INDOLES

XVI * SYNTHESIS OF STRUCTURAL ANALOGS OF PHYSOVENINE

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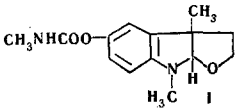
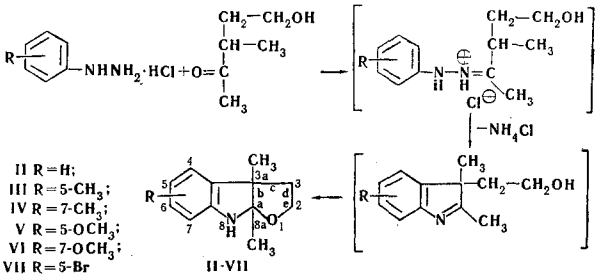
Derivatives of 2,3,3a,8a-tetrahydro-3a,8a-dimethylfuro[2,3-c]indole were synthesized by the reaction of arylhydrazine salts with 3-methylpentan-4-on-1-ol on heating the components in dimethylformamide.

In a continuation of our previously published studies [1] associated with the synthesis of dinordeoxy-9-methyleseroline we have developed a new method for the preparation of compounds that constitute the base of the alkaloid physovenine [2] (I), viz., 2,3,3a,8a-tetrahydro-3a,8a-dimethylfuro[2,3-b]indole and its derivatives (II-VII).



The previously described [2] synthesis of physovenine (I) consisted of the reduction with sodium in alcohol of 3-(β-hydroxyethyl)-5-methoxyl-1,3-dimethylhydroxyindole to 2,3,3a,8a-tetrahydro-5-methoxy-3a, 8a-dimethylfuro[2,3-b]indole with subsequent treatment with anhydrous $AlCl_3$ and methyl isocyanate, respectively. Nakazaki [3] reported an example of the synthesis of II by the reaction of the magnesium derivative of 2-methyltryptophol with methyl iodide, but this method is complicated and gives low yields (of the order of 17%).

A modified variant [4] of the well-known Fischer reaction – the reaction of arylhydrazine salts with carbonyl compounds in neutral media – is the basis for the method proposed by us. 3-Methylpentan-4-on-1-ol is used as the carbonyl compound. The reaction proceeds via the following scheme:



Our method makes its possible to obtain II-VII in 60-80% yields by heating the components in dimethylformamide.

*See [9] for Communication XV.

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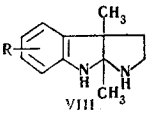
The UV spectra of II-VII, which have the same character as the spectra of compounds of the VIII type [1] and the spectrum [5] of I, were obtained as evidence for their structures.



VIII

In addition, the data from the PMR spectrum of II completely correspond to the data from the spectrum of physovenine [5] and confirm the proposed structure by unambiguous assignment of the proton signals as follows*: singlets at 1.22 ppm (3a-CH_3, three protons), 1.35 ppm (8a-CH_3), three protons), and 4.83 ppm (NH, one proton); multiplets at 1.9-2 ppm (β-CH_2, two protons), 3.1-3.8 ppm (α-CH_2, two protons), and 6.1-6.9 ppm (four aromatic protons). The multiplicity of the proton signals of the α- and β-methylene groups can be explained by the spin-spin coupling of all four nonequivalent protons which make up an ABXY system. The nonequivalency of the protons is due to the rigid cis fusion of the pyrrolidine and tetrahydrofuran rings.

All of the compounds obtained were characterized by means of picrates and R_f values from chromatography on both aluminum oxide and acetylated paper.

EXPERIMENTAL

The degree of purity of the final compounds was monitored by chromatography on a loose layer of a activity II aluminum oxide (thin layer of 0.6-0.7 mm) in a benzene–isopropyl alcohol (9 :1) system (R_{f1}) or in chloroform (R_{f2}). The chromatograms were developed with iodine vapors.

Attempts to carry out paper chromatography were successful only when acetylated paper was used with chloroform as the stationary phase and 80% ethanol as the mobile phase [6] (R_{f3}). The chromatograms were developed with alcoholic ninhydrin with preliminary storage in a cabinet with iodine vapors.

3-Methylpentan-4-on-1-ol. This was obtained by refluxing α-methyl-α-acetylbutyrolactone [1] with 5% hydrochloric acid under the conditions indicated in [7]. The product was obtained in 70% yield and had bp 55-58 deg (1 mm), d_4^{20} 0.9825, and n_D^{20} 1.4417.

Arylhydrazines. These were obtained by reduction of the corresponding diazonium compounds [8] with stannous chloride.

2,3,3a,8a-Tetrahydro-3a,8a-dimethylfuro[2,3-b]indole (II). 3-Methylpentan-4-on-1-ol [5.8 g (0.05 mole)] was added to a solution of 7.23 g (0.05 mole) of phenylhydrazine hydrochloride in 50 ml of dimethylformamide, and the reaction mixture was heated at 50 deg for 30 min, on a boiling water bath for 30 min, and finally refluxed for 30 min. Dimethylformamide was vacuum distilled from the reaction mass, 50 ml of water was added to the residue, and the mixture was extracted with benzene. The benzene extract was evaporated, and the residue was vacuum distilled to give 7.2 g (76.2%) of 2,3,3a,8a-tetrahydro-3a,8a-dimethylfuro[2,3,-b]indole with bp 108-110 deg (0.5 mm) in the form of a yellowish oil; the oil began to crystallize on standing to give a product with mp 46.6-47.5 deg (from hexane). Found %: C 76.09, 76.32; H 7.88; 8.00. $C_{12}H_{15}NO$. Calc. %: C 76.15; H 7.99. UV spectrum,† λ_{max}, nm (log ε): 216 (4.02), 223 (3.87), 243 (3.78). Chromatography: R_{f1} 0.62, R_{f2} 0.16, R_{f3} 0.61. The picrate had mp 137.5-138.5 deg (from alcohol). Found %: N 13.22, 13.48. $C_{12}H_{15}NO \cdot C_6H_3N_3O_7$. Calc. % N 13.39.

