15. H. M. Bogaert, D. J. van den Zwanenburg, and Th. A. M. M. Maas, Recl. Trav. Chim., 94, 218 (1975).
16. A. Hinnen, Ch. Audic, and R. Gautron, Bull. Soc. Chim. Fr., No. 5, 2066 (1968).
17. A. Samat, C. Riou, J. Robillard, and R. Guglielmetti, J. Photogr. Sci., 26, 34 (1978).
18. Yu. M. Chunaev, N. M. Przhiyalgovskaya, L. N. Kurkovskaya, and M. A. Gal'bershtam, Khim. Geterotsikl. Soedin., No. 11, 1501 (1982).
19. G. Kaupp and M. Stark, Chem. Ber., 111, 3608 (1978).
20. T. Masamune, S. Numata, H. Matsue, A. Matsuyuki, T. Sato, and H. Murase, Bull. Chem. Soc. Jpn., 48, 2294 (1975).
21. H. Prinzbach, D. Stusche, M. Breuninger, and J. Markert, Chem. Ber., 109, 2823 (1976).
22. B. M. Howard, W. Fenical, K. Hirotsu, B. Solheim, and J. Clardy, Tetrahedron, 36, 171 (1980).
23. É. R. Zakhs, V. P. Martynova, and L. S. Éfros, Khim. Geterotsikl. Soedin., No. 4, 435 (1979).
24. High-Resolution NMR Spectra Catalog: Varian Associates, National Press (1962), p. 687.
25. M. A. Gal'bershtam, L. M. Mikheeva, and N. P. Samoilova, Khim. Geterotsikl. Soedin., No. 11, 1534 (1972).

INDOLE DERIVATIVES.

125.* SYNTHESIS OF DISUBSTITUTED TRYPTAMINES

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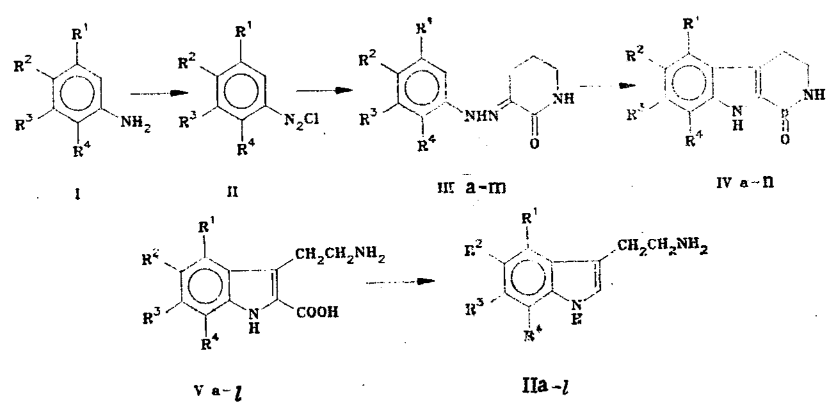
Disubstituted tryptamines, containing methyl, methoxy, nitro, and amino groups, chlorine, and bromine in the benzene ring, were synthesized. The influence of substituents on the course of individual stages of synthesis was noted.

The radioprotective activity chiefly of monosubstituted tryptamines has been studied heretofore [2]. The number of disubstituted tryptamines produced and studied is small. We synthesized disubstituted tryptamines† according to the scheme of Abramovich and Shapiro:



a $R^2=CH_3O$, $R^4=CH_3$; b $R^2=R^4=CH_3$; c $R^1=R^4=CH_3$; d $R^1=R^4=Cl$; e $R^2=R^4=Cl$; f $R^1=R^2=Cl$; g $R^2=R^3=Cl$; h $R^2=CH_3$, $R^4=Br$; i $R^1=NO_2$, $R^4=CH_3$; j $R^2=CH_3$, $R^4=NO_2$; k $R^2=CH_3O$, $R^4=NO_2$; l $R^1=NO_2$, $R^4=CH_3O$; m $R^2=R^4=CH_3O$; n $R^2=R^3=CH_3O$; o $R^1=R^4=CH_3O$; p $R^1=R^3=CH_3O$; q $R^2=CH_3$, $R^4=CH_3O$. Here and henceforth, unless superscripts are indicated, R = H

*For communication 124, see [1].
†The radioprotective activity of the compounds obtained was reported earlier [3].

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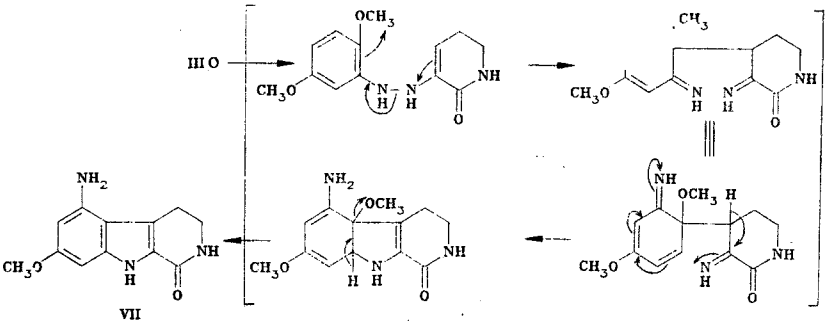
Tryptamines produced according to this scheme contain methyl groups, chlorine, bromine, and one methoxy group in the benzene ring. The presence of a methoxy group (especially two methoxy groups) and a nitro group in the initial hydrazone III hinders the synthesis and in certain cases prevents it. The hindrances are of varied types, determined by the type and arrangement of the substituents.

