INDOLE DERIVATIVES

CI.* SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME TRYPTAMINES

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UDC 547.757.07:541.69

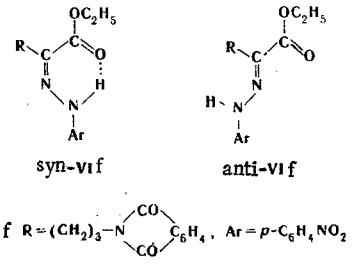
The cyclization of hydrazones obtained by coupling of diazonium salts with ethyl α-acetyl-δ-phthalimidovalerate gives ethyl 5-substituted-3-(2-phthalimidoethyl)indole-2-carboxylates, the successive hydrolysis and decarboxylation of which make it possible to obtain 5-substituted tryptamines. The synthesized hydroxyethyl ester of serotonin was found to have pronounced antiradiation action.

In the synthesis of tryptamines, an aminoethyl group is most often introduced into the prepared indole rings, and this is fraught with a number of difficulties [2]. In order to obtain 5-substituted tryptamines we used hydrazones obtained by coupling p-substituted benzenediazonium salts with ethyl α-acetyl-δ-phthalimidovalerate (I) [3].

In order to synthesize I we used the readily accessible 1,3-chlorobromopropane (II). However, we were unable to alkylate the acetoacetic ester of γ-chloropropylphthalimide (III) obtained by the Gabriel synthesis from chlorobromopropane II. We obtained I in 96% yield [6] only by replacement of the chlorine by iodine by Finkelstein substitution.

We easily obtained the hydroxyethyl ether of p-nitrophenol (V) by synthesis of the starting hydroxyethyl ether of p-aminophenol (IV) from p-nitrophenol, but the described method for its reduction [5] proved to be unsuitable. Much better results were obtained by reduction of the nitrophenol (V) with hydrazine hydrate in the presence of Raney nickel.

Coupling of diazonium salts with ester I in an acetate buffer leads to the corresponding hydrazones (VIa-f) (see Table 1) in greater than 90% yields. It should be noted that the cyclization of the purified phenylhydrazones rather than of the crude hydrazones, as was done in [3], insures considerably higher yields (89% instead of 52% for p-chloro-substituted compounds) and facilitates isolation of the products. We were also able to isolate hydrazones VIa-d,f in analytically pure form. We were also able to isolate the syn and anti forms of the p-nitrophenylhydrazone of ethyl α-keto-δ-phthalimidovalerate (VIf). We assigned the structure of a chelate compound with an intramolecular hydrogen bond to the syn isomer.



syn-VIf anti-VIf

VIf R = $(CH_2)_3$–N(CO)C_6H_4(CO), Ar = p-$C_6H_4NO_2$

* See [1] for communication C.

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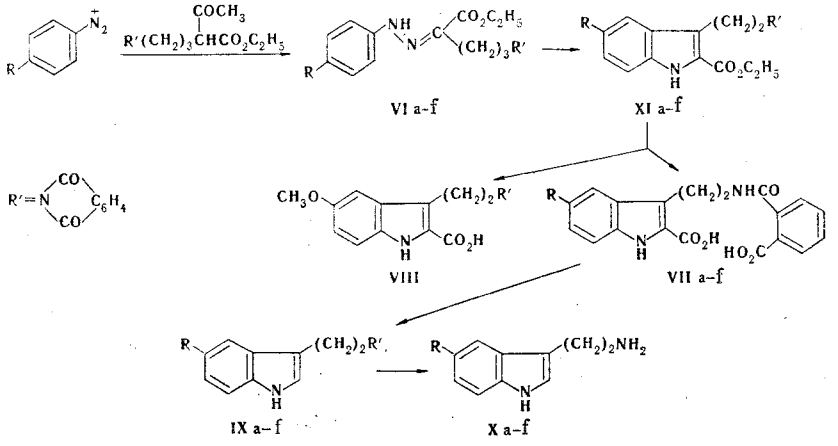
Two absorption bonds of an NH group – the first at 3327 cm^{-1} and the second less-intense band at 3255 cm^{-1} – are observed in the IR spectrum of the anti isomer. The spectrum of the syn isomer has only one NH band at 3240 cm^{-1}; this is in agreement with the data in [7]. However, it is difficult to isolate the pure hydrazones, and we therefore used the crude products for the cyclization in most cases.

We selected a saturated alcohol solution of hydrogen chloride as the cyclizing agent, inasmuch as the use of alcohol solutions of sulfuric acid, sulfosalicyclic acid, formic acid, and boron trifluoride etherate gave poorer yields of the desired product. In the case of hydrazone VIf, we carried out the cyclization in polyphosphoric acid (PPA) [8].