2,3,3a,8a-Tetrahydro-3a,5,8a-trimethylfuro[2,3-6]indole (III). This was obtained under similar conditions from 7.93 g (0.05 mole) of p-tolylhydrazine hydrochloride. The product [8 g (79%)] was a yellowish oil with bp 142-145 deg (2 mm) which began to crystallize on standing to give crystals with mp 82-83.5 deg (from hexane). Found %: C 77.00, 77.03; H 8.31, 8.44. $C_{13}H_{17}NO$ Calc. %: C 76.80; H 8.43. UV spectrum, λ_{max}, nm (log ε): 220 (4.09), 251 (3.75). Chromatography: R_{f1} 0.60, R_{f2} 0.16, R_{f3} 0.67. The picrate had mp 174.5-175 deg (from alcohol). Found %: N 13.24, 13.04. $C_{13}H_{17}NO \cdot C_6H_3N_3O_7$. Calc. %: N 12.96.

*The spectrum was obtained by Yu. A. Ustynyuk with a JNM-60 spectrometer (operating frequency 60 MHz) in carbon tetrachloride. The assignments are given in the δ scale.

†The UV spectra in 80% ethanol were obtained with an EPS-3T spectrometer.

2,3,3a,8a-Tetrahydro-3a,7,8a-trimethylfuro[2,3,-b]indole (IV). This compound [7.5 g (74.2%)] was obtained under similar conditions from 7.93 g (0.05 mole) of o-tolylhydrazine hydrochloride and was a yellowish oil with bp 120-122 deg (0.5 mm) that began to crystallize on standing to give a product with mp 93-94.5 deg (from hexane). Found %: C 76.80, 76.84; H 8.42, 8.36. $C_{13}H_{17}NO$. Calc. %: C 76.80; H 8.43. UV spectrum, λ_{max}, nm (log ε): 221 (4.03), 228 (4.03), 228 (3.91), 244 (373). Chromatography: R_{f1} 0.59, R_{f2} 0.28, R_{f3} 0.51.

2,3,3a,8a-Tetrahydro-5-methoxy-3a,8a-dimethylfuro[2,3-b]indole (V). This compound [7.5 g (68.5%)] was obtained under similar conditions from 8.73 g (0.05 mole) of p-anisylhydrazine hydrochloride in the form of a yellowish oil with bp 148-150 deg (3 mm) that began to crystallize on standing to give a product with mp 55-56 deg (from hexane). Found %: C 70.98, 71.21; H 7.69, 7.70. $C_{13}H_{17}NO_2$. Calc %: C 71.20; H 7.81. UV spectrum: λ_{inf} 217 nm (log ε 4.10), λ_{max} 272 (log λ 3.88). Chromatography: R_{f1} 0.51, R_{f2} 0.07, R_{f3} 0.79. The picrate had mp 162-162.5 deg (from alcohol). Found %: N 12.58, 12.72. $C_{13}H_{17}NO_2 \cdot C_6H_3N_3O_7$. Calc. %: N 12.50.

2,3,3a,8a-Tetrahydro-7-methoxy-3a,8a-dimethylfuro[2,3,-b]indole (VI). This compound [8.5 g (77.5%)] was obtained under similar conditions from 8.73 g (0.05 mole) of o-anisylhydrazine hydrochloride in the form of a yellowish oil with bp 145-146 deg (1 mm) that began to crystallize on standing to give a product with mp 68-70.5 deg (from hexane). Found %: C 71.25, 71.06; H 7.80, 7.73. $C_{13}H_{17}NO_2$. Calc. %: C 71.20; H 7.81. UV spectrum: λ_{inf} 224 nm (log ε 3.92), λ_{max} 231 nm (log ε 3.86), 245 nm (log ε 3.78), 293 nm (log ε 3.40). Chromatography: R_{f1} 0.60, R_{f2} 0.20, R_{f3} 0.50. The picrate had mp 139.140.5 deg (from alcohol). Found %: N 12.58, 12.82. $C_{13}H_{17}NO_2 \cdot C_6H_3N_3O_7$. Calc. %: N 12.50.

2,3,3a,8a-Tetrahydro-5-bromo-3a,8a-dimethylfuro[2,3-b]indole (VII). This compound [7.35 g (55%)] was obtained under similar conditions from 10.18 g (0.05 mole) of p-bromophenylhydrazine hydrochloride in the form of an oil with bp 163-168 deg (3 mm) that crystallized immediately to give a product with mp 122-123.5 deg (from hexane). Found %: C 53.47, 53.71; H 5.12, 5.32. $C_{12}H_{14}NOBr$. Calc. %: C 53.75; H 5.26. UV spectrum: λ_{inf} 228 nm (log ε 3.64), λ_{max} 251 nm (log ε 4.08), 308 nm (log ε 3.30). Chromatography: R_{f1} 0.61, R_{f2} 0.24, R_{f3} 0.37. The picrate had mp 110-111.5 deg (from alcohol). Found %: N 10.98, 11.12. $C_{12}H_{14}NOBr \cdot C_6H_3N_3O_7$. Calc. %: N 11.27.

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