NAPHTHYRIDINES IN HETARYLATION REACTIONS*

A. K. Sheinkman, T. N. Nezdiiminoga, T. S. Chmilenko, and N. A. Klyuev

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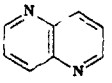
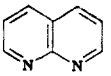
The reaction of indole (2-methylindole) with 1,5-, 1,6-, and 1,8-naphthyridines at 20°C, in the presence of benzoyl chloride, leads to the preferential formation of dihydro structures with one indolyl substituent at the α-position to the hetero atom. With increase in temperature, dibenzoyl and monobenzoyl tetrahydro-substituted naphthyridines with two indolyl residues in both pyridine rings are formed besides the above compounds.

Hetarylation of organic compounds by azines or azoles in the presence of acylating agents takes place in three stages: formation of N-acyl heteroaromatic cations, addition of nucleophiles to them in situ, and aromatization of the N-acyl α(γ)-substituted dihydroheteroaromatic compounds formed [2]. The rate of the first stage is higher, the higher is the basicity of the heterocycle. The higher the basicity, the higher is the current concentration of the N-acyl cations, and hence, the higher is the rate of nucleophilic addition to them. However, with increase in the basicity of the heterocycle, the electrophilicity of its cation decreases, which affects the decrease in the rate of nucleophilic addition. Aromatization becomes more difficult at higher electrophilicity of the heteroaromatic cations thus formed, in other words, at lower basicity of the corresponding heterocycles [3]. Therefore, when the reactions are carried out under standard conditions, there is sometimes an increase in the yields of the hetarylation products with increase in the basicity of the heterocycle [4], and sometimes the yields decrease a little, but nevertheless remain fairly high even in the case of weakly basic heterocycles such as 1,4-diazines [5]. It was interesting to study the behavior of different naphthyridines [6] in this reaction [6].


pK_a 2.91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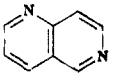
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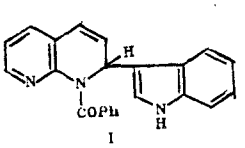
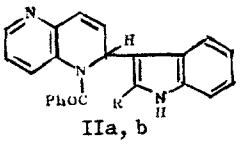
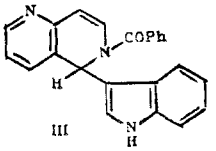
It is known that in the presence of benzoyl chloride, 1,8- and 1,6-naphthyridines add KCN to form the so-called Reissert compounds [7-10]. For the least basic 1,5-naphthyridine, no such reaction is known, and there are no known cases of the addition of other nucleophiles to naphthyridines [6-11].

We studied the reaction of 1,5-, 1,6-, and 1,8-naphthyridines with indole and 2-methylindole in the presence of benzoyl chloride in toluene and DMFA at different temperatures and ratios of the reagents. It was found that in toluene at 20°C, the usual hetarylation products I-III are obtained, and when the reaction is carried out under standard conditions, the yields of products are approximately the same as in the reaction with quinoline and isoquinoline [4], although the basicity of naphthyridine is 2.5 pK units lower.


I


IIa, b

II a R=H b R=CH$_3$


III

*Preliminary communication, see [1].

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TABLE 1. Physicochemical Characteristics of Compounds Synthesized

