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CHEMISTRY OF INDOLE

XLIV.* FORMATION OF CYCLIC AMIDES FROM NITRILES OF THE INDOLE AND INDOLENINE SERIES

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Under the conditions of the Ritter reaction (sulfuric acid), indolylacetonitrile is converted to a tricyclic lactam of the pyrrolo[2,3-b]indole series. Depending on their structure and the reaction conditions, nitriles of the indolenine series form linear amides or cyclic lactams.

We have shown in [2] that nitriles of 3-indolylpropionic acid are protonated primarily at the nitrile group in concentrated sulfuric acid and consequently undergo the Ritter reaction. However, the indole ring itself is capable of protonation in solutions of strong acids to give a carbonium ion with localization of the positive charge in the 2 position. This sort of protonation is responsible for the dimerization and polymerization of indole and gives rise to rearrangements with migration of an alkyl or aryl group bonded to the pyrrole ring [3].

It might have been assumed that the indole molecule is capable of producing the carbonium ion necessary for alkylation in the Ritter reaction. If this protonated molecule also contains a reactive nitrile group, an intramolecular Ritter reaction is possible. However, we did not observe intramolecular cyclization for 3-indolylpropionitriles. Thus 3-indolylpropionitrile, which does not have a substitutent attached to C_2, forms only an amide with a linear structure [2]. 2-Methyl-3-indolylacetonitrile (Ia) also gives only 2-methyl-3-indolylacetamide (IIa) on dissolving in sulfuric acid.

In the case of 3-indolylacetonitrile (Ib) the reaction proceeds ambiguously. An amide (IIb) is formed at room temperature, whereas a three-membered lactam (III) is obtained at higher temperatures. Compound IV is obtained with cyclohexene at high temperatures, i.e., cyclohexene also participates in the Ritter reaction.

The UV spectra of amides IIa, b are characterized by the absorption typical for indoles with the characteristic fine structure of the long-wave maximum. Insofar as the spectra of III and IV are concerned, they are characteristic for indoline systems (243-246 and 295-297 nm; for example, see [4]). The

* See [1] for communication XLIII.

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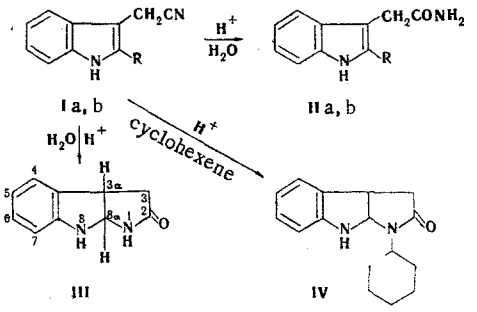
singlet of a CH_2 group is observed in the PMR spectrum of amide IIb (in pyridine) at 3.8 ppm. The spectrum of III contains a triplet at 2.3-2.4 ppm, which we assigned to the signals of 3-CH_2 protons, the multiplet of an 3a-H proton at 3.4-4 ppm, and a broad doublet (5.3 ppm, J = 8 Hz) of an 8a-H proton (cis ring fusion). A diffuse signal of the 8-H proton is found at 4.8-5.1 ppm, and the 1-H signal lies in the region of aromatic proton absorption.

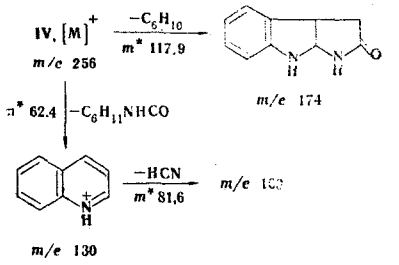


I, II a R=CH_3; b R=H

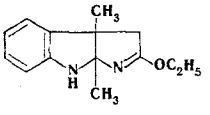
Ions with m/e 44 and 130 (m* 97.0) corresponding to α cleavage with elimination of a carbamide group are characteristic in the mass spectrum of amide IIb. This process is characteristic for primary aliphatic amides. The ion with m/e 130 subsequently loses HCN; this is confirmed by the metastable transition with m* 81.6.

