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SYNTHESIS OF TRYPTAMINES CONTAINING A SULFO GROUP IN THE BENZENE RING

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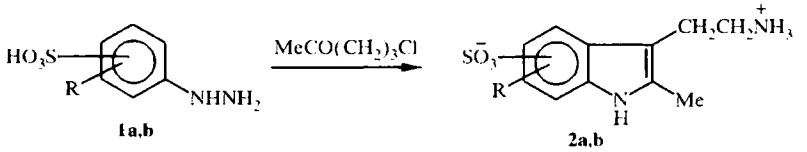
It has been shown that sulfophenylhydrazines can be used successfully in a single stage synthesis of tryptamines from arylhydrazines and γ-chlorocarbonyl compounds.

Keywords: tryptamine-sulfonic acids, phenylhydrazine-sulfonic acids, ω-chlorobutyraldehyde.

In previously published work describing a single stage synthesis of tryptamines from arylhydrazines and γ-chlorocarbonyl compounds, reviewed in [1, 2], it was found that the basic stage of the process (being a modified Fischer indole synthesis) can be considered as a [3,3]-sigmatropic shift. For this reason, we have proposed that the Fischer synthesis of indoles proceeds *via* a [3,3]-sigmatropic shift [3]. It is known that electronic factors have a weak influence on the processes occurring in a scheme of sigmatropic shifts [4]. However, in our previous work there were few examples of tryptamine synthesis from phenylhydrazines which contained powerful electron acceptor substituents. This was caused by the difficulty in separating the nitro substituted tryptamines from the reaction mixtures.

In the work mentioned it was found possible to introduce arylhydrazines containing sulfo groups in different positions of the benzene ring smoothly and with acceptable yields. Moreover, the conditions for the cyclization were usual for these processes. Hydrazine **1a** gave only the one tryptamine **2a**, apparently due to steric hindrance.

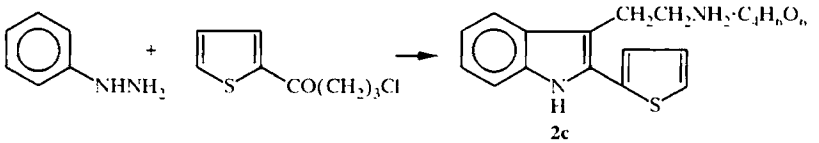


1a,b **2a,b**

1 a 3-SO_3H, R = 4-OPh; b 4-SO_3H, R = H

2 a 6-SO_3^-, R = 5-OPh; b 5-SO_3^-, R = H

This data fully confirms our proposal [1-3] that the Fischer indole synthesis occurs via a [3,3]-sigmatropic shift. It was also possible to introduce the thiophene analog of γ-chloropropyl phenyl ketone into this reaction [5]. The tryptamine was very contaminated and was separated only as the tartrate.



2c

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EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer 577 instrument for KCl tablets, UV spectra were recorded on a Specord M-40 spectrophotometer, and ^{1}H NMR spectra on a Bruker WM-250 using DMSO-d_6 solvent.

2-Methyl-5-sulfotryptamine (2b). A mixture of *p*-sulfophenylhydrazine (5.64 g, 0.03 mol), sodium acetate trihydrate (4.1 g, 0.03 mol), and γ-chloropropyl methyl ketone (4 g, 0.03 mol) in methyl cellosolve (15 ml) and water (6 ml) was heated on a boiling water bath for 6 h. An abundant precipitate was formed in the heating process. After addition of conc. HCl (3 ml) the reaction mixture was evaporated to dryness on a rotary evaporator, placed in a Soxhlet apparatus, and extracted with water over 3 h. Already after 1 h of extraction all of the contaminant was transferred to the aqueous solution and the basic product remained within the filter. It was dried to give the internal tryptamine salt (3.9 g, 51%) as a greyish-brown powder; mp ~350°C (dec.). IR spectrum: 1620, 1480, 1465 cm^{-1}. UV spectrum (H_2O + NaOH), λ_{max} (log ε): 233 (4.69); 270 nm (4.33). ^{1}H NMR spectrum: 2.30 (3H, s, 2-CH_3); 2.8-2.9 (4H, m, CH_2CH_2); 7.16 (1H, d, J = 6 Hz, 7-H); 7.37 (1H, d, J = 6 Hz, 6-H); 7.75-7.90 (br. s, 4-H and NH_3^+); 10.8 ppm (1H, s, NH). Found, %: C 51.4; H 5.4; N 10.6. $C_{11}H_{14}N_2O_3S$. Calculated, %: C 52.0; H 5.5; N 11.0.

