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REACTION OF N-ACYL SALTS OF HETEROAROMATIC CATIONS WITH 4,5,6,7-TETRAHYDROINDOLE — A POSSIBLE PATHWAY TO 2-HETERYLINDOLES

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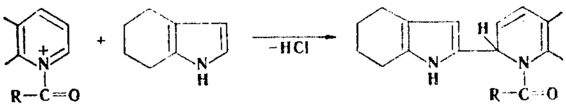
The reaction 4,5,6,7-tetrahydroindole with various N-heteroaromatic bases in the presence of acyl halides proceeds via a mechanism involving hetarylation and leads to corresponding 2-substituted 4,5,6,7-tetrahydroindoles. The structures of the compounds obtained were confirmed by data from the IR, mass, and PMR spectra.

The direct introduction of heterocyclic residues into the indole ring by various methods can be accomplished only in the 3 position, except for hetarylation by heteroaromatic anion radicals, which leads to mixtures of 2- and 3-hetarylindole isomers [1-3].

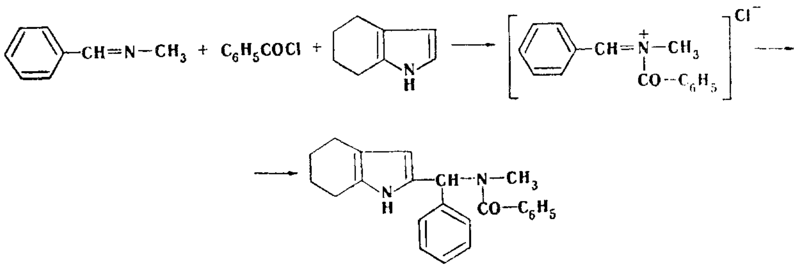
We propose a possible general method for the preparation of 2-substituted indoles from 4,5,6,7-tetrahydroindole, which has recently become accessible [4].

In the present paper we demonstrate the possibilities of the new method in the case of the reaction of N-acyl heteroaromatic cations in situ, which leads to various 2-heterocyclic derivatives of 4,5,6,7-tetrahydroindole (Table 1):



I

4,5,6,7-Tetrahydroindole reacts similarly with N-acylimmonium salts in situ:

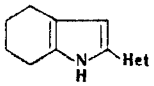


II

Donetsk State University, Donetsk 340055. Irkutsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Irkutsk 664033. Dnepropetrovsk Civil Engineering Institute, Dnepropetrovsk 320092. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 167-169, February, 1978. Original article submitted May 10, 1977.

0009-3122/78/1402-0127$07.50

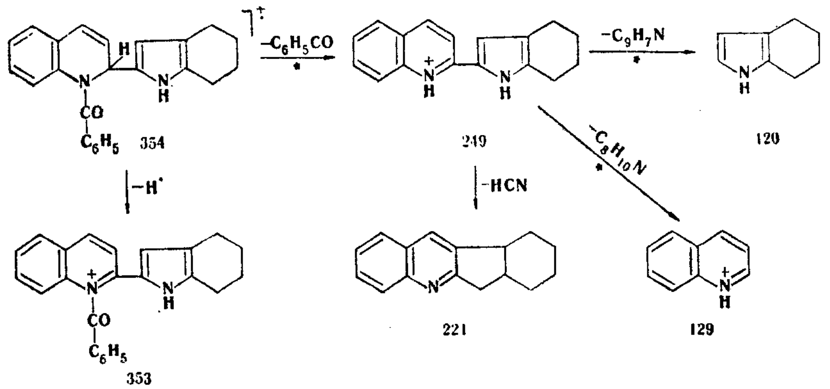
TABLE 1. Heterocyclic Derivatives of 4,5,6,7-Tetrahydroindole (Ia-h)



