SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES. 32.* SYNTHESIS AND SOME TRANSFORMATIONS OF HYDROCHLORIDES OF IMIDO ESTERS OF INDOLECARBOXYLIC ACIDS

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The Pinner reaction with the nitriles of indole-3-carboxylic and 3-indolylacetic acids was studied. The hydrochlorides of the imido esters of these acids, which were converted to the free bases, amides, and esters, were synthesized. Imidazolines, benzimidazoles, and benzoxazoles that contain indole substituents were obtained by condensation of the hydrochlorides of the imido esters of the indolecarboxylic acids with ethylenediamine, o-phenylenediamine, and o-aminophenol.

The hydrochlorides of the imido esters of 3-indolylacetic and 3-indolylpropionic acids are quite widely used to obtain amidines and some heterocycles that contain an indole residue. At the same time, the literature contains only isolated data on the synthesis and further transformations [2, 3] of indole-3-carboxylic acid ethyl imido ester hydrochloride (IIIb).

Assuming that compounds that simultaneously contain indolyl and azole groupings may be of definite interest as biologically active substances, we decided to synthesize compounds of this type from the hydrochlorides of the imido esters of indole-3-carboxylic and 3indolylacetic acids.

We made a systematic study of the behavior of indole-3-carboxylic acid nitrile (I) under the conditions of the Pinner reaction in order to find the best conditions for the synthesis of the hydrochlorides of the methyl (IIIa) and ethyl (IIIb) imido esters of this acid. In the preparation of IIIb via the Pinner reaction under the described conditions [2, 3] - by bubbling a stream of dry HCl into a solution of nitrile I and ethanol in tetrahydrofuran (THF) at $45-50^{\circ}$ C — we isolated a compound with constants that are in agreement with the literature data. When this compound was heated above its melting point, it was converted to indole-3-carboxamide (IV); however, when we subjected the latter to hydrolysis, instead of the expected ethyl indole-3-carboxylate (Vb, mp 126-127°C) we obtained a lowermelting substance (mp 107-108°C) with the composition C13H14C1NO2. The IR spectrum of the latter contained intense absorption bands at 3250 and 1670 cm^{-1} , which are characteristic for the N-H and C=0 stretching vibrations in esters of indole-3-carboxylic acid [4]. The facts noted above, together with the results of elementary analysis and the data from mass spectrometry, made it possible to conclude that the compound formed when the Pinner reaction was carried out with I in THF is indole-3-carboxylic acid 4-chlorobutyl imido ester hydrochloride (IIIc). Opening of the THF ring to give significant amounts of 4-chloro-1-butanol, which also reacts with nitrile I and HCl to give imido ester IIIc, evidently takes place under the reaction conditions $(45-50^{\circ}C)$ under the influence of HCl [5].

The highest yields of IIIa and IIIb (>90%) can be obtained when the reaction is carried out at a molar ratio of nitrile I and the alcohol of 1:5 in nitrobenzene or dimethoxy-ethane at $30-35^{\circ}$ C with a twofold excess of hydrogen chloride and subsequent standing of the reaction mixture for 3 days.

In the case of the preparation of 3-indolylacetic acid ethyl imido ester hydrochloride (VIIa) from 3-indolylacetonitrile (II) one's attention is directed to the fact of the considerably greater ease of its formation as compared with the formation of IIIa,b: the isolation of imido ester VIIa is complete in a few hours at 0°C. This difference in the

*See [1] for communication 31.

I. M. Gubkin Moscow Institute of the Petrochemical and Gas Industry, Moscow 117296. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 645-650, May, 1980. Original article submitted July 26, 1979. behavior of nitriles I and II in the Pinner reaction can be explained by weakening of the electrophilicity of the nitrile group in I as a result of the effect of the electron-donor indolyl group.

