INDOLES

XLVII.* SYNTHESIS OF 2,3,3a,8a-TETRAHYDROFURO[2,3-b]INDOLE DERIVATIVES

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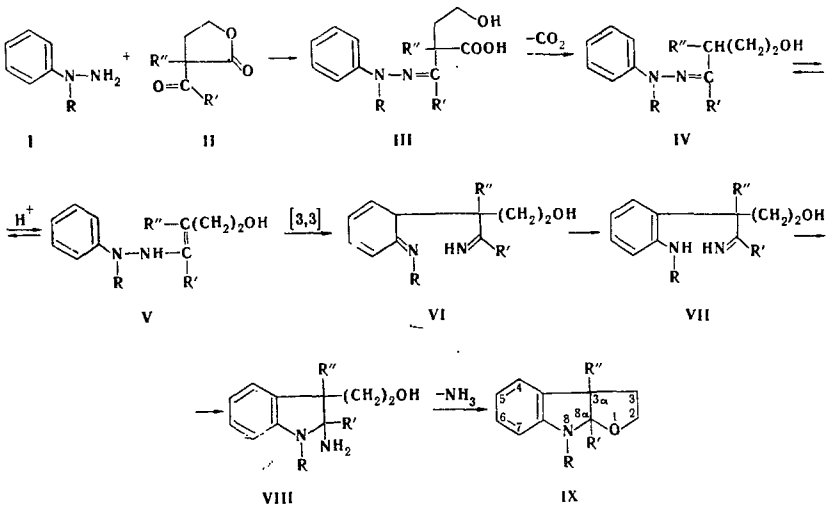
A method is proposed for the synthesis of 2,3,3a,8a-tetrahydrofuro[2,3-b]indole derivatives; the method is based on the reaction of 3-alkyl-3-acyl-γ-butyrolactones with N_1-substituted arylhydrazines in acidic aqueous alcohol media.

2,3,3a,8a-Tetrahydrofuro[2,3-b]indoles (IX) are structural analogs of the alkaloid physovenine. We have previously reported the synthesis of such systems based on the reaction of arylhydrazines with α-alkyl-γ-hydroxy ketones [2]. The latter were obtained by hydrolysis and decarboxylation of the corresponding 3-alkyl-3-acyl-γ-butyrolactones [2].

In the present research we investigated the possibility of the synthesis of 2,3,3a,8a-tetrahydrofuro[2,3-b]indoles using directly 3-alkyl-3-acyl-γ-butyrolactones (II) as the carbonyl compounds, thereby bypassing the step involving the preparation from them of α-alkyl-γ-hydroxycarbonyl compounds, in analogy with our preceding communications [3, 4]. By carrying out the reaction of lactones II with N_1-substituted arylhydrazines (I) by refluxing them in isopropyl alcohol-aqueous hydrochloric acid, we obtained a number of tetrahydrofuroindoles (IXa-e).

The following reaction scheme is assumed:



IIa R′=R″=CH₃; b R′=CH₃, R″=CH₂C₆H₅; c R′=H, R″=CH₃; III—IX a R=CH₂C₆H₅, R′=R″=CH₃; b R=R″=CH₂C₆H₅, R′=CH₃; c R=R″=CH₃, R′=H; d R=i-C₃H₇, R′=H, R″=CH₃; e R=C₆H₅, R′=H, R″=CH₃; f R=CH₂C₆H₅, R′=H, R″=CH₃

*See [1] for communication XLVI.

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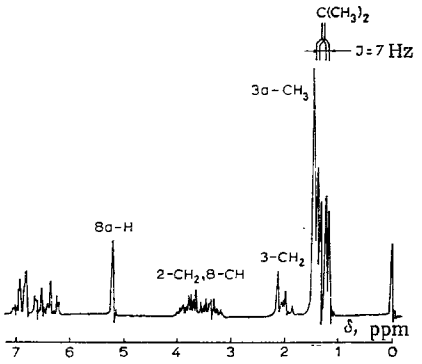

Fig. 1. PMR spectrum of 3a-methyl-8-isopropyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole.

