ppm (4H, m, aromatic protons). Mass spectrum, m/z (%): 247 [M^+] (100), 246 [M − 1] (17.1), 232 [M − 15] (21.3), 220 [M − 1 − C_2H_2] (8.5), and 206 [M − 15 − C_2H_2] (8.5). Found: C 77.6, H 5.7, N 17.2%. $C_{16}H_{13}N_3$. Calculated: C 77.7, H 5.3, N 17.0%.

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SYNTHESIS OF 2-CARBOXY-5,6-ETHYLENEDIOXYINDOLE AND ITS 3-, 4-, AND 7-HALO DERIVATIVES

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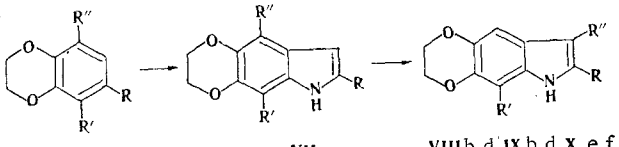
UDC 547.751'841.07:543.422

A method for the synthesis of 2-carboxy-5,6-ethylenedioxyindole and its 4- and 7-chloro derivatives from 3,4-ethylenedioxyaniline and, correspondingly, its 2- and 5-chloro derivatives via the Fischer reaction was developed. It was established that in the case of bromination or chlorination under mild conditions 2-carbethoxy-5,6-ethylenedioxyindole forms 3-halo derivatives, while 5,6-ethylenedioxyindole itself forms only 3,7-dihalo derivatives. The closeness in the reactivities of the 3 and 7 ring positions of 5,6-ethylenedioxyindole (as compared with indole) is in agreement with the results of calculations of the quantum-chemical reactivity indexes for electrophilic substitution.

Derivatives of acids of the ethylenedioxyindole series, particularly those that contain halogens, display anti-inflammatory activity [1, 2]. In connection with the manifestation of anti-inflammatory and analgesic activity by 2-carboxyindole derivatives [3], it therefore seems of interest to develop methods for the synthesis of ethylenedioxy-substituted 2-carboxyindolines and their halo derivatives.

We have developed the following scheme for the synthesis of the previously unknown 4- and 7-halo-2-carboxy-5,6-ethylenedioxyindoles in the preparation of chloro derivatives VIb,c:



I–IIIa–c, IV c V–VIa–c, VII a VIIIb, d, IX b, d, X e, f

I R=NO_2; II R=$NH_2 \cdot HCl$; III R=$NHNH_2 \cdot HCl$; IV R=NHN=$C(CH_3)COOC_2H_5$; V, VIII R=$COOC_2H_5$; VI, IX R=COOH; VII, X R=H; a R′=R″=H; b R′=H, R″=Cl; c R′=Cl, R″=H; d R′=H, R″=Br; e R′=R″=Br; f R′=R″=Cl

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1215-1219, September, 1982. Original article submitted February 3, 1982.

0009-3122/82/1809-0932$07.50

TABLE 1. Quantum-Chemical Reactivity Indexes

Index	Indole				5,6-Ethylenedioxyindole (VIIa)			
	indole ring carbon atoms							
	2	3	4	7	2	3	4	7
q [a]	−0,06	−0,10	−0,00	−0,05	−0,07	−0,11	−0,04	−0,09
f [b]	0,32	0,47	0,39	0,32	0,33	0,39	0,34	0,37
$\bar{E}$, [c] eV	0,41	0,00	0,52	0,41	0,15	0,05	0,11	0,00

[a] Charge on the atom. [b] Electron population of the AO due to the highest filled MO [4, 10]. [c] Energies of the π electrons in the case of increased absolute values of the ionization potentials and the electrostatic integrals of the AO of the ring atom attacked (3 and 1 eV, respectively). The probability of electrophilic substitution increases as the E values decrease [11].

Nitrochloroethylenedioxybenzenes Ib,c [4] are reduced to amines IIb,c, which are converted to diazonium salts and reduced to hydrazines IIIb,c. The latter by reaction with ethyl pyruvate (isolation of the intermediate hydrazones IVb,c is not necessary) are converted to indole derivatives Vb,c and hydrolyzed to acids VIb,c. We obtained acid VIa, which has been previously synthesized by a more complex pathway [6], via this scheme from amine IIa [5].

The presence of strong electron-donor substituents in the benzene ring of indole promotes its electrophilic substitution even when the 3 position of the pyrrole ring is unoccupied [7]. However, despite the presence of a 5,6-ethylenedioxy substituent in the benzene ring and a 2-carbethoxy substituent in the pyrrole ring, ester Va is chlorinated and brominated under mild conditions only in the 3 position and forms derivatives VIIIb,d, which are hydrolyzed to acids IXb,d. It is interesting to note that 5,6-ethylenedioxyindole (VIIa) itself forms only 3,7-dihalo derivatives Xe,f in the case of halogenation under the same conditions or even when the amount of halogen used is half the amount necessary for monohalogenation.