Compound	mp,* °C	R_f	IR spectrum, cm^{-1}				Found, %			Empirical formula	Calculated, %		
			NH_{ind}	NH_{naphth}	C=O	C=N	C	H	N		C	H	N
I	204—205	0,78	3380		1650	1550	78,3	4,4	11,6	$C_{23}H_{17}N_3O$	78,6	4,8	12,0
IIa†	178—179	0,51	3370		1660	1570	79,0	4,7	11,5	$C_{23}H_{17}N_3O$	78,6	4,8	12,0
IIb	261—262	0,64	3380		1660	1570	79,2	4,9	11,2	$C_{24}H_{19}N_3O$	78,9	5,2	11,5
III	191—192	0,64	3360		1670	1550	78,1	5,0	12,1	$C_{23}H_{17}N_3O$	78,6	4,8	12,0
Va	289—290	0,39	3390	3320	1650		79,8	5,1	12,1	$C_{31}H_{24}N_4O$	79,5	5,1	12,0
Vb	240—241	0,60	3390	3290	1640		79,4	5,2	10,9	$C_{33}H_{28}N_4O$	79,8	5,6	11,2
VI	278—279	0,53	3325		1645		79,5	5,2	9,4	$C_{38}H_{28}N_4O_2$	79,7	4,9	9,8
VII	194—195	0,24	3380	3270			79,2	5,5	15,3	$C_{24}H_{20}N_4$	79,1	5,5	15,4
VIII	185—186	0,09	3420	3380			79,5	5,9	15,4	$C_{24}H_{20}N_4$	79,1	5,5	15,4
IXa‡	271—272	0,07	3400	3380			79,2	5,1	14,8	$C_{24}H_{20}N_4$	79,1	5,5	15,4
IXb	209—210	0,25	3390	3340			79,3	6,0	14,6	$C_{25}H_{24}N_4$	79,6	6,1	14,3
X**	204—205	0,16	3440	3345			78,8	5,4	15,0	$C_{24}H_{20}N_4$	79,1	5,5	15,4

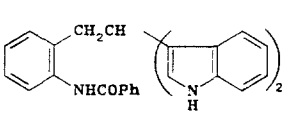
*Compounds IIa, X were recrystallized from acetonitrile, IIb from DMFA, VIII, IXb from methanol, and the remaining compounds from propanol.

†PMR spectrum: 10.90 (s, NH), 8.33-6.95 (13H, m, arom.), 7.07 (1H, dd, J = 7.4 Hz, 4-H), 5.73 (1H, dd, 3-H), 5.07 (1H, d, J = 5.6 Hz, 2-H).

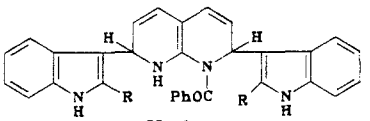
††PMR spectrum: 10.82 (2H, d, NH), 7.75-6.74 (16H, m, naphthyridine and indole ring protons), 4.94, 4.71 (2H, dd, J = 2.6 and 10.3 Hz, dd, J = 6.7 and 11.9 Hz, 3-H).

**PMR spectrum: 10.84 (2H, d, NH); 7.73-6.79 (16H, m, naphthyridine and indole ring protons); 4.60, 4.46 (2H, t, J = 4.7 Hz, J = 4.5 Hz, 3-H).

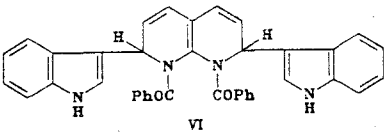
Compounds I-III were obtained at the boiling point of toluene, and in the reaction with 1,5-naphthyridine, β-di-(3-indolyl)ethyl-o-benzanilide (IV) is also formed, while in the reaction with 1,8-naphthyridine, 1-benzoyl-2,7-di-(3-indolyl)-1,2,7,8-tetrahydro-1,8-naphthyridine (V), 1,8-dibenzoyl-2,7-di-(3-indolyl)-1,2,7,8-tetrahydro-1,8-naphthyridine (VI), and 2,7-di-(3-indolyl)-1,2,7,8-tetrahydro-1,8-naphthyridine (VII) are obtained:



