A NEW SYNTHESIS FOR HETARYLINDOLES*

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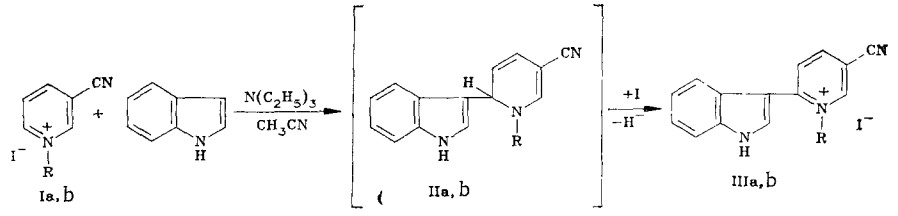
UDC 547.82.832.751:541.635

The reaction of pyridinium quaternary salts and benzopyridiniums with indoles in the presence of bases has been investigated. It has been shown that in this case, the indole molecule is added to the heteroaromatic cation with subsequent elimination of a hydride ion and the formation of either hetarylindoles, their quaternary salts, or anhydro bases, depending on the structure of the cation.

The interest in the chemistry of heterocyclic derivatives of indole, particularly in pyridyl- and benzopyridylindoles, is due to their high biological activity. They are very important intermediates in the synthesis of indole alkaloids, display bactericidal, antifungal, hypoglycemic, and anti-inflammatory activities, have hypotensive and anticonvulsion effects, suppress motor activity, and act on the central nervous system. For this reason, investigations on the development of methods for the synthesis of these heterosystems have been actively conducted for the last 50 years; however, many of them are still extremely difficult to obtain. While 2-pyridyl- and benzopyridylindoles are obtained fairly easily by the Fischer indole synthesis from the phenylhydrazones of the corresponding acetylpyridines and benzopyridines [2, 3], there are no simple universal preparative methods for the synthesis of 3-pyridylindoles. Such structures are formed either according to the Fischer reaction in this case, too, but from difficulty obtained acetonyl- or phenacylpyridines [4, 5] or by a direct method involving the reaction of N-oxides of nitrogenous bases, for example, the N-oxide of quinoline [6] or ethylnicotinate [7], with indole and its homologs in the presence of acylating agents. 3-(4-Pyridyl)indole can be obtained by the direct reaction of pyridine and indole in the presence of acetyl or benzoyl chloride [8, 9]. In addition, some 3-pyridyl- and quinolylindoles form when the corresponding halogenated derivatives of the nitrogenous bases are reacted with organomagnesium derivatives of indole and 2-methylindole [10]. However, all the paths for the synthesis of 3-pyridylindoles just enumerated are extremely unsuccessful, since they either require the use of difficulty obtained reactants or are very tedious, and they are accompanied by a number of secondary competitive processes, which of the suppress the main reaction and preclude the isolation of the product in the individual state. The yields of the pyridylindoles in all the cases described are generally negligible.

In the last few years we developed another method for the synthesis of 3-pyridylindoles, which involves the aromatization of indole derivatives of N-acyl-1,2(1,4)-dihydropyridines and benzopyridines, which are formed in a singlet step according to a hetarylation reaction with the aid the selective hydride-ion acceptor 1-oxo-2,2,6,6-tetramethylpiperidinium perchlorate; however, the realization of this method is limited by the difficulties in obtaining this hydride-ion acceptor [11].

As a result of an investigation of the reactions of 3-cyanopyridinium quaternary salts with several nucleophiles, we found that 1-alkyl-3-cyanopyridinium iodides (I) react in acetonitrile in the presence of triethylamine with indole to form 1-alkyl-3-cyano-6-(3-indolyl)pyridinium iodides:



a $R=CH_3$; b $R=C_{16}H_{33}$

*For preliminary report, see [1].

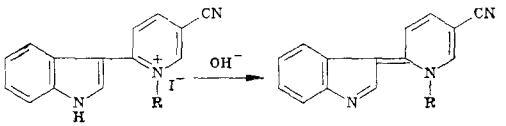
Donetsk State University, Donetsk 340055. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1383-1387, October, 1984. Original article submitted February 15, 1984.

