É. S. Krichevskii and V. G. Granik

We have developed two synthesis routes for 4-amino derivatives of 6-nitro-γ-carbolines: 1) consecutive conversion of 1,2-dimethyl-3-formyl-5-nitroindole to the 3-cyano derivative, condensation of the latter with DMF diethyl acetal, and cyclization of the enamine formed in this case with ammonia and benzylamine; 2) N-oxidation of 9-substituted 6-nitro-γ-carbolines, transformation of N-oxides to the corresponding γ-carbolin-4-ones, from which the target compounds are obtained through the 4-chloro derivatives.

Previously [2] we established that derivatives of 2-methyl-3-formyl-5-nitroindole are easily condensed with DMF diethyl acetals and dimethylacetamide at the 2-CH₃ group with formation of the corresponding enamines. The latter, depending on the reaction conditions and the selected reagents, are converted to substituted γ-carbolines or carbazoles. In this study, we attempted to synthesize the 4-amino derivatives of γ-carboline based on the derivatives of indole and γ-carboline we obtained in [2].

In the first stage of the investigation, as the starting compound we selected 1,2-dimethyl-3-formyl-5-nitroindole (I), which upon reaction with NH₂OH·HCl in pyridine is converted to the oxime II. Upon heating in DMF, the oxime II is easily condensed with DMF diethyl acetal (III), simultaneously undergoing a second-order Beckmann rearrangement. In this case, 1-methyl-2-(β-dimethylamino)vinyl-3-cyano-5-nitroindole (IV) in high yield. We found that an alternative route for obtaining the enamine IV is rather successful. In the first stage, the aldehyde I upon heating with NH₂OH·HCl in DMF is converted to 1,2-dimethyl-3-cyano-5-nitroindole (V), which upon reaction with the acetal III forms the enamine IV in good yield. Cyclization of the latter is done by two routes: 1) upon heating in an autoclave with ammonia; 2) upon boiling in a DMF solution with benzylamine. In the first case, only formation of 4-amino-6-nitro-9-methyl-γ-carboline (VIa) is possible, while in the second case the structure of

*For Communication 72, see [1].


0009-3122/92/2804-0420$12.50 © 1992 Plenum Publishing Corporation
the final compound required special consideration. Under these conditions, apparently in the first stage of the reaction transamination of the enamine IV occurs, and then cyclization, leading to formation of the imino derivative VII, which is isomerized to 4-benzylamino-6-nitro-9-methyl-γ-carboline (VIb).

In the mass spectrum* of compound VIb, in addition to the molecular ion peak M⁺ 332, we observe intense peaks 227 [M⁺-Ph-CH₂NH] and 106 [Ph-CH₂NH], which is evidence in favor of structure VIb. The Dimroth rearrangement occurring during cyclization was proven conclusively by data comparing the physical and spectral characteristics of compound VIb and the substance synthesized by a method (see below) for which formation of the imine VII is excluded.

Our motivation for investigating a different way to obtain derivatives of 4-amino-γ-carboline was not only our intention to unambiguously confirm the structure of the benzyl derivative VIb, but also the fact that the method considered above allows us to use only ammonia and primary amines, and therefore we eliminate the possibility of forming substances with a tertiary amino group in the 4 position of the γ-carboline molecule. An alternative approach is based on using 9-substituted 6-nitro-γ-carbolines VIIIa, b in the reaction of N-oxidation and rearrangement of the N-oxides obtained IXa, b upon heating in acetic anhydride to the carbolin-4-ones Xa, b. The structure of the N-oxides IXa, b clearly follows from the mass spectra, in which we observe intense [M⁺-16] peaks, characteristic for N-oxides (in carbolines Xa, b, such peaks are missing). In principle, we cannot exclude the possibility that rearrangement of N-oxides may also occur in the direction involving formation of carbolin-2-ones. However, the two doublet signals observed in the PMR spectrum (in DMSO-D₆) at 6.81 and 7.82 ppm, assigned to the 1-H and 2-H protons, unambiguously determine the structure of the substances Xa, b obtained as 9-substituted 6-nitro-γ-carbolin-4-ones. Heating the tricyclic lactams Xa, c with phosphorus chloride in the presence of triethylamine hydrochloride leads to the 4-derivatives Xlba, b, which form with amines the 4-amino-γ-carbolines VIb-g. In the PMR spectrum of 4-amino-6-nitro-9-methyl-γ-carboline (Vla) in DMF-d₆ (characteristic for the synthesized amino derivatives), we observe the signals: 3.99 (s, N—CH₃); 6.77 (br. s, NH₂); 7.02 and 8.09 (2 d, C₁H and C₂H); 7.82 (d, C₂H); 8.37 (q, C₇H) and 9.20 ppm (d, C₅H).

**EXPERIMENTAL**

The PMR spectra were obtained on the Varian XL-200 spectrometer, internal standard TMS. The reaction and purity of the substances were monitored chromatographically on Silufol UV-254 plates in the systems 9:1 benzene—methanol, 3:1:5 isopropanol—ammonia—ethylacetate, 1:1 chloroform—acetone; development under UV light.

The elemental analysis data and the mass numbers of the synthesized compounds correspond to the calculated values.

*Here and below, we give the m/z values for the ion peaks.