INDOLE DERIVATIVES.

126.* SUBSTITUTED NITROTRYPTAMINES

L. Kh. Vinograd and N. N. Suvorov

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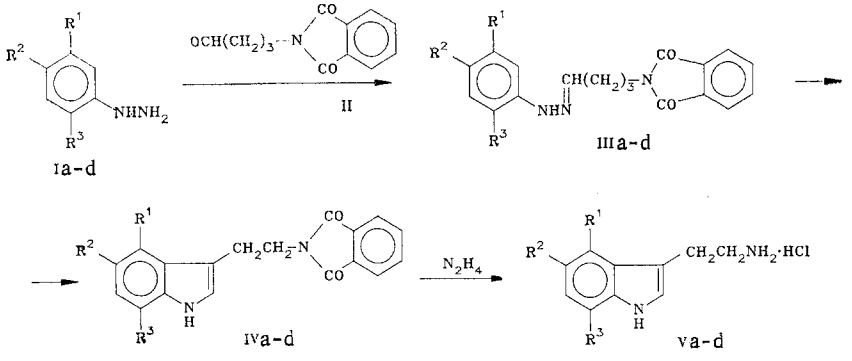
A preparative method has been developed for obtaining substituted nitrotryptamines from the corresponding nitrophenylhydrazones of γ-phthalimidobutyraldehyde.

Abramovich and Shapiro's universal method for obtaining tryptamines is complicated because the starting materials are hydrazones containing a nitro group in a benzene ring. The use of the latter requires the application of severe conditions both in the cyclization of the nitrophenylhydrazones and in the decarboxylation of the nitrotryptaminecarboxylic acids. However, even when these conditions are observed the yield of tryptamines is extremely low [1]. We have found [2] that the difficulties mentioned can be overcome if the substituted nitrotyramines are obtained from the corresponding hydrazones (I) and γ-phthalimidobutyraldehyde (II) by the following scheme:

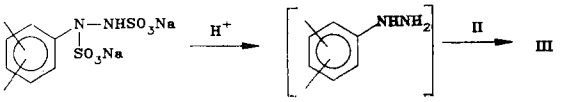


Ia-d; II; IIIa-d; IVa-d; Va-d

a $R^1=NO_2$, $R^3=CH_3O$; b $R^2=CH_3O$, $R^3=NO_2$; c $R^2=NO_2$, $R^3=CH_3O$; d $R^2=Cl$, $R^3=NO_2$; wherever not specified, R = H

As the cyclizing agent we have proposed [2] to use a boiling solution of sulfosalicylic acid in acetic acid. The use of this reagent ensures conditions under which the hydrazone takes part in the reaction practically instantaneously and the heat liberated is removed by the vapors of the boiling solvent. This makes it possible to regulate the intensity of the process by the speed of addition of the hydrazone and to use considerable charges of the latter. On cooling, the phthalimidotryptamines separate out in the fairly pure state. In the proposed method, no decarboxylation is required. The phthalimide protective group is eliminated by hydrazinolysis under the usual conditions.

In the preparation of the initial phenylhydrazines by reducing diazonium salts with sodium sulfite [3], the stage of hydrolyzing the disulfonic acids can conveniently be combined with the formation of the hydrazone



The γ-phthalimidobutyraldehyde (II) was synthesized from γ-aminobutyric acid by phthalylation, conversion into the acid chloride, and the Rosenmund reduction of the latter [4].

*For communication 125, see [1].

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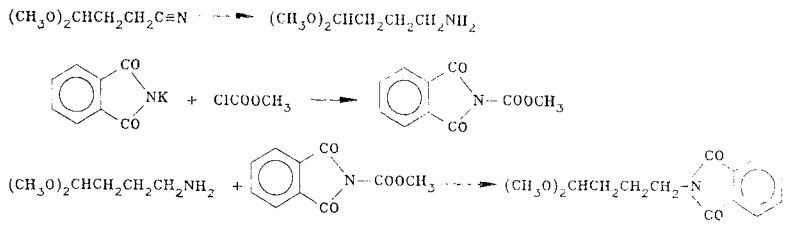
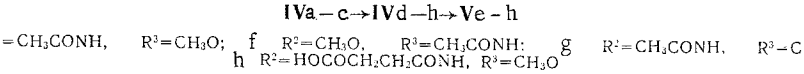
In addition to the aldehyde (II) it was possible to obtain an acetal — for example, the dimethyl acetal — of it. The conditions of performing the reaction and the yields did not change in this case. The acetal was obtained by the following scheme:



Other phenylhydrazones of γ-phthalimidobutyraldehyde containing no nitro group can also be used in the synthesis of tryptamines. For example, 5-benzyloxyphthalyltryptamine — the starting compound for the synthesis of serotonin — has been obtained from 4-benzyloxyphenylhydrazine and the aldehyde (II). In this case, the cyclization of the hydrazone took place so readily that its formation could be observed simply by subjecting the reaction mixture to TLC. A solution of sulfosalicylic acid in boiling acetic acid is convenient also for the cyclization of other hydrazones, not containing nitro groups.