Ejection of an ion with m/e 44 is absent in the spectrum of III, whereas one does observe the fragmentation of the molecular ion characteristic for cyclic amides, namely, the loss of a CO molecule and the formation of an ion with m/e 146; this is confirmed by the metastable transition with m* 122.1.

The molecular ion of IV similarly loses a cyclohexene molecule to give an ion with m/e 174 (m* 117.9), the structure of which is apparently identical to the structure of the molecular ion of III. Correspondingly, an ion with m/e 146 (metastable transition m* 122.1) is formed from it. The second pathway of fragmentation of the molecular ion involves splitting out of a $C_6H_{11}NHCO$ fragment (i.e., 126); this was confirmed by the metastable transition (m* 62.4) and leads to an ion with m/e 130, characteristic for IIb, with subsequent loss of HCN. All of this makes it possible to consider the structures of amides II and III to be established.

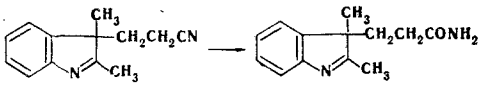


The intramolecular Ritter reaction proceeds even more readily in the indolenine series. It has already been reported [5] that 2,3-dimethyl-3-cyanomethylindolenine on reaction with alcoholic HCl adds an alcohol molecule to give a substance to which a cyclic imino ether structure (V) was assigned on the basis of the results of elementary analysis and the UV spectrum.



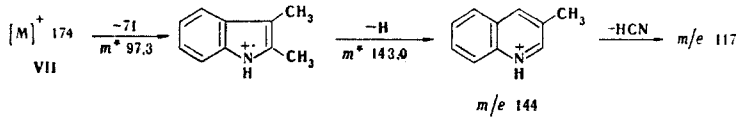
V

We have found that propionitrile VI reacts with methanolic HCl to give a mixture of substances, from which we were able to isolate, by chromatography on aluminum oxide, a substance corresponding with respect to its composition and UV spectrum (λ_{max} 218 and 257 nm) to an open imino ether with an indolenine structure (it was not investigated in greater detail). In sulfuric acid, nitrile VI forms primarily amide VII (isolated in 69% yield), which has the absorption (217 and 258 nm) typical for indolenines.



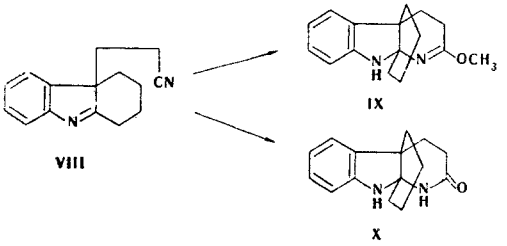
VI VII

Splitting out of an acrylamide fragment (which was confirmed by the metastable transition) to give an ion with m/e 145, which probably has a 2,3-dimethylindole structure, is characteristic in the mass spectrum of amide VII. This ion subsequently loses a hydrogen atom and is converted to a 3-methylquinolinium ion, for which splitting out of HCN is characteristic.



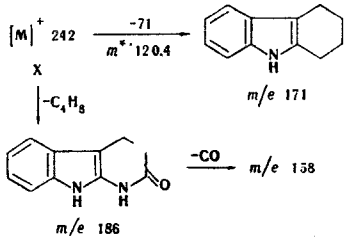
VII m/e 144

Similarly, nitrile VIII reacts with alcoholic HCl to give a mixture of substances, one of which (in 40% yield) corresponds with respect to its composition and UV spectrum (maxima at 240 and 290 nm) to cyclic imino ether IX, i.e., to o-methylated lactam X. Lactam X, i.e., 2-oxo-4a,9a-tetramethylene-1,2,3,4,4a,9a-hexahydro-α-carboline, proved to be the chief reaction product in the reaction of sulfuric acid with nitrile VIII.



VIII IX X

The molecular ion of X does not have high stability. Two fragmentation pathways leading to a stable aromatic system are characteristic for it. Just as in the case of VII, an acrylamide fragment (M − 71) is split out to give an ion with m/e 171, which apparently has a tetrahydrocarbazole structure. This process is confirmed by a metastable transition. The second pathway is a retrograde diene cleavage of the cyclohexane ring with the loss of C_4H_8 and formation of the 2-oxotetrahydro-α-carboline ion (m/e 186), which loses a CO molecule (this is characteristic for lactams).



