INDOLES

X.* METHOD OF SYNTHESIZING HOMOTRYPTOPHOLS†

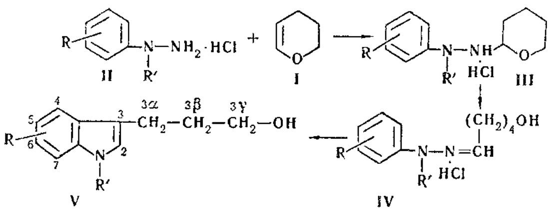
I. I. Grandberg and T. P. Moskvina

UDC 547.754.07:542.953.4

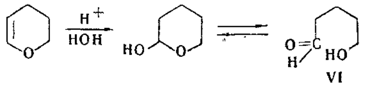
It has been found that the heating of arylhydrazine salts and dihydropyran in dioxane leads to the corresponding homotryptophols.

The nucleophilic addition of amines to an activated double bond is known [1]. We have shown previously that, in the Fischer reaction with arylhydrazine hydrochlorides under anhydrous conditions where hydrolysis is unlikely, noncyclic vinyl ethers behave in a similar manner to carbonyl compounds [2].

On studying the reaction between dihydropyran (I) and arylhydrazine salts (II), we observed the formation of homotryptophols (V). The reaction probably takes place in the following way:



It is known that in aqueous solutions of acids dihydropyran adds water to give 2-hydroxytetrahydropyran and its tautomeric form 5-hydroxyvaleraldehyde (VI) [3].



However, since the reaction takes place in an anhydrous medium, in our opinion it is the dihydropyran itself and not the aldehyde VI that takes part in the reaction with II, forming the intermediate compound III, which isomerizes into the hydrazone IV. The latter is converted by the usual mechanism of the Fischer reaction into the homotryptophol V. A special paper will be devoted to a study of the mechanism of the process.

In a search for the optimum reaction conditions, various solvents and mixtures of them, different temperatures and times, and various arylhydrazine salts were studied. Aqueous dioxane (5-9% water) gave better results than other solvents, but increasing the content of water even to 15% greatly decreased the yield. In anhydrous dioxane the yield was somewhat lower but this was obviously simply because of the lower solubility of the salts. Hydrochlorides and sulfates gave better yield than phosphates and acetates. The optimum time and temperature conditions are given in the Experimental part. Alkylation of the NH group of the arylhydrazine greatly increased the yield – in the case of α-benzylphenylhydrazine even to 92%. This is probably connected with the impossibility of the addition of the dihydropyran to the NH group as well as a side reaction, with the formation of resinous products insoluble in benzene which are almost

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*For Communication IX, see [6].

†See I. I. Grandberg and N. I. Bobrova, USSR Patent No. 239,341, Byull. Izobr., No. 11 (1969).

Timiryazev Agricultural Academy, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 7, pp. 942-944, July, 1970. Original article submitted February 24, 1969.

always present in large amounts. The introduction of methyl and alkoxy groups into the phenylhydrazine nucleus has practically no effect on the yield, with the exception of the ortho-substituted derivatives which, as is usual in the Fischer reaction, give somewhat smaller yields.

EXPERIMENTAL

The PMR spectra were obtained on a JNM-4H-100 instrument with a working frequency of 100 MHz in $CDCl_3$ solution using tetramethylsilane as internal standard. The IR spectra were obtained on a Jasco JR-S instrument with an NaCl prism in CCl_4 solution or in a tablet with KBr. The UV spectra were obtained on a Hitachi EPS-3T instrument in ethanol.

General Method for Obtaining Homotryptophols. A mixture of 0.05 mole of an arylhydrazine hydrochloride or phosphate in a mixture of 80 ml of dioxane and 3 ml of water was heated in the boiling water bath in a 3-necked flask with stirrer and reflux condenser. Then, with vigorous stirring, a solution of 0.075 mole of dihydropyran in 20 ml of dioxane was added to the hot mixture over 5 min, and the resulting mixture was heated in the boiling water bath for 3 h. The dioxane was distilled off in the vacuum of a water pump, the residue was treated with 50 ml of hot water and 50 ml of hot benzene and carefully shaken, and the extraction with 50 ml of benzene was repeated once more. The benzene extract was distilled in vacuum. Then, where necessary, special individual purification processes were used.

Homotryptophol. Yield 35%, bp 182-185°C (1 mm). Found %: C 75.22, 75.30; H 7.45, 7.43. $C_{11}H_{13}NO$. Calculated %: C 75.39; H 7.48. R_f 0.62*; R'_f 0.82.† The substance was purified on a column of Al_2O_3 (activity grade 5), 2 cm in diameter and 50 cm high; elution was performed first with benzene and then with benzene–isopropanol (9 : 1). IR spectrum, cm^{-1}: 3600 (OH), 3480 (NH), 1615, 1600, 1500, 1460 (stretching vibrations of the nucleus). UV spectrum: λ_{max} 224, 280 nm; log ε 4.46, 3.77. Picrate, obtained from absolute benzene, mp 98-99°C. Found %: N 13.50, 13.43. $C_{11}H_{13}NO \cdot C_6H_3N_3O_7$. Calculated %: N 13.61 [4,5].