Hydrolysis with aqueous alcoholic alkali proceeds smoothly, and the corresponding dicarboxylic acids (VIIa-f) were obtained in quantitative yields. The purification of these acids presents considerable difficulties [3]; partial dehydration occurs during crystallization from glacial acetic acid. We were able to obtain analytically pure samples of 5-methoxy-3-[2-(o-carboxybenzamido)ethyl]indole-2-carboxylic acid VIIa and 5-methoxy-3-(2-phthalimido)indole-2-carboxylic acid VIII. Nevertheless, it seemed pointless to us to carry out the laborious purification of all of the hydrolysis products, in all of the remaining cases we heated the crude acids at 280-320° in a stream of argon and obtained 5-substituted 3-(2'-phthalimidoethyl)indoles (IXa-f) (see Table 3) in 70-87% yields.

This method of decarboxylation proved to be unsuitable in the case of 5-nitro-3-[2-(o-carboxylbenzamidoethyl)indole-2-carboxylic acid (VIIf), which we were able to decarboxylate by heating this acid with its copper salt in dimethylacetamide [9].

Heating IXa-f with hydrazine hydrate in methanol gives almost quantitative yields of 5-substituted tryptamines (Xa-f) (see Table 4).



The antiradiation effectiveness of the preparation was tested on mongrel mice weighing 20-24 g under conditions of Co^{60} γ-irradiation at dose rates of 43.4-44.0 R/min. The substances were dissolved in distilled water and injected into the mice intraperitoneally or administered orally 5-10 min prior to irradiation. The radiation-protection properties were evaluated from the survival rate in the course of 30 days after irradiation and the average lifetime of the animals that died. Compound Xe has pronounced antiradiation properties when it is introduced parenterally. The preparation proved to be ineffective when it was administered orally. Antiradiation properties were not found for Xf.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer.

P-aminophenol Hydroxyethyl Ether Hydrochloride (IV). A 1-g sample of Raney nickel was added to a solution of 18.3 g (0.1 mole) of p-nitrophenol hydroxyethyl ether (V) in 250 ml of methanol, and 30 ml (0.6 mole) of hydrazine hydrate was added to the heated mixture in the course of 2 h. The mixture was then stirred at the same temperature for another hour, after which it was cooled and filtered. The filtrate was vacuum evaporated to give 15 g (98%) of the amine. The amine was dissolved by heating in 40 ml of alcohol, and the solution was added slowly to 15 ml of a saturated alcohol solution of hydrogen chloride. The mix-

TABLE 1. p-Substituted Phenylhydrazones of α-Keto-δ-phthalimidovaleric Acid

Compound	Substituent in para position of phenyl ring	mp, °C	Empirical formula	Found, % C	H	N	Calc., % C	H	N	IR spectrum, cm^{-1}	Yield, %
VIa	$-OCH_3$	76—77	$C_{22}H_{23}N_3O_5$	64,3	5,5		64,5	5,6	10,3	3480(NH), 1775 (CO), 1755(CO), 1720(CO)	98
VIb	$-CH_3$	91—92	$C_{22}H_{23}N_3O_4$	67,4	5,8	10,8	67,2	5,8	10,7	3465(NH), 1770 (CO), 1750(CO), 1715(CO)	95
VIc	H	67,5—68,5*								3470(NH), 1770 (CO), 1750(CO), 1712(CO)	98
VId	Cl	147—148	$C_{21}H_{20}ClN_3O_4$	61,1	4,9	10,4 Cl 8,5	60,9	4,8	10,2 Cl 8,6	3330(NH), 1765 (CO), 1725(CO), 1710(CO)	96
VIe syn	$-OCH_2CH_2OH$	An analytically pure product could not be isolated									94
VIf		149—151 (petr. ether)		59,3	4,8	13,2				3240(NH), 1775 (CO), 1710(CO), 1685(CO)	
	$-NO_2$		$C_{21}H_{20}N_4O_6$				59,5	4,7	13,2		93
anti-VIf		176—177		59,5	4,6	13,1				3327(NH), 3265 (NH), 1775(CO), 1730(CO)	

*According to [4], this compound has mp 146°.