Attempts to obtain imido ester hydrochlorides from nitrile I and $HOCH_2CH_2NO_2$ or HOCH_2CH_2Cl under the usual conditions were unsuccessful. This fact can be explained by the inability (under the indicated conditions) of I, which contains a nitrile group with reduced electrophilicity, to react with alcohols in which the hydroxy group has reduced nucleophilicity (as a result of the action of the -I effect of a nitro or chloro substituent in the β position relative to the hydroxy group).



An interesting principle is observed when some transformations of IIIa-c and VIIa are carried out: imido ester hydrochloride VIIa was found to be more reactive in nucleophilic reactions than imido ester III. Thus, the Pinner rearrangement (conversion to amides by heating) for IIIa-c proceeds at 165-190°C, as compared with 105-110°C for VIIa. Heating in boiling water for 12 h is necessary for the hydrolysis of IIIa-c to esters Va-c, whereas imido ester VIIa is converted to ester VIIId after 30 min at room temperature. Imido ester VIIa undergoes resinification under the influence of a strong nucleophilic reagent, viz.,



aqueous potassium hydroxide solution, and it is therefore necessary to treat hydrochloride VIIa with triethylamine in ether to obtain VIIb. At the same time, IIIa-c were converted to imido esters VIa-c by the action of aqueous KOH. The great inertness of imido esters IIIa-c with respect to nucleophilic reagents can evidently be explained by the fact that the electron-donor indolyl group attached to the imido ester group decreases the positive charge on this group, while the indolyl group in VIIa is separated from the imido ester grouping by a methylene group, and its effect is considerably weaker.

The transformations that we carried out and the IR spectra confirm the structures of IIIa-c. In order to identify bases VIa-c and VIIb we converted them to the starting hydrochlorides by the action of dry HCl in absolute ether.

We studied the condensation of imido esters IIIa and VIIa with a number of 1,2-difunctional compounds: o-phenylenediamine, o-aminophenol, ethylenediamine, and N-monosubstituted ethylenediamines. As a result, we synthesized the corresponding benzimidazoles VIIIa,b, benzoxazoles IXa,b, and imidazolines Xa-d and XIa-d, which contain indolyl or indolylmethyl groups in the 2 position, in good yields. We used N-benzyl-, N-(2-cyanoethyl)-, and N-(2-thienylmethyl)ethylenediamine for the synthesis of 1,2-disubstituted imidazolines.



VIIIa, bX=NH; IX a, b X=O; VIII, IX a n=0; b n=1; Xa-d n=0; Xla-d n=1; X, XI a R=H; b R=CH₂C₆H₅; c R=CH₂CH₂CN, d R=2-thienylmethyl

The structures of the heterocyclic compounds obtained were confirmed by data from the IR, UV, and PMR spectra.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform or of KBr pellets were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in deuteroacetone were recorded with a Tesla BS spectrometer (80 MHz) on the δ scale with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with a MKh-1303 spectrometer with direct introduction of the samples into the ion source. The course of the reactions and the purity of the compounds obtained were monitored by means of thin-layer chromatography (TLC) on activity II (Brockmann scale) Al₂O₃ in a benzenemethanol system (5:1) (the chromatograms were developed with iodine vapors).

Indole-3-carboxylic Acid Methyl Imido Ester Hydrochloride (IIIa). A stream of dry HCl was bubbled with stirring at 30-35°C into a solution of 10.4 g (0.07 mole) of I and 11.2 g (0.35 mole) of absolute methanol in 200 ml of nitrobenzene until the gain in weight was 7-8 g. The reaction mixture was then maintained at 20°C for 3 days, and the precipitate was removed by filtration, washed with dry ether, and crystallized from glacial CH₃COOH.

Compound IIIb was similarly synthesized.

Indole-3-carboxylic Acid 4-Chlorobutyl Imido Ester Hydrochloride (IIIc). A stream of dry HCl was bubbled with stirring at 30-35°C for 1 h into a solution of 5.2 g (0.035 mole) of I in 75 ml of absolute THF. After 3 days, the precipitate was removed by filtration, washed with dry ether, and crystallized from glacial CH₃COOH.