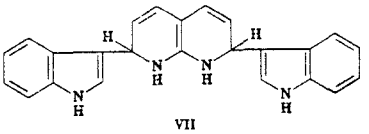
IV



Va,b



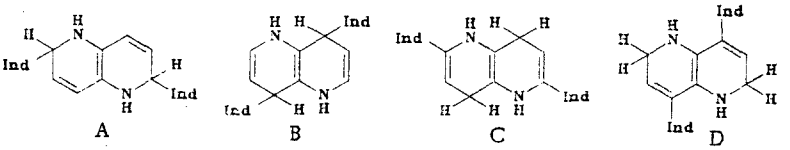
VI



VII

V a R=H, b R=CH_3

In the reaction with 1,8-naphthyridine in DMFA at 20°C, the same compounds I, V-VII are formed as in toluene, but at the boiling point the ratio of their yields changes: the amount of compound VII increases from 5 to 83%, and that of compound V decreases from 15 to 5%, while the dibenzoyl derivative VI and compound I were not detected in the reaction mixture. In the reaction with 1,6-naphthyridine in DMFA at 20°C and at the boiling point, compound III is not formed, but 2,5-di-(3-indolyl)-1,2,5,6-tetrahydro-1,6-naphthyridine (VIII) is. The behavior of 1,5-naphthyridine in DMFA was found to be somewhat unusual. Two isomeric compounds IX and X could be isolated from the reaction mixture in a ratio of 4:3, with a molecular weight of 364 and an empirical formula of $C_{24}H_{20}N_4$. The possible structures of these compounds are represented by the following formulas:



A B C D

TABLE 2. Mass Spectra of Compounds I-III, V-X

Compound	Mass spectrum, m/z (relative intensity, %)								
	$[M]^+$	$[M-COPh]^+$ (A)	$[(A)-Ind]^+$	$[(A)-Ind)-H]^+$	$[M-Ind]^+$	$[(M-Ind)-H]^+$	$[Ind]^+$	$[Ind-H]^+$	$[COPh]^+$
I	351 (12)	246 (100)	130 (24)				117 (12)	116 (2)	105 (33)
IIa	351 (6)	246 (100)	130 (4)				117 (39)	116 (3)	105 (70)
IIb	365 (12)	260 (40)	130 (29)				131 (12)		105 (100)
III*	351 (13)	246 (100)	130 (24)				117 (24)	116 (7)	105 (99)
Va	468 (7)	363 (29)	247 (11)	246 (27)			117 (100)	116 (14)	105 (52)
Vb	496 (21)	391 (100)	261 (17)	260 (64)			131 (38)		105 (48)
VI	572 (8)	467 (8)†					117 (19)	116 (3)	105 (100)
VII	364 (12)				247 (87)	246 (100)	117 (25)	116 (6)	
VIII	364 (18)				247 (95)	246 (100)	117 (31)	116 (6)	
IXa	364 (91)				247 (80)	246 (100)	117 (48)	116 (9)	
IXb	392 (22)				261 (97)	260 (100)	131 (74)		
X	364 (48)				247 (100)	246 (99)	117 (74)	116 (15)	

*For compounds IIb, Vb, IXb, Ind = 2-methylindole.
†The following peaks are in the mass spectrum: $M - 2COPh^+$ 363 (7); $M - 2COPh - Ind^+$ 246 (30); $M - 2COPh - Ind - H^+$ 245 (17); $M - 2COPh - 2Ind^+$ 130 (10).

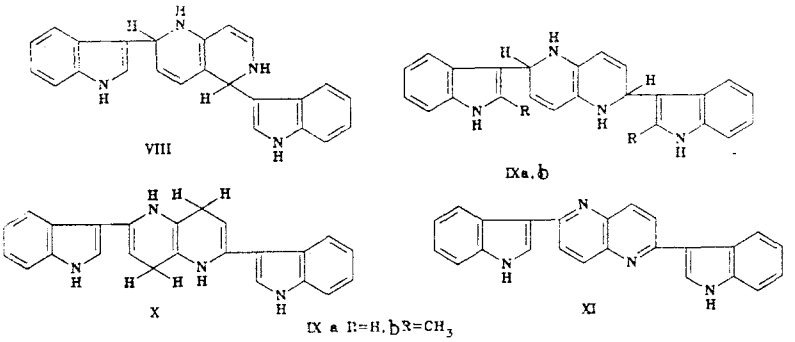
TABLE 3. Reaction Conditions and Yields of Hetarylation Products of Indole