 0009-3122/84/2010-1140$08.50

TABLE 1. Derivatives of Pyridylindoles

Compound	mp, °C (methanol)	IR spectrum, ν, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIIb	235—236	1650 (C=N), 2190 (C≡N), 3485 (NH)	62,0	7,8	7,3	$C_{29}H_{42}IN_3$	62,2	7,6	7,5	55
IVb	122—123	1658 (C=N), 2190 (C≡N)	80,5	9,3	9,5	$C_{29}H_{41}N_3$	80,7	9,6	9,7	98
V	192—194	2205 (C≡N), 3495 (NH)	79,0	7,7	13,1	$C_{14}H_{16}N_2$	79,2	7,6	13,2	95

The reaction apparently takes place with a step involving the intermediate formation of dihydro structure II, which subsequently eliminates a hydride ion under the action of the excess of salt I and gives final product III. The results obtained have an analogy in the literature in the case of the synthesis of N-methyl-3-(2-quinoxalyl) indolium iodide by reacting N-methylquinoxalinium iodide and indole under conditions for oxidation by oxygen [12]. In the case of salt Ia, we were able to isolate a small quantity of the corresponding dihydro derivative IIa along with N-methyl iodide III, proving the correctness of the proposed interpretation. When the salts of type III are treated with a water—methanol solution of an alkali metal hydroxide, they are readily deprotonated with the formation of the corresponding stable anhydro bases IV:

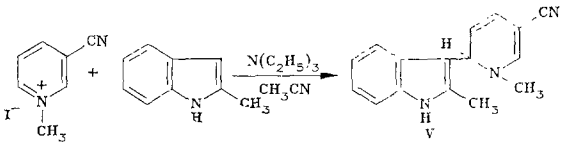


IIIa, b IVa, b

The IR spectra of compounds III show intense absorption maxima at 2200 and 3485 cm^{-1}, which are assigned to stretching vibrations of the C≡N and N—H groups in the molecule. In compounds IV the absorption band corresponding to the NH group of indole disappears, attesting to the complete deprotonation of the system, and there is additional absorption at 1610 cm^{-1}, which characterizes the presence of a C=C bond in the molecule.

When 3-cyanopyridinium salts are reacted with nucleophiles, the latter can become attached either to the $C_{(2)}$ atom or to the $C_{(4)}$ and $C_{(6)}$ atoms of the pyridine ring, which are characterized by a deficiency of electrons. The site of attack depends primarily on the nature of the nucleophile. It was established [13] that the only nucleophile attacking position 2 of the ring is the hydroxyl ion, whereas the other nucleophiles are directed either to the $C_{(6)}$ atom or to the $C_{(4)}$ atom. The attack of the $C_{(2)}$ atom by nucleophiles bulkier than the hydroxyl ion is prevented by the steric hindrances created by the substituent in position 3 and the N-methyl group. The attack of the $C_{(4)}$ atom and the attack of the $C_{(6)}$ atom have practically equal probabilities. However, it should be noted that in the case of the reaction of a 3-substituted pyridinium N-oxide with indole, the latter is added at the $C_{(6)}$ atom of the ring [7]. We also made the choice in favor of the products indicated above on the basis of an analysis of the PMR spectrum of one of them, viz., compound IVa, which was recorded in trifluoroacetic acid. It should be noted that the strong base IVa (its pK_a is 10.56) is protonated at the indolenine nitrogen atom when it is dissolved in trifluoroacetic acid and that a cation of type IIIa, rather than anhydro base IVa, is actually present in trifluoroacetic acid. The PMR spectrum shows the following signals: a singlet for the three protons of the N-methyl group at 3.70 ppm, a singlet formed by the protons at the $C_{(4)}$ and $C_{(5)}$ atoms of the pyridine ring at 7.73 ppm, a singlet at 8.30 ppm, which belongs to the proton at the $C_{(2)}$ atom, a doublet for the proton at the $C_{(2)}$ atom of the indole fragment at 7.90 ppm (J_{HCNH} = 3.0 Hz), and a multiplet for the aromatic protons of the benzene ring of the indole fragment at 6.5-7.4 ppm. The PMR spectrum unequivocally attests to the formation of derivatives of 3-(2-pyridyl)indole alternative variants of the synthesis of the isomeric 3-(4-pyridyl)indoles are possible.

When 2-methylindole is used in this reaction, the process stops at the stage of the formation of dihydro derivative V, which is farily stable and, in contrast to the case described above, is not oxidized by an excess of salt I:



The PMR spectrum of dihydro derivative V differs from the spectrum of IVa described above. It contains the following signals: two singlets at 2.81 and 4.47 ppm, which are formed by the protons of the methyl group in the indole ring and the N-methyl group, respectively, a singlet for the proton at the $C_{(2)}$ atom of the pyridine ring at 9.14 ppm, two singlet signals for the protons at the $C_{(4)}$ and $C_{(5)}$ atoms of the pyridine ring at 8.94 and 8.24 ppm, and singlet for the methine proton in the geminal fragment at 8.76 ppm.

