INDOLES

XLII.* SYNTHESIS OF 1,2-DISUBSTITUTED TRYPTOPHOLS

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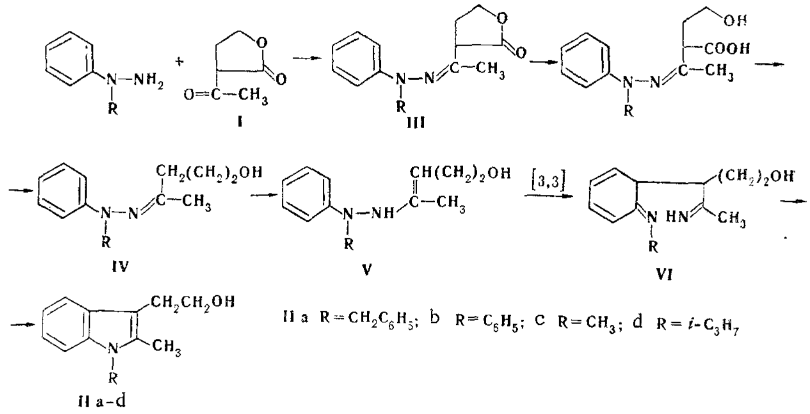
A new method is proposed for the synthesis of 1,2-disubstituted tryptophols by reaction of N_α-substituted arylhydrazines with α-acyl-γ-butyrolactones by refluxing the components in an acidic aqueous alcohol media.

α-Acyl-γ-butyrolactones are the starting materials for the preparation of the corresponding γ-acyl derivatives of alcohols, which can be used for the synthesis of 2-substituted tryptophols [2].

Continuing our research on the synthesis of tryptophols (II) [3], we have investigated the possibility of preparing them directly from acetylbutyrolactone and arylhydrazines in acidic media. It seemed likely that the hydrolysis of the lactone ring and decarboxylation may proceed in parallel with Fischer indolization because of the identical conditions used in carrying out both processes. Refluxing acetylbutyrolactone with N_α-substituted arylhydrazines in a mixture of isopropyl alcohol and aqueous hydrochloric acids leads to a number of 1,2-disubstituted tryptophols (IIa-d).



Hydrazone III is apparently formed in the first step and is then converted to hydrazone IV as a result of acid hydrolysis. After prototropic tautomeric conversion of hydrazone IV to enehydrazine V, the latter, as a consequence of a sigmatropic [3.3] shift [4], is converted to diimine VI, which subsequently gives tryptophol II via the usual Fischer scheme. Hydrolytic opening of the lactone ring and decarboxylation may also occur after the step involving the sigmatropic [3.3] shift.

We used only the acetyl group as the acyl group, since under these conditions cyclization proceeds at the CH_2 group but not at CH_3. When other acylbutyrolactones are used, mixtures of 2- and 3-hydroxyalkylindoles are formed; we will deal with this matter in subsequent papers.

Only 1-phenyl-3-methyl-4-(2-hydroxyethyl)-5-pyrazolone was isolated in 65% yield in an attempt to use phenylhydrazine to obtain 1-unsubstituted tryptophol under the same conditions [5].

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*See [1] for communication XLI.

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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 UR-20 spectrometer. The PMR spectra of CCl_4 solutions were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. Chromatography was carried out in a thin layer of Al_2O_3 (activity II) in benzene–isopropyl alcohol (20 : 1). The individuality of the compounds was also confirmed by gas–liquid chromatography (GLC) with a Yanaco G-800 chromatograph with a 2-m-long column filled with SE-30 silicone (5%) on chezosorb (0.25-0.35 mm); the column temperature was 240°, and the carrier gas (H_2) flow rate was 36.5 ml/min.

Commercial grade α-benzyl-α-phenyl-, α-methyl-α-phenyl-, and α,α-diphenylhydrazine salts were used. α-Isopropyl-α-phenylhydrazine hydrochloride was obtained by the method in [6].

General Method for the Preparation of Tryptophols IIa-d. A solution of 0.05 mole of α-acetyl-γ-butyrolactone and 0.05 mole of arylhydrazine salt in a mixture of 55 ml of isopropyl alcohol, 30 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 8 h, after which the solvents were evaporated on a rotary evaporator, and the residue was treated with 30 ml of benzene and 50 ml of water. The benzene layer was washed several times with water, separated, and dried. The benzene was evaporated, and the residue was vacuum distilled. The crude product was additionally purified by passing 2 g of it through a column (20 cm long and 3 cm in diameter) fillwed with activity II Al_2O_3 with successive elution with hexane, hexane–benzene (1 : 1), and benzene. The yield of pure sample was 1.3-1.5 g.