The possibility of the reduction of the nitro groups in the tryptamines obtained both before and after the elimination of the protective phthalyl group expands the preparative possibilities of the method. Thus, the free tryptamine (Va) has been reduced to 4-amino-7-methoxytryptamine (VI). When the nitrophthalyltryptamines (IVa-c) were reduced in the presence of acetic or succinic anhydride, the acylaminophthalyltryptamines (IVe-h) and, after their hydrazinolysis the acylaminotryptamines (Ve-h), were obtained.



The absorption bands in the IR spectra of the substances obtained did not deviate from the standard positions (cm^{-1}): NH, 3240-3470; CO of an imide, 1760-1765, 1700-1705; NO_2, 1520-1560 and 1310-1330; C=N in hydrazones, 1580-1590. The radioprotective properties of the tryptamines obtained have been reported previously [5].

EXPERIMENTAL

IR spectra were recorded on a Perkin—Elmer instrument in paraffin oil, and PMR spectra on a Varian XL-100 instrument using D_2O as solvent and DSS as internal standard.

γ-Phthalimidobutyric Acid. A mixture of 177.6 g (1.2 mole) of phthalic anhydride and 129.6 g (1.26 mmole) of γ-aminobutyric acid was heated to 180°C (foaming was observed at 130 °C), the melt was poured with stirring into 1.5 liters of water, and the precipitate was washed with dilute hydrochloric acid and with water and dried at 80-90°C to give 264.4 g (94%) of a white powder with mp 114.2°C (from 50% aqueous ethanol); according to the literature [6]: mp 117-118°C.

γ-Phthalimidobutyryl Chloride. At 30-40°C, 0.5 ml of DMFA and 100 ml of purified thionyl chloride were added to 74 g (0.318 mole) of γ-phthalimidobutyric acid, the mixture was gradually heated to 70°C, the excess of thionyl chloride was distilled off in vacuum with the addition of benzene, and 80-82 g (about 100%) of a light yellow oil was obtained which, on crystallization from xylene—petroleum ether, had mp 68-70°C; according to the literature [6], mp 67-69°C (from ligroin).

γ-Phthalimidobutyraldehyde (II) . To a solution of 43.4 g (0.2 mole) of the acid chloride in 300 ml of sulfur-free xylene were added 15 g of $Pd/BaSO_4$ catalyst [7] and 1.2 ml of catalyst poison [8], and a current of hydrogen was passed with stirring and boiling. The course of the reaction was followed from the amount of hydrogen chloride liberated, which was determined by its titration with a solution of caustic soda. After 5-6 h, about 80% of the calculated amount of hydrogen chloride had been evolved. The catalyst was filtered off, and the xylene was distilled off in vacuum. The aldehyde was used without further purification. The yield of technical product was about 100%, mp 70-75°C; according to the literature [4]: mp 72-73°C (after vacuum distillation). 2,4-Dinitrophenylhydrazone, mp 182-183°C; according

