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# XXXIII.* PYRIDYLETHYLATION OF THE NH GROUP OF INDOLE COMPOUNDS

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2-Methyl-5-vinylpyridine, which is usually of low reactivity, pyridylethylates the NH groups of pyrrole, indole and its homologs, carbazole, $\gamma$- and $\alpha$-carbolines, etc. if the process is carried out in dimethyl sulfoxide containing alkaline agents.

2-Vinylpyridine or 4-vinylpyridine in alkaline media readily pyridylethylates the imino group of indole compounds (for example, see [2,3]). However, if the vinyl group is bonded to the 3 position of the pyridine ring, its polarization is considerably lower, and direct pyridylethylation of indoles is not possible [4]. In the meantime, models of precisely this type are of interest, since structures that have strong antihistamine action are found among the products of $\beta$-(3-pyridyl)ethylation [5]. These compounds must be synthesized by a roundabout path [6, 7].

The substantial effect of solvents on the pyridylethylation of the amino group has already been noted [8]. In the present study, we were able to directly pyridylethylate pyrrole, a number of indole compounds, carbazole, and carboline using the capacity of highly polar aprotic solvents [of the dimethyl sulfoxide (DMSO) type] to activate the anion formed by the action of alkaline agents on the NH group to such an extent that even the relatively weak polarization of the bond in 3-vinylpyridine proves to be sufficient for successful reaction. The activation by DMSO consists in the fact that, in contrast to proton solvents, the anions formed in this case are less solvated because of the absence of hydrogen bonds and are therefore more reactive [9].

The reaction proceeds readily with excess 2-methyl-5-vinylpyridine but requires heating to 100-120° (resinification begins at higher temperatures). We used primarily sodium metal or sodium ethoxide as the alkaline agent. In individual cases, for example for 3-methyl-6-methoxy-1,2,3,4-tetrahydro-$\gamma$-carboline, it is necessary to use a stronger alkaline agent of the sodium hydride type. The reaction does not proceed without DMSO even on heating for many hours. According to the IR spectra, the compounds obtained do not have an NH group (the absorption at 3400 $cm^{-1}$ is absent). Their structure was confirmed by elementary analysis and comparison with samples of known structure. The PMR spectrum (in $CHCl_3$) of 9-[2-(2'-methyl-5'-pyridyl)ethyl]carbazole, which was obtained by this route, contains a singlet of a $CH_3$ group at 2.5 ppm and triplets of two methylene groups at 3.05 and 4.37 ppm (J 8 Hz); this is evidence that the addition proceeds precisely at the $\beta$ carbon atom of the vinyl group of 2-methyl-5-vinylpyridine. It follows from the data in Table 1 that the yields in most cases are completely satisfactory. A preparation with antihistamine action – dimeboline (compound 7 in Table 1) – can be obtained by this method from the accessible 3,6-dimethyl-1,2,3,4-tetrahydro-$\gamma$-carboline [5].

It is convenient to follow the reaction by means of thin-layer chromatography (TLC) on activity II aluminum oxide using various solvent systems (see Table 1). The spots were usually developed with iodine, but development can be carried out by means of irradiation with UV light (azure fluorescence) in the case of pyridylethylated $\alpha$-carboline and 6-methoxy-3-methyl-1,2,3,4-tetrahydro-$\gamma$-carboline.

*See [1] for communication XXXII.

