2O has methylene group multiplets at 3.21-3.57 (2H) and 4.37-4.80 (2H) and a singlet for the two equivalent methyl groups at 3.82 ppm (6H). The existence for the amino group in the salt form and significant shift of the C=O group band toward higher frequencies in the IR spectra of IVa and IVb indicate that the positive charge in cyclic quaternary salts IVa and IVb which arises as a result of intramolecular nucleophilic substitution of the chlorine atom is localized to a considerable extent on N-2.

The formation of cyclic compounds upon reaction with hydrazines is characteristic for propionic acid derivatives. Thus, phenylhydrazine reacts with β-chloropropionyl chloride to give the corresponding 1-phenylpyrazolidone-3 [4], while the reaction of unsymmetrical dimethylhydrazine with the acid chlorides of α,β-unsaturated acids leads to 3-oxo-1,1-dimethylpyrazolidinium chlorides [5]. However, we are the first to report the extremely facile cyclization of hydrazides IIIa and IIIb to give quaternary salts IVa and IVb. Such ready formation of these salts is apparently a consequence of the favorable steric configuration of hydrazides IIIa and IIIb and the lack of steric hindrance to ring formation. Indeed, the substitution of the methyl group by a phenyl group in hydrazide IIIc completely eliminates the possibility of cyclization, likely due to the reduced nucleophilicity of the nitrogen atom and increases steric hindrance. In its physicochemical properties, IIIc is analogous to hydrazides I although upon reaction with $POCl_3$, it does not form the corresponding 2-aminoindole, but rather undergoes decomposition with the formation of highly colored polymer products. The structure of these products was not determined. Salts IVa and IVb are rather stable and do not react with phosphorus halides even after prolonged heating at reflux. For example, salt IVa was isolated unchanged from the reaction mixture after heating with $POCl_3$ and PCl_5 in various solvents.

In order to evaluate the applicability of chloro derivatives II for the introduction of other functional groups, we studied the reactivity of the chlorine atom in several nucleophilic substitution reactions. In light of the high sensitivity of 2-aminoindole derivatives toward atmospheric oxygen in alkaline media [6], II were initially converted to N-acyl derivatives V. The reaction of chloro derivative Va reacts under relatively mild conditions with triethylamine and thiourea. More vigorous conditions are required for the preparation of quaternary salts IVa-c. The Gabriel reaction proceeds with only the greatest difficulty and requires heating at reflux in DMF for 14 h (for Va), while chloro derivatives Vc did not yield the corresponding product IX, apparently as a result of steric factors.

The structures of all the compounds studied were confirmed by physicochemical methods and elemental analysis. The structure of IXa, in addition, was confirmed by convergent synthesis involving the acetylation of the hydrochloride salt of 2-amino-3-phthalimidoethylindole X [2]. The IR spectra of the compounds obtained by both methods were identical.

Thus, chloro derivatives V may be used for the synthesis of bifunctional indole derivatives.



a n=2, R=CH_3; b n=3, R=C_6H_5; c n=3, R=C_6H_4—OCH_3-*o*

EXPERIMENTAL

The UV spectra were taken on a Perkin—Elmer 402 spectrometer. The IR spectra were taken on a Perkin—Elmer spectrometer in vaseline. The PMR spectra were taken on a Tesla BS-467 spectrometer. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates with 10:1 benzene—isopropyl alcohol and 1:4:1 benzene—butanol—ammonia eluents.

N-Methyl-N-phenylhydrazides of ω-chloroalkylcarboxylic acids (Ia-c, Table 1). A sample of 50 mmoles of the acid chloride of the ω-chloroalkylcarboxylic acid was added with stirring and cooling to a mixture of 50 mmoles N-methyl-N-phenylhydrazine and 50 mmole triethylamine in 50 ml absolute benzene. The reaction mixture was stirred for 1 h and 100 ml water was added. The benzene layer was separated, washed with water, and dried over sodium sulfate. The benzene was distilled off. Ether was added to the residue and the precipitate formed was filtered off. Products Ia and Ic were recrystallized from 10:1 ether—ethanol. Product Ib was purified on a columm packed with alumina having grade II activity and benzene eluent.