TABLE 1. Characteristics of the Compounds Synthesized

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	Cl		C	H	N	Cl	
IIIa	144—145	59,3	4,8	14,6		$C_{19}H_{18}N_4O_5$	59,3	4,7	14,6		82
IIIb	158—160	58,9	4,8	14,5		$C_{19}H_{18}N_4O_5$	59,6	4,7	14,6		89
IIIc	151—152	59,3	5,0	14,8		$C_{19}H_{18}N_4O_5$	59,6	4,7	14,6		92
IIId	175—176			14,4		$C_{18}H_{15}ClN_4O_4$			14,5		76
IVa	237—239	62,2	4,1	11,3		$C_{19}H_{15}N_3O_5$	62,5	4,1	11,5		82
IVb	244—246	62,0	4,1	11,4		$C_{19}H_{15}N_3O_5$	62,5	4,1	11,5		84
IVc	238—239	62,2	4,2	11,4		$C_{19}H_{15}N_3O_5$	62,5	4,1	11,5		49
IVd	279—280	58,8	4,0	11,2	9,5	$C_{18}H_{12}ClN_3O_4$	58,5	3,3	11,4	9,6	84
IVe	267—268	66,4	5,0	11,3		$C_{21}H_{19}N_3O_4$	66,8	5,1	11,1		80
IVf	213—215	66,4	4,8	10,9		$C_{21}H_{19}N_3O_4$	66,8	5,1	11,1		81
IVg	238—240	66,1	4,8	10,9		$C_{21}H_{19}N_3O_4$	66,8	5,1	11,1		93
Va	250*	48,4	5,0	15,4	12,9	$C_{11}H_{13}N_3O_3 \cdot HCl$	48,6	5,2	15,4	13,1	83
Vb	260—261	48,7	5,3	15,4	13,0	$C_{11}H_{13}N_3O_3 \cdot HCl$	48,6	5,2	15,4	13,1	83
Vc	250*	48,2	4,9	15,8	12,9	$C_{11}H_{13}N_3O_3 \cdot HCl$	48,6	5,2	15,4	13,1	76
Vd	250*	43,6	3,6	15,3	25,2	$C_{10}H_{10}ClN_3O_2 \cdot HCl$	43,5	4,0	15,2	25,7	86
Ve	270—273	54,8	6,0	14,6	13,1	$C_{13}H_{17}N_3O_2 \cdot HCl$	55,0	6,4	14,8	12,5	50
Vf	262—264	55,0	6,1	14,4	12,6	$C_{13}H_{17}N_3O_2 \cdot HCl$	55,0	6,4	14,8	12,5	44
Vg	275—276	54,2	6,4	14,6	12,5	$C_{13}H_{17}N_3O_2 \cdot HCl$	55,0	6,4	14,8	12,5	51

*With decomposition.

to the literature [4], mp 183.5-184°C. According to GLC, the substance contained 88-96% of the aldehyde, and 4-8% of N-propylphthalimide.

γ-Phthalimidobutyric Anhydride. When the acid chloride was reduced under similar conditions over Pd/C, which probably contained traces of water instead of the aldehyde (II), γ-phthalimidobutyric anhydride was obtained, in the form of colorless crystals with mp 108-110 °C. IR spectrum, cm^{-1}: 1700, 1760 (CO of an imide), 1800 (CO of an acid anhydride). Found, %: C 63.0, H 4.9, N 5.8. $C_{24}H_{20}N_2O_7$. Calculated, %: C 63.2, H 4.5, N 6.2.

N-Methoxycarbonylphthalimide. Over 1 h 30 min, 60.5 g (0.64 mole) of methyl chloroformate was added to a suspension of 92.5 g (0.5 mole) of potassium phthalimide in 200 ml of DMFA at 5-10°C, the mixture was stirred at 20°C for 1 h and at 70-75°C for 2 h, the solvent was distilled off in vacuum, and the residue was diluted with water to give 47.6 g (45%) of colorless crystals with mp 174-175°C; after recrystallization from DMFA, mp 183°C; according to the literature [9], mp 183°C.

Dimethyl Acetal of γ-Aminobutyraldehyde. With stirring, 37.5 g of a crushed 50% alloy of nickel and aluminum was added to a solution of 25 g of the dimethyl acetal of β-cyanopropionaldehyde [10] and 40 g of caustic soda in 50 ml of methanol and 500 ml of water. The intensely foaming suspension was heated to 65°C, the alloy was filtered off, the ethanol was evaporated off, the aqueous layer was extracted with chloroform, the solvent was evaporated off, and the residue was distilled to give 16.15 g (62%) of the amino acetal with bp 82-90°C (30 mm); according to the literature [11], bp 82°C (22 mm).

Dimethyl Acetal of γ-Phthalimidobutyraldehyde. A solution of 5.6 g (0.043 mole) of the dimethyl acetal of γ-aminobutyraldehyde and 9.83 g (0.048 mole) of N-methoxycarbonylphthalimide in 70 ml of ethanol was boiled for 2 h, the small amount of phthalimide impurity was filtered off in vacuum, and 10.5 g (about 93%) of a colorless liquid was obtained which was used in the synthesis of the hydrazones (III) without purification. 2,4-Dinitrophenylhydrazone, mp 183-184°C; according to the literature [4]: mp of the 2,4-dinitrophenylhydrazone of γ-phthalimidobutyraldehyde, 183.5-184°C.

