INDOLE DERIVATIVES.

130.* SYNTHESIS OF DISUBSTITUTED TRYPTAMINES BY NITRATION OF 5-METHOXY-N-PHTHALYLTRYPTAMINE

I. A. Petrunin, L. Kh. Vinograd,
N. M. Przhiyalgovskaya, and N. N. Suvorov

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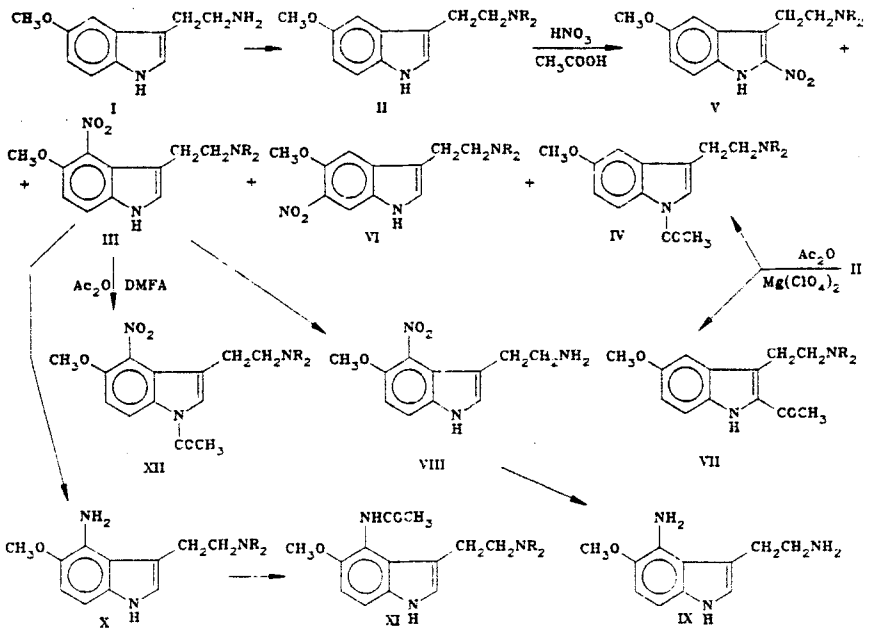
It was shown that nitration of 5-methoxy-N-phthalyltryptamine in acetic acid gives principally the 4-nitro derivative. The 4-nitro, 4-amino-, and 4-acetylamino-derivatives of 5-methoxy-N-phthalyltryptamine were also prepared.

The monosubstituted tryptamines, which include some highly active amines (serotonin, mexamine, psilocyn, etc.), are usually synthesized from the corresponding hydrazone by the Fischer reaction, using the modification described in [2, 3]. These methods are also used for the synthesis of di- and polysubstituted tryptamines [4, 5]. However, substituents which are present in the starting hydrazones affect the position of the newly formed C–C bonds, thus limiting the synthetic possibilities of these methods. In order to synthesize previously unknown compounds in this series, or compounds which are difficult to obtain, direct methods of introducing new substituents into already substituted tryptamines have been studied.

In this communication we have shown that it is possible to nitrate 5-methoxytryptamine (I) directly, when the amino group is first protected with phthalylation.

Nitration of 5-methoxy-N-phthalyltryptamine (II) with a solution of nitric acid in acetic acid gave 4-nitro- (III, 42%), 1-acetyl- (IV, 5%), 2-nitro- (V, 4.1%), 6-nitro- (VI, 6%)-5-methoxy-N-phthalyltryptamines.



*For Communication 129 see [1].

D. I. Mendeleev Chemical-Technological Institute, Moscow 125047. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1050-1053, August, 1987. Original article submitted November 3, 1986.

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The formation of the acetyl derivative IV by nitration in acetic acid in the absence of acetic anhydride is unexpected, since acetylation of the phthalyl derivative II cannot be achieved even on refluxing the mixture with acetic anhydride.

Acetylation of 5-methoxy-N-phthalyltryptamine (II) was carried out with acetic anhydride in the presence of a catalytic amount of magnesium perchlorate. This reaction gave 1-acetyl-5-methoxy-N-phthalyltryptamine (IV), identical with that described above,and also 2-acetyl-5-methoxy-N-phthalyltryptamine (VII).