1-Benzyl-2-methyltryptophol (IIa). This compound, with mp 80-80.5° (from hexane) and R_f 0.51, was obtained in 58% yield.* UV spectrum: λ_{max} 226, 285 nm (log ε 4.48, 3.83). IR spectrum: 3637 (OH), 1618, 1496 cm^{-1} (ring stretching vibrations). PMR spectrum,† δ, ppm: 1.67 s (OH), 2.20 s (2-CH_3), 2.86 t (J = 7 Hz, 3-α-CH_2), 3.63 t (J = 7 Hz, 3-β-CH_2), 5.12 s (1-CH_2), 6.70-7.50 m (aromatic protons). Found, %: C 81.1; H 7.1. $C_{18}H_{19}NO$. Calculated, %: C 81.5; H 7.2.

1-Phenyl-2-methyltryptophol (IIb). This compound, with bp 195-210° (1 mm), mp 69-70°, and R_f 0.46, was obtained in 57% yield. UV spectrum: λ_{max} 223, 267, 285 nm (log ε 4.65, 4.14, 4.08). IR spectrum: 3637 (OH), 1600, 1505 cm^{-1} (ring stretching vibrations). PMR spectrum, δ, ppm: 1.83 s (OH), 2.19 s (2-CH_3), 2.90 t (J = 7 Hz, 3-α-CH_2), 3.70 t (J = 7 Hz, 3-β-CH_2), 6.90-7.50 m (aromatic protons). Found, %: C 80.3; H 6.6. $C_{17}H_{17}NO$. Calculated, %: C 81.2; H 6.8.

1,2-Dimethyltryptophol (IIc). This compound, with bp 170-180° (1 mm) and R_f 0.47, was obtained in 41% yield. UV spectrum: λ_{max} 229, 284 nm (log ε 4.61, 3.87). IR spectrum (liquid film): 3400 (OH_{bonded}), 1610, 1480 cm^{-1} (ring stretching vibrations). PMR spectrum, δ, ppm: 2.03 s (OH), 2.23 s (2-CH_3), 2.77 t (J = 7 Hz, 3-α-CH_2), 3.47 (1-CH_3), 3.56 t (J = 7 Hz, 3-β-CH_2), 6.8-7.3 m (aromatic protons). Found, %: C 74.8; H 8.0; N 7.3. $C_{12}H_{15}NO$. Calculated, %: C 76.2; H 8.0; N 7.4.

1-Isopropyl-2-methyltryptophol (IId). This compound, with R_f 0.49, was obtained in 55% yield. UV spectrum, λ_{max}: 230, 284 nm (log ε 4.53, 3.81). IR spectrum: 3600 (OH), 1600, 1500 cm^{-1} (ring stretching vibrations. PMR spectrum, δ, ppm: 1.53 d [J = 8 Hz, $(CH_3)_2C$], 1.79 s (OH), 2.30 s (2-CH_3), 2.81 t (J = 7 Hz, 3-α-CH_2), 3.61 t (J = 7 Hz, 3-β-CH_2), 4.58 m (1-CH), 6.8-7.4 m (aromatic protons). Found, %: C 77.2; H 8.8. $C_{14}H_{19}NO$. Calculated, %: C 77.4; H 8.8.

1-Phenyl-3-methyl-4-(2-hydroxyethyl)-5-pyrazolone. This compound was obtained from phenylhydrazine hydrochloride. After removal of the solvent from the reaction mixture, the residue was dissolved in hydrochloric acid (1 : 1), and the solution was washed several times with chloroform. It was then made alkaline with KOH until the initially formed emulsion had dissolved, after which it was washed several times with chloroform. The alkaline solution was neutralized with acetic acid and extracted with chloroform. The solution of the pyrazolone in chloroform was filtered through a layer of aluminum oxide, the solvent was evaporated, and the residue was obtained in 65% yield as a chromatographically pure sample with bp 209-211° (2 mm) (dec.) and R_f 0.23 [benzene–isopropyl alcohol (9 : 1)]. UV spectrum: λ_{max} 248 nm (log ε 4.23). IR spectrum (in KBr): 3400 (OH_{bonded}), 1700 cm^{-1} (C = O). Found, %: C 65.2; H 6.3. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.0; H 6.5.

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*Here and elsewhere, the yields indicated are for the products obtained after distillation.

† The abbreviations used here and elsehwere are as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

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