INVESTIGATION OF SOME TRANSFORMATIONS OF 1-KETO-1,2,3,4-TETRAHYDROCARBAZOLE DERIVATIVES

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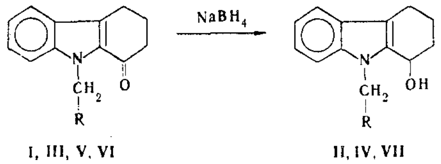
The reduction of 9-substituted functional derivatives of tetrahydrocarbazoles with sodium borohydride was investigated. 9-Carbazolylacetonitrile was obtained instead of the expected pyrazinocarbazole derivatives in an attempt to cyclize 1-keto-1,2,3,4-tetrahydro-9-carbazolylacetamide.

The reduction of 1-keto-1,2,3,4-tetrahydrocarbazole derivatives with sodium borohydride was studied in [1]. 1-Hydroxy-1,2,3,4-tetrahydro-9-methylcarbazole (II) was obtained by the action of sodium borohydride in 1-keto-1,2,3,4-tetrahydro-9-methylcarbazole (I). The reduction of ethyl 1-keto-1,2,3,4-tetrahydro-9-carbazolylacetate (III) [2] with sodium borohydride gives 1-hydroxy-1,2,3,4-tetrahydro-9-(β-hydroxyethyl)carbazole (IV). The latter was also synthesized by reduction of 1-keto-1,2,3,4-tetrahydro-9-(β-hydroxyethyl)carbazole (V) [2] with sodium borohydride. An attempt to cyclize IV to an oxazinoindole derivative by the action of p-toluenesulfonic acid was unsuccessful. Only the keto group is reduced in the reduction of 1-keto-1,2,3,4-tetrahydro-9-carbazolylacetamide (VI) [2] with sodium borohydride to give 1-hydroxy-1,2,3,4-tetrahydro-9-carbazolylacetamide (VII).



I, II R=H; III R=COOC$_2$H$_5$; IV, V R=CH$_2$OH; VI, VII R=CONH$_2$

9-Carbazolylacetonitrile (IX) was obtained instead of the expected pyrazinocarbazole derivative (VIII) in an attempt to cyclize VI by means of phosphorus oxychloride.

The PMR spectrum of nitrile IX contains a singlet of protons of the methylene group at 4.81 ppm and a multiplet at 7.08-8.9 ppm corresponding to eight aromatic protons. The mass spectrum contains a molecular-ion peak (M^+) at m/e 206, a second peak at m/e 180 (M − 26) corresponds to elimination of CN^-, and a more intense peak at m/e (M − 40) corresponds to ion A. A very weak absorption band is found at 2250 cm^{-1} in the IR spectrum. A shift in the absorption maxima to the longer-wave region is observed in the UV spectrum, and this indicates a longer conjugation chain in IX than in the starting VI.

The reduction of IX with lithium aluminum hydride gives the previously unknown 9-(β-aminoethyl)carbazole hydrochloride (X). Acid hydrolysis of IX gives 9-carbazolylacetic acid (XI). No melting-point depression was observed for a mixture of samples of XI obtained by hydrolysis of IX by the method described in [3]; the IR, PMR, and mass spectra of the samples of XI are identical.

In connection with the fact that the synthesis of IX from VI is unusual, we obtained IX from 9-carbazaolylacetamide (XII) by the action of phosphorus oxychloride. No melting-point depression was observed

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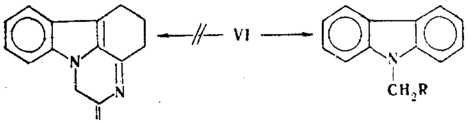

IX-XI

IX $R=CH_2CN$; X $R=CH_2NH_2 \cdot HCl$; XI $R=COOH$

for a mixture of samples of IX obtained by the various methods, and their UV, IR, PMR, and mass spectra were identical.

EXPERIMENTAL

The IR spectra of the compounds were recorded with Perkin-Elmer and UR-10 spectrometers. The UV spectra of ethanol solutions were recorded with a Hitachi EPS-3T spectrophotometer. The PMR spectra were recorded with JNM-4H100 and C-60HL spectrometers with dimethyl sulfoxide (DMSO) as the internal standard for IX and XI and tert-C_4H_9OH as the internal standard for X. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates.