In the cyclization of 2,4-dimethoxyphenylhydrazone IIIa by hydrogen chloride and methanol, together with the "normal" dimethoxycarbolinone IVm, up to 25% methoxychlorocarbolinone impurity is also formed, as indicated by the data of elementary analysis, mass spectrum (presence of M^+ 246 and 250-252), and PMR spectrum. Conducting the reaction in a mixture of sulfuric and acetic acids gives the pure carbolinone IVm, but with an extremely low yield. The addition of chlorine and other nucleophilic particles in the course of the Fischer reaction was observed earlier and was explained by intermediate formation of stable carbocations on account of cyclization at the orthoposition, occupied by a methoxy group [4].

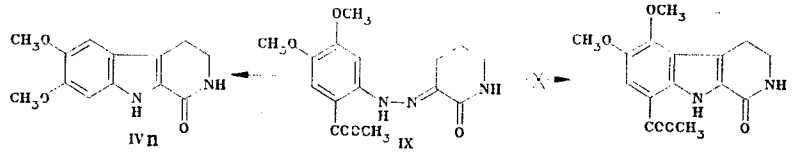
In the cyclization of 2,5-dimethoxyphenylhydrazone IIIo, instead of the expected 5,8-dimethoxycarbolinone, aminomethoxycarbolinone VII is formed with a yield of 77%. An analogous conversion was observed in Fischer cyclization of the 2-methoxy-5-chlorophenylhydrazone of the ethyl ester of pyruvic acid [5]. In our case the formation of aminomethoxycarbolinone VII can presumably be explained by the following conversions:



VII

Evidently here too cyclization occurs at the ortho-position, occupied by a methoxy group, but the pyrrole ring is formed not by the elimination of ammonia but as a result of intramolecular nucleophilic addition of an imino group to a ring with impaired aromaticity and stabilization of the cyclization product by the elimination of methanol with the formation of 5-amino-7-methoxycarbolinone (VII). It should be noted that together with the unusual carbolinone VII, 2,5-dimethoxy-1,4-phenylenediamine VIII is also formed. This diamine, according to the data of [6], is the main reaction product in an attempt at cyclization of the 2,5-dimethoxyphenylhydrazone of the ethyl ester of pyruvic acid.

An attempt to synthesize 4,5-dimethoxytryptamine, which we hoped to obtain from 3-(2-carbomethoxy-4,5-dimethoxyphenylhydrazone)piperidinedione-2,3 (IX), also did not get by without complications. Theoretically the carbomethoxy group should have prevented cyclization at the 2-position, that, is, should have played the role of a protective group; however, in the course of the reaction this group is eliminated, and 6,7-dimethoxycarboline (IVn) is formed.



IVn IX

We were also unable to carry out the cyclization of the 3,5-dimethoxyphenylhydrazone IIIp, and in an attempt to synthesize 5-methyl-7-methoxytryptamine we were unable to decarboxylate the corresponding carboxylic acid Vq.

An attempt to synthesize 5,6- and 5,7-dimethoxytryptamines according to the scheme cited below [7, 8] where hydrazones with the formula X are used for cyclization, proved more successful.

Difficulties were also encountered in the synthesis of disubstituted tryptamines, when one of the substituents was a nitro group. Cyclization of the corresponding hydrazones IIIj-l occurs only under rigorous conditions during heating in polyphosphoric acid is accompanied by

