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Abstract

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SYNTHESIS OF PYRIDYLETHYLOXINDOLES

The increased recent interest in the chemistry of pyridylindoles is explained, on the one hand, by the closeness of these compounds to alkaloids and, on the other hand, by their varied pharmacological activity. It may be expected that γ-carbolines of type I and pyridylindoles of type II will find broad application as substitutes for reserpine (^{1,2}).

(I) (II)

It was of interest to obtain similar systems in which pyridine and oxindole rings would be present simultaneously. It is known that the structures of such alkaloids as mitraphylline (^{3}) and rhynchophylline (^{4}) contain an oxindole system as a constituent part, while compounds of the 3-(2-aminoethyl)oxindole type are effective serotonin antagonists (^{5}).

As preliminary tests already carried out at the Minsk Medical Institute under the direction of Prof. K. S. Shadurskii have shown, pyridylethyloxindole III in the form of the iodomethylate possesses a very strong curare-like action at dilutions of the order of 1 : 10 000. This action is rather specific, since the iodomethylate of an oxindole not containing a methyl group in position 3 is almost inactive.

We carried out the synthesis of such compounds according to the following scheme:

(III)

$$\text{2-methyl-5-(2-arylaminoethyl)pyridine} \xrightarrow{ClCH_2COCl} \text{chloroacetyl derivative} \xrightarrow{AlCl_3} \text{oxindole derivative, where } R_1 = CH_2CH_2\text{-(2-methylpyridyl) and } CH_2CH_2\text{-(pyridyl).}$$

By adding the acid chlorides of halo-substituted acids ($ClCH_2COCl$ and $CH_3CHBrCOCl$) to 2-methyl-5-(2-arylaminoethyl)pyridine and 2-phenylaminoethylpyridine, we obtained, in quantitative yield, the hydrochlorides of co-

corresponding haloacylated amines, which were introduced into the Stolle reaction.

The structure of the pyridylethyloxindoles obtained was demonstrated by the presence of an intense absorption band in the region 1705-1715 cm^{-1}, corresponding to vibrations of the carbonyl group. Only in the case of N-(2-(2-methylpyridyl-5)-ethyl)-oxindole was a line found in the region 3370 cm^{-1}, corresponding to the hydroxyl group, which indicates the presence of an enolized form. The structure was also confirmed by reduction to the corresponding pyridylethylindoles described previously. For this purpose, in the oxindoles oxygen was replaced by sulfur with the aid of phosphorus pentasulfide, followed by treatment with skeletal nickel. Other reduction methods (Baeyer, Clemmensen) did not give the desired results.

It should be noted that pyridylethyloxindoles possess a characteristic color reaction, giving an intense raspberry coloration with chromic acid.

Experimental part

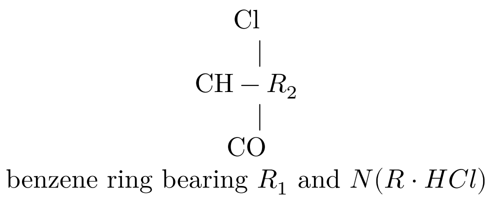
2-Methyl-5-(2-phenylaminoethyl)-pyridine, 2-methyl-5-(2-*p*-toluidinoethyl)-pyridine, and 2-methyl-5-(2-*p*-anisidinoethyl)-pyridine were obtained by pyridylethylation of the corresponding aromatic amines in the presence of metallic sodium (^{1}).

The synthesis of 2-(2-phenylaminoethyl)-pyridine was carried out by the method of Reich and Levine by pyridylethylation in an acidic medium (^{6}).

N-(pyridyl)-oxindoles. 1. To 0.1 mole of arylaminoethylpyridine in 120 ml of anhydrous benzene, with vigorous stirring and cooling with ice water, a solution of 0.1 mole of the acid chloride of an α-halo-substituted acid in 50 ml of benzene was added dropwise. After the addition was complete, the mixture was stirred for another hour and left overnight. The separated oil gradually turned into a white amorphous powder. The filtered hydrochloride was washed with benzene and petroleum ether. The yield ranges from 95% to quantitative. The hydrochlorides obtained are presented in Table 1. Melting points are given after recrystallization from anhydrous alcohol.

Table 1

Derivatives of the type



$$\begin{array}{c}\text{Cl}\\ |\\ \text{CH} - R_2\\ |\\ \text{CO}\\ \text{benzene ring bearing } R_1 \text{ and } N(R \cdot HCl)\end{array}$$

Compound No.	R	R_1	R_2	m.p., °C	Empirical formula	Found, % C	Found, % H	Calculated, % C	Calculated, % H
I	2-methyl-5-pyridyl-CH_2CH_2-	H	H	158	$C_{16}H_{18}ON_2Cl_2$	59.68; 59.78	5.61; 5.97	59.08	5.58
III	Same	OCH_3	H	146.5–147	$C_{17}H_{20}ON_2Cl_2$	58.44; 58.59	5.98; 6.17	58.04	5.68
V	Same	H	CH_3	126.5–127*	$C_{17}H_{20}ON_2BrCl$	53.86; 53.96	5.26; 5.33	53.59	5.25
VII	2-pyridyl-CH_2CH_2-	H	H	157–158	$C_{15}H_{16}ON_2Cl_2$	58.10; 58.20	5.38; 5.60	57.88	5.18

* Recrystallized from acetone.