This phenomenon is evidently due to orbital control of the course of the halogenation reaction, which is promoted by the high nucleophilicity of the VIIa molecule, and to the small difference between the reactivities of the 3 and 7 positions of its ring, since the reactivity indexes calculated within the π-electron approximation [Pariser–Parr–Pople (PPP)] of the self-consistent field (SCF) MO LCAO method (Table 1) indicate the increased capacity for electrophilic substitution of the 3 position in indole and the small differences in this respect between the 3 and 7 positions in the VIIa molecule.

The parameters in the calculations were taken from the data in [8]. The bond lengths and bond angles were standard values [9]. The ethylenedioxy group was examined in the half-chair conformation [10].

The structures of Xe,f are confirmed by the absence in their PMR spectra of signals of protons in the 3 and 7 positions of the ring, which are observed at 6.44 and 7.03 ppm in the spectrum of starting VIIa.

Compound VIIa was obtained by decarboxylation of acid VIa. The yield of VIIa was increased from 63% [6] to 75% by raising the temperature and decreasing the reaction time.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Tesla BS-487C spectrometer (80 MHz) with tetramethylsilane as the internal standard.

2(or 5)-Chloro-3,4-ethylenedioxyaniline Hydrochlorides (IIb,c). A mixture of 1 liter of 80% ethanol, 215 g (1 mole) of Ib or Ic [4], 280 g (5 moles) of reduced iron powder, and 32 g (0.5 mole) of copper turnings was refluxed with stirring, and 40 ml (0.4 mole) of con-

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C (solvent)	UV spectrum		IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm[a]		Found, %				Empirical formula	Calculated, %				Yield, %
		λ_{max}, nm	lg ε	C=O	NH	OH	H_{Ar}	H_{NH} (s)	C	H	Hal	N		C	H	Hal	N	
II b	195—197 (ethanol)	212, 309	4,47; 3,43	—	3400	—	7,01 (s)[b]; 7,18 (s)	7,35	43,4	4,1	31,9	6,4	$C_8H_8ClNO_2 \cdot HCl$	43,3	4,1	31,9	6,3	79
II c	220—222 (ethanol)	208, 303	4,51; 3,54	—	3400	—	6,88 (d, 6-H)[b,c]; 7,16 (d, 5-H)[c]	7,83	43,1	3,9	31,9	6,4	$C_8H_8ClNO_2 \cdot HCl$	43,3	4,1	31,9	6,3	72
III a	144 (dec., isopropyl alcohol)	206, 227—246, 294	4,23 shoulder 3,76	—	3230	—	6,5—6,9 (m)[b]	3,46 10,16	47,3	5,5	17,2	13,8	$C_8H_{10}N_2O_2 \cdot HCl$	47,4	5,5	17,5	13,8	66
III b	121 (dec., ethanol)	213, 298	4,34; 3,50	—	3400	—	6,63 (d)[b,d] 6,75 (d)[d]	3,78 10,38	40,3	4,3	30,2	11,9	$C_8H_9ClN_2O_2 \cdot HCl$	40,5	4,3	29,9	11,8	61
III c	165 (dec., ethanol)	214, 290	4,44; 3,76	—	3400	—	6,75 (d, 6-H)[b,c] 6,90 (d, 5-H)[c]	3,55 10,18	40,5	4,3	30,0	11,8	$C_8H_9ClN_2O_2 \cdot HCl$	40,5	4,3	29,9	11,8	53
IV c	125—126 (ethanol)	206, 350	4,34; 4,26	1690	3280	—	6,66 (d)[c,e,f,g]; 7,01 (d)[c]	12,20	52,3	5,2	11,6	9,4	$C_{13}H_{15}ClN_2O_4$	52,3	5,1	11,9	9,4	96
V a	135—136 (benzene)	213, 305, 320	4,19; 4,03; 4,01	1695	3330	—	6,83 (s, 7-H)[b,g] 6,91 (s, 3-H); 7,00 (s, 4-H)	11,40	63,2	5,2	—	5,7	$C_{13}H_{13}NO_4$	63,2	5,3	—	5,7	60
V b	175—177 (CCl_4)	213, 222—236, 298, 310—330,	4,45 shoulder 4,30 shoulder	1705	3340	—	6,83 (s, 7-H)[b,g]; 6,91 (s, 3-H)	11,96	55,2	4,2	12,5	5,1	$C_{13}H_{12}ClNO_4$	55,4	4,3	12,6	5,0	42
V c	140—141 (benzene)	212, 220—230, 315	4,40 shoulder 4,25	1710	3310	—	7,01 (s)[b,g]	11,63	55,4	4,4	12,5	4,9	$C_{13}H_{12}ClNO_4$	55,4	4,3	12,6	5,0	50
VI a[h]	250 [dec., acetone — isooctane 1 : 4)	212, 320	4,20; 4,01	1700	3360	3310	6,8—7,1 (m)[b]	11,31	60,3	4,1	—	6,2	$C_{11}H_9NO_4$	60,3	4,1	—	6,4	98
VI b	230 (dec., 80% ethanol)	212, 219—233, 303	4,21 shoulder 4,06	1695	3410	3000	—	—	51,9	3,1	13,9	5,5	$C_{11}H_8ClNO_4$	52,1	3,2	14,0	5,5	96
VI c	261 (dec., 80% ethanol)	212, 218—227, 312	4,50 shoulder 4,33	1690	3410	3000	—	—	52,3	3,1	13,9	5,6	$C_{11}H_8ClNO_4$	52,1	3,2	14,0	5,5	97
VIIa[i]	148—149 (isooctane)	216, 283, 304	4,31; 3,76; 3,87	—	3420	—	6,44 (m, 3-H)[j]; 7,03 (s, 7-H); 7,22 (m 2-H); 7,26 (s, 4-H)	11,32	—	—	—	—	—	—	—	—	—	75