1-Hydroxy-1,2,3,4-tetrahydro-9-methylcarbazole (II). A solution of 1.9 g (0.05 mole) of sodium borohydride in 200 ml of water was added to a solution of 7.9 g (0.04 mole) of I in 200 ml of methanol, after which the mixture was refluxed for 30 min. It was then cooled and poured over ice, and the resulting precipitate was removed by filtration to give 5 g (62%) of a product with mp 129-130° (from methanol). IR spectrum: 3225 cm^{-1} (OH). The product had R_f 0.6 [acetone–hexane (1:1)]. Found: C 77.8; H 7.8; N 6.7%. $C_{13}H_{15}NO$. Calculated: C 77.5; H 7.5; N 6.9%.

1-Hydroxy-1,2,3,4-tetrahydro-(β-hydroxyethyl)carbazole (IV). A) A solution of 1.64 g (0.043 mole) of sodium borohydride in 40 ml of water was added to 6 g (0.22 mole) of ester III in 40 ml of methanol, after which the mixture was refluxed for 30 min. It was then poured over ice, and the resulting precipitate was removed by filtration to give 4 g (80%) of a product with mp 103-104° (from methanol) and R_f 0.27 [acetone–hexane (1:1)]. IR spectrum: 3200 cm^{-1} (OH). Found: C 72.5; H 7.1; N 5.9%. $C_{14}H_{17}NO_2$. Calculated: C 72.7; H 7.4; N 6.0%.

B) A solution of 0.72 g (0.018 mole) of sodium borohydride in 100 ml of water was added to 3.5 g (0.015 mole) of V in 100 ml of methanol, after which the mixture was refluxed for 16 h. It was then cooled and diluted with water. The liberated oily substance began to crystallize on cooling. Workup gave 1.8 g (53%) of a product with mp 104-105° (from methanol) and R_f 0.27 [acetone–hexane (1:1)]. IR spectrum: 3200 cm^{-1} (OH). Found: C 72.8; H 7.2; N 6.0%. $C_{14}H_{17}NO_2$. Calculated: C 72.7; H 7.4; N 6.0%. No melting-point depression was observed for a mixture of samples of IV obtained by methods A and B.

1-Hydroxy-1,2,3,4-tetrahydro-9-carbazolylacetamide (VII). A solution of 0.16 g (0.0045 mole) of sodium borohydride in 50 ml of water was added to 1 g (0.004 mole) of VI in 50 ml of methanol, after which the mixture was refluxed for 3 h, cooled, and poured over ice. The resulting precipitate was removed by filtration to give 0.8 g (80%) of a product with mp 218-219° (from methanol) and R_f 0.15 [acetone–hexane (1:1)], IR spectrum: 3480 cm^{-1} (OH). Found: C 68.5; H 6.7; N 11.5%. $C_{14}H_{16}N_2O_2$. Calculated: C 68.8; H 6.6; N 11.4%.

9-Carbazolylacetonitrile (IX). A) A 5-g (0.02 mole) sample of amide VI was mixed with 250 ml of phosphorus oxychloride, and the resulting solution was refluxed for 3 h. The excess phosphorus oxychloride was then removed by vacuum distillation to dryness, and the residue was dissolved in the minimum amount of dioxane. The dioxane solution was mixed with water, and the precipitated crystals were removed by filtration and dissolved in chloroform. The chloroform solution was passed through a column filled with silica gel for purification, and the solution was evaporated to give 4.3 g (84%) of a product with mp 137-138° (from alcohol) and R_f 0.66 (chloroform). PMR spectrum (CD_3CN): 4.81 (CH_2) s,* 7.08-8.09 (1,2,3,4,5,6,7,8H) m ppm. UV spectrum, λ_{max} (in alcohol), nm (log ε): 234(4.69); 250(4.30); 258(4.03); 292(4.29; 324(3.61); 338(3.61). IR spectrum: 2250 cm^{-1} (CN). Found: C 81.6; H 4.8; N 13.5%. $C_{14}H_{10}N_2$. Calculated: C 81.5; H 4.8; N 13.5%.