The IR spectra of hydrochlorides IIIa-c contain characteristic absorption bands at 3180-3220 (stretching vibrations of indole NH) [6], 3100-3120 (C=N⁺-H) [7], 2970-2980 (C-H stretching vibrations), 1675-1680 (C=N⁺)[7], 1590-1625 (aromatic system of indole ring bonds), 1015-1030 (C-O-C), and 750-760 cm⁻¹ (C-H).

<u>3-Indolylacetic Acid Ethyl Imido Ester Hydrochloride (VIIa).</u> A stream of dry HCl was bubbled withstirring at 0°C in the course of an hour into a solution of 11.2 g (0.05 mole) of 3-indolylacetonitrile (II) and 2.3 g (0.05 mole) of absolute ethanol in 150 ml of dry ether, after which the mixture was allowed to stand in the refrigerator for 12 h. Workup gave 10.7 g (90%) of hydrochloride VIIa with mp 126-127.5°C (dec., from CH₃COOH-ether; mp 128°C [8]). IR spectrum: 3250 (indole NH); 1670 (C=N);1595, 1510, 1485, 1350 (indole ring); 1475 (CH₂); 1420 (CH₃); 1015 (C-O-C); 750 cm⁻¹ (C-H). Found: Cl 14.6%. $C_{12}H_{13}N_2O$. HCl. Calculated: Cl 14.8%.

<u>Indole-3-carboxylic Acid Methyl Imido Ester (VIa, Table 1).</u> A 5-ml sample of a 10% solution of KOH was added dropwise to a stirred suspension of 0.77 g (0.0036 mole) of hydrochloride IIIa in 50 ml of ether, after which the ether layer was separated, washed with water, and dried over MgSO₄. The solvent was removed at reduced pressure. PMR spectrum: 8.35-8.90 (m, NH), 6.9-7.72 (m, aromatic protons), 7.52 (d, 2-H), and 3.38 ppm (s, C-O-CH₃).

The ethyl (VIb) and 4-chlorobutyl(VIc) imido esters were similarly obtained (Table 1).

<u>3-Indolylacetic Acid Ethyl Imido Ester (VIIb)</u>. A solution of 0.50 g (0.005 mole) of triethylamine in 5 ml of ether was added dropwise at 0°C to a stirred suspension of 1.0 g (0.0043 mole) of hydrochloride VIIa in 50 ml of dry ether, and the mixture was stirred at 0°C for 1 h. The precipitate was removed by filtration, and the solvent was removed from the filtrate in vacuo to give 0.8 g (92%) of imido ester VIIb with mp 132-133°C (mp 134°C [9]).

Indole-3-carboxyamide (IV). Samples (0.01 mole) of hydrochlorides IIIa-c were heated 10-15°C above their melting points for 15 min, after which they were cooled, and the residues were crystallized from water with activated charcoal. Amide IV, with mp 195-195.5°C (mp 196-197°C [2]), was obtained in 80-82% yield.

Amide VIIc, with mp 147.5-148°C (from alcohol-ether; mp 149-150°C [11]), was similarly obtained in 72% yield.

4-Chlorobutyl Indole-3-carboxylate (Vc). A suspension of 1.94 g (0.006 mole) of hydrochloride IIIc in 40 ml of water was refluxed with stirring for 12 h, after which it was cooled and filtered to give 1.3 g (85%) of ester Vc with mp 107-108°C (from cyclohexane). IR spectrum: 3250 (N-H); 1670 (C==0); 1580, 1480, 1355 cm⁻¹ (indole ring). Found: C 62.1;

