INDOLES

XLIV.* SYNTHESIS OF 1-SUBSTITUTED TRYPTOPHANS

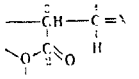
I. I. Grandberg and G. P. Tokmakov

UDC 547.755.07

1-Substituted tryptophans were obtained by heating α-formyl-γ-butyrolactone with N_1-substituted arylhydrazines in aqueous acidic media.

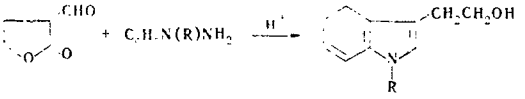
The known methods for the synthesis of tryptophols are based either on the use of an already existing indole ring or on the reaction of arylhydrazines with γ-acylpropyl alcohols, which are obtained from α-acyl-γ-butyrolactones. However, γ-hydroxybutryaldehyde cannot be obtained by hydrolysis and decarboxylation of α-formyl-γ-butyrolactone (I), inasmuch as acid cleavage to butyrolactone and formic acid occurs. Thus, tryptophols that do not have substituents in the 2-position cannot be synthesized by this method.

We have previously reported the synthesis of 1,2-disubstituted tryptophols directly from α-acetyl-γ-butryolactone [2], by-passing the step involving the production of acetylpropyl alcohol. We therefore assumed that hydrolysis and decarboxylation of arylhydrazones of α-formyl-γ-butyrolactone would occur under similar conditions because of the decrease in the polarity of the C_3-C_4 bond in structure A when the oxygen atom (X=O) is replaced by a nitrogen atom (X=NR).



A

By carrying out the reaction of lactone I with N_1-substituted phenylhydrazines we were able to obtain 2-unsubstituted tryptophols (IIa-d) in good yields. The assumed reaction scheme is presented in [2].



I II

IIa R=C_6H_5; b R=$CH_2C_6H_5$; c R=CH_3; d R=$CH(CH_3)_2$

EXPERIMENTAL

The UV spectra of isopropyl alcohol solutions of the compounds were recorded with an Hitachi EPS-3T spectrophotometer. The IR spectra of CCl_4 solutions were recorded with a UR-20 spectometer. The PMR spectra of CCl_4 solutions were recorded with a Varian T-60 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The melting points were determined with a Mettler F-P5 apparatus. Analysis by gas-liquid chromatography (GLC) was carried out with a Yanaco-G 800 T chromatograph at a carrier gas (H_2) flow rate of 40 ml/min. Column I consisted of 5% SE-30 silicone on Chezosorb (Czechoslovakian SSR), 0.25-0.36 mm, washed with acid and silanized with HMDS; the packing had a polarity of 12% with respect to β,β'-dihydroxydipropionitrile [3]. Column II consisted of 5% poly-

*For Communication XLIII see [1].

K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1083-1084, August, 1974. Original article submitted August 6, 1973.

©1976 Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for $15.00.

ethylene glycol (molecular weight 6000) on Porolit (Czechoslovakian SSR), 0.25-0.35 mm, containing 5% KOH with a relative polarity of 39%. Corrected retention times (t_r^I and t_r^{II}) were obtained, and the Kovacs retention indices (I_I and I_{II}) were calculated for the 1-alkyltryptophols (200 and 220°) and for the 1-aryltryptophols (220 and 240°). Chromatography was carried out in a thin layer of activity II Al_2O_3 in benzene–isopropyl alcohol (20:1). The chromatograms were developed with iodine vapors.

Commercial-grade salts of 1-benzyl-1-phenyl-, 1-methyl-1-phenyl-, and 1,1-diphenylhydrazines were used. 1-Isopropyl-1-phenylhydrazine hydrochloride was obtained by the method in [4]. α-Formyl-γ-butyrolactone (I) was obtained by the method in [5].

General Method for the Preparation of Tryptophols (IIa-d). A solution of 0.04 mole of lactone I and 0.04 mole of N_1-substituted phenylhydrazine in a mixture of 50 ml of isopropyl alcohol, 30 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 5 h, after which the solvents were evaporated with a rotary evaporator, and 40 ml of benzene and 60 ml of water were added to the residue. The benzene was evaporated, and the residue was vacuum distilled. The resulting crude product (2 g) can be subjected to additional purification with a chromatographic column (50 by 2.5 cm) filled with activity II Al_2O_3 by elution initially with benzene and then with benzene–isopropyl alcohol (40:1). The yield of pure sample from the column was 1.4-1.5 g.