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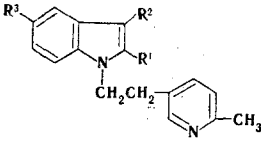
TABLE 1. Pyridylethylation Conditions and Physical Constants of the Compounds Obtained

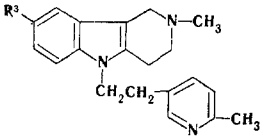
| No. | Reaction products | Reaction temp., °C | Reaction time, h | Method of isolation | mp, °C | $R_f$[f] (system) | Empirical formula | Found, % | | Calc., % | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | C | H | |
| 1 | 1-[2-(2'-Methyl-5'-pyridyl)ethyl]indole | 95—97 | 5 | A | 66—67 | 0,6 (4)<br>0,69 (5) | $C_{20}H_{18}N_2$ | 81,4 | 6,8 | 81,3 | 6,8 | 38 |
| 2 | 1-[2-(2'-Methyl-5'-pyridyl)ethyl[-2,3-dimethylindole | 95—97 | 5 | A | 70—71[a] | 0,24 (1) | | | | | | 50 |
| 3 | 1-[2-(2'-Methyl-5'-pyridyl)ethyl]carbazole | 110—115<br>120—130 | 9<br>1 | B | 160—161 | 0,52 (1)<br>0,77 (5) | $C_{20}H_{16}N_2$ | 84,0 | 6,7 | 83,8 | 6,3 | 59 |
| 4 | 1-[2-(2'-Methyl-5'-pyridyl)ethyl]pyrrole | 95—97 | 5[b] | A | bp 145—148 (2 mm) | 0,54 (2) | $C_{12}H_{14}N_2$ | 76,9 | 7,8 | 77,3 | 7,6 | 46 |
| 5 | 9-[2-(2'-Methyl-5'-pyridyl)ethyl]-2,3-dimethyl-α-carboline | 115 | 6 | A | 98—100 | 0,7 (6) | $C_{21}H_{21}N_3$ | 79,6 | 6,5 | 79,9 | 6,7 | 54 |
| 6 | 9-[2-(2'-Methyl-5'-pyridyl)ethyl]-3-methyl-1,2,3,4-tetrahydro-γ-carboline | 90—95 | 9 | C | 91—92[c] | 0,84 (3)<br>0,65 (5) | | | | | | 53,5 |
| 7 | 9-[2-(2'-Methyl-5'-pyridyl)ethyl]-3,6-dimethyl-1,2,3,4-tetrahydro-γ-carboline | 90—95 | 5 | A | 121—122[d] from absolute alcohol—absolute ether | 0,49 (3)<br>0,59 (5) | | | | | | 46 |
| | | 110—115<br>120—130 | 9<br>1 | | | | | | | | | 55 |
| 8 | 9-[2-(2'-Methyl-5'-pyridyl)ethyl]-6-bromo-3-methyl-1,2,3,4-tetrahydro-γ-carboline | 90—95 | 10 | e | 112—114 | 0,65 (3)<br>0,59 (5) | $C_{20}H_{22}N_3Br$ | 62,5 | 5,5 | 62,5 | 5,7 | 19 |
| 9 | 9-[2-(2'-Methyl-5'-pyridyl)ethyl]-6-methoxy-3-methyl-1,2,3,4-tetrahydro-γ-carboline | 90—95 | 15 | C | 103—105 | 0,81 (3)<br>0,65 (5) | $C_{21}H_{25}N_3O$ | 75,3 | 7,3 | 75,2 | 7,1 | 10 |

[a]According to [4], mp 70.5° (from petroleum ether). [b]The reaction was carried out in a stream of nitrogen. [c]According to [7], mp 92-93° (from heptane). [d]According to [7], mp 121-122° (from heptane). The yield increases to 55% when the reaction is carried out with sodium ethoxide. [e]Isolated from the mother liquor after crystallization from benzene–petroleum ether (the starting material precipitates initially). [f]Chromatography in a thin layer of activity II aluminum oxide was carried out with 13 by 18 cm plates and a layer thickness of 1 mm in the following systems: benzene (1); 20:1 benzene–ethyl acetate (2); chloroform saturated with ammonia (3); 9:1 benzene–methanol (4); 8:1 carbon tetrachloride–absolute ethanol (5); 1:1 benzene–ethyl acetate (6).