TABLE 1. Characteristics of the Compounds Synthesized

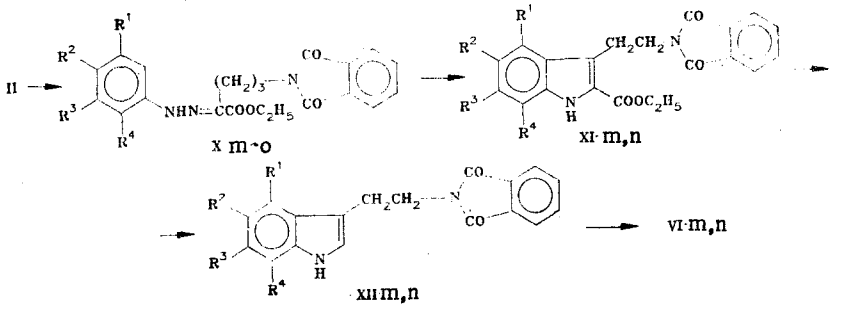
Compound	mp, [a] °C	Found, %				Gross formula	Calculated, %				Yield, %	Procedure
		C	H	N	Cl (Br)		C	H	N	Cl (Br)		
IIIc	169—170	67,7	7,1	18,2		$C_{13}H_{17}N_3O$	67,5	7,4	18,2		68	A
IIId	208—209	47,8	4,4	15,5	26,8	$C_{11}H_{11}Cl_2N_3O$	48,5	4,1	15,4	26,1	85	A
IIIh	133—136	47,9	5,1	13,2	(25,8)	$C_{12}H_{14}BrN_3O$	48,7	4,8	14,2	(27,0)	84	A
IIIi	185—189	54,6	5,3	22,0		$C_{12}H_{14}N_4O_3$	54,9	5,4	21,4		81	A-1
IIIj	238—239	54,6	5,4	21,4		$C_{12}H_{14}N_4O_3$	55,0	5,4	21,4		67	A
IIIk	229—230	51,4	4,9	20,0		$C_{12}H_{14}N_4O_4$	51,8	5,1	20,1		91	A
IIIm	185—186	59,2	7,3	16,4		$C_{13}H_{17}N_3O_3$	59,3	6,5	16,0		63	A
IIIo	153—154	59,3	6,5	15,6		$C_{13}H_{17}N_3O_3$	59,3	6,5	16,0		29	A
IIIp	205—210	59,1	6,7	15,6		$C_{13}H_{17}N_3O_3$	59,3	6,5	16,0		51	A
IIIq	162—163	63,2	6,8	17,0		$C_{13}H_{17}N_3O_2$	63,1	6,9	17,0		86	A
IVc	234—235	73,0	6,5	13,1		$C_{13}H_{14}N_2O$	72,9	6,6	13,1		32	B-3
IVd	227—228	50,9	3,5	10,1	27,2	$C_{11}H_8Cl_2N_2O$	51,8	3,2	11,0	28,0	44	B-1
IVe	175—180	51,2	3,7	10,3		$C_{11}H_8Cl_2N_2O$	51,8	3,2	11,0		84	B-1
IVf,g[b]	244—246	51,8	3,2	11,0	26,9	$C_{11}H_8Cl_2N_2O$	51,8	3,2	11,0	28,0	67	B-1
IVh	122—126	50,9	3,9	10,8	(28,8)	$C_{12}H_{11}BrN_2O$	51,6	4,0	10,0	(28,6)	61	B-2
IVi	273—278	58,0	4,5	17,0		$C_{12}H_{11}N_3O_3$	58,8	4,5	17,1		91	B-1
IVj	288—290	57,4	4,3	17,2		$C_{12}H_{11}N_3O_3$	58,8	4,5	17,1		89	B-1
IVk	233—234	54,5	4,5	16,1		$C_{12}H_{11}N_3O_4$	55,2	4,2	16,1		68	B-1
IVl	285—287	54,8	4,2	15,8		$C_{12}H_{11}N_3O_4$	55,2	4,2	16,1		50[c]	B1
IVn	282—283	62,6	5,8	11,1		$C_{13}H_{14}N_2O_3$	63,4	5,7	11,4		64	B-3
IVq	310	67,5	5,7	12,5		$C_{13}H_{14}N_2O_2$	67,8	6,1	12,2		92	B-3
Vd	322[d]	47,6	3,6	9,7	26,6	$C_{11}H_{10}Cl_2N_2O_2$	48,4	3,7	10,3	26,0	94	C
Vh	265—270	47,8	4,6	9,8	(25,9)	$C_{12}H_{13}BrN_2O_2$	48,5	4,4	9,4	(27,0)	91	C
Vk	310	51,8	4,6	14,0		$C_{12}H_{13}N_3O_5$	51,6	4,7	15,0		59	C
VIa	164,4[e]	71,4	8,0	13,7		$C_{12}H_{16}N_2O$	70,5	8,0	13,7		67[f]	[11]
VIb	237—238[g]	64,4	7,6	12,4		$C_{12}H_{16}N_2 \cdot HCl$	64,1	7,6	12,5		70[f]	[12]
VIc	265—267	63,7	7,2	12,0	15,5	$C_{12}H_{16}N_2 \cdot HCl$	63,4	7,6	12,5	15,8	19	D-2
VId	322—323	45,4	4,2	10,6	39,0	$C_{10}H_{10}Cl_2N_2 \cdot HCl$	45,2	4,2	10,6	40,1	40f	D-3
VIe	257	45,2	4,2	10,2	39,4	$C_{10}H_{10}Cl_2N_2 \cdot HCl$	45,2	4,2	10,6	40,1	42f	D-3
VIf,g[b]	265—270	45,1	4,2	10,5	40,1	$C_{10}H_{10}Cl_2N_2 \cdot HCl$	45,2	4,2	10,6	40,1	44f	D-3
VIh	268	45,2	4,7	9,6		$C_{11}H_{13}BrN_2 \cdot HCl$	45,6	4,9	9,7		57f	D-1
VIi	253—255	51,8	5,4	16,4	13,6	$C_{11}H_{13}N_3O_2 \cdot HCl$	51,7	5,5	16,4	13,9	23f	D-3
VIj	277—278	51,3	5,5	14,8	13,8	$C_{11}H_{13}N_3O_2 \cdot HCl$	51,7	5,5	16,4	13,9	20f	D-2
VIk	260—261	48,7	5,3	15,4	13,2	$C_{11}H_{13}N_3O_3 \cdot HCl$	48,6	5,2	15,5	13,1	20f	D-3
VIm	224—225			11,0		$C_{12}H_{16}N_2O_2 \cdot HCl$			10,9		48f	C-1,E
VIn	228—230[h]	56,2	6,7	10,9		$C_{12}H_{16}N_2O_2 \cdot HCl$	56,1	6,7	10,9		28i	E
VII	245—246	61,7	5,7	18,1		$C_{12}H_{13}N_3O_2$	62,3	5,7	18,2		77	B-5
IX	237	55,5	6,1	13,4		$C_{15}H_{19}N_3O_5$	56,0	6,0	13,1		93	A
Xm	145—146	62,0	5,5	8,8		$C_{23}H_{25}N_3O_6$	62,9	5,7	9,6		74	A-2[8]
Xo	103—106[b]	62,8	5,6	8,9		$C_{23}H_{25}N_3O_6$	62,9	5,7	9,6		80	A-2
XIn	230[d]	64,6	5,4	6,5		$C_{23}H_{22}N_2O_6$	65,4	5,3	6,6		46	B-6
XIm	183—185[b]	64,7	4,8	7,0		$C_{23}H_{22}N_2O_6$	65,4	5,3	6,6		19	B-6
XIIo	138—140[b]	69,5	4,1	8,6		$C_{20}H_{18}N_2O_4$	68,6	5,2	8,0		24	C-1
XIII	330[f]	62,5	5,6	18,0		$C_{12}H_{13}N_3O_2$	62,3	5,7	18,2		84	F
XIV		50,2	6,5	16,3		$C_{11}H_{13}N_3 \cdot 2HCl$	50,8	5,8	16,1		41	F-1