X m/e 171 m/e 186

Thus, although the same cation (charge localization on C_2) should be formed in the ring protonation of indoles and indolenines, nitriles of the indole series are evidently protonated at the nitrile group (after which they are saponified to amides), whereas nitriles of the indolenine series are primarily protonated at the carbon−ring nitrogen double bond to give lactams. We were unable to directly determine the site of protonation, inasmuch as the PMR spectra of indolenine nitriles dissolved in sulfuric acid are difficult to interpret in view of rapid chemical transformations.

The facile and even tautomeric cyclization of similarly constructed 3-(2-aminoethyl)- [6] and 3-(3-aminopropyl)indolenines [7] has been previously noted. In our case, the process is more complex, apparently because of the simultaneous hydrolysis of the amide. Thus the UV spectrum of amide VII (in 80% ethanol) at pH 8.0 has absorption maxima at 217 and 258 nm (indolenine), and at pH 1.5 it acquires the character of the spectrum of the indolinium ion (maxima at 230, 236, and 278 nm); however, the spectrum changes irreversibly upon reverse transformation at pH 7.5-8.0, and the position of the maxima (at 217, 223, and 245 nm in the first minutes) changes with time. We have not observed cases of migration of the substituent bonded to the pyrrole portion of the molecule.

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		UV spectrum		IR spectrum, cm⁻¹		Mass spectrum, m/e (intensity, %) (m* indicates the metastable transitions)	Yield, %
			C	H	C	H	λ_{max}, nm	lg ε	NH	CO		
IIa	126–127 (benzene)	$C_{11}H_{12}N_2O$	70,2	6,3	70,2	6,3	223 282 289	4,64 3,89 3,83	3350 3500	1646 1682	—	64
IIb	153[a] (benzene–hexane)	$C_{10}H_{10}N_2O$	—	—	—	—	222 274 281 290	4,78 3,82 3,85 3,77	3200 3420	1645 1682	[M]+ 174 (100); 130 (100); 103 (8); 115 (1); 77 (10) m* = 126; 97,1; 81,6; 57,4	50
III	199–201 (benzene–heptane)	$C_{10}H_{10}N_2O$	68,8	5,8	69,0	5,8	242 293	3,83 3,43	3300	1620 1660 1680	[M]+ 174 (100); 146 (43); 145 (43); 118 (32); 105 (18); 91 (8); 77 (13) m* = 172; 122,1; 97; 81,6; 57,4	20
IV	210–212 (heptane)	$C_{16}H_{20}N_2O$	75,2	7,8	75,0	7,8	246 297	3,81 3,40	3350	1620 1665	[M]+ 256 (37); 174 (35); 147 (60); 146 (42); 130 (100); 117 (17); 98 (10); 77 (8) m* = 172; 122,1; 117,9; 97; 81,6; 84,4; 62,4	38[b]
VII	259 (benzene)	$C_{13}H_{16}N_2O$	72,5	7,7	72,2	7,4	217 258	4,30 3,81	3300 3160	1670	[M]+ 216 (21); 201 (1,8); 158 (28); 145 (49); 144 (100); 130 (4); 128 (4); 115 (12); 91 (6); 77 (7) m* = 214,5; 183,5; 169; 155,2; 143–144; 114,2; 97,3	69[c]
X	188 (benzene–heptane)	$C_{15}H_{18}N_2O$	74,4	7,5	74,4	7,4	225 239 289	3,76 3,85 3,46	3300 3160	1645	[M]+ 242 (37); 214 (0,8); 199 (14); 198 (11); 186 (27); 171 (45); 170 (100); 158 (4); 156 (6); 143 (23); 130 (8); 115 (10); 77 (4,5) m* = 167; 142; 119,5; 120,5	92[d]

[a] According to the data in [8], this compound has mp 153° and R_f 0.40 [chloroform–methanol (10 : 1)].