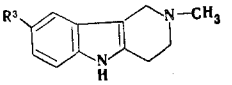
TABLE 2. Qualitative Reactions for the Compounds Obtained



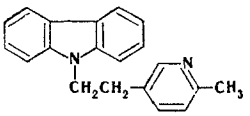
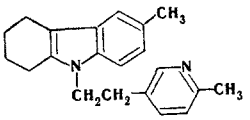
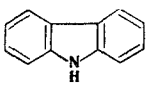
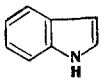
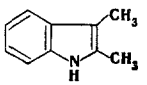
I



II



III

| Compound | R¹ | R² | R³ | Reagents | | | |
|---|---|---|---|---|---|---|---|
| | | | | Procházka | Ehrlich | Fischer | 2,6-Dichloroquinone-4-chloroimide |
| Ia | H | H | H | Rose | Crimson | Cherry-red | Cherry-red |
| Ib | $CH_3$ | $CH_3$ | H | — | — | — | Light-violet |
| Ic | $CH_3$ | $CH_3$ | $OCH_3$ | — | Light-azure | Gray | Blue |
| Id | $CH_3$ | $CH_3$ | $CH_3$ | — | — | — | Violet |
| Ie | $CH_3$ | $C_6H_5$ | H | — | — | Light-yellow | — |
| If | H | $CH_3$ | H | Yellow | Violet | Rose | Dark-red |
| Ig | $CH_3$ | H | H | Yellow | Crimson | Dark-yellow | Cherry-red |
| Ih | $CH_3$ | $CH_2CN$ | H | — | — | — | Dark-red |
| Ii | $CH_3$ | $C_3H_7$ | H | — | — | Rose | Dark-gray |
| Ij | H | $C_2H_5$ | H | Yellow | Azure | — | — |
| IIa | | | $OCH_3$ | | | Rose | Light-brown |
| IIb | | | H | | | — | Light-brown |
| IIc | | | Br | | | — | Light-brown |
| IId | | | $CH_3$ | | | Light-yellow | — |
|  | | | | — | — | — | Cherry-red |
|  | | | | Rose | — | — | Violet |
| IIIa | | | H | — | — | Light-brown | — |
| IIIb | | | $CH_3$ | — | — | Light-brown | — |
| IIIc | | | Br | — | — | Light-brown | — |
| IIId | | | $OCH_3$ | — | — | Dark-brown | — |
|  | | | | — | — | Greenish | Rose |
|  | | | | Bright-rose | Crimson | Cherry-red | Cherry-red |
|  | | | | — | Light-azure | Light-green | — |

All of the pyridylethylated compounds give the characteristic (for pyridines) orange-red color with the Dragendorff reagent, which the starting indoles do not give. However, α-carboline and 1,2,3,4-tetrahydro-γ-carbolines, which have a pyridine or piperidine ring, are not colored by the action of this reagent. The Procházka reagent gives a bright-rose color with compounds that have unsubstituted 2 and 3 positions of the pyrrole ring. If one of these positions is substituted, the color given is yellow; it is practically absent for 2,3-disubstituted compounds. The introduction of a pyridylethyl group into the nitrogen atom does not affect the character of the coloration and alters the sensitivity of the reagent only slightly. Similarly, the Ehrlich reagent gives a bright color from crimson to violet or even azure with unsubstituted indoles or indoles substituted only in the 2 and 3 positions. The Fischer reagent and 2,6-dichloroquinone 4-chloroimide proved to be just as unspecific with respect to the introduction of a pyridylethyl group, although it was

difficult to establish a correlation between the structure and color for them. The data in Table 2 may be useful in the search for methods for the qualitative detection of these sorts of structures.

## EXPERIMENTAL

Pyridylethylation (General Method). A 0.02-mole sample of finely ground sodium metal was added in small portions to a mixture of 0.02 mole of a compound with a pyrrole ring, 0.22 mole of 2-methyl-5-vinylpyridine, 20 ml of DMSO, and a small amount of hydroquinone, and the mixture was heated at 90-120° with constant stirring for 5-10 h. It was then cooled, and 8 ml of alcohol was added. The mixture was then worked up via one of the methods indicated below. The reaction conditions yields, physical constants, and analytical results are presented in Table 1.