We suggest that the difference between the properties of dihydropyridine II and V is due to the steric shielding of the 2-methyl group of the indole part of the molecule, which would occur in planar structures of types III and IV and which is absent in compound V owing to the free rotation around the C—C bond between the heterocycles. We confirmed this hypothesis by constructing molecule V with the aid of Stuart—Briegleb models, and, as a result, it became clear that the indole ring with the 2-methyl group is located in a plane perpendicular to the plane of the pyridine ring.

The formation of derivatives of pyridylindoles when pyridinium quaternary salts are reacted directly with indoles takes place only when there is an electron-acceptor substituent in the ring of the slats, and unsubstituted pyridinium quaternary salts do not react with indole under similar conditions. We postulated that annelation of the pyridine ring can produce an effect similar to the effect of an electron-acceptor substituent in the ring of the salt, and, using this hypothesis, we were able to obtain quaternary salts of various benzopyridylindoles by the direct method from the correpsonding and indole. However, N-methylquinolinium iodide (VI), N-methyl-isoquinolinium iodide (VII), and N-methylbenzoquinolinium iodide (VIII) do not react with indole under the conditions described above. We were able to conduct this reaction only by reacting salts VI-VIII with indole in an ethanol solution in the presence of sodium ethoxide.

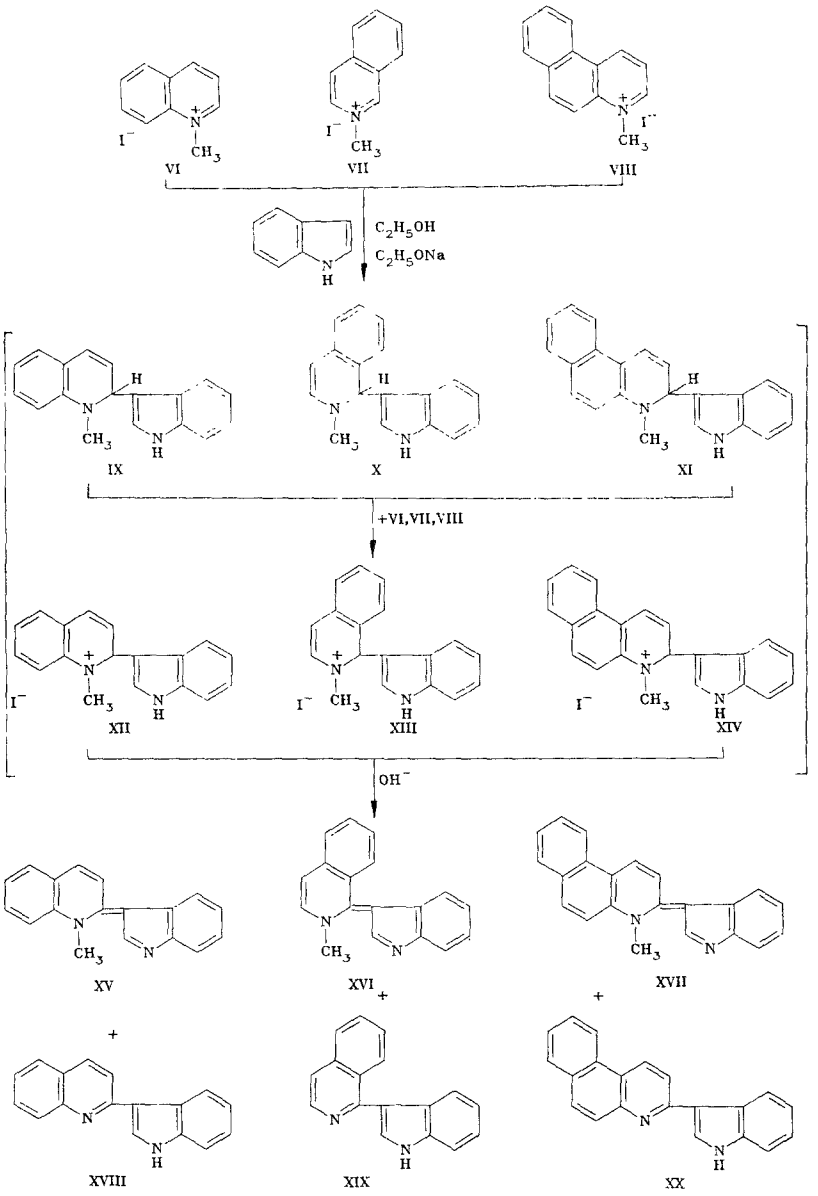
From the scheme presented it follows that the reaction does not stop at the stage of the formation of quaternary salts XII-XIV, as in the preceding case, or at dihydro structures IX-XI and that it proceeds further with the realization of deprotonation and dealkylation processes, which give mixtures of the corresponding anhydro bases XV-XVII and bases XVIII-XX. These compounds form in the ratios which we previously observed in a study of the reactions of purposely synthesized quaternary salts XII-XIV with an alkali metal hydroxide [14]. The ratio between the deprotonation and dealkylation products is dictated, as was shown in [14], by the difference between the partial positive π-electronic charges on the nitrogen atoms in cations XII-XIV.