TABLE 1. Indole-3-carboxylic Acid Imido Esters and Their Hydrochlorides

Com - pound	mp, ^a °C	Found, %				Empirical formula	Calc., %				Yield,
		с	н	CI	N		c	Н	CI	N	9%
IIIa VIa IIIb VIb IIIc VIc	$\begin{smallmatrix} 167,5-168^b\\ 159-159,5\\ 152-153,b\\ 112,5-113\\ 172-174b\\ 84-85 \end{smallmatrix}$	69,1 70,1 62,4	5,7 6,5 6,0	16,5 16,0 25,0 14,4	16,0 15,0 11,3	$\begin{array}{c} C_{10}H_{10}N_2O\cdot HCl\\ C_{10}H_{10}N_2O\\ C_{11}H_{12}N_2O\cdot HCl\\ C_{11}H_{12}N_2O\\ C_{13}H_{15}ClN_2O\cdot HCl\\ C_{13}H_{15}ClN_2O\end{array}$	69,0 70,2 62,3	5.7 6,4 6,0	16,8 	16,1 14,9 11,2	95 81 92 78 96 78

^aCompounds VIa and VIb were crystallized from isopropyl alcohol-H₂O (1:2.5), while VIc was crystallized from CCl₄. bWith decomposition.

TABLE 2. 2-(3-Indoly1)- and 2-(3-Indoly1methy1)benzazoles

Com - pound	mp, ^a °C	Found, %			Empirical	Calc., %			· · · · · · · · · · · · · · · · · · ·		
		с	н	N	formula	С	н	N	ⁿ max, IIIII (18 E)	Yield	
VIIIa VIIIb	219—220 193—193,5b	77,1 77,8	4,7 5,2	17,8 16,7	$\begin{array}{c} C_{15}H_{11}N_{3}\\ C_{16}H_{13}N_{3} \end{array}$	77,3 77,7	4,7 5,3	18,0 17,0	221 (4,55), 314 (4,40) 210 (4,68), 221 (4,67), 252 (4,17), 266 (4,21),	90 85	
IXa	185—186	77,0	4,3	11,9	$C_{15}H_{10}N_2O$	76,9	4,3	12,0	290 (3,84) 218 (4,55), 264 (4,14),	87	
IXÞ	166—167	77,2	4,7	11,1	$C_{16}H_{12}N_2O$	77,4	4,8	11,2	$\begin{array}{c} 316 \ (4,51) \\ 209 \ (4,69), \ 221 \ (4,68), \\ 244 \ (3,94), \ 275 \ (4,15), \\ 282 \ (4,17), \ 290 \ (3,81) \end{array}$	80	

aThe compounds were crystallized: VIIIa from 30% ethanol, VIIIb from nitromethane, and IXa and IXb from 50% ethanol. ^bAccording to the data in [9], this compound has mp 193-195°C.

H 5.5; Cl 14.3, N 5.7%; M (by mass spectrometry) 251. C₁₃H₁₄ClNO₂. Calculated: C 62.0, H 5.6; Cl 14.1, N 5.6%; M 251.5.

Methyl ester Va, with mp 145-146°C (from aqueous ethano1; mp 147-148°C [14]), was similarly obtained in 88% yield, and ethyl ester Vb, with mp 122-123.5°C (from aqueous ethano1; mp 124°C [4]), was obtained in 80% yield. No melting-point depressions were observed for mixtures of Va and Vb with genuine samples of the esters, and their IR and UV spectra were identical.

<u>Ethyl 3-Indolylacetate (VIId).</u> A 2.38-g (0.01 mole) sample of VIa in 25 ml of water was stirred at room temperature for 30 min, and the resulting oil was extracted with benzene. The extract was dried over MgSO₄, the benzene was removed by distillation, and the residue was vacuum distilled to give 1.54 g (76%) of ester VId with bp $177-183^{\circ}C$ (9.6. 10^{3} mm) [12].