Method A. The DMSO and vinyl pyridine were removed from the reaction mixture by vacuum distillation (1 mm), and the residue was recrystallized from petroleum ether (70-100°) or heptane. Preparative separation on activity II aluminum oxide in a benzene–methanol (9:1) system (elution with ethyl acetate) is required in the case of indole.

Method B. The residue resulting from the removal of DMSO and pyridine by vacuum distillation was extracted with ether or chloroform, the extract was evaporated, and the residue was recrystallized twice from hexane and petroleum ether.

Method C. At the end of the reaction, the mixture was poured into water, and the aqueous mixture was extracted with ether. The extract was dried with calcined magnesium sulfate and vacuum evaporated. The excess 2-methyl-5-vinylpyridine was removed from the residue by distillation, and the residue was crystallized from heptane.

3-Methyl-6-methoxy-1,2,3,4-tetrahydro-$\gamma$-carboline. A solution of 24.6 g (0.2 mole) of p-anisidine in 380 ml of concentrated HCl was diazotized by adding a solution of 13.8 g (0.2 mole) of $NaNO_2$ at 0-3°. A solution of 120 g (0.53 mole) of $SnCl_2 \cdot 2H_2O$ in 100 ml of water (0-8°) was then added to the cooled (0-8°) solution of the diazonium salt, and the mixture was allowed to stand at room temperature for 4 h. The precipitate was removed by filtration, washed with a saturated salt solution, and shaken with 30% aqueous sodium hydroxide (without cooling). The alkaline solution was extracted with ether, and the extract was dried with magnesium sulfate and vacuum evaporated. A 16.5-g (0.146 mole) sample of 1-methyl-$\gamma$-piperidone was added to the residue (21 g), and the mixture was refluxed with benzene with azeotropic removal of water. The benzene was vacuum evaporated, and 300 ml of absolute alcohol saturated with HCl was added to the residue. The mixture was allowed to stand overnight. The alcohol was vacuum evaporated, and the residue was dissolved in water. The aqueous solution was made alkaline with potassium carbonate, and the alkaline solution was extracted with ether. The extract was dried with calcined magnesium sulfate and vacuum evaporated. The residue was recrystallized from benzene to give 19.25 g (54%) of 3-methyl-6-methoxy-1,2,3,4-tetrahydro-$\gamma$-carboline with mp 170-171°. Found,%: C 72.5; H 7.6. $C_{13}H_{16}N_2O$. Calculated,%: C 72.2; H 7.5.

9-[2-(2'-Methyl-5'-pyridyl)ethyl]-6-methoxy-3-methyl-1,2,3,4-tetrahydro-$\gamma$-carboline. A solution of 2 g (0.01 mole) of 6-methoxy-3-methyl-1,2,3,4-tetrahydro-$\gamma$-carboline in 15 ml of DMSO was added by drops to a suspension of 500 mg (0.02 mole) of sodium hydride in 20 ml of DMSO, after which 12 ml of 2-methyl-5-vinylpyridine was added and the mixture was heated at 90-95° with constant stirring for 15 h. It was then cooled, and the excess sodium hydride was decomposed by the addition of 5-10 ml of alcohol. The mixture was poured into water, and the aqueous solution was extracted thoroughly with ether. The extract was dried with calcined magnesium sulfate and evaporated. The unchanged vinylpyridine was removed by vacuum distillation, and the residue was recrystallized from petroleum ether (bp 30-70°) to give 350 mg (10%) of 9-[2-(2'-methyl-5'-pyridyl)ethyl]-6-methoxy-3-methyl-1,2,3,4-tetrahydro-$\gamma$-carboline with mp 103-105°. Found,%: C 75.3; H 7.3. $C_{21}H_{25}N_3O$. Calculated,%: C 75.2; H 7.1.

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