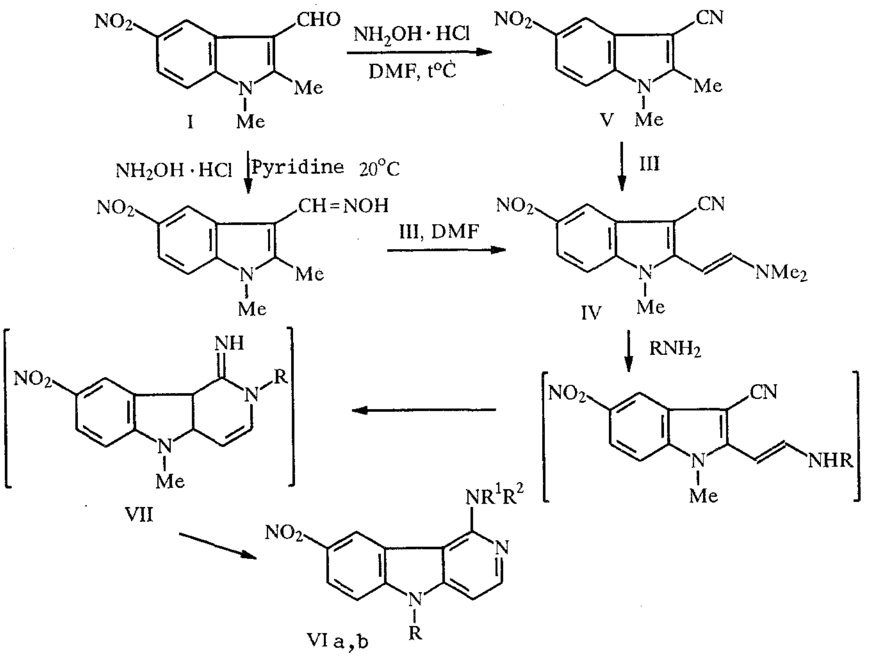
ACETALS OF LACTAMS AND ACID AMIDES.
73.* SYNTHESIS AND SOME PROPERTIES OF DERIVATIVES OF 6-NITRO-γ-CARBOLINE

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-CH_3 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].



VIa,bR = Me, R^1 = H; a R^2 = H, b R^2 = CH_2Ph; VII R = CH_2Ph

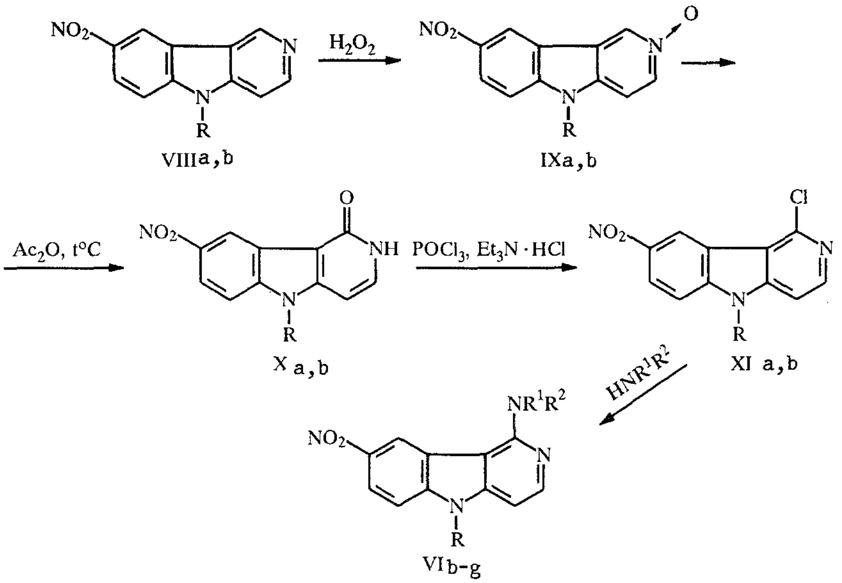
In the first stage of the investigation, as the starting compound we selected 1,2-dimethyl-3-formyl-5-nitroindole (I), which upon reaction with $NH_2OH \cdot HCl$ in pyridine is converted to the oxime II. Upon heating in DMF, the oxime II is easily condensed with DMF diethyl acetal (III), simultaneously 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 $NH_2OH \cdot HCl$ 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].

Center for Drug Chemistry, S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 502-505, April, 1992. Original article submitted October 30, 1990.

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).