TABLE 2. Ethyl 5-R-3-(2-Phthalimidoethyl)indole-2-carboxylates

Compound	R	mp, °C	Empirical formula	Found, % C	H	N	Calc., % C	H	N	IR spectrum, cm^{-1}	Yield,* %
XIa	$-OCH_3$	238—240	$C_{22}H_{20}N_2O_5$	67,7	5,1	7,1	67,4	5,1	7,1	3328(NH), 1775 (CO), 1723(CO), 1685(CO)	54
XIb	$-CH_3$	223—224	$C_{22}H_{20}N_2O_4$	70,2	5,6	8,0	70,2	5,3	7,5	3330(NH), 1775 (CO), 1715(CO), 1685(CO)	57
XIc	H	190—191†								3330(NH), 1775 (CO), 1715(CO), 1695(CO)	45,8
XId	Cl	265—266	$C_{21}H_{17}ClN_2O_4$	63,4	4,3	7,2 Cl 8,8	63,6	4,3	7,0 Cl 8,9	3330(NH), 1765 (CO), 1710(CO), 1675(CO)	52
XIe	$-OCH_2CH_2OH$	187—188 (methanol)	$C_{23}H_{22}N_2O_6$	65,5	5,2	6,4	65,4	5,2	6,6	3330(NH), 1774 (CO), 1715(CO), 1687(CO)	60
XIf	$-NO_2$	316—317 (glycerol-methanol)	$C_{21}H_{17}N_3O_6$	61,6	4,1	10,6	61,9	4,2	10,3	3310(NH), 1778 (CO), 1710(CO) 1695(CO), 1550 (NO_2), 1330(NO_2)	51

*The yield was calculated on the basis of the starting amine.
†According to [4], this compound has mp 195°.

ture was cooled, and the resulting precipitate was removed by filtration and washed with alcohol to give 15.95 g (85%) of hydrochloride IV with mp 203-205°.*

Ethyl α-Keto-δ-phthalimidovalerate Phenylhydrazones (VIa-f). A solution of 7 g (0.1 mole) of sodium nitrite in 20 ml of water was added to a cooled (205°) solution of 0.1 mole of the amine in 100 ml of water, 100 ml of methanol, and 40 ml of concentrated hydrochloric acid in such a way that the temperature did not rise above 5°. The reaction mixture was stirred at 0-5° for 20 min, and the completion of the reaction was monitored with starch-iodide paper. At the end of the diazotization, the mixture was filtered,

*According to [5], this compound has mp 204-205°.

TABLE 3. 5-R-3-(2-Phthalimidoethyl)indoles

Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				IR spectrum, cm^{-1}	Yield, %
				C	H	Cl	N	C	H	Cl	N		
IXa	$-OCH_3$	160—161 (methanol—acetone)	$C_{19}H_{16}N_2O_3$	71,1	5,1	—	9,1	71,2	5,0	—	8,8	3390(NH), 1770(CO), 1710(CO)	79
IXb	$-CH_3$	163,5—164,5 (methanol—acetone)	$C_{19}H_{16}N_2O_2$	75,0	5,4	—	9,2	75,0	5,2	—	9,2	3380(NH), 1770(CO), 1710(CO)	87
IXc	H	162—163* (methanol)										3390(NH), 1770(CO), 1710(CO)	83
IXd	Cl	200—201 (methanol)	$C_{18}H_{13}ClN_2O_2$	66,2	3,9	10,6	8,9	66,5	4,0	11,0	8,6	3330(NH), 1770(CO), 1710(CO)	74
IXe	$-OCH_2CH_2OH$	An analytically pure product could not be isolated											
IXf	$-NO_2$	229—230 (methanol)	$C_{18}H_{13}N_3O_4$	64,3	3,9	—	12,4	64,3	3,9	—	12,5	3440(NH), 1776(CO), 1715(CO), 1525(NO_2), 1330(NO_2)	76

*According to [10], this compound has mp 164-165°.

and a solution of 34 g (0.25 mole) of sodium acetate trihydrate in 100 ml of methanol was added to the filtrate. The mixture was then poured rapidly into a solution of I prepared as follows: 32 g (0.1 mole) of ester I was dissolved by heating in 200 ml of methanol, the solution was filtered, and the filtrate was cooled to 5°; immediately prior to coupling, a solution of 6.6 g (0.1 mole) of potassium hydroxide in 100 ml of methanol was added to it with stirring and cooling. The pH must be strictly maintained at 5. The reaction mixture was stirred at the same temperature for 1 h, after which it was allowed to warm to room temperature. The oily layer was separated by decantation, and the mother liquor was diluted to twice its volume with water and extracted with benzene (three 500-ml portions). The benzene extracts were combined with the previously isolated product, the mixture was filtered, and the benzene was removed from the filtrate by distillation to give the corresponding hydrazone. The hydrazones were recrystallized from methanol for analysis. The physical constants of the substances obtained are presented in Table 1.

Ethyl 5-substituted-3-(2-Phthalinimidoethyl)indole-2-carboxylates (XIa-f). 1) Cyclization with an alcohol solution of hydrogen chloride. The hydrazone obtained from 0.1 mole of amine was added to 100 ml of a saturated alcohol solution of hydrogen chloride heated to 60-70°. After the addition of the hydrazone, the reaction mixture was stirred and refluxed for 2 h. It was then cooled to room temperature, and the resulting precipitate was separated and washed thoroughly and successively with methanol, water, and methanol and dried. The product was recrystallized for analysis from the acetic acid, and the precipitate was washed on the filter with hot methanol. Ethyl esters XIa-e were obtained in this way.