Hydrazinolysis of the phthalyl derivative of 4-nitro-5-methoxytryptamine (III) gave 4-nitro-5-methoxytryptamine (VIII, 67.5%), which was reduced with hydrogen on a palladium catalyst to 4-amino-5-methoxytryptamine (IX, 87%). Reduction of the nitro group in compound III using hydrogen on Raney nickel in tetrahydrofuran gave a high yield of 4-amino-5-methoxy-N-phthalyltryptamine (X, 90%). In the reduction of compound III in DMFA using the same catalyst, the amine X was not isolated, but was immediately acetylated with acetic anhydride to give 4-acetylamino-5-methoxy-N-phthalyltryptamine (XI, 34%). Because of incomplete reduction of the starting nitrocompound, a small quantity of 4-nitro-5-methoxy-1-acetyl-N-phthalyltryptamine (XII, 12%) was also isolated.

EXPERIMENTAL

PMR spectra of compounds II, V, VI, VIII-XII were taken on a Bruker WP-200SY, compounds III, IV, and VII on a Varian XL-200. Solvents and standards are given in Table 2. Mass spectra were recorded on an MX-1303 with direct introduction of the sample to the ion source at 50 eV. IR spectra were taken on a UR-20; compounds were prepared as mulls with mineral oil. Analytical data and PMR spectra are given in Tables 1 and 2, respectively.

5-Methoxy-3-(2-phthalimidoethyl)indole (II). A ground mixture of 50 g (26 mmole) 5-methoxytryptamine (I) and 42.9 g (29 mmole) of phthalic anhydride was gradually heated to 206°. The hot viscous liquid was poured into cold water, and after 1 h the precipitate filtered off, and washed with 2% hydrochloric acid and with 5% sodium carbonate solution to give 74.5 g (88%) of product.

Nitration of 5-Methoxy-3-(2-phthalimidoethyl)indole (II). A solution of 3.0 g (47 mmole) of nitric acid (d = 1.5) in 27 ml of acetic acid was added to a stirred suspension of 15 g (47 mmole) of the phthalic derivative II in 192 ml of glacial acetic acid over a period of 3 h, during which time the temperature was maintained at 21-23°. The mixture was then heated to 75°, held at this temperature for 45 min and left overnight at 20°. The precipitate formed was filtered off to give 4-nitro-5-methoxy-3-(2-phthalimidoethyl)indole (III). The filtrate was evaporated in vacuum, the residue chromatographed on silica gel, and eluted with a 20:1 benzene:acetone mixture to give 1-acetyl-, 2-nitro- (mp 241-242°), and 6-nitro-5-methoxy-N-phthalyltryptamines (IV-VI), and the nitrocompound III (1.22 g).

Acetylation of 5-Methoxy-3-(2-phthalimidoethyl)indole (II). A solution of 0.05 g of magnesium perchlorate (anhydrone) in 4 ml of acetic anhydride was added to 1 g (3 mmole) of compound II. The mixture was stirred for 6 h at 20°, left to stand overnight, and 20 ml of ether added. The precipitated material was filtered off and dried. Chromatography on silica gel (chloroform–hexane, 1:1) gave 0.1 g (9%) of colorless crystals of 1-acetyl-5-methoxy-3-(2-phthalimidoethyl)indole (IV). Further elution gave 0.3 g (26%) of pale yellow crystals of 2-acetyl-5-methoxy-3-(2-phthalimidoethyl)indole (VII).

Hydrochloride of 4-Nitro-5-methoxytryptamine (VIII). To a solution of 5.8 g (16 mmole) of the phthalyl derivative III in 150 ml of alcohol was added 2.4 g (48 mmole) of hydrazine hydrate. The mixture was refluxed for 3 h, the solvent distilled off, and to the residue was added 1.5 g of sodium carbonate and 50 ml of water. This was heated for 1 h at 80°, and then cooled to give the base, which was dissolved in 30 ml of water, and brought to pH 3 by the addition of hydrochloric acid. The insoluble material was filtered off and the filtrate evaporated in vacuum. The residue was dried over solid potassium hydroxide to give 3.0 g (68%) of crystals of the hydrochloride VIII.

