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INDOLE DERIVATIVES.

133.* SYNTHESIS OF 5-(2-PYRIDYL)INDOLE

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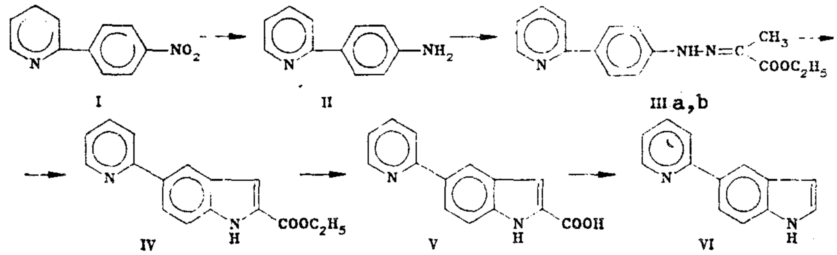
Starting from 2-(4-nitrophenyl)pyridine, the product of the Gomberg arylation of pyridine, 5-(2-pyridyl)indole was prepared by the Japp–Klingman reaction. ^{13}C NMR indicated an inductively transmitted interaction between the pyridine and indole rings.

Continuing our investigations in the field of multinuclear heterocyclic systems containing an indole ring, we have synthesized 5-(2-pyridyl)indole, an open analog of the pyrrolo[f-, g-, and h-]quinolines, which we reported earlier [2-5]. The presence in the molecule of 5-(2-pyridyl)indole of both the π-excessive pyrrole and the π-deficient pyridine rings makes it interesting both from the point of view of reactivity, and also because of the possibility of creating new physiologically active substances.

5-(2-Pyridyl)indole was prepared from 2-(p-nitrophenyl)pyridine by the following scheme:



The starting 2-(p-nitrophenyl)pyridine (I) was synthesized by the arylation of pyridine with p-nitrophenyldiazonium chloride using the conditions for the Gomberg–Bachmann–Hey reaction [6-8]. Reduction of 2-(p-nitrophenyl)pyridine with iron filings in ammonium chloride solution gave 2-(p-aminophenyl)pyridine (II) in good yield. The reaction of II with methylacetoacetic ester, (Japp–Klingmann reaction), gave the p-(2-pyridyl)phenylhydrazone of ethyl pyruvate (III). The hydrazone was separated into the syn-IIIa and anti-IIIb forms by column chromatography on silica gel and the quantitative ratio of the two isomers in the mix-

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ture was determined to be (1:9). The IR spectra of the minor syn-isomer IIIa showed no absorption band in the NH region, due to intramolecular hydrogen bonding; for the anti-isomer IIIa the NH absorbs at 3370 cm^{-1}. Unexpectedly, the stretching vibrations of the carbonyl group (mineral oil) for both isomers occur in the same region (at 1720 for IIIb and 1725 cm^{-1} for IIIa). All the IR absorption bands undergo considerable displacement on dilution (chloroform and methylene chloride) — apparently, because of intermolecular interaction involving the unshared electron pair on the pyridine ring nitrogen atom, in contrast to the energy of the intramolecular hydrogen bond.

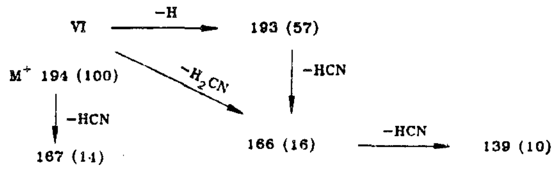
In the UV spectra, the long-wave absorption maximum of the syn-form of IIIa is shifted by 28 nm toward the long-wave region compared to the maximum of the isomer IIIb. The configuration of the syn-anti-isomers was shown more exactly by the ^1H NMR spectral data (see experimental part), where the down-field shift of the signal from the NH group proton of the syn-isomer (12.5 ppm) is larger than that of the corresponding proton of the anti-form (9.41 ppm).

Studying the indole formation of the individual isomeric forms of p-(2-pyridyl)phenylhydrazone, showed that the configuration of the hydrazone has a significant effect on the result of the reaction. The anti-isomer IIIb is cyclized by reaction with the ester of polyphosphoric acid at 130-140°C. The syn-isomer IIIa under these conditions does not cyclize. The formation of the corresponding indole IV was recorded chromatographically by heating the isomer IIIa with polyphosphoric acid at 180-190°C.