2) Cyclization with polyphosphoric acid. A total of 108 g of phosphorus pentoxide was added with stirring at a temperature no higher than 30° to 164 ml (sp.gr. 1.73 g/cm^3) of phosphoric acid, the mixture was cooled to 10°, and 42.4 g (0.1 mole) of hydrazone VIf (recrystallized from methanol) was added. The reaction mixture was heated and stirred to 70-80°, during which the temperature rose to 120°. Stirring was continued at this temperature, after which the mixture was cooled and poured over ice. The resulting precipitate was separated, washed with water, and dried. Ester XIf was obtained in quantitative yield.

5-substituted-3-[2-0-Carboxybenzamido)ethyl]indole-2-carboxylic Acids (VIIa-f). A total of 75 ml of a 2 N solution of sodium hydroxide was added to a suspension of 3.92 g (0.01 mole) of ester XIa in 20 ml of methanol, and the mixture was refluxed for 3 h until the solid had dissolved completely. The solution was cooled to 10° and filtered, and the filtrate was poured over ice. The aqueous mixture was acidified with 4 N hydrochloric acid solution until it gave an acid reaction with respect to Congo red. The resulting precipitate was separated, washed with water, and vacuum dried at 80-100° to give 3.7 g (97%) of acid VIIa with mp 240-241° (after recrystallization from acetic acid, methyl ethyl ketone, and methanol). IR spec-

TABLE 4. 5-R-Tryptamine Hydrochloride

Compound	R	mp, °C	Yield, %	Literature citation
Xa	$-OCH_3$	118—120 (benzene)	99	13
	Hydrochloride	241—242		
Xb	$-CH_3$	92—95 (cyclohexane)	97	11
	Hydrochloride	284—286		
Xc	H	114—116 (benzene)	94	13
	Hydrochloride	248—250		
Xd	Cl	—	99	13
	Hydrochloride	287—289	93,5	
Xe	$-OCH_2CH_2OH$	—	75	—
	Hydrochloride	157—158,5		
Xf	$-NO_2$	136—138 (benzene)	91	12
	Hydrochloride	284—286		

trum: 3415 (NH), 3355 (NH), 2625 (OH), 1710 (CO), 1675 (CO), and 1615 cm^{-1} (CO). Found, %: C 62.4; H 4.6; N 7.6. $C_{20}H_{18}N_2O_6$. Calculated, %: C 62.8; H 4.7; N 7.3.

In the recrystallization of dibasic acid VIIa, acid VIII, with mp 253-253.5°, was obtained as a result of dehydration. IR spectrum: 3335 (NH), 1770 (CO), 1710 (CO), and 1670 cm^{-1} (CO). Found, %: C 66.0; H 4.4; N 8.2. $C_{20}H_{16}N_2O_5$. Calculated, %: C 66.0; H 4.4; N 7.7.

The remaining acids (VIIb-f), which were decarboxylated without additional purification, were similarly obtained in quantitative yield.

5-substituted 3-(2-Phthalimidoethyl)indoles (IXa-f) (Table 3). Compounds VIIa-e were heated at 280-320° in a stream of argon for 1 h. The mixture was cooled to 80° and extracted with 250 ml of methyl ethyl ketone, after which it was filtered, and the filtrate was refluxed with activated charcoal. The methyl ethyl ketone was removed by distillation to give IXa-e. A suspension of acid VIIf and 1 g of its copper salt was refluxed in dimethylacetamide for 2 h, after which it was cooled and poured over ice. The resulting precipitate was separated and washed successively with water, ammonium hydroxide, and water. The solid was dissolved in acetone, the solution was filtered, and the acetone was removed from the filtrate by distillation to give IXf.

Tryptamines Xa-f (Table 4). A suspension of 0.02 mole of phthalimidoethylindoles IXa-f in 50 ml of methanol was heated to the boiling point, and a solution of 1.5 ml (0.03 mole) of hydrazine hydrate in 5 ml of methanol was added. The mixture was refluxed for 2 h, the methanol was removed by vacuum distillation to dryness, and 100 ml of 2 N sodium hydroxide solution was added to the residue. The mixture was extracted with methylene chloride (three 350-ml portions), and the extract was filtered. The methylene chloride was removed by distillation, dry benzene was added to the residue, and the mixture was again evaporated to dryness to give tryptamines Xa-f. For purification, the tryptamines were converted to hydrochlorides, and aqueous solutions of them were refluxed with activated charcoal. The solutions were made alkaline with 2 N sodium hydroxide solution and extracted with methylene chloride. Tryptamine Xe was characterized as the hydrochloride with mp 157.5-158°. Found, %: C 56.0; H 6.7; Cl 13.6; N 11.1. $C_{12}H_{16}N_2O_2 \cdot HCl$. Calculated, %: C 56.1; H 6.6; Cl 13.9; N 10.9.

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