[b] R_f 0.48 [benzene–ethyl acetate (2 : 1), Al_2O_3].

[c] R_f 0.32 [chloroform–methanol (10 : 1), Silufol].

[d] R_f 0.90 [chloroform–methanol (5 : 1), Silufol].

EXPERIMENTAL

The course of the reactions and the purity of the compounds were monitored by means of thin-layer chromatography (TLC) on activity II-III (Brockmann classification) aluminum oxide and on Silufol UV-254. The IR spectra of mineral oil suspensions of the compounds were recorded with IKS-22 and UR-20 spectrometers. The UV spectra of methanol solutions of the compounds were recorded with a Cary-15 spectrophotometer. The PMR spectra of pyridine solutions were recorded with a Varian T-60 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer at 20-50 eV, 130-180°, and a current strength of 150 mA.

Synthesis of Amides II, III, VII, and X (Table 1). Concentrated sulfuric acid (2-5 ml) was added with cooling and stirring to 0.5 g of the corresponding nitrile, after which the mixture was allowed to stand at room temperature for 24 h (in the case of III, the reaction was carried out at 50° for 1 h). The mixture was then poured over ice, and the aqueous mixture was made alkaline with concentrated ammonium hydroxide. It was then extracted with chloroform, and the extract was dried with calcined sodium sulfate. The chloroform was removed by distillation, and the residue was recrystallized.

1-Cyclohexyl-2-oxo-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole (IV). A mixture of 1.2 g (7.7 mmole) of 3-indolylacetonitrile (Ib), 10 ml of concentrated sulfuric acid, and 1 g (12 mmole) of cyclohexene was heated at 60° for 30 min, after which it was allowed to stand at room temperature overnight. It was then poured over ice, and the aqueous mixture was made alkaline with concentrated ammonium hydroxide. The alkaline mixture was extracted with chloroform, and the extract was dried with sodium sulfate. The chloroform was removed from the extract by distillation, and the residue was recrystallized from heptane to give 0.75 g (38%) of 1-cyclohexyl-2-oxo-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole. Its physical constants and spectral data are presented in Table 1.

Alcoholysis of Nitrile VI. A solution of 1.98 g (0.01 mole) of nitrile VI in 20 ml of absolute methanol was saturated with dry HCl at −10° and allowed to stand overnight. The alcohol was then removed by distillation, and the residue was treated with 5% potassium carbonate solution. The oily layer was then extracted with ether, and the extract was dried with magnesium sulfate. The solvent was removed by distillation to give 2 g of an oily mixture of substances with R_f 0.68 and 0.53 [heptane–methyl ethyl ketone (2 : 1), Al_2O_3]. A substance with an indistinct melting point and R_f 0.53, the composition of which corresponded to the methyl imino ether of 3-(2,3-dimethyl-3-indolenyl)propionic acid, was isolated after preparative separation on Al_2O_3 (elution with the system indicated above). UV spectrum, λ_{max} (log ε): 218 (4.29) and 257 nm (3.81). Found: C 72.8; H 7.7%. $C_{14}H_{18}N_2O$. Calculated: C 73.0; H 7.8%.

Alcoholysis of Nitrile VIII. A solution of 1.12 g (5 mmole) of 11-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazolenine (VIII) in 10 ml of absolute methanol was saturated at −10° with dry HCl. Workup of the reaction mixture as described in the preceding experiment gave a solid residue, from which 0.52 g (40%) of 2-methoxy-4a,9a-tetramethylene-3,4,4a,9a-tetrahydro-α-carboline (IX), with mp 158° and R_f 0.3 [heptane–methyl ethyl ketone (2 : 1), Al_2O_3], was isolated by crystallization from aqueous ethanol. UV spectrum, λ_{max} (log ε): 240 (3.83) and 290 nm (3.50). Found: C 75.1; H 8.1%. $C_{10}H_{20}N_2O$. Calculated: C 75.0; H 7.8%. A waxy substance (0.15 g) with R_f 0.56 was isolated from the residue after evaporation and preparative separation on Al_2O_3 in the same solvent system. UV spectrum, λ_{max}: 257 nm (log ε 3.85).

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