VIIIb	165—166 (CCl_4)	213, 325	4,36; 4,24	1700	3340	—	6,86 (s) b,g 6,91 (s)	11,69	55,4	4,2	12,6	5,1	$C_{13}H_{12}ClNO_4$	55,4	4,3	12,6	5,0	70
VIIId	174—175 (CCl_4)	213, 320	4,54; 4,44	1695	3245	—	6,84 (s) b,g 6,88 (s)	11,76	47,8	3,8	24,3	4,3	$C_{13}H_{12}BrNO_4$	47,9	3,7	24,5	4,3	84
IXb	217 (dec., ethanol)	215, 320	4,46; 4,34	1695	3410	2990	—	—	52,3	3,3	13,7	5,6	$C_{11}H_8ClNO_4$	52,1	3,2	14,0	5,5	95
IXd	197 (dec., acetone—octane 1 : 3)	214, 321	4,46; 4,31	1690	3400	2990	—	—	44,5	2,7	26,8	4,8	$C_{11}H_8BrNO_4$	44,3	2,7	26,8	4,7	97
Xe	190—192 (CH_2Cl_2—CCl_4, 1 : 1)	212, 312	4,37; 3,85	—	3200	—	7,55 (s) i	11,50	36,1	2,1	47,8	4,2	$C_{10}H_7Br_2NO_2$	36,1	2,1	48,0	4,2	79
Xf	183—185 (CH_2Cl_2—CCl_4, 1 : 1)	213, 310	4,40; 3,81	—	3200	—	7,48 (s) i; 7,51 (s)	11,45	49,1	2,9	29,2	5,7	$C_{10}H_7Cl_2NO_2$	49,2	2,9	29,1	5,7	71

[a] Signal at 4.0-4.3 ppm (s, OCH_2CH_2O). [b] In deuterodimethyl sulfoxide. [c] J = 9 Hz. [d] J = 3 Hz. [e] In CCl_4. [f] Signal at 2.04 ppm (s, CH_3). [g] Signals at 1.3-1.4 ppm (t, J = 6-7 Hz, CH_2CH_3) and 4.2-4.5 ppm (q, J = 6-7 Hz, OCH_2). [h] According to the data in [6], this compound had mp 244-245°C (dec.), λ_{max} 315 nm, and log ε 3.82. [i] According to the data in [6], this compound had mp 148.4-149°C, λ_{max} 305 nm, and log ε 3.78. [j] In deuteropyridine.

centrated HCl was added in the course of 1.5 h. After 4 h, the mixture was filtered, the filtrate was acidified with hydrochloric acid, the ethanol was removed by distillation, and the residue was made alkaline with NaOH and extracted with benzene. Gaseous HCl was then bubbled into the dried extract.

3,4-Ethylenedioxyphenylhydrazine Hydrochloride and Its 2- and 5-Chloro Derivatives (IIIa-c). A solution of 6.9 g (0.1 mole) of $NaNO_2$ in 10 ml of water was added at 0°C to a solution of 0.1 mole of amines IIa-c in 120 ml of dilute (1:1) hydrochloric acid, and the mixture was added at 0°C to a solution of 38 g (0.2 mole) of $SnCl_2$ in 40 ml (0.4 mole) of concentrated HCl. The precipitate was suspended in 100 ml of water, and the suspension was made alkaline to pH 10 with NaOH at 5-10°C. The mixture was extracted with ether, and gaseous HCl was bubbled into the dried extract.