Starting naphthyridine	Reaction conditions			Reaction product (yield, %)	Eluent for chromatography and separation of reaction products
	naphthyridine–indole–benzoyl chloride ratio, mole	solvent	T, °C		
1,6-Naphthyridine	1:1:1*	Toluene	25, bp	III (91)	Ether–chloroform–hexane–alcohol 30:10:5:1
	1:2:1	DMFA	25, bp	VIII (90)	
1,8-Naphthyridine	1:1:1	Toluene	25	I (57)	As above
	1:2:1	Toluene (DMFA)	bp (25)	I (17), V (15), VI (9), VII (5)	
	1:2:1	DMFA	bp	V (5), VII (83)	
1,5-Naphthyridine	1:1:1	Toluene	25	II (55)	
	1:2:1	Toluene	bp	II (68)	Ether–chloroform–hexane, 3:1:1
	1:2:1	DMFA	bp	IX (40), X (30)	

*At a 1:2:2 ratio of reagents, the yield of reaction products was the same.

Aromatization of isomers IX and X by chloranil leads to one and the same compound XI, which indicates that the position of the indolyl substituent is identical in the two isomers, and hence structures A and C or B and D are possible. We assigned the structures by analysis of their PMR spectra. In the spectra, the most characteristic feature is the difference in the multiplicity of signals in 4.4-5.0 ppm region. For compound IX there are in this region two doublets of doublets with centers at 4.94 and 4.71 ppm and SSCC J = 2.6 and 10.3 Hz for one of the isomers, and 6.7 and 11.9 Hz for the other, with an overall intensity of 2H. The multiplicity and SSCC indicate that these signals can be assigned to 3-H protons of structures A or B, while their overall intensity and absence of changes in multiplicity when double resonance is superimposed on each of them indicate the presence of two conformers. In the spectrum of compound X there are two triplets at 4.60 and 4.46 ppm with SSCC of 4.7 and 4.5 Hz, respectively, with an overall intensity of 2H. Structure D presumes the presence of two triplets with an overall intensity of 4H for NH and 3-H protons. Therefore, the observed overall intensity of triplets and absence of changes in addition of D_2O show that it is possible to assign the signals to the resonance of 3-H protons of structure C, 2,6-di-(3-indolyl)-1,4,5,8-tetrahydro-1,5-naphthyridine, and their independence of one another (according to the

double resonance data) shows that in this case also we can assume the existence of two conformers. A partner in the pair to this compound is 2,6-di-(3-indolyl)-1,2,5,6-tetrahydro-1,5-naphthyridine, A.



VIII IXa,b X XI

IX a R=H, b R=CH_3

The PMR spectra of the remaining compounds also confirm the α-disposition of the indolyl substituent. For compound IIa, the relative disposition of the 2-H, 3-H and 4-H protons is at 5.07, 5.73, and 7.07 ppm, respectively, and the SSCC J = 5.6 and 7.4 Hz are similar to those for 1,2-dihydroquinoline structures with an α-substituent [12, 13]. Thus, the α- and not the γ-position in the naphthyridine cation is subjected to the nucleophilic attack, which agrees with all the above cases [6-11].

In the IR spectra of the compounds obtained there are absorption bands of the NH groups of indole and dihydronaphthyridine rings, carbonyl group, and C=N double bonds (Table 1). The fragmentation of the molecular ions of compounds I-X is characteristic of these compounds and analogous to the fragmentation of N-benzoyl-2-(3-indolyl)-1,2-dihydrobenzopyridine derivatives by the action of an electron impact [14]. Besides molecular ions, ions of benzoyl (m/z 105) and indole (m/z 117) fragments are observed in the mass spectrum. They are formed as the result of cleavage of the amide and internuclear C—C bonds, which are not labile in the molecule (Table 2).

EXPERIMENTAL

The IR spectra were run on a Specord IR-75 spectrophotometer, and the mass spectra on a Varian MAT-311 spectrometer with a direct introduction system of the samples into the ionic source, energy of ionizing electrons 70 eV, temperature of the ionization chamber 100-300°C. The PMR spectra were recorded on a Bruker WH-90 spectrometer in DMSO-D_6.