VIc $R = R^2 = CH_2Ph$, $R^1 = H$; d $R = CH_2Ph$, $R^1 + R^2 = (CH_2)_5$; e $R = CH_2Ph$, $R^1 + R^2 = CH_2CH_2OCH_2CH_2$; f $R = Me$, $R^1 + R^2 = CH_2CH_2NCH_2CH_2$; g $R = Me$, $R^1 = H$, $R^2 = CH_2CH_2Et_2$; VIIIa $R = Me$, b $R = CH_2Ph$

In the mass spectrum* of compound VIb, in addition to the molecular ion peak M^+ 332, we observe intense peaks 227 [$M^{+\cdot}$-Ph-CH_2NH] and 106 [Ph-CH_2NH], 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 [$M^{+\cdot}$-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-D_6) 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 chloroxide in the presence of triethylamine hydrochloride leads to the 4-derivatives XIa, 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 (VIa) in DMF-d_6 (characteristic for the synthesized amino derivatives), we observe the signals: 3.99 (s, N—CH_3); 6.77 (br. s, NH_2); 7.02 and 8.09 (2 d, C_1H and C_2H); 7.82 (d, C_3H); 8.37 (q, C_7H) and 9.20 ppm (d, C_5H).

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.

1,2-Dimethyl-3-formyl-5-nitroindole (I) was obtained previously in [2].

1,2-Dimethyl-3-cyano-5-nitroindole (V, $C_{11}H_9N_3O_2$). A mixture of 2.18 g (10 mmoles) compound I, 0.8 g (11 mmoles) $NH_2OH \cdot HCl$ in 10 ml DMF was boiled for 9 h. This mixture was cooled and poured into water. The residue was filtered off, washed with water and alcohol, and dried. T_{mp} 184-185°C (from alcohol). Yield 1.9 g (88%).

1-methyl-2-(β-dimethylamino)vinyl-3-cyano-5-nitroindole (IV, $C_{14}H_{14}N_4O_2$). A mixture of 4.3 g (20 mmoles) compound V, 6 ml (40 mmoles) DMF diethyl acetal (III) in 10 ml DMF was boiled for 8 h. This mixture was cooled, the residue was filtered off and washed with alcohol. T_{mp} 260-263°C (from a DMF—alcohol mixture). Yield 4.4 g (81%).

The same compound was obtained in 83% yield upon boiling the oxime of 1,2-dimethyl-3-formyl—5-nitroindole (II) with the acetal III. The substance does not give a depression of the meting point when mixed with the sample obtained previously.

Oxime of 1,2-Dimethyl-3-formyl-5-nitroindole (II, $C_{11}H_{11}N_3O_3$). A mixture of 2.18 g (10 mmoles) of compound I, 1.1 g (15 mmoles) $NH_2OH \cdot HCl$ in 50 ml anhydrous pyridine was allowed to stand for 24 h at 20°C. Then the reaction mass was poured into ice and allowed to stand for 5 h. The residue was filtered off and washed with water and alcohol. T_{mp} 238-240°C (from alcohol). Yield 2 g (86%).

4-Amino-6-nitro-9-methyl-γ-carboline (VIa, $C_{12}H_{10}N_4O_2$). A mixture of 5.4 g (20 mmoles) compound IV in 50 ml of a saturated solution of ammonia in alcohol was heated in an autoclave (110-120°C, 6 h). This was cooled and then the residue was filtered off and washed with alcohol. T_{mp} 349-352°C (from an alcohol—DMF mixture). Yield 4.2 g (87%).

4-Benzylamino-6-nitro-9-methyl-γ-carboline (VIb, $C_{19}H_{16}N_4O_2$). A. 2.7 g (10 mmoles) of compound IV, 3.2 g (30 mmoles) benzylamine in 20 ml DMF were boiled for 10 h. The mixture was then cooled and the residue was filtered off. T_{mp} 233-235°C (from a DMF—alcohol mixture). Yield 2.8 g (85%).

B. The same compound is formed in 82% yield upon heating (130-140°C, 11 h) 4-chloro-5-nitro-9-methyl-γ-carboline with 3000 mmoles benzylamine. The carboline VIb obtained according to this method does not give a depression of the melting point when mixed with the material obtained previously.

9-Methyl- and 9-benzyl-5-nitro-γ-carboline (VIIIa and VIIIb) are obtained by the method in [2].

N-Oxide of 9-Methyl-5-nitro-γ-carboline (IXa, $C_{12}H_9N_3O_3$). A mixture of 4.54 g (20 mmoles) of carboline VIIIa, 5 ml of a 30% H_2O_2 solution in 25 ml glacial AcOH were mixed for 8 h at 95°C. This was then cooled, the residue was filtered off and washed with water. T_{mp} 295-297°C (from an alcohol—chloroform mixture). Yield 4.2 g (85%).