A hydrazone, the lactone ring of which is hydrolyzed under acidic conditions (III) and decarboxylated to give the hydrazone of α-alkyl-γ-hydroxycarbonyl compound IV, which is in equilibrium with its tautomeric form $(V)_t$ is evidently formed in the first steps. Tautomeric form V, as a consequence of a sigmatropic [3, 3] shift [5] is converted to diimine VI, which is stabilized by aromatization to substituted aniline VII. Aniline VII undergoes intramolecular addition to the C=N bond to give aminoindoline VIII, which ejects ammonic and undergoes cyclization to a three-ring tetrahydrofuroindole system (IX).

In order to obtain tetrahydrofuro[2,3-b]indoles without substituents in the 8a position and similar to natural physovenine, it was necessary to obtain 3-alkyl-3-formyl-γ-butyrolactone in DMSO with methyl iodide. The sodium salt of 3-formyl-γ-butyrolactone was in turn obtained by acylation of butyrolactone with ethyl formate by means of the Claisen reaction. It should be noted that the α-methyl-γ-hydroxybutyraldehyde (IV) necessary for the preparation of 8a-unsubstituted furoindoles as in the method in [2] cannot be obtained by hydrolysis and decarboxylation of lactone IIc. We obtained these compounds by subjecting lactone IIIc directly to the above-described reaction (without prior preparation of the hydroxy aldehyde).

The PMR spectrum of lactone C contains a singlet of protons of a methyl group with a chemical shift of 1.40 ppm. The two nonequivalent H_A and H_B protons have chemical shifts of 2.01 and 2.73 ppm, respectively, and, by coupling with one another and with the γ protons, give signals in the form of two multiplets, each with geminal coupling constant $J_{H_AH_B} = 13$ Hz and with vicinal coupling constants $J_{H_AH_\gamma} = 7.5$ Hz and and $J_{H_BH_\gamma} = 6.5$ Hz. The γ-methylene protons give a signal at 4.17 ppm in the form of two superimposed doublets. A singlet of the proton of an aldehyde group at 9.20 ppm is observed at weak field. In the case of the spectrum of fluoroindole IXd, it is seen in the PMR spectra of furoindoles IXa-f (Fig. 1) that a signal of protons of methyl groups of an isopropyl group is observed at strong field in the form of two doublets (1.27 and 1.30 ppm). The methyl groups are apparently nonequivalent as a consequence of hindrance to rotation. The 3a-CH_3 group gives a singlet with a chemical shift of 1.38 ppm. The multiplet at 1.85-2.11 ppm belongs to the protons of the 3-CH_2 group. The signals of the protons of the 2-CH_2 group and the methylidyne proton of the isopropyl group are overlapped and give a complex multiplet at 3.19-4.00 ppm. The 8a-H signal appears at 5.18 ppm as a singlet. A multiplet of aromatic protons lies at 6.17-7.07 ppm.

The methylene protons of the benzyl groups in furoindole IXb are nonequivalent because of hindrance to rotation. This methylene group appears in the PMR spectrum as two doublets (see the Experimental section).

EXPERIMENTAL

The UV spectra of isopropyl alcohol solutions of the compounds were recorded with a Hitachi EPS-3T spectrophotometer. The IR spectra of CCl_4 solutions were recorded with a Jasco-IR-S spectrometer. The PMR spectra of CCl_4 solutions were recorded with Varian T-60 or JEOL C-60HL spectrometers with hexamethyldisiloxane (HMDS) as the internal standard. The physovenine systems were chromatographed in a thin layer of activity II Al_2O_3 in hexane–ether (10 : 1). The chromatograms were developed with iodine vapors.