Typical Procedure for Hetarylation of Indole. A mixture of 0.65 g (5 mmoles) of naphthyridine, benzoyl chloride and indole in 15 ml of a solvent is stirred for 3-5 h, and then poured into a dilute ammonia solution. The precipitate is filtered and washed with water. The reaction products are separated by chromatography on aluminum oxide (Tables 1-3).

In the reaction with 1,5-naphthyridine, compound IV is obtained as a byproduct, yield 27%, mp 210-211°C [15] (from propanol). Found, %: C 82.0, H 5.4, N 10.1. $C_{31}H_{25}N_3O$. Calculated, %: C 81.8, H 5.5, N 9.2.

2,6-Di-(3-indolyl)-1,5-naphthyridine (XI). A mixture of 0.18 g (0.5 mmole) of 2,6-di-(3-indolyl)-1,2,5,6-tetrahydro-1,5-naphthyridine and 0.25 g (1 mmole) of chloranil in 15 ml of benzene is boiled to a complete dissolution of the materials. The reaction is treated with alkali, the solvent is evaporated, and the precipitate is recrystallized from propanol. Yield 51%, mp 183-185°C. Mass spectra, m/z, %: 360 (100), 359 (34), 358 (50), 246 (7), 245 (19), 244 (20), 218 (13), 180 (27), 179.5 (30), 179 (12), 166 (5), 165.5 (10), 165 (5). Found, %: C 79.6, H 4.5, N 15.9. $C_{24}H_{16}N_4$. Calculated, %: C 80.0, H 4.4, N 15.6.

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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 1,4-DIHYDROPYRIMIDINE-5-CARBOXYLIC ACID

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1,4-Dihydropyrimidines were synthesized by reductive dethionation of the corresponding 2-thiono-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives, and some of their properties were studied.

1,4-Dihydropyrimidines are 3-aza analogs of 1,4-dihydropyridines, which attracted attention because of their broad spectrum of biological action. However, until now, there are no suitable methods available for the synthesis of 1,4-dihydropyrimidines, and only individual representatives of this class are known. The synthesis of derivatives of 1,4-dihydropyrimidine by intramolecular rearrangement of 1,2,3,4-tetrahydropyrimidine-2-thiones [1, 2] is not very promising, since it is complicated by splitting of the pyrimidine ring and recyclization into 1,3-thiazine derivatives. This method is also unsuitable for synthesizing 2-unsubstituted 1,4-dihydropyrimidines. The existence of 1-N-unsubstituted dihydropyrimidines in the form of 1,4-dihydro isomer has been strictly proved only in separate cases [3] because of tautomeric transitions [4]. In 1983 [5, 6], 1-substituted 4-methyl-1,4-dihydropyrimidines were synthesized by reductive dethionation of pyrimidine-2-thiones over a Raney nickel catalyst. We used this method for synthesizing 4-aryl derivatives of 1-substituted 1,4-dihydro-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid, which have so far been unknown. The reductive dethionation of 2-thiono-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives (I) which we synthesized was carried out in acetone and methanol. The reaction is complicated by side-processes. In the reduction of the bromo derivative Ib, debromination takes place, and the reaction product is 1,4-diphenyl-1,4-dihydropyrimidine (IIa). In the reduction of a methoxy derivative Id in methanol, a mixture of dihydropyrimidine IId and tetrahydropyrimidine IV is formed (in a 1:3 ratio, according to liquid chromatography data), and the main product of the reduction of the nitro derivative IIc is tetrahydropyrimidine III. Reduction of 1,2,3,4-tetrahydropyrimidine-2-thiones over Raney nickel in a hydrogen atmosphere (p = 1 atm, T = 60°C) does not lead to increase in the yield of II (see scheme on following page).

The synthesis of IIa by reductive splitting of 1,4-diphenyl-2-methylthio-5-ethoxy-6-methyl-1,4-dihydropyrimidine (V) is not explicitly preferential, since the starting compound V was obtained by alkylation of Ia. We took compounds IIa, e as an example, and showed that derivatives of 1,4-dihydropyrimidine-5-carboxylic acid have characteristic chemical properties. The ester grouping in IIa is readily hydrolyzed in an alkaline medium to 1,4-diphenyl-

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