3-Oxo-1-methyl-1-phenylpyrazolidinium chloride (IVa) was obtained analogously to Ia-c from N-methyl-N-phenylhydrazine and β-chloropropionyl chloride in 54% yield, mp 168-169°C (from ethanol). Found: C, 56.7; H, 6.2; N, 13.4%. Calculated for $C_{10}H_{13}ClN_2O$: C, 56.5; H, 6.1; N, 13.2%.

Hydrochloride salts of 2-amino-1-methyl-3-chloroalkylindoles (IIa-c, Table 2). A mixture of 10 mmoles N-methyl-N-phenylhydrazide I and 20 mmoles $POCl_3$ in 40 ml absolute ether or chloroform was heated at reflux. At the completion of the reaction, the reaction mixture was evaporated to dryness and the residue was recrystallized from 1:1 ethanol—benzene.

2-Acetylamino-1-methyl-3-(2-chloroethyl)indole (Va). A mixture of 2.45 g (10 mmoles) hydrochloride salt of 2-amino-1-methyl-3-(2-chloroethyl)indole and 0.82 g (10 mmoles) sodium acetate in 25 ml acetic anhydride was stirred at room temperature for 25 h. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform, washed consecutively with water, aqueous sodium bicarbonate, and water, dried over potassium carbonate, and evaporated. Hexane was added to the residue. The precipitate was filtered off and recrystallized from ethanol to yield 1.73 g (69%) Va with mp 152.3-153.5°C. IR spectrum: 3280 (NH), 1670 cm^{-1} (C=O). Found: C, 62.5; H, 6.4; N, 11.1%. Calculated for $C_{13}H_{15}ClN_2O$: C, 62.3; H, 6.0; N, 11.2%.

2-Benzoylamino-1-methyl-3-(γ-chloropropyl)indole (Vb). A sample of 5 ml benzoyl chloride and 50 ml 2 N NaOH were added simultaneously with stirring and cooling to a solution of 2.59 g (10 mmoles) hydrochloride salt of 2-amino-1-methyl-3-(γ-chloropropyl)indole in 10 ml water and stirred for 1 h. The oily residue was removed and ether was added to it. The crystals formed were recrystallized from benzene—hexane to yield 1.43 g (46%) Vb with mp 160-161°C. IR spectrum: 3240 (NH), 1650 cm^{-1} (C=O). Found: C, 69.9; H, 5.7; N, 8.7%. Calculated for $C_{19}H_{19}ClN_2O$: C, 69.8; H, 5.8; N, 8.6%.

2-(o-Methoxybenzoyl)amino-1-methyl-3-(γ-chloropropyl)indole (Vc) was obtained by analogy to Vb in 50% yield, mp 75°C (from ethanol—chloroform). IR spectrum: 3300 (NH), 1660 cm^{-1} (C=O). Found: C, 67.4; H, 5.8%. Calculated for $C_{20}H_{21}ClN_2O_2$: C, 67.3; H, 5.9%.

TABLE 1. N-Methyl-N-phenylhydrazides of ω-chloroalkylcarboxylic acids

Compound	n	mp, deg C	IR spectrum, cm^{-1}		Found, %			Chemical formula	Calculated, %			Yield, %
			NH	C=O	C	H	N		C	H	N	
Ia	0	72—73	3180	1660	54,4	5,8	13,9	$C_9H_{11}ClN_2O$	54,4	5,5	14,1	55
Ib	2	Oil	3250	1670	58,5	7,0	12,5	$C_{11}H_{15}ClN_2O$	58,3	6,6	12,4	57
Ic	3	53—55	3220	1660	59,5	7,1	11,7	$C_{12}H_{17}ClN_2O$	59,9	7,1	11,6	60