2-Methoxy-5-nitrophenylhydrazone of γ-Phthalimidobutyraldehyde (IIIa). A mixture of 36.7 g (0.2 mole) of 2-methoxy-5-nitrophenylhydrazine, 44.4 g (0.205 mole) of γ-phthalimidobutyraldehyde or the corresponding amount of its dimethyl acetal, 300 ml of absolute ethanol, 60 ml of benzene, and 23 ml of 85% phosphoric acid was boiled for 3 h and was then left at 20°C for 48 h, and the precipitate was filtered off and washed with ethanol to give 62.6 g (82%) of the hydrazone (IIIa). The hydrazones (IIIb-d) (see Table 1) were obtained similarly.

7-Methoxy-4-nitro-N-phthalyltryptamine (IVa). With stirring, 38.2 g (0.1 mole) of the hydrazone (IIIa) was added in portions to a boiling (about 120°C) solution of 38.2 g of sulfosalicylic acid dihydrate in 382 ml of acetic acid, the mixture was boiled for another 10 min,

and after 16 h at 20°C the precipitate was filtered off and washed with acetic acid and with water to give 26 g of greenish-brown crystals. A further 3.9 g of the substance was isolated from the mother solution after evaporation. The total yield of the phthalyltryptamine (IVa) was 29.9 g (82%). The phthalyltryptamines (Vb-d) (see Table 1) were obtained similarly.

7-Methoxy-4-nitrotryptamine Hydrochloride (Va). A suspension of 6 g (0.0165 mole) of the phthalyltryptamine (IVa), 2.68 g (0.535 mole) of hydrazine hydrate, and 200 ml of absolute ethanol was boiled for 2 h, the solvent was distilled off, the residue was heated with 3 g of sodium carbonate and 40 ml of water at 70-80°C for 1 h, 20 ml of water was distilled off in vacuum, and the precipitate was filtered off, washed with ice water, and dried in vacuum over sulfuric acid to give 3.8 g of free 7-methoxy-4-nitrotryptamine in the form of yellow crystals with mp 174-176°C. The base was dissolved in 15 ml of acetic acid and a saturated solution of hydrogen chloride in ethanol was added to give pH 4.5-5, the mixture was cooled, and the precipitate was washed with acetic acid and dried in vacuum over caustic potash to give 7.72 g (83%) of the hydrochloride (Va) with mp about 250°C (decomp.). The tryptamine hydrochlorides (Vb-d) and, from the corresponding acetylamino derivatives (IVe-g), the tryptamine hydrochlorides (Ve-g) (see Table 1) were obtained similarly.

PMR spectra (ppm): (Va): 7.62 (d, 5-H), 6.34 (d, 6-H, J = 9 Hz), 7.29 (s, 2-H), 4.01 (s, OCH_3), 3.13 (br.s, CH_2CH_2); (Vc): 8.16 (d, 4-H), 7.44 (d, 6-H, J = 2.5 Hz), 7.35 (s, 2-H), 4.0 (s, OCH_3), 3.10-3.35 (m, CH_2CH_2); (Vd): 8.01 (d, 4-H), 7.93 (d, 5-H,* J = 2.5 Hz), 7.42 (s, 2-H), 3.05-3.35 (m, CH_2CH_2); (Ve): 7.23 (s, 2-H), 6.83-6.74 (AB system, 5- and 6-H), 3.97 (s, OCH_3), 3.05-3.25 (m, CH_2CH_2), 2.26 (s, $COCH_3$).†

7-Acetylamino-5-methoxy-N-phthalyltryptamine (IVf). A suspension of 3 g (0.0082 mole) of 5-methoxy-7-nitro-N-phthalyltryptamine (IVb), 5 ml of acetic anhydride, 40 ml of DMFA, and 0.5 g of skeletal nickel catalyst was reduced with hydrogen at 20°C and atmospheric pressure. After the absorption of hydrogen had ceased, the catalyst was filtered off, the solvent was distilled off in vacuum, and the residue was triturated with 20 ml of ethanol to give 2.43 g (81%) of the acetylamino derivative (IVf). The acetylamino derivatives (IVe and g) (see Table 1) were obtained similarly.

Dihydrochloride of 4-Amino-7-methoxytryptamine (VI). A suspension of 4.11 g (0.0174 mole) of 7-methoxy-4-nitrotryptamine (Va) and 1 g of 10% Pd/C in 30 ml of acetic acid was reduced with hydrogen at 20°C and atmospheric pressure (3 h), the catalyst was filtered off in an atmosphere of argon, the filtrate was acidified with a solution of hydrogen chloride in ethanol to pH 4.5-5, and the precipitate was filtered off, washed with acetic acid, and dried in vacuum over caustic potash to give 3.12 g (65%) of light green crystals with mp 245-246°C. Found, %: C 46.9, H 6.5, N 14.8. $C_{11}H_{15}N_3O \cdot 2HCl$. Calculated, %: C 47.5, H 6.2, N 15.1.

