SYNTHESIS AND AROMATIZATION OF INDOLE DERIVATIVES OF N-IMIDOYLDIHYDROAROMATIC COMPOUNDS\*

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The reaction of indole (methylindoles) with a number of pyridine bases, imidazole, and benzimidazole in the presence of benzimidazolyl chlorides gave N-imidoyl derivatives of dihydro- $\alpha(\gamma)$ -3-indolylheterocyclic compounds, the aromatization of which under the influence of triphenylmethyl perchlorate or 1-oxo-2,2,6,6-tetramethylpiperidinium perchlorate leads to perchlorates of N-imidoyl heteroaromatic cations.

In reactions involving hetarylation by means of N-acyl heteroaromatic cations in situ the acyl halides in some cases can be successfully replaced by substituted amides of carboxylic acids in the presence of  $POCl_3$ , i.e., by chloroiminium salts [2].



\*See [1] for our preliminary communication.

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These results have made it possible to assume that ordinary imidoyl chlorides, like acyl chlorides, upon reaction with N-heteroaromatic bases would form sufficiently electrophilic N-imidoyl heteroaromatic cations that can be used *in situ* for the introduction of **heteroaromatic residues into** nucleophilic organic compounds. In fact, as we have shown in a preliminary communication [1], ordinary hetarylation products are formed in the reaction of pyridine, quinoline, or isoquinoline with indole in the presence of N-phenylbenzimidoyl chloride.

We found that in this reaction one can use various imidoyl chlorides and N-heteroaromatic bases, viz., pyridine, benzo- and dibenzopyridines, imidazole, and benzimidazole. In analogy with hetarylation in the presence of acyl halides [3] N-imidoyl salts of N-heteroaromatic bases (I) are evidently formed as intermediates. Such salts cannot be obtained by the direct reaction of imidoyl chlorides with pyridine bases as a consequence of their instabilities. We have found that stable N-phenylsulfonylbenzimidoylisoquinolinium and -quinolinium perchlorates (VIII-XI) can be obtained as a result of aromatization of the compounds (II-VII) obtained via hetarylation.

Unsubstituted N-imidoylisoquinolinium salt VIII was obtained in the reaction of dihydroisoquinoline IIIe with triphenylmethyl perchlorate, while in the reaction of 1-oxo-2,2,6,6tetramethylpiperidinium perchlorate one observes dihydroaromatization to give substituted salt IX, just as occurs under similar conditions in the aromatization of benzoyl derivatives of dihydroisoquinoline [4].

In the **aromatization of dihydroquinoline** IVb we observed an unusual reaction: Triphenylmethyl perchlorate induced dihydroaromatization to give substituted salt X, whereas detachment of indole to give unsubstituted salt XI occurred under the influence of 1-oxo-2,2,6,6tetramethylpiperidinium perchlorate:



Thus the direct hetarylation of indole in the presence of imidoyl chlorides with subsequent aromatization of the resulting N-imidoyl dihydro derivatives may serve as a universal method for the preparation of N-imidoyl salts of nitrogenous heteroaromatic compounds.

The IR spectra of II-IV, in which  $R^1 = C_6H_5$  and  $R^2 = H$ , contain intense characteristic C=N bands of an imidoyl residue at 1600-1660 cm<sup>-1</sup> and of an indole N-H bond at 3230 cm<sup>-1</sup>, whereas bands of SO<sub>2</sub> vibrations at 1090, 1290, and 1150 cm<sup>-1</sup> and of an indole N-H bond at 3350-3400 cm<sup>-1</sup> are observed in the IR spectra of compounds with  $R^1 = SO_2C_6H_5$ ; however, the band of C=N vibrations of the imidoyl residue at 1600-1640 cm<sup>-1</sup> is expressed very weakly (with an intensity of 7-10%), as in the case of arenesulfonamide amides of the ArSO<sub>2</sub>N=C(NR<sup>1</sup>-R<sup>2</sup>)Ar type [5].

The NMR spectrum of IIIa contains two doublets of olefin protons at 5.2 and 5.54 ppm ( $H^b$  and  $H^c$  protons) with a spin-spin coupling constant (SSCC) of 7.5 Hz and a singlet at 4.06 ppm ( $H^a$  proton).