TABLE 2. Hydrochloride Salts of 2-Amino-1-methyl-3-chloroalkylindols

Compound	Reaction time	Reac. temp., deg C	mp, dec C	IR spectrum, cm^{-1}		Found, %			Chemical formula	Calculated, %			Yield, %
				$\overset{+}{N}H_3$	C=N	C	H	N		C	H	N	
IIa	18	40	220 (dec.)	3200—2500	1710	49,3	4,8	12,6	$C_9H_9ClN_2 \cdot HCl$	49,7	4,6	12,9	48
IIb	10	60	230 (dec.)	3300—2600	1690	53,3	6,1	11,3	$C_{11}H_{13}ClN_2 \cdot HCl$	53,8	5,7	11,4	66
IIc	20	40	216—218	3300—2500	1690	55,1	6,4	10,7	$C_{12}H_{15}ClN_2 \cdot HCl$	55,6	6,2	10,8	92

N-[3'-(2-Benzoylamino-1-methylindolyl-3)propyl]pyridinium chloride (VIb). A mixture of 0.086 g (260 mmoles) 2-benzoylamino-1-methyl-3-(γ-chloropropyl)indole and 5 ml pyridine was heated at reflux for 5 h and the excess pyridine was evaporated off. Absolute ether was added to the residue. The crystals formed were filtered off and recrystallized from ethanol—ether. The yield was 76%, mp 250-251°C. IR spectrum 3500-3320 br (NH), 1670 (C-O), 1640 cm^{-1}. Found: C, 70.7; H, 5.9; N, 10.5%. Calculated from $C_{24}H_{24}ClN_3O$: C, 71.0; H, 6.0; N, 10.4%.

N-{3'-[2-(o-Methoxybenzoyl)amino-1-methylindolyl-3]propyl}pyridinium chloride (VIc) was obtained by analogy to VIb in 67% yield, mp >230°C (dec., from ethanol—ether). IR spectrum: 3500-3150 br (NH), 1660 cm^{-1} (C=O). Found: C, 68.2; H, 5.3%. Calculated from $C_{26}H_{26}ClN_3O_2$; C, 68.8; H, 5.9%.

N-{2'-[2-Acetylamino-1-methylindolyl-3]}ethylpyridinium chloride (VIa) was obtained analogously in 70% yield, mp >250°C (from ethanol—ether). IR spectrum: 3490 (NH), 1680 cm^{-1} (C=O). Found: C, 65.2; H, 6.1%. Calculated for $C_{18}H_{19}ClN_3O$: C, 65.7; H, 5.8%.

N-{β-[2-Acetylamino-1-methylindolyl-3]ethyl}triethylammonium chloride (VIIa). A mixture of 0.75 g (3 mmoles) 2-acetylamino-1-methyl-3-(2-chloroethyl)indole and 0.42 ml (3 mmoles) triethylamine in 30 ml methanol was heated at reflux for 16 h. The reaction mixture was evaporated. A sample of 1:1 chloroform—ether was added to the oily residue, cooled, and the precipitate was filtered off to yield 0.71 g (67%) VIIa with mp 144-145°C (from ethanol—benzene). IR spectrum: 3500-3360 (NH), 1670 cm^{-1} (C=O). Found: C, 64.3; H, 8.5; N, 11.4%. Calculated from $C_{19}H_{30}ClN_3O$: C, 64.8; H, 8.5; N, 11.9%.

S-{β-[2-Acetylamino-1-methylindolyl-3]ethyl}thiouronium chloride (VIIIa). A mixture of 0.5 g (2 mmoles) 2-acetylamino-1-methyl-3-(2-chloroethyl)indole and 0.152 g (2 mmoles) thiourea in 15 ml 95% ethanol was heated at reflux for 30 h. The reaction mixture was evaporated. Chloroform was added to the oily residue, cooled, and the precipitate formed was filtered off and recrystallized from ethanol to yield 0.52 g (80%) VIIIa with mp 225-226°C (dec.). IR spectrum: 3340-3200 br, 3150 (NH), 1640 cm^{-1} (C=O). Found: C, 54.4; H, 5.9; N, 16.7%. Calculated for $C_{14}H_{19}ClN_4SO$: C, 51.5; H, 5.8; N, 17.2%.