[a]Compounds IIIc, h, j, k, m-q, VIc, i-k, IX, Xm from alcohol; IIId from methanol; IVc from chloroform; IVd-g, l, Vd, h, VId-h, XIn from acetic acid; IVi-k, n, q, XIII from dimethylformamide; VIm, n from methylene chloride. [b]Mixtures of isomers, 65-70% of isomer IVf or VIf. [c]The yield is cited converted to the amine I. [d]Mp 327°C [10]. [e]Mp of the base: mp 163-164°C [11]; mp of the hydrochloride 209-210°C. [f]The yield is cited calculated for the hydrazone IV. [g]According to the data of [12], mp of the acetate 154-155°C. [f]The yield is cited calculated for the hydrazone IV. [g]According to the data of [12], mp of the acetate 154-155°C. [h]The tryptamine has been described [13] in the form of an unstable base. [i]The yield is cited calculated for the ester XIn.

side reactions, which appreciably lower the yield of the carbolinones IV. The presence of a nitro group in the amino acid V hinders decarboxylation or even makes it impossible.

The PMR spectra confirmed the structure of the carbolinones (Table 2) and tryptamines (Table 3) obtained. As it follows from the table data, substituents in the benzene ring have a stronger effect on the chemical shifts of the proton in the 2-position (in tryptamines) than on the chemical shifts of the protons of the methylene groups (in tryptamines and carbolinones). Exceptions are 5-substituted carbolinones, in which a strong unshielding influence of the substituent in the 5-position on the chemical shift of the 4-H protons is observed. This effect has the same sign and comparable magnitude for a strong acceptor (NO_2), a strong

donor (NH_2), and substituents intermediate in electronic effects (CH_3, Cl). Evidently the influence on the chemical shifts is transmitted not along the bonds but through space and is due to steric interactions of the substituent in the 5-position and the 4-H protons, which are close together. In the ^{13}C NMR spectra (Table 4), this interaction is manifested in the form of an appreciable (~2 ppm) weak-field shift of the signal of the carbon $C_{(4)}$. In sign and magnitude the effect observed in 5-substituted carbolinones is analogous to the weak-field "δ-effect" which the substituent exerts on the chemical shift of the δ-carbon atom in the case of a syn-axial orientation of this atom and the substituent [9].



m $R^2=R^4=CH_3O$; n $R^2=R^3=CH_3O$; o $R^1=R^4=CH_3O$

We used the peculiarities of the ^1H and ^{13}C NMR spectra of 5-substituted carbolinones noted to establish the structure of the rearrangement product VII. According to the data of Table 4, the signal of the 4-H protons in this compound (3.07 ppm) is substantially shifted in the weak-field direction in comparison with the analogous signal in 5-unsubstituted carbolinones, in particular, in compound XIII (2.81 ppm) with the same substituents (NH_2 and OCH_3) in the benzene ring. This is an indication of the presence of a substituent in the 5-position of the carbolinone ring in compound VII, which is also confirmed in the ^{13}C NMR spectra by a weak-field shift of the signal of the carbon $C_{(4)}$ (22.5 ppm) relative to the corresponding signal in carbolinones unsubstituted in the 5-position (20.1-20.6 ppm). The value of the SSIC of the two protons of the benzene ring in compounds VII ($J \approx 2$ Hz) is evidence of a meta-position of the substituents in the ring, which, considering the other chemical and physicochemical data, permits an unambiguous conclusion to be drawn about the structure of the rearrangement product.

EXPERIMENTAL

The PMR spectra of compounds IVb-h, *l*, n, VIc-k were recorded on a Varian XL-100 instrument, compounds IVk, m, VIm on a Jeol JNM-4H-100 instrument, compounds VIa, b, XIII, XIV on a Varian XL-200 instrument. The ^{13}C NMR spectra were recorded on an XL-100A spectrometer with working frequency for ^{13}C nuclei 25.2 MHz. The solvents and standards are indicated in Tables 2-4.

3-(2,4-Dimethoxyphenylhydrazone)piperidinedione-2,3 (IIIm). A. To a solution of 15.3 g (0.1 mole), 2,4-dimethoxyaniline in 180 ml of water and 27 ml (0.3 mole) conc. HCl, a solution of 7.2 g (0.105 mole) sodium nitrite in 20 ml of water was added with mixing at 2-3°C. After 15 min a solution of soda or sodium acetate was added to pH 5-5.5, then a solution of the potassium salt of 3-carboxypiperidone-2 [produced by mixing 17.1 g (0.1 mole) 3-carbethoxypiperidone-2 and a solution of 5.7 g (0.102 mole) potassium hydroxide in 185 ml of water 1-2 h before the coupling]. Acetic acid was used to establish pH 5; the mixture was mixed for 5 h without cooling, after 16 h the precipitate was filtered off, washed with water, and recrystallized from 400 ml of absolute alcohol. Yield of the hydrazone IIIa 16.5 g (63%).

