

ABOUT REACTIVITY OF ISOMERIC AZAINDOLES

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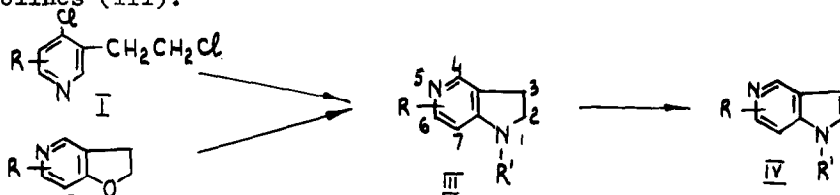
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Isomeric azaindoles are convenient models for an investigation of intramolecular electronic interactions between π -electron deficient and π -electron excessive rings in bicyclic heteroaromatic systems. In order to study the relative reactivity of this type of compound we have developed new general methods for the syntheses of the 4- and 5-azaindoles and investigated their reactions with various electrophilic agents.

5-Azaindoles were synthesized from the 3-(β -chloroethyl)-4-chloropyridines (I) or 2,3-dihydro-5-azabenzofuranes (II) via the corresponding 5-azaindoles (III):



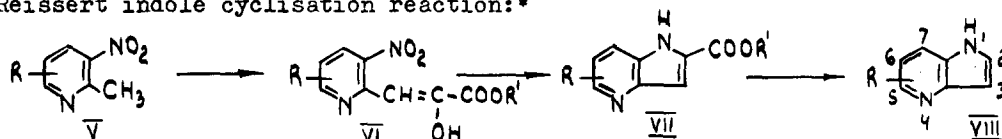
For example, the interaction of I (R=6Cl) (2) with ammonia in ethanol at 200°(4 hours) gave in 71,5% yield III(R=6-Cl, R'=H), m.p.106-107°(ethylacetate), b.p.152-154°(I,5mm), λ_{max} 260m μ (lg ϵ 3,96)*, NMR: two triplets 3,05 and 3,77 ppm (J ~ 8 cps), two singlets of I proton each 6,40 ppm and 7,77 ppm, broad signal NH 5,15-5,50 ppm. The reaction of II (R=6-OH) with 3 moles of benzylamine at 190°(8 hours) led in 72% yield to III (R=6-OH, R'=CH₂Ph), m.p.187-188°(dioxan). Oxoderivative III (R=6-OH, R'=CH₂Ph) was transformed by treat-

* All compounds described in this paper gave complete elementary analyses in good agreement with calculated values and the positions of the substituents were confirmed by NMR-spectra. All UV-spectra were determined in ethanol on the spectrophotometer CQ-4, NMR-spectra were measured on spectrometer JNM-100 in CDCl₃ with TMS as the inner reference compound.

ment with POCl_3 at 150° (5 hours) into the chlorocompound (III, $\text{R}=\text{Cl}$, $\text{R}'=\text{CH}_2\text{Ph}$), m.p. $75-76^\circ$ (ethylacetate). By the following catalytical reduction with Pd both III ($\text{R}=\text{Cl}$, $\text{R}'=\text{H}$) and III ($\text{R}=\text{Cl}$, $\text{R}'=\text{CH}_2\text{Ph}$) were converted in quantitative yields to 5-azaindoline (III, $\text{R}=\text{R}'=\text{H}$), m.p. $102-103^\circ$ (cyclohexane), $\lambda_{\text{max}} 260 \text{ m}\mu$ ($\lg \epsilon 3,96$), NMR: two triplets 2,89 ppm and 3,50 ppm ($J \sim 8 \text{ cps}$), doublet 6,47 ppm ($J \sim 7 \text{ cps}$) and coincided by chemical shifts (7,7 ppm) singlet and doublet ($J \sim 7 \text{ cps}$).

Dehydrogenation of III ($\text{R}=\text{R}'=\text{H}$) with 9% Pd/C under N_2 at $215-225^\circ$ (15 min.) led in 70,5% yield to 5-azaindole (IV, $\text{R}=\text{R}'=\text{H}$), m.p. $109,5-110^\circ$ (water) (3). In the similar way from II and aniline (8 hours at 250°) III ($\text{R}=\text{OH}$, $\text{R}'=\text{Ph}$), m.p. $215-216^\circ$ (ethanol) was obtained in 78,8% yield. The latter was transformed via III ($\text{R}=\text{Cl}$, $\text{R}'=\text{Ph}$), m.p. $99-100^\circ$ (ethanol), into 1-phenyl-5-azaindoline (III, $\text{R}=\text{H}$, $\text{R}'=\text{Ph}$), m.p. $59-60^\circ$ (petr. ether). The dehydrogenation of this compound at $255-265^\circ$ gave in 80,7% yield 1-phenyl-5-azaindole (IV, $\text{R}=\text{H}$, $\text{R}'=\text{Ph}$) m.p. $58-59^\circ$ (petr. ether).