1-Phenyltryptophol (IIa). This compound, with bp 170-173° (1 mm and R_f 0.58 was obtained in 62% yield* from 1,1-diphenylhydrazine hydrochloride. GLC: 220° (t_r^I=7.92, I_I=2268: t_r^{II}=37.5, I_{II}=3543), 240° (t_r^I=3.64, I_I=2261; t_r^{II}=19.50, I_{II}=3557). Found: C 81.1; H 6.4%. $C_{16}H_{15}NO$. Calculated: C 81.0; H 6.4%. According to [6], this compound has bp 185° (1 mm).

1-Benzyltryptophol (IIb). This compound, with mp 53° (ether–pentane) and R_f 0.59, was obtained in 58% yield from 1-benzyl-1-phenylhydrazine hydrochloride. GLC: 220° (t_r^I=9.30, I_I=2320; t_r^{II}=50.0, I_{II}=3623), 240° (t_r^I=4.40, I_I=2333; t_r^{II}=24.80, I_{II}=3651). According to [6], this compound has mp 51° (from pentane).

1-Methyltryptophol (IIc). This compound, with bp 130-133° (0.5 mm) and R_f 0.55, was obtained in 46% yield from 1-methyl-1-phenylhydrazine hydrosulfate. GLC: 200° (t_r^I=2.70, I_I=1733; t_r^{II}=22.91, I_{II}=2718), 220° (t_r^I=1.67, I_I=1758; t_r^{II}=4.36, I_{II}=2755). PMR spectrum,† δ, ppm: 2.41 s (OH), 2.78 t (J=7 Hz, 3-α-CH_2), 3.47 s (1-CH_3), 3.63 t (J=7 Hz, 3-β-CH_2), 6.59 s (2-H), and 6.80-7.50 m (aromatic protons). Found: C 75.0; H 7.5%. $C_{11}H_{13}NO$. Calculated: C 75.4; H 7.5%. According to [6], this compound has bp 158-160° (1 mm).

1-Isopropyltryptophol (IId). This compound, with mp 78.3° (from hexane) and R_f 0.60, was obtained in 54% yield from 1-isopropyl-1-phenylhydrazine hydrochloride. GLC: 200° (t_r^I=3.51, I_I=1813; t_r^{II}=32.60, I_{II}=2829), 220° (t_r^I=2.075, I_I=1829; t_r^{II}=5.43, I_{II}=2834). UV spectrum, λ_{max}: 226, 280 (infl) nm (log ε: 4.52, 3.67, 3.72, and 3.68). IR spectrum: 3630 (OH), 1612 cm^{-1} (ring stretching vibrations). PMR spectrum, δ, ppm: 1.38 d [J=7 Hz $(CH_3)_2C$], 2.15 s (OH), 2.83 t (J=7 Hz, 3-α-CH_2), 3.68 t (J=7 Hz, 3-β-CH_2), 4.48 m (J=7 Hz, 1-CH), 6.70-7.50 m (2-H and aromatic protons). Found: C 77.0; H 8.5%. $C_{13}H_{17}NO$. Calculated: C 76.8; H 8.4%.

LITERATURE CITED

1. R. A. Khmel'nitskii, N. A. Klyuev, A. F. Dolgikh, N. I. Bobrova, and I. I. Grandberg, Izv. Timiryazev. Sel'skokhoz. Akad., 1, 176 (1974).
2. I. I. Grandberg and G. P. Tokmakov, Khim. Geterotsikl. Soedin., 204 (1974).
3. B. A. Rudenko, É. L. Il'kova, V. F. Kucherov, and N. A. Kerimova, Zh. Analit. Khim., 25, 1405 (1970).
4. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 342 (1971).
5. T. Kaneko, K. Wakabayashi, and H. Katsura, Bull. Chem. Soc. Japan, 35, 1149 (1962).
6. I. I. Grandberg and T. P. Moskvina, Khim. Geterotsikl. Soedin., 1366 (1972).

*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.