3-(2-Methyl-5-nitrophenylhydrazone)piperidinedione-2,3 (IIIi). A-1. Produced analogously to the hydrazone IIIm, but for diazotization the amine Ii was dissolved in a mixture of 100 ml of water and 50 ml of methanol; diazotization was conducted at 14-15°C.

6-Methoxy-8-nitro-1,2,3,4-tetrahydro-β-carbolinone-1 (IVk). B-1. In a one-liter flask with a mixer we placed 240 ml of 85% phosphoric acid, and 440 g of phosphoric anhydride was loaded in ~1 h without access to moisture at 70-105°C (first cooling then heating is necessary); the mixture was heated to 120°C until it dissolved completely, and 77 g (0.275 mole) of the hydrazone IIIk was gradually added at 65-70°C (no lower), waiting until complete dissolution of each portion. The mixture was heated to 110°C (at 80-82°C there is a sharp spontaneous temperature jump to 107°C). The hot dense mass was poured out into 5 liters of cold

TABLE 2. PMR Spectra of Carbolinones[a]

Compound	Substituents in ring				Chemical shifts, δ, ppm									SSIC, Hz
	R⁵	R⁶	R⁷	R⁸	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	all other	
IVb		CH_3		CH_3	7,40 br[b]	3,49 t	2,86 t	7,15 n.s[c]		6,83 n.s[c]		11,30 br.	2,44 s (CH_3); 2,34 s (CH_3)	$J_{34}=6,8$
IVc	CH_3			CH_3	7,43 br	3,50 t	3,14 t		6,84 d[d]	6,66 d[d]		11,30 br	2,42 s (CH_3); 2,53 s (CH_3)	$J_{34}=6,8$; $J_{76}=7,5$
IVd	Cl			Cl	7,75 br.	3,54 t	3,21 t		7,25 d[d]	7,09 d[d]		12,25 br		$J_{34}=6,7$; $J_{76}=8,0$
IVe		Cl		Cl	7,67 br.	3,52 t	2,92 t	7,70 d		7,35 d		12,15 br.		$J_{34}=6,8$; $J_{57}=2,0$
IVf[e]	Cl	Cl			7,70 br.	3,52 t	3,20 t			7,36 f	7,36 f	12,10 br		
IVg[e]		Cl	Cl		7,70 br.	3,52 t	2,91 t	7,90 s			7,57 s	11,87 br.		$J_{34}=6,8$
IVh		CH_3		Br	7,58 br.	3,50 t	2,88 t	7,29 n.s.[c,d]		7,40 n.s[c,d]		11,47 br	2,38 s (CH_3)	$J_{34}=6,8$
IVi		CH_3O		NO_2	7,75 br.	3,58 t	2,97 t	7,73 d[d]		7,62 d[d]		10,75 br	3,90 s (CH_3O)	$J_{34}=6,5$; $J_{57}=2,0$
IVl	NO_2			CH_3O	7,84 br.	3,48 t	3,16 t		8,03 d	6,91 d			4,04 s (CH_3O)	$J_{34}=6,5$; $J_{57}=2,0$
IVm		CH_3O		CH_3O	7,50 br.	3,47 t	2,86 t	6,55 d		6,38 d		11,25 and	3,76 s (CH_3O); 3,85 s (CH_3O)	$J_{34}=6,5$; $J_{57}=2,0$
IVn		CH_3O	CH_3O		7,29 br.	3,48 t	2,86 t	7,03 s			6,85 s	11,24 br	3,77 s (CH_3O, CH_3O)	
VIIo	NH_2		CH_3O		7,15 br.	3,45 t	3,07 t		5,87 d		6,12 d	11,0 br	3,68 s (CH_3O)	$J_{34}=6,7$; $J_{68}=2,0$
XIII		CH_3O		NH_2	7,38 br.	3,48 t	2,81 t	6,25 d		6,07 d		11,0 br	3,69 s (CH_3O); 5,28 br. (NH_2)	$J_{34}=6,7$; $J_{57}=2,0$

[a]Solvent DMSO-D_6, internal standard TMS. [b]br.) Broad signal. [c]Signal broadened as a result of interaction with the protons of the 6-CH_3 group. [d]Possibly reverse assignment of signals. [e]Studied in a mixture of 5,6- and 6,7-dichloroisomers, ~1:1. [f]Random coincidence of the chemical shifts.

TABLE 3. PMR Spectra of Tryptamines[a]