<u>2-(3-Indoly1)-</u> and <u>2-(3-Indoly1methy1)benzazoles</u> (VIIIa,b and IXa,b). A mixture of o-phenylenediamine or o-aminophenol with an equimolar amount of imido esters IIIa or VIa was refluxed with stirring in absolute alcohol for 7-8 h, after which it was cooled and poured into water containing the calculated amount of NaHCO₃. The resulting precipitate was removed by filtration and dried. The IR spectra of the benzazoles contain intense absorption at 3200-3380 (N-H stretching vibrations in the indole and benzimidazole rings) [6], 1610-1635 (C=N), and 725-735 cm⁻¹ (C-H). The absorption bands at 1020 and 1250 cm⁻¹ in the IR spectra of IXa,b characterize the stretching vibrations of the =C-O-C group of the benzoxazole ring [12]. PMR spectrum of benzimidazole VIIIa: 8.62 (q, NH), 8.12 (s, NH), 7.02-7.60 (m, aromatic protons), and 7.58 ppm (d, 2-H). PMR spectrum of benzoxazole IXb: 10.45 (s, NH), 6.75-7.50 (m, aromatic protons), and 4.92 ppm (s, CH₂).

2-(3-Indoly1)- and 2-(3-Indoly1methy1) imidazolines (Xa-d and XIa-d). A 0.01-mole sample of imido ester IIIa or VIa was added in portions with stirring to a solution of 0.52 g (8.5 mmole) of 100% ethylenediamine in 20 ml of absolute methanol, and the mixture

TABLE 3. 1-Substituted 2-(3-Indoly1)- and 2-(3-Indoly1methy1)imidazolines

Com - pound	mp,°C, pic- rates ^a and hydro- chlorides ^b	R _f	Four C	nd, d	% N	Empirical formula	Cal c	с., Н	% N	yield, %
Xa Xb Xc Xd XIa XIb XIc XId	267268 214215 178179 172173 c 169170 c 148149 190191 111112	0,20 0,22 0,30 0,35 0,12 0,26 0,28 0,40	49,2 57,1 51,4 51,6 	$ \begin{array}{c} 3,4\\3,9\\3,6\\3,6\\-\\6,0\\6,0\\3,8\end{array} $	20,2 16,6 20,9 16,6 19,5 — 15,9	$\begin{array}{c} C_{11}H_{11}N_3\cdot C_6H_3N_3O_7\\ C_{18}H_{17}N_3\cdot C_6H_3N_3O_7\\ C_{14}H_{14}N_3\cdot C_6H_3N_3O_7\\ C_{16}H_{15}N_3S\cdot C_6H_3N_3O_7\\ C_{12}H_{13}N_3\cdot C_6H_3N_3O_7\\ C_{19}H_{19}N_3\cdot HCl\\ C_{15}H_{16}N_4\cdot HCl\\ C_{17}H_{17}N_3S\cdot C_6H_3N_3O_7\\ \end{array}$	49,3 57,1 51,4 51,7 50,5 70,0 62,4 52,7	3,4 4,0 3,6 3,5 3,7 6,1 5,9 3,8	20,3 16,7 21,0 16,5 19,6 16,0	81 80 90 85 85 74 92 77

^aThe picrates were crystallized: the picrate of Xa from nitrobenzene (dec.), the picrate of Xb from DMF-water (2:1), the picrate of Xc from 50% DMF (dec.), the picrate of Xd from 50% ethanol (dec.), the picrate of XIa from aqueous acetone, and the picrate of XId from 50% ethanol. ^bThe hydrochlorides of XIb and XIc were crystallized from absolute ethanol-ether. ^cBase Xd melted at 113-113.5°C. Found: M (by mass spectrometry) 281. $C_{16}H_{15}N_{3}S$. Calculated: M 281. Base XIa melted at 130.5-131.5°C (from absolute ethanol-benzene) (mp 131-133°C [13]).

was refluxed for 10 h. It was then cooled to 0°C, and a solution of sodium methoxide obtained from 0.2 g (0.0085 g-atom) of sodium in 8 ml of absolute methanol was added dropwise. The mixture was then maintained at 0°C for 2 h, and the precipitate was removed by filtration. The filtrate was evaporated, and the residue was extracted with hot acetone (two 25-ml portions). The extract was evaporated to 5-7 ml, and the concentrate was chromatographed with a column (1.5 by 30 cm) filled with Al_2O_3 [elution with benzene-methanol (5:1)]. Removal of the solvent in vacuo gave imidazoline IXa in the form of a slightly yellowish very viscous oil, which in some cases crystallized when it was triturated with ether and allowed to stand in the cold for a long time.