Comp.	Heterocyclic residue	mp, °C	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1}		Yield, %
			C	H	N		C	H	N	ν_{CO}	ν_{NH}	
Ia	1-Benzoyl-1,2-dihydro-2-quinolyl	178—179	81,2	6,4	7,8	$C_{24}H_{22}N_2O$	81,5	6,2	7,9	1642	3430	51
Ib	2-Benzoyl-1,2-dihydro-1-isoquinolyl	110—111	82,1	6,4	8,1	$C_{24}H_{22}N_2O$	81,5	6,2	7,9	1650	3430	48
Ic	9-Acridinyl	295—297	83,9	6,0	8,9	$C_{21}H_{18}N_2$	84,5	6,0	9,4	—	3450	67
Id	1-Acetyl-1,2-dihydro-2-quinolyl	181—183	78,1	7,2	9,8	$C_{19}H_{20}N_2O$	77,8	6,8	9,6	1638	3432	49
Ie	2-Acetyl-1,2-dihydro-1-isoquinolyl	197—198	77,3	7,3	9,6	$C_{19}H_{20}N_2O$	77,2	6,8	9,6	1645	3425	55
Ie	1-Acetyl-1,4-dihydro-4-pyridyl	202—203	75,0	7,2	11,9	$C_{15}H_{18}N_2O$	74,5	7,4	11,8	1620	3455	62
Iж	1,3-Diacetyl-2-benzimidazolyl	215—216	70,5	6,6	13,1	$C_{19}H_{21}N_3O_2$	70,6	6,5	13,0	1670	3433	98
Ih	1,3-Diacetyl-4-imidazol-2-yl	206—207	65,5	7,2	15,1	$C_{13}H_{19}N_3O_2$	65,7	6,9	15,3	1650	3420	97
II	N-Methylbenzamidobenzyl	101—102	80,7	6,8	7,9	$C_{23}H_{24}N_2O$	80,2	6,9	8,1	1632	3470	75

We proved the structures of the products by means of their IR and mass spectra. In particular, the presence of intramolecular hydrogen bonding in solutions of I provides evidence for substitution in the 2 position (rather than in the 3 position). Thus the IR spectrum of unsubstituted 4,5,6,7-tetrahydroindole contains a narrow strong band (ν_{NH}) at 3480 cm^{-1}, whereas this band is shifted to the long-wave region (3430 cm^{-1}) and broadened in the spectra of I. When solutions of I in chloroform are diluted by factors of two, four, and eight, the character of the NH absorption band remains unchanged; this excludes the formation of an intermolecular hydrogen bond.

The mass spectra of I and II contain molecular ion peaks and peaks of principal fragment ions [(M — RCO), (M — tetrahydroindole fragment), (M — heterocyclic residue), etc.]; this confirms the structures of the synthesized substances. The fragmentation Ia can be cited as a typical example of the dissociative ionization of I and II under the influence of electron impact:



The following signals are observed in the PMR spectra of I: two signals at 1.73 (4H) and 2.47 ppm (4H), which can be assigned to the protons of the cyclohexane ring; a doublet at 5.75 ppm (2H), which is related to the proton in the β position of the pyrrole ring and in the α position of the partially hydrogenated heteroring; a singlet at 7.17 ppm (1H) due to the NH group; and a complex multiplet of aromatic protons at 7.10-8.80 ppm (10H).

Compounds I and II can be dehydrogenated by Pd^{2+} salts by a procedure similar to that previously described for the hydrogenation of piperazine [5] and cyclohexane [6]; information regarding this dehydrogenation will be reported separately.

EXPERIMENTAL

The IR spectra of $CHCl_3$ solutions of all of the compounds obtained were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Hitachi—Perkin—Elmer spectrometer at an ionizing-electron energy of 70 eV. The PMR spectra of $CDCl_3$ solutions of the compounds were recorded at 25°C with a YaMR-5535 spectrometer (40 MHz) with tetramethylsilane as the internal standard. Chromatography in a thin layer of aluminum oxide (activity II on the Brockmann scale) was carried out in all cases with elution with benzene—hexane—chloroform (6:1:30); the chromatograms were developed with iodine vapors and in UV light.

The starting 4,5,6,7-tetrahydroindole was obtained by the method in [4].

Typical Method for the Hetarylation of 4,5,6,7-Tetrahydroindole. A three-necked 100-ml flask equipped with a mechanical stirrer with a liquid seal and a dropping funnel was charged with 0.05 mole of dry N-heteroaromatic base, 0.025 mole of acyl halide or carboxylic acid anhydride, and 0.025 mole of 4,5,6,7-tetrahydroindole, and the mixture was stirred at room temperature in an inert gas atmosphere for 24 h. The precipitate was removed by filtration or the reaction mixture was subjected to steam distillation until the odor of the nitrogen base was no longer present in the distillate. The solid residue in the distillation flask was separated, dried, and recrystallized from a suitable solvent. The physical constants of the product are presented in Table 1.

2-(1',3'-Diacetyl-2'-benzimidazolyl)-4,5,6,7-tetrahydroindole. A mixture of 1.18 g (0.01 mole) of benzimidazole, 0.58 g (0.005 mole) of 4,5,6,7-tetrahydroindole, 0.64 g (0.01 mole) of acetyl chloride, and 25 ml of dry benzene was refluxed for 2 h, after which it was cooled and diluted with 50 ml of water. The benzene layer was removed by distillation, and the residue was recrystallized from n-butanol (Table 1).

2-(1',3'-Diacetyl-4'-imidazolyl)-4,5,6,7-tetrahydroindole was similarly obtained (Table 1).

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