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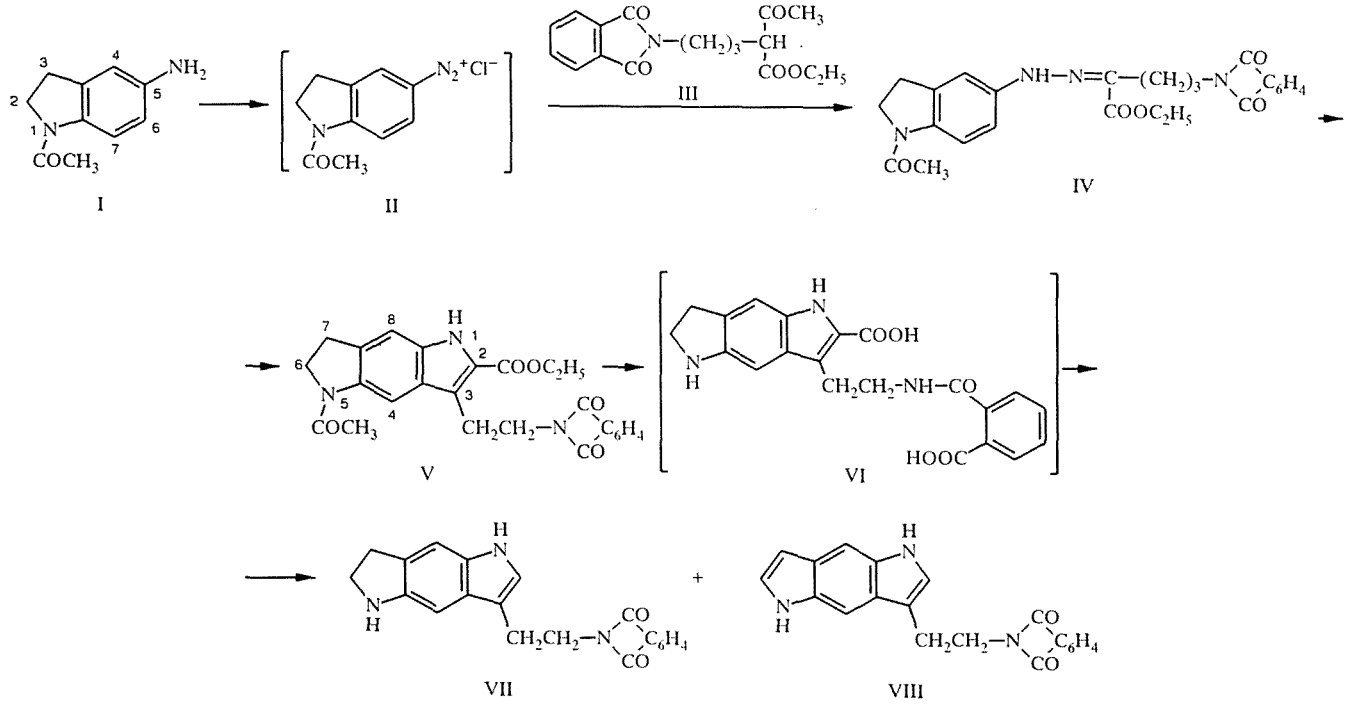
PYRROLOINDOLES.
15.* SYNTHESIS OF TRYPTAMINE ANALOGS. 6,7-DIHYDRO-3-(2-PHTHALIMIDOETHYL)-1H,5H-PYRROLO[2,3-f]INDOLE AND 3-(2-PHTHALIMIDOETHYL)-1H,5H-PYRROLO[2,3-f]INDOLE

D. O. Kadzhrishvili, E. N. Gordeev, Sh. A. Samsoniya, and N. N. Suvorov

Diazotization of 1-acetyl-5-aminoindoline and reaction of the diazonium salt with ethyl α-acetyl-δ-phthalimidovalerate gave the 1-acetyl-5-indolinyl hydrazone of ethyl α-keto-δ-phthalimidovalerate. Cyclization of the hydrazone and subsequent hydrolysis, decarboxylation, and dehydrogenation of the pyrroloindoline gave the corresponding tryptamines.

The aim of this work was to synthesize a tryptamine analog based on 1-acetyl-5-aminoindoline (I).

Literature methods for preparation of tryptamines can be divided into two groups. 1) Synthesis involving closure of the indole ring using a suitable side chain and 2) synthesis using compounds already having the indole nucleus. Syntheses of type 1) have been described by Fischer [2, 3].



*For Communication 14, see [1].