N-Oxide of 9-benzyl-5-nitro-γ-carboline (IXb, $C_{18}H_{13}N_3O_3$) was obtained in the same way as compound IXa from carboline VIIIb in 84% yield. T_{mp} 246-248°C (from an alcohol—DMF mixture).

6-Nitro-9-methyl-1,2-dehydro-γ-carboline-4-one (Xa, $C_{12}H_3N_3O_3$). 4.86 g (20 mmoles) N-oxide IXa and 30 ml acetic anhydride were boiled for 10 h. The mixture was evaporated under vacuum and the residue was boiled for 1 h with 50 ml alcohol. This was cooled and the residue was filtered off and washed with water. T_{mp} >330°C (from a DMF—alcohol mixture). Yield 4.2 g (86%).

6-Nitro-9-benzyl-1,2-dehydro-γ-carboline-4-one (Xb, $C_{18}H_{13}N_3O_3$) was obtained in the same way as compound Xa from IXb and acetic anhydride in 84% yield. T_{mp} 284-286°C (from an alcohol—DMF mixture).

4-Chloro-6-nitro-9-methyl-γ-carboline (XIa, $C_{12}H_8ClN_3O_2$). A mixture of 2.45 g (10 mmoles) carboline Xa, 18 ml freshly distilled $POCl_3$, 0.75 g $Et_3N \cdot HCl$ in 40 ml absolute dioxane was boiled for 5 h. The reaction mass was evaporated under vacuum, the residue was treated with water and saturated with an $NaHCO_3$ solution in water. The residue was filtered off and washed with water until neutral reaction. The yield of the chlorocarboline XIa was 2.05 g (78%). This was recrystallized from a dioxane—DMF mixture with carbon. T_{mp} 301-305°C (decomp.).

4-Chloro-6-nitro-9-benzyl-γ-carboline (XIb, $C_{18}H_{12}ClN_3O_2$) was obtained in the same way as compound XIa from Xb in 75% yield. T_{mp} 212-214°C (from a DMF—dioxane mixture).

4-Benzylamino-6-nitro-9-benzyl-γ-carboline (VIc, $C_{25}H_{20}N_4O_2$) was obtained under the conditions of method **B** from compound XIb and $PhCH_2NH_2$ in 78% yield. T_{mp} 205-207°C (from an alcohol—DMF mixture).

4-Piperidino-6-nitro-9-benzyl-γ-carboline (VId, $C_{23}H_{22}N_4O_2$) was synthesized by reaction of IXb with piperidine according to method **B** in 74% yield. T_{mp} 177-179°C (from alcohol).

4-Morpholino-6-nitro-9-benzyl-γ-carboline (VIe, $C_{22}H_{20}N_4O_3$) was obtained by reaction of compound XIb with morpholine under the conditions of method **B**. T_{mp} 213-215°C (from an alcohol—DMF mixture). 75% yield.

4-Benzhydrylpiperazino-6-nitro-9-methyl-γ-carboline (VIf, $C_{29}H_{27}N_5O_2$). A mixture of 2.61 g (10 mmoles) of the chloride XIa, 1.8 g (10 mmoles) benzhydrylpiperazine n 20 ml DMF were boiled for 20 h. The DMF was evaporated under vacuum, the residue was crystallized from a DMF—alcohol mixture with carbon. T_{mp} 218-220°C. Yield 4.28 g (90%).

Hydrochloride VIf ($C_{29}H_{27}N_5O_2 \cdot HCl$). T_{mp} 233-235°C (decomp., from water).

4-Diethylaminoethylamino-6-nitro-9-methyl-γ-carboline (VIg, $C_{18}H_{23}N_5O_2$). A mixture of 2.61 g (10 mmoles) of chloride XIa in 20 ml diethylaminoethylamine was boiled for 16 h and evaporated under vacuum. 20 ml alcohol was added to the residue. The solution was boiled for 10 min and cooled; the residue was filtered off and compound VIg was obtained in a yield of 3.16 g (93%). T_{mp} 208-210°C (from alcohol).

Hydrochloride VIg ($C_{18}H_{23}N_5O_2 \cdot HCl$). T_{mp} 242-244°C (decomp., from water).

LITERATURE CITED

1. V. M. Lyubchanskaya, L. S. Sarkisova, L. M. Alekseeva, and V. K. Granik, *Khim. Geterotsikl. Soedin.*, No. 3, 357 (1992).
2. É. S. Krichevskii, L. M. Alekseeva, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, No. 11, 1483 (1990).