Attempts were made to cyclize the hydrazone IIIb at different temperatures using the media commonly used in the E. Fischer reaction: mineral acids, a mixture of sulfuric and acetic acids, zinc chloride, polyphosphoric acid, ethyl ester of polyphosphoric acid, etc. The best results were achieved with the ethyl ester of polyphosphoric acid as cyclization catalyst. Hydrolysis of the cyclic ester IV followed by thermal decarboxylation of the acid V gave 5-(2-pyridyl)indole (VI).

The presence of a weak interaction between the pyridine ring and the indole molecule was confirmed by the absorption spectrum, in which there was a bathochromic shift of the long-wave band of 17 nm compared with the long-wave bands of the unsubstituted indole and 5-phenylindole [9]. In this respect 5-(2-pyridyl)indole behaves like 5-(4-pyridyl)indole [10], which was obtained by the pyridylation of a 1-alkyl-2,3-dihydroindole and subsequent dehydrogenation.

The mass spectrum of the indole VI contained a strong peak from the molecular ion M^+ 194, corresponding to the molecular weight. The decay of 5-(2-pyridyl)indole occurs in the same way as the decay of indole and of pyridine [11], the decay processes were confirmed by the metastable transitions:*



As can be seen from Table 1, in the ^1H NMR spectrum of 5-(2-pyridyl)indole (V) the chemical shifts and the coupling constants, are characteristic for protons both of the indole and the pyridine part of the molecule. Information on the nature of the reciprocal effect of the pyridine and indole rings was obtained by studying the ^{13}C NMR spectra of 5-phenyl- (VII) and 5-(2-pyridyl)indoles (VI). The signals were assigned based on selective and resonance-decoupled spectra.† It was surmised that the transfer of the acceptor effect of the pyridine ring to the indole nucleus is accomplished through both mesomeric and inductive effects. An analysis of the spectra shows that as in the diphenyl molecule both aromatic structures in compounds VI and VII are weakly linked to each other. This is confirmed first of all by the negligible change in the chemical shift of the carbon atoms $C_{(9)}$ and $C_{(5)}$,

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*Here and subsequently, m/z values are given for ion peaks; the relative intensities of the ion peaks in % of the maximum are given in parentheses.

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TABLE 1. Chemical Shifts (δ, ppm) and Spin–Spin Interaction Constants for the 5-(2-Pyridyl)indoles

Compound	R	1-H	2-H	3-H	4-H	6-H	7-H	3-H	4-H	5-H	6-H	Coupling constant, Hz
IV	$COOC_2H_5$	11,06	4,39 (CH_2) 1,39 (CH_3)	7,30	8,47	8,14	7,63	7,95	7,83	7,26	8,66	$J_{13}=1,83$; $J_{14}=0,73$; $J_{46}=1,83$; $J_{37}=0,73$; $J_{67}=8,77$; $J_{34}=8,04$; $J_{35}=1,1$; $J_{45}=7,31$; $J_{56}=4,75$; $J_{46}=1,83$
V*	COOH	11,03	—	7,29	8,47	8,13	7,63	7,96	7,83	7,26	8,65	$J_{46}=1,83$; $J_{67}=8,77$; $J_{34}=8,04$; $J_{45}=8,04$; $J_{56}=4,4$; $J_{46}=1,83$
VI	H	8,3	7,25	6,64	8,28	7,88	7,48	7,78	7,70	7,18	8,69	$J_{12}=2,14$; $J_{13}=2,44$; $J_{23}=3,3$; $J_{17}=0,91$; $J_{46}=1,8$; $J_{56}=4,88$; $J_{67}=8,54$; $J_{34}=8,04$

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*Coupling constant in NH is not observed from fast NH–ND exchange.