2-Methyl-5-phenoxy-6-sulfotryptamine (2a). A mixture of 3-sulfo-4-phenoxyphenylhydrazine (14 g, 0.05 mol), sodium acetate trihydrate (6.8 g, 0.05 mol), and γ-chloropropyl methyl ketone (6.6 g, 0.05 mol) was heated at reflux on a boiling water bath for 8 h in methyl cellosolve (25 ml) and water (6 ml). Conc. HCl (5 ml) in water (10 ml) was added to the reaction mixture and the product was evaporated to dryness on a rotary evaporator. The residue was extracted with water using the Soxhlet apparatus for 20 h. Dark grey crystals (4.8 g, 28%) were obtained from the extract. For purification they were refluxed for 0.5 h with benzene (15 ml), the benzene was discarded, and the operation was repeated a further time with ethanol (15 ml) to give the tryptamine (3.8 g, 22%); mp 278-279°C (with decomposition in a sealed capillary). IR spectrum: 1630, 1600, 1480, 1450 cm^{-1}. UV spectrum (water + NaOH), λ_{max} (log ε): 239 (4.55); 292 nm (4.33). ^{1}H NMR spectrum: 2.30 (3H, s, 2-CH_3); 2.7-2.9 (4H, m, CH_2CH_2); 6.8-6.9 (5H, m, OPh); 7.15 (1H, s, 4-H); 7.85 (1H, s, 7-H); 7.75 (3H, br. s, NH_3^+); 10.8 ppm (1H, s, NH). Found, %: C 59.4; H 5.3. $C_{17}H_{18}N_2O_4S$. Calculated, %: C 58.9; H 4.9.

2-(α-Thienyl)tryptamine Tartrate (2c). A mixture of γ-chloropropyl α-thienyl ketone (5 g, 0.0265 mol), acetic acid (three drops), and freshly distilled phenylhydrazine (2.86 g, 0.0265 mol) in ethylene glycol (20 ml) was heated on an oil bath for 5 h at 150°C. The reaction mixture was acidified with HCl (5 ml) and evaporated to dryness in vacuo. The cooled, oily mass was extracted with water in the Soxhlet apparatus for 20 h. The aqueous extract was basified with sodium hydroxide and an tared mass of the tryptamine separated. An equimolar amount of the dry tryptamine and tartaric acid were triturated in absolute methanol and the tared salt separated was triturated with absolute ether (up to 7 times) to give the tartrate as a grey powder (3.6 g, 34%). For purification the substance was heated at reflux for 15 min with ethyl acetate (15 ml), the ethyl acetate was discarded and the whole operation was repeated with absolute alcohol (15 ml). Mp 167-169°C. IR spectrum: 1710, 1600, 1500 cm^{-1}. UV spectrum (alcohol), λ_{max} (log ε): 245 (4.20); 323 nm (4.22). ^{1}H NMR spectrum: 3.0, 3.2 (4H, m, CH_2CH_2); 7.1-7.8 (7H, m, Ar); 11.0 ppm (1H, s, NH). Found, %: C 54.6; H 4.9; N 6.8. $C_{18}H_{20}N_2O_6S$. Calculated, %: C 55.1; H 5.1; N 7.1.

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