Dihydrochloride of 4-Amino-5-methoxytryptamine (IX). To a solution of 2.46 g (10.4 mmole) of 4-nitro-5-methoxytryptamine in 20 ml of acetic acid was added 0.8 g of 5% Pd/C and this was reduced with hydrogen at 20° and atmospheric pressure. When the absorption of hydrogen was complete, the catalyst was filtered off in a current of argon. The filtrate was acidified with a solution of hydrogen chloride in alcohol. The precipitated material was filtered off and washed with acetic acid to give 2.4 g (87%) of the dichloride of 4-amino-5-methoxytryptamine (IX) as light brown crystals, which quickly darkened in air.

TABLE 1. Physical Data for Synthesized Compounds

Compound	mp[a], °C	Found				Empirical formula	Calculated				Yield, %
		C, %	H, %	N(Cl), %	M+		C, %	H, %	N(Cl), %	M+	
II	158[b]	71.1	5.4	8.5	320	$C_{19}H_{16}N_2O_3$	71.2	5.0	8.7	320	88
III	239—240	62.1	4.1	11.3	365	$C_{19}H_{15}N_3O_5$	62.4	4.1	11.5	365	42
IV	166	68.5	5.0	7.4	362	$C_{21}H_{18}N_2O_4$	68.8	5.0	7.7	362	5[c]
VI	245—246	62.3	3.7	11.5	365	$C_{19}H_{15}N_3O_5$	62.4	4.1	11.5	365	6
VII	210—211	68.6	5.1	7.6	362	$C_{21}H_{18}N_2O_4$	68.8	5.0	7.7	362	26
VIII	230—233	48.5	5.2	15.3 (13.7)	235	$C_{11}H_{13}N_3O_3 \cdot HCl$	48.7	5.2	15.5 (13.1)	235	67
IX	179	47.1	5.9	14.8 (23.9)	205	$C_{11}H_{17}N_3O_5 \times \times 2HCl$	47.5	6.1	15.1 (24.5)	205	87
X	229—231	67.81	5.01	12.12	335	$C_{19}H_{18}N_2O_3$	68.05	5.07	12.53	335	90[d,e]
XI	267—268	66.66	4.57	10.76	377	$C_{21}H_{19}N_3O_4$	66.8	5.0	11.1	377	34[d]
XII	221	61.74	4.61	10.22	407	$C_{21}H_{17}N_3O_6$	61.9	4.17	10.31	407	12[d]

[a]Compounds II, III, VI, XI, and XII were recrystallized from acetic acid, VII from alcohol, IV from acetic anhydride, VIII from a mixture of CH_2Cl_2 and alcohol.
[b]mp 156-158° [5].
[c]Nitration of compound II in acetic acid; acylation with acetic anhydride, yield 9%.
[d]Yield is based on the nitrocompound III.
[e]On reduction by method B, yield is 83%.

TABLE 2. PMR Spectra of Compounds II-XII

Compound	Chemical shifts, δ, ppm [a]										Coupling constant, Hz
	phthalyl	C—CH_2	CH_2N	1-H	2-H (s)	4-H	6-H	7-H	CH_3O (s)	$COCH_3$ (s)	
II	7,83 s	3,10	3,94	9,86	7,18	7,18 s	6,74 d	7,25 d	3,79		$J_{67}=9.0$; $J_{45}=2.5$, $J_{12}=2.0$
III	7,82 m	3.31	3,77	11,34	7.33		7,09 d	7,54 d	3,87		$J_{67}=8,9$
IV	7,65—7,68	3,06	4,02		7,32	7,10 d	6,93 dd	8,28 d	3,86	2,57	$J_{67}=9,0$, $J_{46}=2.45$
V	7,75 s	3,55	4,08	11,5		7.03 s	6,97 d	7,35 d	3,70		$J_{46}=1,75$, $J_{67}=8,77$
VI	7,81 s	3,06	3,86	11,05	7,44	7,28 s		7,90 s	3,84		
VII	7,65—7,68	3,40	3,90	9,4		7,16 s	6,96 d	7,25 d	3,85	2,74	$J_{45}=2.3$, $J_{67}=8,2$
VIII		2,79	2,97	11,6	7,47		7,13 d	7,53 d	3,88		$J_{12}=2,19$, $J_{67}=8,77$
IX		3,18 m		11.32	7,35		7.03 d	7,33 d	3,87		$J_{67}=8,13$
X	7,83 s	3,14	3.87	10.29	6,90		6.57 d	6,75 d	3,73	4.51[b]	$J_{67}=8,68$
XI	7,82 s	3,02	3,83	10,56	7,02		6,88 d	7,20 d	3,74	2,09	$J_{67}=8,58$
XII	7,84 s	2,76	3,78		7,93		7,35 d	8,49 d	3,92	2,54	$J_{67}=9.2$

[a]For compounds II and V the solvent was acetone-D_6, for IV and VII, $CDCl_3$, and for the remaining tryptamines, DMSO-D_6. For all the compounds the internal standard was TMS.
[b]NH_2.