I. Dzhavakhishvili State University, Tbilisi 380028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 209-212, February, 1994. Original article submitted July 20, 1993.

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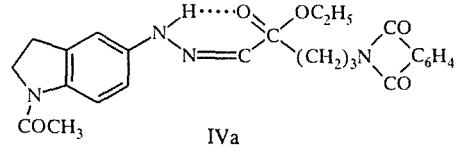
TABLE 1. Some Parameters for Compounds IV, V, VII, and VIII

Compound	Empirical formula	mp, °C	R_f*	IR Spectrum, ν, cm^{-1}		UV Spectrum, λ_{max}, nm (log ε)	Yield, %
				NH	CO		
IVa	$C_{25}H_{26}N_4O_5$	143...144	0,53	3150	1755, 1690 1655, 1620	220 (4,82) 266 (4,31) 370 (4,41)	9
IVb	$C_{25}H_{26}N_4O_5$	267...268	0,38	3220	1760, 1700 1685, 1630	220 (4,70) 242 (4,30) 350 (4,37)	68
V	$C_{25}H_{23}N_3O_5$	280...281	0,58	3330	1775, 1720 1690, 1650	—	70
VII	$C_{20}H_{17}N_3O_2$	234...235	0,23	3280 3250	1760, 1700	220 (4,91) 290 (4,46) 303 (4,45)	5
VIII	$C_{20}H_{15}N_3O_2$	247...248	0,35	3360 3340	1750, 1700	222 (4,80) 232 (4,65) 303 (4,22)	15

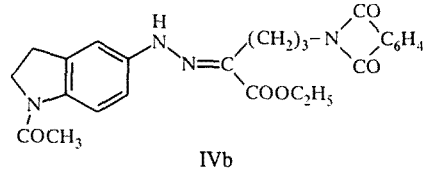
*Benzene–acetone, 3:1.

Preparation of a tryptamine analog based on 1-acetyl-5-amino-indoline (I) was carried out by us according to the above scheme.

Diazotization of I and Japp–Klingermann reaction of the diazonium salt II with ethyl α-acetyl-δ-phthalimidovalerate (III) gave the 1-acetyl-5-indolinyl hydrazone of ethyl α-keto-δ-phthalimidovalerate (IV) as a mixture of syn and anti isomers (IVa and IVb).



IVa



IVb

In the IR spectrum of cis isomer IVa the NH absorption band is shifted to lower wave number by 70 cm^{-1} when compared with the corresponding band in the anti isomer due to the presence of an intramolecular hydrogen bond in the syn form (Table 1). The intramolecular hydrogen bond also causes a 20 nm bathochromic shift of the long wavelength absorption maximum for the IVa when compare with the IVb (Table 1). In the syn configured isomer IVa the NH proton NMR signal is seen at lower field than in the anti isomer IVb (Table 2).

Cyclization of hydrazone IV was carried out with different cyclizing agents. The best results were obtained using a mixture of acetic and sulfuric acids (yield 60-70%); differences in the cyclization of hydrazone isomers IVa, b were not observed.

Hydrolysis of the cyclization product 5-acetyl-2-carbethoxy-3-(2-phthalimidoethyl)-6,7-dihydro-1H,5H-pyrrolo-[2,3-f]indole (V) in aqueous base gives a 91% yield of 2-carboxy-3-(2-O-carboxybenzamidoethyl)-6,7-dihydro-1H,5H-pyrrolo[2,3-f]indole (VI). Acid VI is used in subsequent reactions without further purification. The structure of VI was assumed on the basis of our previous publication [3].

Decarboxylation and dehydrogenation were carried out in one stage by heating acid VI in an inert gas atmosphere using 10% Pd/C. The two compounds separated from the reaction mixture were 6,7-dihydro-3-(2-phthalimidoethyl)-1H,5H-pyrrolo-[2,3-f]indole (VII) and 3-(2-phthalimidoethyl)-1H,5H-pyrrolo[2,3-f]indole (VIII) (see Tables 1 and 3).