The shift to the weak-field region is evidently due to the effect of the indole and benzene rings; this is in agreement with the data in [2]. The H<sup>d</sup> proton is not visible in our case but is included in a complex multiplet of aromatic protons centered at 7.4 ppm.

The structures of II-VII are also confirmed by their mass spectra, in which molecular ions  $(M^+)$ , as well as principal molecular fragments that are formed under the influence of electron impact, are recorded:



Intense  $Clo_4^{-}$  bands at 1090 cm<sup>-1</sup>, which differ with respect to their widths from the SO<sub>2</sub> bands at 1170 and 1230 cm<sup>-1</sup> and the C=N band at 1600-1660 cm<sup>-1</sup>, are observed in the IR spectra of imidoyl salts VIII-XI; an indole N-H band is observed in the spectra of salts IX and X at 3400 cm<sup>-1</sup>. The structures of compounds obtained are also confirmed by their alkaline hydrolysis:

VIII 
$$\xrightarrow{1. \text{ OH}}_{2. \text{ H}^+}$$
  $\xrightarrow{N}_{N}$  +  $C_6H_5SO_2NH-C-C_6H_5$ 

As a result of alkaline hydrolysis, substituted salt IX is converted to the known 1-(3indoly1)isoquinoline XIII and benzoic acid benzenesulfonamide XII; this confirms its structure completely:



Salts VIII-XI react with aniline to **give** amidine XIV and the corresponding isoquinoline and indolylisoquinoline bases XIII, which also confirms their structures:



\*The m/z values and the intensities of the ion peaks in percent are given.

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TABLE 1. N-Imidoylheterocyclic Derivatives (II-VII) of Indole

Com- pound	R1	R²	R <sup>3</sup>	mp, deg C	Found, %				Empirical	Calculated, %				Yield,
					с	н	N	s	formula	с	н	N	s	10
II IIIa IIIb IIIc IIId <sup>4</sup> IVa IVb IVc V VIa VIb VIIa VIIb	$\begin{array}{c} C_{6}H_{5}\\ C_{6}H_{5}\\ C_{6}H_{5}\\ C_{6}H_{5}\\ C_{6}H_{5}\\ C_{6}H_{5}\\ C_{6}H_{5}\\ SO_{2}\\ \end{array}$	— H CH₃ CH₃ H H H H H H H H H	H CH <sub>3</sub> H CH <sub>3</sub> H H CH <sub>3</sub> H CH <sub>3</sub> CH <sub>3</sub>	$\begin{array}{c} 158 - 159\\ 122 - 123\\ 135 - 136\\ 75 - 78\\ 146 - 150\\ 182 - 184\\ 143 - 145\\ 197 - 199\\ 212 - 213\\ 219 - 222\\ 240 - 242\\ 245 - 247\\ 222 - 230\\ 238 - 239\\ \end{array}$	83,5 84,7 84,4 84,2 81,9 73,6 73,6 73,6 75,8 65,8 66,1 68,3 68,2	5,7 5,6 5,5 5,7 5,0 5,0 5,0 5,0 5,0 4,4 4,4 4,4 4,4	10,8 9,9 9,4 9,3 9,0 8,8 9,9 8,8 8,5 8,0 10,0 10,0 9,9 9,8	$\begin{array}{c} \\ \\ \\ 6,4 \\ 6,5 \\ 5,8 \\ 9,3 \\ 9,5 \\ 9,5 \\ 9,0 \\ 9,0 \\ \end{array}$	$\begin{array}{c} C_{27}H_{23}N_3\\ C_{30}H_{23}N_3\\ C_{31}H_{25}N_3\\ C_{31}H_{25}N_3\\ C_{33}H_{29}N_3O\\ C_{30}H_{23}N_3O_2S\\ C_{30}H_{23}N_3O_2S\\ C_{30}H_{23}N_3O_2S\\ C_{31}H_{25}N_3O_2S\\ C_{31}H_{25}N_3O_2S\\ C_{31}H_{25}N_3O_2S\\ C_{32}H_{25}N_3O_2S\\ C_{32}H_{23}N_3O_2S\\ C_{32}H_{23}N_3O_2S\\ C_{32}H_{23}N_3O_2S\\ C_{32}H_{23}N_3O_2S\\ C_{32}H_{23}N_3O_4S_2\\ C_{42}H_{33}N_5O_4S_2\\ C_{42}H_{33}N_5O_4S_2\\ \end{array}$	83,3 84,5 84,7 84,7 81,9 73,6 73,9 75,7 66,6 66,6 68,3 68,6	5,53 5,77 5,70 4,73 4,7 5,7 4,7 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 5,5 5,5 5,5 5,7 5,5 5,5 5,7 5,5 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 5,7 4,7 5,7 4,7 5,7 4,7 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 4,5 5,5	10,8 9,8 9,6 9,6 8,7 8,6 8,8 8,6 8,8 7,8 10,2 9,7 9,5		$\begin{array}{c} 60\\ 50\\ 35\\ 25\\ 60\\ 73\\ 63\\ 59\\ 35\\ 50\\ 60\\ 35\\ 35\\ 28\\ \end{array}$