4-Amino-5-methoxy-3-(2-phthalimidoethyl)indole (X). A suspension of 6.65 g (18.3 mmole) of the phthalyl derivative III in 120 ml of tetrahydrofuran was reduced with hydrogen as described above over 3 g of Raney nickel over a period of 20 h. The catalyst was filtered off and washed with THF. The solvent was evaporated, and the residue was washed with a small quantity of THF to give 5.5 g (90%) of the amine X as red crystals.

4-Acetylamino-5-methoxy-N-phthalyltryptamine (XI). A. A solution of 5 g (13.7 mmole) of the phthalic derivative III in 40 ml of DMFA was reduced with hydrogen as described above over ~1 g Raney nickel. After absorption of the calculated amount of hydrogen, 2 ml of acetic anhydride was added, the mixture stirred for 2 h, and the catalyst filtered off and washed many times with DMFA. The filtrate and the washings were evaporated to dryness in air. The residue was dissolved in 25 ml of acetic acid and cooled to give 4.5 g of yellow crystals. The residue was chromatographed on silica gel, and eluted with chloroform to give 0.66 g (12%)

of colorless crystals of 1-acetyl-5-methoxy-4-nitro-3-(2-phthalimidoethyl)indole (XII). Further elution gave 1.78 g (34%) of colorless crystals of 4-acetylamino-5-methoxy-3-(2-phthalimidoethyl) indole (XI).

B. To a solution of 4 g (12 mmole) of phthalic derivative X in 40 ml of pyridine was added 2.82 ml (28 mmole) acetic anhydride and mixed for 6 h at 40°. The precipitated material was filtered off, washed with ether, and dried under vacuum over solid KOH to give 3.74 g (83%) of compound XI.

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REACTIONS OF DERIVATIVES OF N-ARYL-2-METHYL-3-ETHOXYCARBONYL-4,5-DIHYDROXY-6-BROMOINDOLES

A. N. Grinev* and I. K. Sorokina

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Some 4,5-dihydroxyindoles, with an acetoacetic ester substituent at the 7 position were used to synthesize 7-acetonyl-4,5-dihydroxyindoles. Methylation of these compounds gave 4-hydroxy-5-methoxy- and 4,5-dimethoxyindoles. On reaction with hydroxylamine, these compounds were converted to the oximes. Oxidation of 4,5-dihydroxyindoles with nitric acid gave 4,5-indolequinones.

The o-quinones of the benzofuran and indole series react with ketoenols in the presence of zinc chloride to give 4,5-dihydroxyfurans (and indoles), substituted at the 7 position with a ketoenol group [1]. The resulting o-dihydroxy derivatives of benzofuran and indole can be used as starting compounds in the synthesis of heterocyclic analogs of some biologically active catechol derivatives [2, 3], and they are therefore of interest in the search for new drugs.

The present work is devoted to a study of 4,5-dihydroxyindoles. Acid hydrolysis of N-aryl-4,5-dihydroxyindoles (Ia-c) [1] with an acetoacetic ester group at position 7, gave N-aryl-7-acetonyl-4,5-dihydroxyindoles (IIIa-c) in 36-59% yield. The reaction was carried out by heating compounds Ia-c in acetic acid in the presence of a catalytic amount of orthophosphoric acid. In addition, the intermediate reaction products — indolylacetoacetic acids IIa-c — were isolated in 16-21% yield. Under similar reaction conditions the ketonic splitting of 4,5-dihydroxybenzofurans [1, 4] was accompanied by tarring. On increasing the reaction time, the yield of the substances decreased sharply.

o-Dihydroxyderivatives of indole are unstable in both acid and strongly alkaline media. In the preparation of 4,5-dimethoxyderivatives of 4,5-dihydroxyindoles, IIIb and c were first converted to the more alkali-stable 4-hydroxy-5-methoxyindoles (IVa and b); in the case of

*Deceased.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021.

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