Compound	Substituents in ring				Chemical shifts, δ, ppm							SSIC, Hz
	R⁴	R⁵	R⁶	R⁷	CH_2CH_2	2-H	4-H	5-H	6-H	7-H	all other	
VIa		CH_3O		CH_3	3,10—3,30	7,28 s	7,01 d		6,75 d		3,86 s (CH_3O), 2,44 s (CH_3)	$J_{46}=2,5$
VIb		CH_3		CH_3	3,10—3,30	7,27 s	7,33 n.s[b]		6,94 n.s[b]		2,41 s (CH_3), 2,46 s (CH_3)	
VIc	CH_3			CH_3	3,25 n.s	7,22 s		6,80 d[c]	6,90 d[c]		2,41 s (CH_3), 2,59 s (CH_3)	$J_{56}=7,6$
VId	Cl			Cl	3,25—3,30	7,26 s		6,99 d[c]	7,11 d[c]			$J_{56}=8,2$
VIf[c,d]	Cl	Cl			3,00—3,30	7,21 s			7,14 d[c]	7,19 d[c]		$J_{67}=8,7$
VIg[c,d]		Cl	Cl		3,00—3,30	7,20 s	7,56 s			7,43 s		
VIh		CH_3		Br	3,05—3,30	7,23 s	7,37 n.s[b]		7,17 n.s[b]		2,43 s (CH_3)	
VIi	NO_2			CH_3	3,05—3,35	7,46 s		7,78 d	7,00 d		2,59 s (CH_3)	$J_{56}=8,0$
VIj		CH_3		NO_2	3,00—3,30	7,18 s	7,52 n.s[b,c]		7,48 n.s[b,c]		2,29 s (CH_3)	
VIk		CH_3O		NO_2	2,90—3,30	7,15 s	7,07 d[b]		7,13 d[c]		3,76 s (CH_3O)	$J_{46}=2,5$
VIm		CH_3O		CH_3O	3,00—3,25	7,14 s	6,65 d		6,26 d		3,77 (CH_3O), 3,80 (CH_3O)	$J_{46}=2,5$
XIV		CH_3		NH_2	3,15—3,35	7,39 s	7,14 n.s[b]		7,58 n.s[b]		2,47 s (CH_3)	

[a]For VIh, i, the solvent was CD_3OD, standard TMS; for the remaining tryptamines the solvent was D_2O, the standard $(CH_2)_3COH$ (δ 1.23 ppm). [b]The broadening of the signal was caused by interaction with the protons of the methyl group. [c]Possibly reversed assignment of the signals. [d]A mixture of 4,5- and 5,6-dichlorotryptamines, ~1:1, was studied.

TABLE 4. Parameters of the ^{13}C NMR Spectra of Carbolinones[a]

Compound	Substituents				Chemical shifts, δ, ppm						
	R^5	R^6	R^7	R^8	$C_{(1)}$	$C_{(3)}$	$C_{(4)}$	$C_{(9a)}$[b]	$C_{(4a)}$[b]	$C_{(4b)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, $C_{(8a)}$[c]	all others
IVb		CH_3		CH_3	162,1	41,3 t	20,6 t	125,0	118,5	135,4, 128,3, 127,2, 126,5, 121,8 d, 116,8 d	21,1 q (CH_3); 17,1 q (CH_3)
IVc	CH_3			CH_3	162,0	41,3 t	22,6 t	124,0	119,3	136,8, 128,6, 126,9, 124,3 d, 120,4 d, 119,5	19,2 q (CH_3)
IVd	Cl			Cl	160,7	41,0 t	21,8 t	125,0	118,8	135,0, 129,5, 124,0 d, 123,7, 120,5 d, 116,2	
IVe		Cl		Cl	160,9	41,0 t	20,3 t	124,0	119,1	132,9, 129,9, 127,2, 123,2 d, 118,5 d, 117,9	
IVf[d]	Cl	Cl			161,0	41,0 t	21,8 t	126,1	117,3		
IVg[d]		Cl	Cl		161,1	41,0 t	20,1 t	124,7	117,8		
VII	NH_2		CH_3O		162,1	41,4 t	22,5 t	124,0	119,1	159,1, 143,9, 139,6, 109,7, 93,8 d, 84 d	54,9 q (CH_3O)

[a]Solvent DMSO-D_6, the signal of which was used for counting the chemical shifts (δ 39.6 ppm); d, t, q) multiplicity of the signals in a spectrum with incomplete uncoupling from protons; absence of a letter indicates a singlet. [b]Probable assignment. [c]In this work the signals were not assigned. [d]Studied in a mixture of 5,6- and 6,7-dichloroisomers.

water; after 16 h the precipitate was filtered off, washed with water and alcohol, and 48.7 g (68%) of the carbolinone IVk was obtained.

6-Methyl-8-bromo-1,2,3,4-tetrahydro-β-carbolinone-1 (IVh). B-2. A mixture of 20 g (0.0677 mole) of the hydrazone IIIi, 20 g (0.0735 mole) 80% sulfosalicyclic acid, 100 ml of water, and 100 ml of alcohol was boiled for 7 h, diluted with water, the precipitate washed with water and alcohol, and 11.5 g (61%) of the carbolinone IVh was obtained.

5,8-Dimethyl-1,2,3,4-tetrahydro-β-carbolinone-1 (IVc). B-3. A mixture of 23.1 g (0.1 mole) of the hydrazone IIIc in 100 ml 97-99% formic acid was boiled for 2 h, evaporated under vacuum, the residue dissolved in chloroform, washed with a 5% aqueous solution of sodium hydroxide, filtered through a layer of aluminum oxide, the solvent distilled off, and 6.95 g (32%) of the carbolinone IVc was obtained.

6,8-Dimethoxy-1,2,3,4-tetrahydro-β-carbolinone-1 (IVm). B-4. A solution of 3 g (0.0114 mole) of the hydrazone IIIm and 0.8 ml (0.015 mole) sulfuric acid in 12 ml acetic acid was heated for 2 h at 70°C, diluted with water, extracted with chloroform, the solvent distilled off, the residue washed with alcohol, and 0.31 g (11%) of the carbolinone IVm, mp 113-135°C (from benzene) was obtained. Found: M^+ 246. $C_{13}H_{14}N_2O_3$. Calculated: M 246.