TABLE 2. Chemical Shift Values (δ, ppm) and Spin–Spin Couplings (J, Hz) in the PMR Spectra of IVa, b in $CDCl_3$

Compound	2-H_2	3-H_2	4-H	6-H	7-H	NH	$COCH_3$	$\underline{CH_3}CH_2$	$CH_3\underline{CH_2}$	$(CH_2)_3$	C_6H_4	J, Hz
IVa	4,03 t	3,16 t	7,7 d	7,7 dd	8,11 d	12,0 br s	2,19 s	1,31 t	4,23 q	(a) 2,58 t (b) 2,10 m (c) 3,77 t	7,22 br s	J_{23} = 9,0; J_{67} = 7,9; $J_{CH_2CH_3}$ = 7,0 J_{46} = 1,4
IVb	4,04 t	3,17 t	7,18 d	7,09 dd	8,09 d	8,9 br s	2,19 s	1,35 t	4,27 q	(a) 2,63 t (b) 1,97 m (c) 3,74 t	7,77 br s	J_{23} = 7,7; J_{67} = 8,5; $J_{7,NH}$ = 2,0; $J_{CH_3CH_2}$ = 6,9; $J_{CH_2CH_2}$ = 7,4; $J_{CH_2CH_2}$ = 6,3; J_{46} = 1,4

TABLE 3. PMR Spectra of V, VII, and VIII in DMSO-d_6 (δ, ppm)

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	$COCH_3$	$\underline{CH_2}CH_3$	$CH_2\underline{CH_3}$	3-CH_2	N-CH_2	C_6H_4	J, Hz
V	11,1 br s	–	–	8,11 d	–	4,1 t	3,2 t	7,17 d	2,15 s	4,20 q	1,28 t	3,31 t	3,83 t	7,70 br s	$J_{CH_2CH_2}$ = 6,1; $J_{CH_2CH_3}$ = 7,1; J_{48} = 0,6; J_{67} = 8,0
VII	10,7 br s	6,97 d	–	7,0 d	10,5 br s	3,9 t	3,1 t	7,20 d	–	–	–	2,90 t	3,80 t	7,79 br s	J_{12} = 2,5; J_{48} = 0,8; $J_{CH_2CH_2}$ = 7,0
VIII	10,2 br s	7,05 d	–	7,35 d	10,5 br s	7,20 dd	6,31 dd	7,45 d	–	–	–	2,92 t	3,87 t	7,80 br s	J_{12} = 2,6; J_{48} = 0,7; J_{57} = 1,9; J_{67} = 3,1; $J_{CH_2CH_2}$ = 8,2

EXPERIMENTAL

The reaction course and compound purities were monitored on Silufol UV-254 plates. IR spectra were recorded on vaseline oil on a UR-20 instrument and PMR spectra on a WP-200 SY instrument with TMS internal standard.

Elemental analytical data for the compounds synthesized agreed with those calculated.

1-Acetyl-5-indolinyl Hydrazone of Ethyl α-Keto-δ-phthalimidovalerate (IV). A solution of the diazonium salt obtained by diazotiation of 1-acetyl-5-aminoindoline (I, 1 g, 6 mmoles) was added slowly with stirring to a cooled (−10°C) solution of ethyl α-keto-δ-phthalimidovalerate (III) in acetic acid (20 ml). The pH was maintained at 5 by adding sodium acetate. The product was stirred for 10 h and the precipitate filtered, washed with water, and dried to give a mixture of stereoisomers. The mixture was separated on a column, eluting with chloroform (Table 1).

5-Acetyl-2-carbethoxy-3-(2-phthalimidoethyl)-6,7-dihydro-1H,5H-pyrrolo[2,3-f]indole (V). The 1-acetyl-5-indolinyl hydrazone of ethyl α-keto-δ-phthalimidovalerate (IV, 1.0 g, 2 mmoles) was dissolved in glacial acetic acid. It was heated to 80°C and concentrated H_2SO_4 (3-4 drops) added. After cooling, the precipitate was filtered, washed with water, dried, and recrystallized from acetic acid (Table 1).

3-(2-Phthalimidoethyl)-1H,5H-pyrrolo[2,3-f]indole (VIII) and 6,7-Dihydro-3-(2-phthalimidoethyl)-1H,5H-pyrrolo[2,3-f]indole (VII). A suspension of V (10 g, 0.02 mole), KOH (13 g), and water (100 ml) was stirred under reflux for 2-3 h. The product was cooled, filtered, and acidified with acetic acid to pH 4-5. The precipitate was filtered, washed with water, and dried. A mixture of the unpurified VI (8 g, 91%) and 10% Pd/C (4 g) was heated at 330°C and 30 min in an argon stream. The product was cooled, extracted with acetone, and evaporated. Separation of this mixture was carried out on a column eluting with benzene−ether (20:1) (Table 1).

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3. N. N. Suvorov, E. N. Gordeev, and M. V. Vanin, Khim. Geterotsikl. Soedin., No. 11, 1496 (1974).