Table 2

N-pyridyloxindoles of the general formula

general oxindole skeleton with R_1, R_2, and $N-R$

Compound no.	R	R_1	R_2	Reaction temp., °C	Yield, %	M.p., °C	B.p., °C/mm	Gross formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	M.p. of iodomethylates, °C
II[2]	2-methyl-5-pyridylethyl–	H	H	125–135	95	97.5 (from pet. ether), 103.6 (from water)		$C_{16}H_{16}ON_2$	75.91; 76.09	6.73; 6.61	11.05; 11.15	76.16	6.39	11.10	198.5[3]
IV[4]	Same	CH_3	H	130–135	88		215/25	$C_{17}H_{18}ON_2$	76.36; 75.93	6.95; 7.11	10.31; 10.39	76.66	6.81	10.52	167–168

Compound no.	R	R_1	R_2	Reaction temp., °C	Yield, %	M.p., °C	B.p., °C/mm	Gross formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	M.p. of chloromethylates, °C
VI	Same	OH	H	170—180		165—166 (from alcohol)		$C_{16}H_{16}O_2N_2$	71.72	6.97		71.62	6.41		
VIII	Same	H	CH_3	160—170	85	52—54	189—191/1.5	$C_{17}H_{18}ON_2$	77.06; 77.13	6.88; 7.06		76.66	6.81		150—151
X	2-pyridylethyl—	H	H	120—125	88	99.5 (from water)		$C_{15}H_{14}ON_2$	75.45; 75.38	5.78; 5.87		75.60	5.92		256—257

[1] Recrystallized from anhydrous alcohol. [2] λmax 250 mμ; lg ϵ 4.12 (in methanol). [3] Found, %: C 52.16, 52.20; H 4.97, 5.05; N 7.36, 7.20. $C_{17}H_{19}ON_2J_2$. Calculated, %: C 51.79; H 4.85; N 7.16. [4] 2-methyl-5-(N-chloroacetyl-2-*p*-tolylaminoethyl)pyridine hydrochloride with m.p. 148—150° was introduced into the reaction.

2. A thoroughly mixed mixture of 0.1 mole of the hydrochloride of an N-halogenated 2-arylaminoethylpyridine and 0.4 mole of anhydrous aluminum chloride was placed in a two-necked flask equipped with a reflux condenser with a calcium chloride tube and with a thermometer immersed in the mixture, and was heated on a silicone bath. At 40-45° the reaction mass begins to foam and hydrogen chloride is evolved; at this point the temperature rapidly rises to 95-100°. It was gradually brought to the required temperature (see Table 2) and maintained there until the evolution of hydrogen chloride had completely ceased (4-5 h). The mixture was poured onto ice with hydrochloric acid, the solution was alkalinized with sodium acetate, and extracted with chloroform.

N-(2-(2-Methylpyridyl-5)ethyl)-3-methylindole (XI). In a three-necked flask equipped with a stirrer, reflux condenser, and thermometer, a solution of 2.66 g of N-(2-(2-methylpyridyl-5)ethyl)-3-methyloxindole (VIII) and 6.8 g of phosphorus pentasulfide (P_4S_{10}) in 65 ml of pyridine was heated for three hours at 110-114°. To the cooled mixture were added 160 ml of water, and it was extracted with benzene. The green oil obtained after removal of the solvent was heated on a water bath for 1 h with 9 g of Raney nickel in 98 ml of alcohol. The filtered solution was evaporated to 3 ml, cooled to 0°, and 1.4 g of N-(2-(2-methylpyridyl-5)ethyl)-3-methylindole (XI) was isolated (58%), mp 70–71° (from petroleum ether); it gives no depression of the mixed melting point with indole obtained by Fischer' s method from α-N-(2-(2-methylpyridyl-5)ethyl)phenylhydrazine and propionaldehyde (^{2}).

$$\lambda_{\max} 235,\ 270\ \text{m}\mu;\ \lg\varepsilon\ 4.45,\ 3.88\ \text{(in methanol)}.$$

N-(2-(2-Methylpyridyl-5)ethyl)indole (XII). A mixture of 5 g of N-(2-(2-methylpyridyl-5)ethyl)oxindole (II) and 13.6 g of P_4S_{10} in 135 ml of pyridine was heated, with stirring, for 3 h at 108-110°. The cooled mixture was diluted with 240 ml of water and extracted with ether. The solvent was distilled off, and the remaining yellow crystalline precipitate was boiled for 1 h in 175 ml of alcohol with 18 g of Raney nickel. After the usual work-up, 0.5 g of N-(2-(2-methylpyridyl-5)ethyl)indole (XII) was isolated, mp 65.5–66° (from *n*-hexane).

Found, %:	C 81.32, 81.59; H 7.06, 6.97
$C_{16}H_{16}N_2$. Calculated, %:	C 81.32; H 6.82

$$\lambda_{\max} 222,\ 270\ \text{m}\mu;\ \lg\varepsilon\ 4.44,\ 3.97\ \text{(in methanol)}.$$

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named after M. V. Lomonosov

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Note: Figure translations are in progress. See original paper for figures.

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