5-Amino-7-methoxy-1,2,3,4-tetrahydro-β-carbolinone-1 (VII). B-5. An intense flow of hydrogen chloride was passed for 40 min through a boiling solution of 2.98 g (0.0114 mole) of the hydrazone IIIm in 20 ml of methanol, cooled, the precipitate washed with methanol and 4% hydrochloric acid, dried under vacuum, and 2.33 g (77%) of colorless crystals of the hydrochloride of VII was obtained, mp 209-210°C. The hydrochloride was alkalinized with aqueous sodium hydroxide, yielding the base VII. Found: M^+ 231. $C_{12}H_{13}N_3O_2$. Calculated: M 231.

2,5-Dimethoxy-1,4-phenylenediamine. The mother liquor after isolation of the hydrochloride VII was evaporated to 5 ml, the precipitate filtered off, and 0.6 g (22%) 2,5-dimethoxy-1,4-phenylenediamine dihydrochloride was obtained. Found: C 40.0; H 5.3; N 11.6; Cl 28.8%; M^+ 168. $C_8H_{14}N_2O_2 \cdot 2HCl$. Calculated: C 39.8; H 5.8; N 11.6; Cl 29.5%; M 168. PMR spectrum (D_2O): 2.72 (s, 6H, $2CH_3O$; 6.4 ppm (s, 2H, aromatic protons). Diacetyl derivative (pyridine, acetic anhydride, 2 h at 100°C), mp 283-284°C; according to the data of [5], mp 281°C.

Ethyl Ester of 3-Phthalimidoethyl-5,7-dimethoxyindole-2-carboxylic Acid (XIm). B-6. To 60 ml of a saturated solution of hydrogen chloride in alcohol, 26.74 g (0.061 mole) of the hydrazone Xm was added at 40-50°C heated for 2 h on a boiling water bath, cooled, the precipitate washed with methanol, and 4.93 g (19%) of the ester XIm was obtained.

3-(2-Aminoethyl)-5-methyl-7-bromoindole-2-carboxylic Acid (Vh). C. A mixture of 11.5 g (0.0412 mole) of the carbolinone IVh, 11.5 g sodium hydroxide, 115 ml of alcohol, and 115 ml of water was boiled for 20 h, the alcohol distilled off, the precipitate acidified to pH 5 with acetic acid, and the acid Vh was obtained, mp 265-267°C, yield 11.4 g (91%).

5-Methyl-7-bromotryptamine hydrochloride (VIh). D-1. A mixture of 1.5 g of the amino acid Vh, 7 ml of acetic acid, and 7 ml of conc. HCl was boiled for 10 h in a stream of argon, the solvent distilled off, the residue crystallized from 2 ml of acetic acid, and 0.67 g (46%) of the hydrochloride VIh was obtained.

4,7-Dimethyltryptamine Hydrochloride (VIc). D-2. A 9.3-g portion of the carbolinone IVc was treated according to procedure C; 40 ml of water and 2 ml of conc. H_2SO_4 were added to the precipitate of the amino acid IVc, the mixture boiled for two days, alkalinized with sodium hydroxide, tryptamine extracted with toluene, the solvent evaporated, the residue acidified in alcohol with hydrogen chloride to pH 6, and 1.86 g (19%) of the hydrochloride VIc was obtained.

4,7-Dichlorotryptamine Hydrochloride (VId). D-3. A 3.94-g (0.0155 mole) portion of the carbolinone IVd was treated according to procedure C; the amino acid Vd obtained was dried and boiled for 2 h with 20 ml of 85% phosphoric acid, alkalinized with sodium hydroxide, repeatedly extracted with chloroform, the solvent distilled off, and the tryptamine base dissolved in 10 ml of absolute alcohol and acidified with an alcohol solution of hydrogen chloride to pH 5.5-6, yielding 1.53 g (37%) of the hydrochloride VId.

3-(2-Phthalimidoethyl)-5,7-dimethoxyindole (XIIm). C-1. A mixture of 4.22 g (0.01 mole) of the ester XIm, 20 ml of 20% sodium hydroxide, 60 ml of water, and 10 ml of methanol was boiled for 6 h, acidified at 5-10°C to pH 3-4 with dilute hydrochloric acid, the precipitate of the acid XIm obtained was dried, heated at 280-320°C until the evolution of carbon dioxide ceased (1-3 h), and chromatographed on aluminum oxide in chloroform, yielding 2.21 g (63%) of compound XIIm.

5,7-Dimethoxytryptamine Hydrochloride (VIm). E. A suspension of 3.5 g (0.01 mole) 3-phthalimidoethyl-5,7-dimethoxyindole (XIIm), 1 ml (0.0206 mole) hydrazine hydrate, and 30 ml of alcohol was boiled for 3 h, cooled, and 30 ml of 20% sodium hydroxide and 50 ml of water were added, the mixture repeatedly extracted with methylene chloride, the solution dried, concentrated, and acidified with an alcohol solution of hydrogen chloride. The precipitate of the hydrochloride VIm obtained was dried under vacuum over potassium hydroxide. Yield, 1.97 g (77%).

6-Methoxy-8-amino-1,2,3,4-tetrahydro-β-carbolinone-1 (XIII). F. A suspension of 3 g of the carbolinone IVl in 25 ml of alcohol was reduced with hydrogen at 20°C and 760 mm Hg in the presence of 0.5 g 2% Pd/Al_2O_3 for 12 h, the mixture of the amine XIII and the catalyst filtered off, extracted with boiling dimethylformamide, evaporated, and 2.22 g (84%) of the aminocarbolinone XIII was obtained. Found: M^+ 231. $C_{12}H_{13}N_3O_2$. Calculated: M 231.