TABLE 2. Chemical Shifts (δ, ppm) in ^{13}C NMR

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
VII	124,78	103,07	119,27	133,35	121,92	111,19	128,44	135,35	127,40	142,58	127,40	128,64	126,31	128,64
VI	125,10	103,27	119,60	131,47	121,33	111,37	128,35	136,53	—	158,97	120,51	136,62	121,11	149,31
Indole	125,2	102,8	121,3	120,3	122,3	118,8	128,8	136,1	—	—	—	—	—	—
Pyridine	—	—	—	—	—	—	—	—	—	150,6	124,5	136,4	124,5	150,6

in the para-positions of the substituted pyridine and indole rings, perhaps the most informative indication of coupling. Moreover, the effect of the substituent at the $C_{(9)}$ (the numbering of the indole ring includes the quaternary carbon atoms) is negligible: $\Delta\delta C_{(9)}$ = 0.4, −0.7, and −1.2 ppm for VI, VII, and diphenyl, respectively. For $C_{(4)}$ and $C_{(6)}$ in the ortho-position, the effect of the substituent at position 5 of the indole ring is similar to that of diphenyl (−1.1 ppm) [12]; −2.0 and 0.4 (average −1.2 ppm) for 5-diphenylindole and −1.7 and −1.0 (average −1.3 ppm) for 5-pyridylindole. The chemical shifts of the pyrrole carbon atoms in compounds VI and VII are virtually unchanged (see Table 2).

The donor properties of the indole molecule in relation to the benzene ring (compound VII) are approximately the same (with accuracy of 0.5 ppm) as for the phenyl substituent in the diphenyl molecule, but more strongly marked in relation to the π-deficient system of pyridine (compound VI). However, this effect does not exceed 4 ppm and most probably causes an inductive type transfer: the effect of the change in the chemical shift for $C_{(5)}$ (−3.4 ppm) is analogous to that for the para-carbon atom in the toluene molecule (−2.9 ppm) [12].

EXPERIMENTAL

IR spectra of the compounds in mineral oil or chloroform were taken on a UR-20, electronic spectra on a Specord UV-vis and a Perkin-Elmer (using ethanol as a solvent). NMR spectra were recorded on a WP-200 SY Bruker, using TMS as an internal standard. Mass spectra were obtained on an MX-1303 with direct introduction of the sample into the ion source, cathode emission current 1.5 mA, ionizing voltage 50 eV, accelerating voltage 2 kV.

2-(p-Nitrophenyl)pyridine (I). To a stirred suspension of 28 g (0.22 mole) of p-nitroaniline in 70 ml of water and 70 ml of concentrated HCl at 5°C was added a solution of 14 g (0.22 mole) of sodium nitrite in 40 ml of water. The resulting suspension of p-nitrophenyldiazonium chloride was stirred at 40-60°C and added to 170 ml of pyridine. The reaction mixture was stirred for a further 1 h at 65-70°C, poured into 1.5 liter of cold water and allowed to stand overnight. The precipitated material was filtered off, washed with water, and dried to give a mixture of p-nitrophenylpyridines, which by column chromatography on silica gel (40/100 µm; elution with benzene) gave 10.3 g (25%) of 2-(p-nitrophenyl)pyridine (I), mp 129-130°C. Literature value [6], mp 130.5°C, IR spectra (mineral oil): 1535, 1350 cm^{-1} (NO_2).

2-(p-Aminophenyl)pyridine (II). To 12.8 g of iron filings was added 280 ml of 0.78 N ammonium chloride solution, the mixture heated to 95°C and 8 g (0.04 mole) of 2-(p-nitrophenyl)pyridine added all at once. The mixture was vigorously stirred for 30 min at 90-95°C, the hot solution filtered, the filtrate set aside, and the precipitated material extracted with hot ethanol. The ethanol was evaporated and the residue recrystallized from ethanol to give 2 g of the amine II. The filtrate, on repeated extraction with ether, gave an additional 2.77 g of 2-(p-aminophenyl)pyridine (II). A total yield of 70% was obtained, mp 95°C. Literature value [6], mp 95-97°C. IR spectra (mineral oil): 3440, 3380, and 3220 cm^{-1} (NH_2).