4-azaindoles were synthesized from 2-methyl-3-nitropyridines (V) by using Reissert indole cyclisation reaction:*



For example, ethyl 3-nitropyridyl-2-pyruvate (VI, $\text{R}=\text{H}$, $\text{R}'=\text{Et}$), m.p. $126-127^\circ$, was obtained in 70% yield by condensation of V ($\text{R}=\text{H}$) with diethyl-oxalate in presence of $\text{C}_2\text{H}_5\text{OK}$ in benzene at room temperature for 24 hours. Reduction (with 9% Pd/C) of VI ($\text{R}=\text{H}$, $\text{R}'=\text{Et}$) in ethanol led in quantitative yield to ethyl 4-azaindole-2-carboxylate (VII, $\text{R}=\text{H}$, $\text{R}'=\text{Et}$), m.p. $173-173,5^\circ$. The ester VII ($\text{R}=\text{H}$, $\text{R}'=\text{Et}$) was saponificated by boiling with 1,5 moles of the 1% aqueous sodium hydroxide into 4-azaindole-2-carboxylic acid (VII, $\text{R}=\text{R}'=\text{H}$), m.p. $302-303^\circ$ dec. (94% yield). In the similar way VI ($\text{R}=\text{OEt}$, $\text{R}'=\text{Et}$), m.p. $131-132^\circ$ (ethanol) was synthesized in 58,8% yield starting from 2-methyl-3-nitro-6-ethoxypyridine (V, $\text{R}=\text{OEt}$), m.p. $39-40^\circ$. The latter was

* After this paper had been prepared for publication an article by american chemists on application of the Reissert reaction for the 4-azaindole synthesis appeared in press (4).

transformed in 93% yield into VII (R=5-OEt, R'=Et), m.p. 148-149,5° (ethanol) and then via VII (R=5-OEt, R'=H), m.p. >300° dec. (yield 85%), - to 5-ethoxy-4-azaindole (VIII, R=5-OEt), m.p. 148-150°, λ_{\max} 302 m μ (lg ϵ 4,07).

The nitration, bromination, cyanomethylation and Mannich reaction were used as the electrophilic substitution reactions. These reactions were made in conditions which have given the best yields for the corresponding 7-azaindole-derivatives (6-8). The nitration was carried out using the excess of HNO₃ (d=1,52), 1 hour at 0°. The bromination was realized by addition of 1 mole of Br₂ in dioxan 1 hour at 15°. The cyanomethylation was made by heating with 1 mole HCHO and 1,5 moles KCN in the aqueous ethanolic solution 4 hours at 120° in the presence of 0,35 moles CH₃COOK and Al₂O₃ under the starting pressure 10 atm. (N₂). The cyanomethylated products were converted during the reactions and the following treatments into azaindoly-3-acetic acids, which were isolated and described as their ethyl esters. The Mannich reactions were carried out with 20% excess of paraform and with 3 moles of (CH₃)₂NH.HCl in boiling butanol (15 minutes). The obtained results are given in the table I.

Table I.

| Compounds | The yield in % electrophilic substitution at position 3 | | | | m.p. of the 3-substituted (solvent for the crystallisation) | | |
|--------------|---|-------------|------------------|------------------|---|-----------------------|-----------------------------------|
| | nitration | bromination | Mannich reaction | cyanomethylation | nitro | bromo | dimethylaminomethyl |
| 4-azaindole | 99 | 89 | 99 | 52** | 348° dec. (HCONMe ₂) | 228° (ethanol) | 127-128,5° (benzene) |
| 5-azaindole | 99 | 99 | 53 | 37*** | 296-297° dec. (HCONMe ₂ -H ₂ O) | 184-185° (benzene) | 236-237°**** (benzene-ethanol) |
| 7-azaindole* | 83 | 81 | 99 | - | - | - | - |

* The yields of the 3-substituted 7-azaindoles are taken from (6,7).

** Side by side with ethyl 4-azaindoly-3-acetate, m.p. 142-144° (benzene) in this case bis-(4-azaindoly-3)-methane, m.p. 292-293° (HCONMe₂), was obtained in 45% yield.

*** Side by side with ethyl 5-azaindoly-3-acetate, m.p. 79-80°, in this case the starting 5-azaindole in 25,5% yield and bis-(5-azaindoly-3)-methane, m.p. >320° (HCONMe₂-water), in 22,8% yield were obtained.

**** m.p. is given for the dihydrochloride.

The comparison of the experimental results obtained for 4-, 5- and 7-azaindoles allows to say that all these isomers at the first approximation show the similar reactivity in the electrophilic substitution reactions at position 3 of the pyrrol ring. These data show that into isomeric azaindoles the general type of interactions between the " π -electron deficient"-pyridine- and the " π -electron excessive"-pyrrol-rings take place. This conclusion is also in good agreement with the results of made at our request by D.A.Bochvar and A.A.Bagaturyants (9,10) MO-calculations of the isomeric azaindoles by Hückel and Parizer-Parr-Pople-methods. According to these calculations π -electron-density displacement into the pyrrol parts of the molecules of isomeric azaindoles also undergoes a little change depending on the position of the nitrogen into the sixmember ring.

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