2-Acetylamino-1-methyl- 3-(2-phthalimidoethyl)indole (IXa). A. A mixture of 0.5 g (2 mmole) acetylamino-1-methyl-3-(2-chloroethyl)indole and 0.37 g (2 mmoles) potassium phthalimide in 10 ml DMF was heated at reflux for 14 h. The dimethylformamide was evaporated off. The residue was dissolved in chloroform, transferred to a column packed with silica gel (100/250 μ), and eluted with chloroform to yield 0.4 g (55%) IXa with mp 203-204°C. IR spectrum 3180 (NH), 1770, 1705, 1660 cm^{-1} (C=O). Found: C, 69.5; H, 5.4%. Calculated for $C_{21}H_{19}N_3O_3$: C, 69.8: H, 5.3%.

B. A mixture of 1.06 g (3 mmoles) hydrochloride salt of 2-amino-1-methyl-3-(2-phthalimidoethyl)indole [2] and 0.25 g (3 mmoles) sodium acetate in 15 ml acetic anhydride was stirred for 24 h. The reaction mixture was treated analogously to Va to yield 0.75 g (69%) IXa with mp 203-204°C. The IR spectrum was identical to the spectrum of the sample obtained by method A.

N,N-Diphenylhydrazide of β-chloropropionic acid (IIIc) was obtained analogously to Ia-c from N,N-diphenylhydrazine and β-chloropropionyl chloride in 60% yield, mp 133-135°C (from ethanol). IR spectrum: 3220 (NH), 1665 cm^{-1} (C=O). Found: C, 65.8; H, 6.0; N, 10.6%. Calculated for $C_{15}H_{15}ClN_2O$: C, 65.6; H, 5.5; N, 10.2%.

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SYNTHESIS OF 2-ACYLINDOLES FROM α-(N-ISATINYL) KETONES

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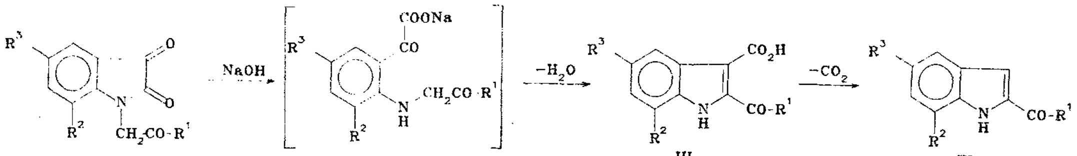
2-Acylindoles were synthesized by the recyclization of N-phenacyl- and N-acetonylisatins in alkaline media and the decarboxylation of 2-acylindolyl-3-carboxylic acids or their salts in basic or neutral media.

2-Acylindoles are used as starting compounds for the synthesis of sedatives [1] and the study of their rearrangement to give 3-acylindoles [2]. These compounds, nevertheless, are not readily available despite a number of special or multistep methods for their preparation [1-8].

We have developed a simple general method for the synthesis of 2-acylindoles by the action of alkali on α-(N-isatinyl) ketones [10].* This reaction may be carried out in water or in a mixture of water and an organic solvent. At 60-70°C and 5% NaOH, the reaction is complete in 3-4 h. 2-Aroylindoles are obtained in high yields (Table 1), while 2-acetylindole and 2-acetyl-5-bromoindole are obtained in 29 and 38% yield, respectively. This decrease in yield is the result of an intermolecular aldol—crotonic condensation of 2-acetylindoles. (We did not carry out a special study of this reaction). If the synthesis of 2-aroylindoles is carried out in a homogeneous medium (1:1 water—DMF, 5% NaOH), purification of the reaction products is significantly simplified. In this case, the precipitate of analytically pure compound is easily separated from the colored impurities which remain in solution.

The formation of 2-acylindoles involve the opening of the five-membered ring of isatin (I) by the action of alkali, the spontaneous cyclization of N-phenacyl- and N-acetonyl-o-aminophenylglyoxylic acids (II) into 2-acylindolyl-3-carboxylic acids (III), and the decarboxylation of III without their separation from the reaction mixture:



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*After the publication of our work [10, 11, 14-16], the brief communication of Black and Wong [9] appeared on the same subject.

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