The 1-benzyl-1-phenyl-, 1-methyl-1-phenyl-, and 1,1-diphenylhydrazine salts used in this research were commercial preparations. 1-Isopropyl-1-phenyl-hydrazine hydrochloride was obtained by the method in [6]. 3-Methyl- and 3-benzyl-3-acetyl-γ-butyrolactones were obtained by the method in [2].

3-Methyl-3-formyl-γ-butyrolactone (IIc). A 24-g (1.05 g-atom) sample of sodium was pulverized in hot xylene, after which the mixture was cooled, the xylene was decanted, 400 ml of absolute ether and 400 ml of absolute ethanol were added to the sodium, and the mixture was stirred for 4 h. Another 200 ml of absolute ether was then added to the suspension of sodium, and a solution of 86 g (1 mole) of γ-butyrolactone and 82 g (1.1 mole) of ethyl formate (fractionated over P_2O_5) in 300 ml of absolute ether was added dropwise slowly with stirring in the course of 3 h. The mixture was then stirred until the sodium had dissolved completely, and the solution was allowed to stand overnight. The resulting precipitate was removed

by filtration, washed on the filter with absolute ether, and dried in a desiccator over KOH to give 133 g of the crude sodium salt of 3-formyl-γ-butyrolactone. The salt was pulverized, dried additionally, and dissolved in 350 ml of absolute DMSO in a 2-liter flask equipped with a powerful stirrer. A 215-g (1.5 mole) sample of methyl iodide was added dropwise with stirring to the solution (the reaction was exothermic), and the thickened reaction mass was heated on a water bath at 50° for 1 h. Benzene (1 liter was then added, and the mixture was filtered. The precipitate on the filter was washed thoroughly with benzene, dissolved in the minimum amount of water, and additionally extracted with benzene. All of the benzene fractions were combined, the benzene was evaporated, and the residue was vacuum distilled with a large fractionating column. The fraction boiling at 75-85° (2 mm), which was redistilled, was collected to give 25 g (20%) of pure 3-methyl-3-formyl-γ-butyrolactone with bp 76.5-77.5° (2 mm), n_D^{20} 1.4567, d_4^{20} 1.1610, R_{f1} 0.27 [activity II Al_2O_3, benzene–isopropyl alcohol (24 : 1)], and R_{f2} 0.58 [Silufol UV-254, benzene–isopropyl alcohol (6 : 1)]. UV spectrum: λ_{max} 222, 288 nm (log ε 2.28, 1.52). IR spectrum: 1778 (lactone C=O and 1733 cm^{-1} (aldehyde C=O). Found: C 56.1; H 6.3%. $C_6H_8O_3$. Calculated: C 56.2, H 6.3%. The 2,4-dinitrophenylhydrazone had mp 169.5° (from alcohol). Found: C 46.7; H 3.9; N 18.8%. $C_{12}H_{12}N_4O_6$. Calculated: C 46.8; H 3.9; N 18.2%.

General Method for the Preparation of 2,3,3*a*,8*a*-Tetrahydrofuro[2,3-b]-indoles (IXa-f). A solution of 0.04 mole of lactone II and 0.04 mole of N_1-substituted phenylhydrazine salt in a mixture of 65 ml of isopropyl alcohol, 40 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 6 h, after which the solvent was vacuum evaporated, and 70 ml of benzene and 70 ml of water were added to the residue. The benzene layer was separated, washed several times with water, and dried with $MgSO_4$. The benzene was evaporated, and the residue was vacuum distilled or recrystallized. The crude product can be subjected to additional purification by preparative chromatography in a thin layer of activity II Al_2O_3; 0.20-0.25 g of the substance was purified with hexane–ether (10 : 1) on an 18 × 24-cm plate with a layer thickness of 2 mm. The edge of the chromatogram was developed with iodine vapors, and the product was washed out with benzene.