5-(3-Carboxypropanoylamino)-7-methoxy-N-phthalyltryptamine (IVh). A suspension of 5 g (0.0137 mole) of 7-methoxy-5-nitro-N-phthalyltryptamine, 5 g of succinic anhydride, and 0.5 g of skeletal nickel in 50 ml of DMFA was treated with hydrogen at 20°C and at atmospheric pressure (3 h), the catalyst was filtered off, and the solvent was evaporated in vacuum to give 5.44 g (91%) of yellow crystals of the tryptamine (IVh), mp 213-214°C (from ethanol). Found, %: C 63.2, H 4.9, N 9.6. $C_{23}H_{21}N_3O_6$. Calculated, %: C 63.4, H 4.9, N 9.7.

Hydrochloride of 5-(3-Carboxypropanoylamino)-7-methoxytryptamine (Vh). A mixture of 5.44 g (0.0125 mole) of the phthalyl derivative (IVh), 1.25 ml of hydrazine hydrate, and 150 ml of ethanol was boiled for 28 h, the solvent was distilled off, water and hydrochloric acid to pH 1 were added, the precipitate was filtered off, the filtrate was made alkaline with sodium bicarbonate to pH 5.7 and evaporated to a volume of 15 ml, the precipitate was filtered off and was washed with water, ethanol, chloroform, and acetone, and was mixed with 5 ml of ethanol, and the solution was acidified with hydrogen chloride in ethanol to pH 1. The hydrochloride obtained was washed with ether and dried over caustic potash in vacuum to give 1.62 g (38%) of a white powder of compound (Vh) with mp 217-220°C (decomp.). Found, %: C 52.5, H 5.7, N 12.2, Cl 10.5%. $C_{15}H_{19}N_3O_4 \cdot HCl$. Calculated, %: C 52.8, H 5.8, N 12.3, Cl 10.4.

5-Benzyloxy-N-phthalyltryptamine. A solution of 1 g (4.77 mmole) of 4-benzyloxyphenylhydrazine and 1.2 g (0.0055 mole) of γ-phthalimidobutyraldehyde in 20 ml of ethanol was treated with 0.4 ml of 85% phosphoric acid and the mixture was boiled for 4 h. With the aid

*The opposite assignment of the signals is possible.
†Without an internal standard, recalculated from the signal of HOD (4.80 ppm) of the solvent.

of TLC [Silufol, benzene—acetone (4:1), spraying with a solution with p-dimethylaminobenzaldehyde] a decrease in the concentration of the initial hydrazine (R_f 0.75, orange coloration), the formation and participation in the reaction of the 4-benzyloxyphenylhydrazone of γ-phthalimidoburyraldehyde (R_f 0.7, yellow coloration), and the formation of 5-benzyloxy-N-phthalyltryptamine (R_f 0.55, blue coloration) were observed. The mass was diluted with water and extracted with chloroform, the solvent was evaporated off, and the residue was triturated with 10 ml of ethanol to give 1.37 g (74%) of cream-colored crystals of 5-benzyloxy-N-phthalyltryptamine, mp 181-183°C; according to the literature [12], mp 179-181°C.

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REACTIONS OF 2-ACETYLINDOLE-3-CARBOXYLIC ACIDS

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UDC 547.757+547.756

Information is given on the synthesis and establishment of the structures of previously unreported 2-acetyl-3-bromoindoles formed by the action of bromine on 2-acetylindole-3-carboxylic acids. The reduction of the latter with sodium tetrahydroborate leads to the formation of 2-(1-hydroxyethyl)indole-3-carboxylic acids.

2-Acetylindole-3-carboxylic acids (I) [1, 2] are convenient compounds for the synthesis of previously unknown or difficultly accessible indole derivatives. For example, the synthesis of 5H-pyridazo[4,5-b]indol-1-ones (II) by the condensation of the acids (I) with hydrazine has been described [3]. An acetyl group in a pyrrole ring promotes ready decarboxylation, which has enabled a convenient synthesis of the 2-acetylindoles (III) to be developed [4].

When solutions of compounds (I) in DMFA were treated with elementary bromine, decarboxylation products containing one atom of bromine in the molecule were formed. The UV spectra of these compounds showed three absorption maxima of different intensities in the 208-214, 240-246, and 310-313 nm regions, which are characteristic for 2-acetylindoles [4]. In the IR spectra there were signals in the 1630-1650 cm^{-1} region that could be assigned to a carbonyl group conjugated with an indole nucleus, and the band of a NH group in the 3290-3300 cm^{-1}

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