4-(2-Pyridyl)phenylhydrazone Ethyl Pyruvate (IIIa and b). To a solution of 10 g (0.059 mole) of 2-(p-aminophenyl)pyridine (II) in 20 ml of concentrated HCl and 46 ml of water at 0-5°C was added dropwise over the course of 20 min, 4 g (0.059 mole) of $NaNO_2$ in 16 ml of water at 5-10°C, and the mixture stirred for 30 min at 10°C. The solution was brought to pH 5 by the addition of sodium acetate and quickly poured into a cooled (−10°C) mixture of 58 ml of ethanol, 58 ml of water, and 3.7 g of KOH, to which had previously been added 58 g of crushed ice and 8.3 ml (0.06 mole) of methyl acetoacetic ester. The mixture was stirred for 2 h at −5°C and allowed to stand overnight in the refrigerator. The following day, the reaction product was extracted with benzene, washed with water, dried, and the solvent evaporated. The 16.7 g of oil obtained was transferred to a silica gel column and eluted with a 2:1 mixture of ether and petroleum ether to give 5 g (31%) of the anti-isomer IIIb, mp 130-131°C. Found, %: C 68.2; H 6.3; N 15.1. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.8; H 6.0; N 14.8. ^1H NMR spectrum (acetone-D_6): 9.41 (1H, s, NH); 2.13 (3H, s, CH_3); 4.25 (2H, q, CH_2CH_3, $J_{CH_2CH_3}$ = 6.95 Hz); 1.33 ppm (3H, t, CH_2CH_3). IR spectrum (in CH_2Cl_2): 1720 (CO), 3370 cm^{-1} (NH). UV spectrum, λ_{max} (log ε); 209 (4.21), 233 (4.05), 351 nm (4.61). The syn-isomer IIIa: 0.6 g (4%), mp 105-106°C. ^1H NMR spectrum (acetone-D_6): 12.5 (1H, s, NH), 2.55 (3H, s, CH_3); 4.32 (2H, q, CH_2CH_3, $J_{CH_2CH_3}$ = 6.85 Hz); 1.37 ppm (3H, t, CH_2CH_3). IR spectrum (in CH_2Cl_2): 1725 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 209 (4.11), 246 (3.96), 270 inflexion (3.86), 278-292 shoulder (3.84), 379 nm (4.37).

Ethyl Ester of 5-(2-pyridyl)indole-2-carboxylic Acid (IV). To 5 g (0.018 mole) of 4-(2-pyridyl)phenylhydrazone ethyl pyruvate was added 70 ml of the ethyl ester of polyphosphoric acid, the mixture stirred and heated to 130-140°C and maintained at this temperature for 1 h, then cooled, and dissolved in water. The solution was made alkaline with ammonia and extracted with ethyl acetate. Removal of the solvent gave 1.18 g (25%) of the ester IV mp 178-179°C (from ethyl acetate). IR spectrum (mineral oil): 1720 (CO), 3410 cm^{-1} (NH). Found, %: C 72.2; H 5.6; N 10.5. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.2; H 5.3; N 10.5.

5-(2-Pyridyl)indole-2-carboxylic Acid (V). A mixture of 2 g (8 mmoles) of the ester IV and 30 ml of alcoholic KOH was refluxed for 5 h. The reaction mixture was cooled, and after the addition of 30 ml of water, acidified with acetic acid in pH 5. The precipitated material was filtered off, washed first with water and then with ether, and dried to give 1.59 g (95%) of 5-(2-pyridyl)indole-2-carboxylic acid, mp 278°C (from ethanol). IR spectrum (mineral oil): 1700 (CO), 3330 cm^{-1}. Found, %: C 70.3; H 4.4; N 11.4. $C_{14}H_{10}N_2O_2$. Calculated, %: C 70.6; H 4.2; N 11.8.

5-(2-Pyridyl)indole (VI). The acid V (1 g, 4.2 mmoles) was quickly heated to 290-295°C in argon and maintained at this temperature for 25-30 min. When cool, the dark brown melt was dissolved in acetone, transferred to a silica gel column and eluted with benzene. After removal of the solvent, 0.24 g (30%) of VI was obtained, mp 120-124°C. IR spectrum (mineral oil): 3295 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 206 (3.98), 254 (4.49), 302 nm (4.14). Found, %: C 80.4; H 5.4; N 14.6. $C_{13}H_{10}N_2$. Calculated, %: C 80.4; H 5.2; N 14.4.

5-Phenylindole [9], mp 69-70°C (from hexane). IR spectrum ($CHCl_3$): 3490 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 207 (4.39), 252 (4.56), 283 nm (3.97) shoulder.

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