7-Methylhomotryptophol. Yield 24%, bp 195-200°C (1 mm), mp 90.5-91°C (from hexane). Found %: C 75.39; H 7.89. $C_{12}H_{15}NO$. Calculated %: C 76.17; H 7.99. R_f 0.59; R'_f 0.85. IR spectrum, cm^{-1}: 3580 (OH), 3280 (NH), 1620, 1590, 1500, 1465 (stretching vibrations of the nucleus). UV spectrum: λ_{max} 222, 274, 280, 290 nm; log ε 4.39, 4.10, 4.01, 4.09.

PMR spectrum, ppm: OH 1.80 (broad singlet); 3β-CH_2 (multiplet with a center) 1.99; 7-CH_3 2.37; 3α-CH_2 2.78 (triplet) (J = 7 Hz); 3γ-CH_2 3.65 (triplet) (J = 7 Hz); 6.84-7.20 (multiplet, aromatic protons); NH 7.96 (diffuse singlet).

5-Methylhomotryptophol. Yield 35%, bp 205-215°C (1 mm). Found %: C 75.58, 75.38; H 8.18, 8.19. $C_{12}H_{15}NO$. Calculated %: C 76.17; H 7.99. R_f 0.63, R'_f 0.86, n_D^{20} 1.5924. The substance was purified on a column of Al_2O_3 2 cm in diameter and 40 cm high; elution was carried out first with benzene and then with benzene–isopropanol (9 : 1). IR spectrum, cm^{-1}: 3480 (OH), 3360 (NH), 1615, 1590, 1520, 1480 (stretching vibrations of the nucleus). UV spectrum: λ_{max} 227, 282, 287, 297 nm; log ε 4.21, 3.62, 3.63, 3.56.

7-Methoxyhomotryptophol. Yield 25%, bp 206-218°C (1 mm). The substance was purified preparatively on 23 × 18 cm^2 plates with a 3-mm layer of Al_2O_3 in the benzene–isopropanol (9 : 1) system. IR spectrum, cm^{-1}: 3617 (OH), 3500 (NH), 1640, 1585, 1505, 1450 (stretching vibrations of the nucleus), 1260 and 1030 (OCH_3). UV spectrum: λ_{max} 223, 270, 280, 290 nm; log ε 4.53, 3.72, 3.66, 3.58.

N-Methylhomotryptophol. Yield 72%, bp 195-200°C (1 mm). It was purified on a column of Al_2O_3 as described above. Found %: C 75.78, 75.65; H 8.10, 8.17. $C_{12}H_{15}NO$. Calculated %: C 76.17; H 7.99. R_f 0.65, R'_f 0.83. IR spectrum, cm^{-1}: 3620 (OH), 1615, 1550, 1470 (stretching vibrations of the nucleus). UV spectrum: λ_{max} 226, 290 nm; log ε 4.46, 3.69. Picrate, mp 65-67°C (from benzene). Found %: N 13.50. $C_{12}H_{15}NO \cdot C_6H_3N_3O_7$. Calculated %: N 13.32.

N-Phenylhomotryptophol. Yield 56%, bp 203-210°C (1 mm). Purified preparatively on 23 × 18 cm plates of Al_2O_3 with a layer thickness of 3 mm. R_f 0.64, R'_f 0.86, 0.85, n_D^{20} 1.6322. Found %: C 80.78; H 6.90. $C_{17}H_{17}NO$. Calculated %: C 81.24; H 6.82. IR spectrum, cm^{-1}: 3360 (OH), 1600, 1560, 1480 (stretch-

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*Here and below, chromatography in a thin layer of Al_2O_3 [activity degree 5; benzene–isopropanol (9 : 1)], the spots being revealed with iodine.

† Here and below, chromatography on dimethylformamide-impregnated "rapid" type paper of the Volodarskii mill in the ethanol–tert-butanol–water (10 : 5 : 6) system, the spots being revealed with Ehrlich's reagent.

ing vibrations of the nucleus). UV spectrum: λ_{max} 220, 259, 294, 299 nm; log ε 4.46, 4.27, 3.99, 4.00.

N-Benzylhomotryptophol. Yield 92%, bp 208-216°C (1 mm), bp 79-80°C (from hexane). Found %: C 81.67; H 7.17. $C_{18}H_{19}NO$. Calculated %: C 81.47; H 7.21. R_f 0.62, R'_f 0.85. IR spectrum, cm^{-1}: 3340 (OH), 1615, 1600, 1565, 1500. (stretching vibrations of the nucleus). UV spectrum: λ_{max} 225, 290, 331 nm; log ε 4.95, 4.28, 2.92.

PMR spectrum: OH 1.63 (broad singlet); 3β-CH_2 (multiplet with a center) 1.99; 3α-CH_2 2.88 (triplet) (J = 6 Hz); 3γ-CH_2 3.69 (triplet) (J = 6 Hz); 1α-CH 5.23 (singlet); 2H 6.88 (singlet); 7.07-7.22 (aromatic protons).

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