\*1-Phenylbenzimidoy1-2-(1,2-dimethy1-5-methoxy-3-indoly1)-1,2dihydroisoquinoline.

## EXPERIMENTAL

The IR spectra of KBr pellets and mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of solutions in d<sub>6</sub>-DMSO were recorded with a Tesla spectrometer (60 MHz) with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-311 spectrometer under standard conditions (an ionizing voltage of 70 eV, a cathode emission current of 300 uA, and an accelerating voltage of 3 kV) with direct introduction of the samples into the ion source. Chromatography in a thin layer of aluminum oxide and on Silufol was accomplished by elution with benzene-hexane-chloroform (6:1:30) and petroleum ether-ether-acetone (1:1:1) systems.

Hetarylation of Indoles with Pyridinium, Benzopyridinium, Imidazolium, and Benzimidazolium N-Imidoyl Salts (general method). A solution of 0.05 mole of indole and 0.115 mole of benzopyridine in 40 ml of dry benzene was stirred for 15 min, after which 0.05 mole of phenylsulfonylbenzimidoyl chloride was added in the course of 10 min, and the mixture was stirred for 1 h and heated at 70-80°C for 2 h. It was then cooled and treated with 50 ml of water and 50 ml of hexane, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from propanol (ethanol). Compounds VIa-b and VIIa-b were similarly obtained, but the reaction was carried out in the presence of an equimolar amount of triethylamine and with refluxing in benzene for 4.5-5 h. The yields, characteristics, and results of analysis of the compounds obtained by this method are presented in Table 1.

<u>2-Phenylsulfonylbenzimidoylisoquinolinium Perchlorate (VIII)</u>. A 0.25-g (5 mmole) sample of IIIe was added to a solution of 0.17 g (5 mmole) of trityl perchlorate in 5 ml of acetonitrile, and the mixture was refluxed for 15 min. It was then poured into 70 ml of dry ether, and the resulting white precipitate was washed with ether to give 0.196 g (82%) of a product with mp 163-165°C. Found: C 56.2; H 3.7; N 5.5; S 6.3%.  $C_{22}H_{17}CIN_2O_6$ . Calculated: C 55.9; H 3.6; N 5.9; S 6.8%. A 0.5-ml sample of aniline was added to 0.02 g (4 mmole) of salt VIII in 2 ml of acetonitrile, and the mixture was refluxed for 1 h, cooled, and poured into water to give 0.007 g (50%) of amidine XIV with mp 145-147°C (mp 148°C [6]). The fil-trate was made alkaline to pH 9 and extracted with ether. The ether extracts were evaporated, and 3 ml of an ethanol solution of picric acid was added to the residue to give the isoquino-line picrate with mp 226-227°C; no melting-point depression was observed for a mixture with a genuine sample.