Compounds Xa-d and XIa,d were characterized in the form of the picrates, while imidazolines XIb,c were characterized in the form of the hydrochlorides (Table 3). All of the synthesized imidazolines are quite soluble in alcohol, acetone, CS₂, and chloroform but insoluble in hydrocarbons and ether. Absorption bands at 1605-1620 (C=Nstretching vibrations in imidazolines) [6], 1020-1030 (C-N), and 1430-1450 cm⁻¹ ("scissors" vibrations of CH₂ in imidazolines) [6] appear in the IR spectra of Xa-d and XIa-d (in CHCl₃). In addition, absorption bands that are characteristic for indole and groupings in the 1 position of the imidazoline ring are present in the spectra.

PMR spectrum of 1-(2-cyanoethyl)-2-(3-indolyl)imidazoline (Xc): 8.82 (s, NH), 7.02-8.0 (m, aromatic protons), 3.90-9.47 (m, CH₂), and 2.80 ppm (q, CH₂). PMR spectrum of 1-(2-thienylmethyl)-2-(3-indolyl)imidazoline (Xd): 8.76 (s, NH), 6.90-8.17 (m, aromatic protons), 7.97 (s, 2-H), 4.67 (s, CH₂), and 3.82 ppm (q, CH₂).

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REACTION OF 2- AND 4-VINYLPYRIDINES WITH

PHENACYLPYRIDINIUM YLIDS

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The reaction of 2- and 4-vinylpyridines with 3-substituted phenacylpyridinium ylids takes place regioselectively with the formation of only 6-substituted 1-pyridyl-3-aroylindolizines. The reaction of the same ylids with dimethyl acety-lenedicarboxylate gives a mixture of isomeric 6- and 8-substituted 1,2-dicarbo-methoxy-3-aroylindolizines. In the analogous reaction of 2-bromo-1-phenacyl-pyridinium ylid, in addition to the corresponding 5-bromoindolizine, the product of its spontaneous cyclization, viz., 4,5-dicarbomethoxy-6-oxo-(6H)-10c-aza-acephenanthrylene, was isolated.

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We have previously shown that the double bond in vinylpyridine is capable of undergoing 1,3-dipolar cycloaddition with dipolar compounds such as diazomethane; the cycloaddition proceeds regioselectively and is controlled primarily by electronic factors [1].

In order to study the regioselectivity of the cycloaddition of other dipolarophiles to vinylpyridines we studied the reaction of 2- and 4-vinylpyridines (I, II) with phenacylpyridinium ylids III.





I, VIa - f Py = 2-pyridyl; II, VIIa - f Py = 4-pyridyl; I--VII a $R^1 = R^2 = H$; b $R^1 = NO_2$, $R^2 = H$; c $R^1 = H$, $R^2 = COOC_2H_5$; d $R^1 = NO_2$, $R^2 = COOC_2H_5$; e $R^1 = H$, $R^2 = Br$; f $R^1 = H$, $R^2 = CH_3$

The fundamental possibility of the use of phenacylpyridinium ylids in 1,3-dipolar cycloaddition reactions was demonstrated in the case of their reaction with acrylonitrile [2]; Fröhlich and Kröhnke were able to isolate the primary products of cycloaddition, viz., the tetra- and dihydro derivatives (of the IV and V type), which are readily converted to 1-cyano-3-aroylindolizines. However, the effect of a substituent in the pyridine ring on

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