EXPERIMENTAL

The IR spectra of recorded on a UR-20 spectrometer in chloroform, the PMR spectra were recorded on a Tesla-80 spectrometer in trifluoroacetic acid (the internal reference was HMDS), and the potentiometric determination of the pK_a was carried out on a pH-340 instrument by titrating a water—methanol solution of the compound ($c = 10^{-2}$ M, the methanol content was 10%) with a 0.1 N HCl solution. The pK_a was assumed to be equal to the pH at the half-neutralization point. The chromatography in an unfixed thin layer of aluminum oxide (Brockmann)s second activity level) was carried out with elution by 30:6:1 chloroform—benzene—hexane (A) and 5:1 chloroform—methanol (B) solvent systems.

Reaction of N-Methyl-3-cyanopyridinium Iodide with Indole. A mixture of 5 g (0.01 mole) of N-methyl-3-cyanopyridinium iodide, 1.17 g (5 mmole) of indole, and 1 ml of triethylamine in 10 ml of dry acetonitrile is held at boiling for 1 h, and the precipitate of 1-methyl-3-cyano-6-(3-indolyl)pyridinium iodide (IIIa) formed upon cooling is filtered out and recrystallized from dimethylformamide. The yield is 1.8 g (50%), mp 270-271°C, R_f 0.45 (B). IR spectrum, ν, cm^{-1}: 2200 (C≡N), 1670 (C=N), 3480. Found: C, 49.7; H, 3.5; N, 11.3%. Calculated for $C_{15}N_{12}IN_3$: C, 49.9; H, 3.4; N. 11.6%. The filtrate remaining after the separation of IIIa yielded 0.28 g (12%) of 1-methyl-3-cyano-6- (3-indolyl)-1,6-dihydropyridine (IIa), mp 175-176°C (from methanol, R_f 0.35 (A). IR spectrum, ν, cm^{-1}: 2210 (C≡N), 3485 (NH).

Scheme



Found: C, 76.6; H, 5.7; N, 17.6%. Calculated for $C_{15}H_{13}N_3$: C, 76.6; H, 5.6; N, 17.9%.

The reactions of the other 3-cyanopyridinium quaternary salts with indoles are carried out in a similar manner. The main characteristics of the compounds obtained are presented in Table 1.

1-Methyl-3-cyano-6-(3-indolenylidene)-1,6-dihydropyridine (IVa). A suspension of 3.6 g (0.01 mole) of IIIa is held in 10 ml of a saturated methanolic solution of KOH at room temperature for 2 min, then water is added to the reaction mixture, and the precipitate formed is filtered and recrystallized from methanol. ν, cm^{-1}: 1680 (C=N), 2200 (C≡N). PMR spectrum: 3.70 (3H, s, N–CH_3), 7.73 (2H, s, C_4–C_5pyr), 8.30 (1H, s, C_2pyr), 7.90 (1H, d, C_2ind) (J_{NHHC} = 3.0 Hz), 6.5-7.4 ppm (m, arom. protons). Found: C, 77.1; H, 4.5; N, 17.7%. Calculated for $C_{15}H_{11}N_3$: C, 77.2; H, 4.8; N, 18.0%.

Anhydro base IVb is obtained in a similar manner, and the main characteristics are given in Table 1.

Reaction of N-methylquinoline Iodide with Indole. A mixture of 5.4 g (0.02 mole) of N-methylquinoline iodide, 1.2 g (0.01 mole) of indole, and 0.5 g of IIa in 20 ml of dry ethanol is held at the boiling point for 2 h, after which water is added to the reaction mixture. Thr precipitate formed is filtered out, dried, and separated in a column with aluminum oxide with successive elution by chloroform and methanol. This gives 0.2 g (10%) of 2-(3-indolyl)-

quinoline (XVIII) with mp 190-191°C (from n-butanol) and R_f 0.25 (A) and 1.8 g(70%) of 1-methyl-2-(3-indolenylidene)-1,2-dihydroquinoline (XVI) with mp 173-174°C and R_f 0.35 (B). Neither compound produces any melting point depression in mixed samples with known specimens.

The reactions of the N-methyl iodides and other benzopyridines with indole take place in a similar manner. The main characteristics of the compounds obtained are not presented here, since they correspond completely to the data obtained in [14].

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