<u>l-(3-Indoly1)-2-phenylsulfonylbenzimidoylisoquinolinium Perchlorate (IX).</u> A 0.13-g (2.5 mmole) sample of IIIe was added gradually to a solution of 0.1 g (4 mmole) of piperidine oxide perchlorate in 4 ml of acetonitrile, and, after the solid material had dissolved, the mixture was heated at 50°C for 30 h. It was then cooled and poured into 70 ml of ether, and the precipitate was reprecipitated twice from acetonitrile by the addition of ether to give 0.066 g (40%) of a red product with mp 136-139°C. Found: C 61.7; H 3.5; N 7.4; S 5.6%. C<sub>30</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>6</sub>S. Calculated: C 61.3; H 3.8; N 7.15; S 5.45%. A 0.5-ml sample of aniline was added to 0.03 g (0.5 mmole) of salt IX in 3 ml of acetonitrile, and the mixture was refluxed for 1.5 h. It was then cooled and poured into water, and the precipitate was separated and crystallized from aqueous alcohol solution to give 0.005 g (40%) of amidine XIV with mp 144-

146°C; no melting-point depression was observed for a mixture with a genuine sample. The filtrate was treated with ether, the ether extracts were combined and evaporated, and the residue was crystallized from n-butanol to give a product with mp 200-201°C; the picrate had mp 210-212°C, which corresponds to 1-(3-indoly1)isoquinoline (XIII) [7].

<u>1-Phenylsulfonylbenzimidoyl-2-(3-indolyl)quinolinium Perchlorate (X).</u> A 0.489-g (0.001 mole) sample of IVb was added gradually to a solution of 0.343 g (0.001 mole) of  $(C_6H_5)_3CC10_4$  in 10 ml of acetonitrile, and, after the solid material had dissolved, the solution was refluxed on a water bath for 5 min. It was then cooled to 20-25°C and maintained at that temperature for 30 min, after which it was cooled to 4-5°C and poured into 100 ml of ether. The red precipitate (which darkened to cherry red in the **air**) was reprecipitated from acetonitrile by the addition of ether to give 0.28 g (60%) of a product with mp 185-187°C. Found: C 61.9; H 4.1; N 6.7; S 5.0%.  $C_{30}H_{22}ClN_3O_6S$ . Calculated: C 61.3; H 3.6; N 7.1; S 5.4%.

<u>l</u>-Phenylsulfonylbenzimidoylquinolinium Perchlorate (XI). A 0.489-g (0.001 mole) sample of IVb was added in portions as each portion dissolved to a solution of 0.384 g (0.001 mole) of piperidine oxide perchlorate in 8 ml of acetonitrile, and the mixture was then heated on a water bath at 50°C for 2.5 h. It was then cooled and poured into 100 ml of ether, and the precipitate was reprecipitated twice from solution in acetonitrile by the addition of ether to give 0.25 g (50%) of an orange product with mp 178-180°C. Found: C 56.4; H 3.9; N 5.3; S 6.6%.  $C_{22}H_{17}ClN_2O_6S$ . Calculated: C 55.9; H 3.6; N 5.9; S 6.8%.

Alkaline Hydrolysis of 1-Phenylsulfonylbenzimidoyl-2-(3-indolyl)quinolinium Perchlorate (X). A 5-ml sample of 20% KOH solution was added to 0.1 g (1.5 mmole) of salt X in 5 ml of ethanol, and the mixture was refluxed for 2.5 h. It was then cooled, and the precipitate was removed by filtration to give 0.04 g (80%) of quinolineindole [sic] with mp 188-190°C; the picrate had mp 245-247°C. The filtrate was acidified to pH 2 with concentrated hydrochloric acid, and the precipitate was removed by filtration to give 0.03 g (60%) of N-benzoylbenzene-sulfonamide with mp 144-146°C; no melting-point depression was observed for a mixture with a genuine sample.

Alkaline Hydrolysis of 2-Phenylsulfonylbenzimidoylisoquinolinium Perchlorate (VIII). A 5-ml sample of a 20% solution of KOH was added to a solution of 0.1 g (2 mmole) of salt VIII in 5 ml of ethanol, and the mixture was refluxed for 2.5 h. It was then cooled and extracted with ether, and the ether extracts were combined and evaporated. The residue was treated with 3 ml of an ethanol solution of picric acid to give the isoquinoline picrate with mp 226-227°C; no melting-point depression was observed for a mixture with a genuine sample. The aqueous ethanol alkaline solution was acidified to pH 2 with concentrated HCl, and the **precipitate was** removed by filtration to give 0.02 g (75%) of N-benzoylbenzenesulfonamide with mp 144-146°C; no melting-point depression was observed for a mixture with a genuine sample.

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