3*a*,8*a*-Dimethyl-8-benzyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXa). This compound with mp 32-33°, bp 152-154° (1 mm), and R_f 0.47 [4], was obtained in 48% yield* from lactone IIa and 1-benzyl-1-phenylhydrazine hydrochloride.

3*a*,8-Dibenzyl-8*a*-methyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXb). This compound, with mp 103-104° (from hexane) and R_f 0.31, was obtained in 46% yield from lactone IIb and 1-benzyl-1-phenylhydrazine hydrochloride. UV spectrum: λ_{max} 250 and 300 nm (log ε 3.97 and 3.38). PMR spectrum,† δ, ppm: 1.48 s (8a-CH_3), 1.90-2.35 m (3-CH_2), 2.75 d and 3.09 d (J = 13 Hz, 3a-CH_2), 3.09-3.91 m (2-CH_2), 4.11 d and 4.67 d (J = 18 Hz, 8-CH_2), and 6.05-7.30 m (aromatic protons). Found: C 84.7; H 7.1%. $C_{25}H_{25}NO$. Calculated: C 84.5; H 7.1%.

3*a*,8-Dimethyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXc). This compound, with bp 80-86° (1 mm) and R_f 0.45, was obtained in 22% yield from lactone IIc and 1-methyl-1-phenylhydrazine hydrosulfate. UV spectrum: λ_{max} 250, 303 nm (log ε 4.04, 3.46). PMR spectrum, δ, ppm: 1.41 s (3a-CH_3), 1.83-2.10 m (3-CH_2), 2.84 s (8-CH_3), 3.13-3.97 m (2-CH_2), 4.90 s (8a-H), and 6.10-7.05 m (aromatic protons). Found: C 76.2; H 8.2%. $C_{12}H_{15}NO$. Calculated: C 76.2; H 8.0%.

3*a*-Methyl-8-isopropyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXd). This compound, with mp 20° and R_f 0.60, was obtained in 45% yield from lactone IIc and 1-isopropyl-1-phenylhydrazine hydrochloride. UV spectrum: λ_{max} 253, 306 nm (log ε 4.17, 3.56). Found: C 77.5; H 8.8%. $C_{14}H_{19}NO$. Calculated: C 77.5; H 8.8%.

3*a*-Methyl-8-phenyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXe). This compound, with bp 150-160° (1 mm) and R_f 0.54, was obtained in 46% yield from lactone IIc and 1,1-diphenylhydrazine hydrochloride. UV spectrum: λ_{max} 240 inf, 278, 311 inf nm (log ε 3.53, 4.24, and 3.64). PMR spectrum, δ, ppm: 1.48 s (3a-CH_3), 1.93-2.20 m (3-CH_2), 3.27-4.07 m (2-CH_2), 5.23 s (8a-H), and 6.53-6.71 m (aromatic protons). Found: C 81.7; H 7.0%. $C_{17}H_{17}NO$. Calculated: C 81.2, H 6.8%.

3*a*-Methyl-8-benzyl-2,3,3*a*,8*a*-tetrahydrofuro[2,3-b]indole (IXf). This compound, with mp 26.5-27.5°, bp 168-173° (2 mm), and R_f 0.39, was obtained in 42% yield from lactone IIc and 1-benzyl-1-phenylhydra-

*Here and subsequently, the yields are indicated for the product obtained after distillation. The spectral characteristics are given for substances purified by chromatography.

† The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, and m is multiplet.

zine hydrochloride. UV spectrum: λ_{max} 251, 303 nm (log ε 4.09, 3.46). PMR spectrum, δ, ppm: 1.38 s (3a-CH_3), 1.82-2.08 m (3-CH_2), 3.18-3.92 m (2-CH_2), 4.30 s (8-CH_2), 4.90 s (8a-H), and 5.93-7.00 m (aromatic protons). Found: C 82.0; H 7.2%. $C_{18}H_{19}NO$. Calculated: C 81.5; H 7.2%.

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