B) A mixture of 3 g (0.12 mole) of XII and 30 ml of phosphorus oxychloride was refluxed for 1 h, after which the excess phosphorus oxychloride was evaporated to dryness, and the residue was dissolved in the

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*Abbreviations: s is singlet and m is multiplet.

minimum amount of dioxane. The dioxane solution was mixed with water, and the resulting emulsion was extracted with chloroform. The solution of IX in chloroform was subjected to azeotropic distillation to remove the water, and the residual solution was passed through a layer of silica gel. The solution was then evaporated to dryness, and the residue was dissolved in the minimum amount of chloroform. The chloroform solution was subjected to preparative chromatography on a loose layer of silica gel. A substance with R_f 0.66 (chloroform) was eluted with chloroform, the eluate was evaporated to two thirds of its original volume, and the resulting precipitate was removed by filtration to give 0.3 g (10%) of a compound with mp 136-137° (from alcohol). Found: C 81.4; H 5.1; N 13.6%. $C_{14}H_{10}N_2$. Calculated: C 81.5; H 4.8; N 13.5%. No melting-point depression was observed for a mixture of samples of IX obtained by methods A and B.

9-(β-Ethylamino)carbazole Hydrochloride (X). A solution of 2.0 g (0.009 mole) of nitrile IX in 15 ml of dioxane was added to a suspension of 1.7 g (0.045 mole) of lithium aluminum hydride in absolute ether, after which the mixture was stirred and refluxed for 3 h. Water was then added carefully, the organic layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried with magnesium sulfate, half of the solvent was removed by distillation, and the residual solution was acidified with an ether solution of hydrogen chloride. Workup gave 1.8 g (81%) of a product that decomposed above 300°. IR spectrum of the base: 3350 (NH_2) and 3180 cm^{-1} (NH_2). PMR spectrum (in D_2O): 3.34 (NH_2) t, 4.64 (CH_2) s, 6.0-7.3 (1,2,3,4,5,6,7,8H) m. Mass spectrum: M^+ 210, m/e 180 (M-30), and m/e 166 (M-46). Found: C 68.3; H 6.1; N 11.5%. $C_{14}H_{15}N_2Cl$. Calculated: C 68.1; H 6.1; N 11.3%.

9-Carbazolylacetic Acid (XI). A solution of 4 g of nitrile IX in 35 ml of dioxane was mixed with 10 ml of concentrated hydrochloric acid, and the mixture was refluxed for 1 h. It was then cooled and diluted with water, and the resulting precipitate was removed by filtration. The product was purified through the sodium salt to give 3.8 g (88%) of XI. IR spectrum: 1730 cm^{-1} (C=O). PMR spectrum (in CD_3CN): 5.00(CH_2) s and 7.3-8.1 (1,2,3,4,5,6,7,8H) m. Mass spectrum: M^+ 225, m/e 180 (M-45), and m/e 166 (M-59). Found: C 47.7; H 5.1; N 6.6%. $C_{14}H_{11}NO_2$. Calculated: C 74.6; H 4.9; N 6.2%. The product had mp 212-213° (from alcohol) [mp 215° (from alcohol) [3]].

9-Carbazolylacetamide (XII). Sodium methoxide, prepared from 0.076 g-atom of sodium, was added to a solution of 13 g (0.07 mole) of carbazole in 70 ml of dry dimethylformamide, the alcohol was removed from the solution by distillation, a solution of 1.9 g (0.2 mole) of chloroacetamide in 100 ml of dry DMF was added to it, and the mixture was refluxed for 3 h. It was then diluted with water, and the resulting precipitate was removed by filtration. A solution of XII in chloroform was passed through a column filled with silica gel for purification, after which the solution was evaporated to give 3 g (17%) of product. IR spectrum: 1640 (C=O), 3440 (NH_2), 3200 (NH_2) cm^{-1}. The product had mp 241-242° (from alcohol) [mp 244° (from alcohol [4]].

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