5-Methyl-7-aminotryptamine Dihydrochloride (XIV). F-1. A solution of 1.1 g of the hydrochloride VIIl in 20 ml of methanol was reduced by hydrogen with boiling at atmospheric pressure over 1 g of skeletal nickel; the catalyst was filtered off, the solvent distilled off, the residue dissolved in alcohol, acidified with an alcohol solution of hydrogen chloride, diluted with ether, and the dihydrochloride XIV was obtained.

LITERATURE CITED

1. L. N. Chupina, V. F. Shner, G. I. Gritsina, A. I. Terekhina, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 4, 466 (1984).
2. N. N. Suvorov, V. S. Shashkov, Chemistry and Pharmacology of Agents for the Prophylaxis of Radiation Sickness [in Russian], Atomizdat, Moscow (1975).
3. N. N. Suvorov, G. A. Chernov, L. Kh. Vinograd, M. M. Vigdorchik, G. N. Il'ina, and N. I. Lisina, Fifth All-Union Colloquium: Chemistry, Biochemistry, and Pharmacology of Indole Derivatives. Summaries of Reports [in Russian], Izd. Tbilissk. Univ. (1981), p. 110.
4. H. Ishii, J. Murukami, K. Hosoya, H. Takeda, I. Suzuki, and N. Ikeda, Chem. Pharm. Bull. (Tokyo), 21, 1481 (1973).
5. H. Ishii, J. Murukami, H. Takeda, and T. Furuse, Chem. Pharm. Bull. (Tokyo), 22, 1981 (1974).
6. H. Ishii, J. Murukami, S. Toni, K. Abe, and X. Ikeda, J. Pharm. Soc. Jpn., 90, 724 (1970); Ref. Zh. Khim. 4Zh365 (1971).

7. L. Britherick, K. Geimster, and W. R. Wragg, J. Chem. Soc., No. 7, 2919 (1961).
8. N. N. Suvorov, E. N. Gordeev, and M. V. Vasin, Khim. Geterotsikl. Soedin., No. 11, 1496 (1974).
9. F. W. Wehrli and T. Wirtlin, Interpretation of Carbon-13 NMR Spectra, Heyden, New York (1976), p. 38.
10. Roussel-UCLAF, Pat. 888413 (GB), 1962; Chem. Abstr., 64, 15890 (1966).
11. G. Muller, A. Allais, and R. Bardoneschi, Pat. 1366721 (FRG); Chem. Abstr., 62, 2803 (1965).
12. A. Allais, G. Muller, and R. Bardoneschi, Pat. 1366723 (FRG); Chem. Abstr., 62, 603 (1965).
13. Ch. F. Huebner, H. A. Troxler, and D. S. Schroeder, J. Am. Chem. Soc., 75, 5887 (1953).

INTERACTION OF ACYL DERIVATIVES OF THE FISCHER BASE WITH meta-SUBSTITUTED PHENOLS. SYNTHESIS OF 2H- and 4H-SPIROCHROMENES OF THE INDOLINE SERIES

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Acyl derivatives of the Fischer base react in the presence of phosphorus oxychloride with m-diethylaminophenol or resorcinol, forming spiro(indoline-2,2'-[2H]chromenes) and spiro(indoline-2,4'-[4H]chromenes). The ratio of the isomers depends on the solvent and the substituent in the phenol. The structure of the compounds obtained was established on the basis of the data of the ^1H and ^{13}C NMR spectra.

According to the data of [1], previously unknown 4-substituted spiro-2H-chromenes of the indoline series (V) can be produced by heating an acylated Fischer base (I) with meta-diethylaminophenol in the presence of phosphorus oxychloride. To study the synthetic possibilities of the indicated conversion we considered reactions of compound I with other m-substituted phenols: resorcinol and its monoesters. In this case, in supplementation to the patent [1], it was established that, as a rule, in addition to the 2H-chromene spiro compound (Va-d), the 4H-spirochromene (VI) isomeric to it is formed. The occurrence of the investigated reaction along two pathways is probably explained by the fact that the acylated Fischer base, being an enamine, can react with m-substituted phenols with two electrophilic sites (C_α and C_γ), correspondingly forming the intermediate compounds III and IV. The latter undergo cyclization under the action of alkali, accompanied by elimination of a phosphate ester group, which leads to the synthesis of spiro-2H- and -4H-chromenes (V and VI).

The ratio of isomers V and VI formed depends on the conditions of the reaction and the nature of the substituent in the phenol. Thus, the interaction of acyl derivatives of the Fischer base (I) with m-diethylaminophenol [II, X = $N(C_2H_5)_2$] in dichloroethane leads only to spiro-2H-chromene (Va). When 1,4-dioxane is used as the solvent, a mixture of isomers Va and VIa is formed, with yields of 34 and 19%, respectively. At the same time, the reaction of merocyanine (I, R = H) with resorcinol in dichloroethane already gives two isomers Vb and VIb. In this case the main product is not spiro-2H- but spiro-4H-chromene (yields of 10 and 40%, respectively).

Monoesters of resorcinol (II, X = OCH_3, OC_6H_5) do not react with the acylated Fischer base under the same conditions.

The structure of spiro-2H- and -4H-chromenes (V, VI) was established on the basis of the ^1H and ^{13}C NMR spectra, the data of elementary analysis, mass spectra (Table 1), and IR spectra. In the ^1H NMR spectrum (Table 2) of spiro-2H-pyrans (V) there are signals of the

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