Ethyl Pyruvate 2-Chloro-3,4-ethylenedioxyphenylhydrazone (IVc). Gaseous HCl was bubbled for 20 min into a solution of 3 g (0.012 mole) of hydrochloride IIIc and 1.5 g (0.012 mole) of ethyl pyruvate in 30 ml of absolute ethanol, and the hydrazone was removed by filtration.

2-Carbethoxy-7-chloro-5,6-ethylenedioxyindole (Vc). Gaseous HCl was bubbled for 2 h into a solution of 3 g (0.01 mole) of hydrazone IVc in 50 ml of absolute ethanol, after which the mixture was refluxed for 1 h, 20 ml of water was added, and the indole was extracted with ether.

2-Carbethoxy-5,6-ethylenedioxyindole and Its 4-Chloro Derivative (Va, b). Gaseous HCl was bubbled for 1 h into a solution of 0.025 mole of hydrochloride IIIa or IIIb and 2.9 g (0.025 mole) of ethyl pyruvate in 45 ml of absolute ethanol, and the mixture was refluxed for 4 h. It was then concentrated to a volume of 20 ml and treated with 50 ml of water. The aqueous mixture was extracted with ether, and the extract was washed with 10% Na_2CO_3 solution and water and dried with $CaSO_4$. The ether was removed by distillation, and the product was extracted with hot octane.

2-Carboxy-5,6-ethylenedioxyindole and Its Halo Derivatives (VIa-c, IXb,d). A mixture of 0.01 mole of esters Va-c or VIIIb,d, 1.7 g (0.03 mole) of KOH, and 20 ml of water was refluxed for 3 h, after which it was acidified with hydrochloric acid.

5,6-Ethylenedioxyindole (VIIa). Acid VIa was heated to 300°C on a bath, and VIIa was removed by vacuum distillation.

3-Halo-2-carbethoxy-5,6-ethylenedioxyindoles (VIIIb,d) and 3,7-Dihalo-5,6-ethylenedioxyindoles (Xe,f). A solution of 0.07 mole or, respectively, 0.14 mole of the halogen in 100 ml of CCl_4 was added with stirring at −20°C to a solution of 0.07 mole of VA or VIIa in 100 ml of CH_2Cl_2, after which the mixture was allowed to stand in the cold for 2 h. The solvent was then removed by vacuum distillation.

The characteristics of the synthesized compounds are presented in Table 2.

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SYNTHESIS AND PHOTOCHROMIC PROPERTIES OF INDOLINOSPIROCHROMENES WITH ELECTRON-DONOR SUBSTITUENTS IN THE INDOLINE PART OF THE MOLECULE

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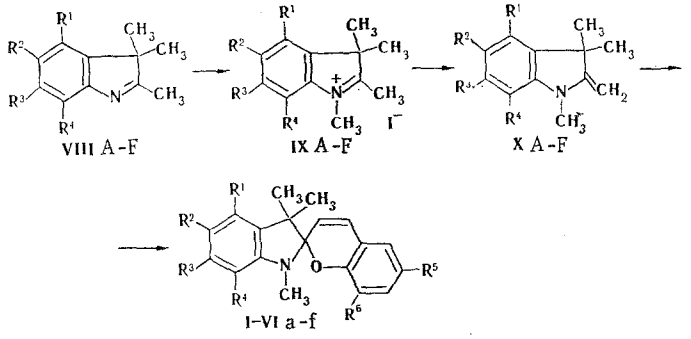
UDC 547.753:541.143

1,3,3-Trimethylspiro(indoline-2,2'-[2H]chromenes) with CH_3 and CH_3O groups in the 4-7 positions and NO_2 and CH_3O groups in the 6' and 8' positions were obtained by the reaction of 4,6-, 4,7-, 5,6-, and 6,7-dimethoxy- and 4-methyl-7-methoxy-2-methyleneindolines and 1,3,3,4,5,6,7-heptamethyl-2-methyleneindoline with 3- and 5-nitrosalicylaldehydes and their derivatives. Most of the compounds have photochromic properties. The introduction of electron-donor groups into the indoline fragment of the spirochromene molecules changes the rate of the dark reaction within the limits of one order of magnitude and has a small effect on the position of the long-wave absorption band of the photomerocyanine.

A large amount of research has been devoted to the study of the relationship between the structure of indolinospirochromenes and their photochromic properties [1]; however, the peculiarities of the effect of substituents from the 4-7 positions of the indoline part of the molecule have not been adequately revealed. In order to study the problem of the degree to which the introduction of electron-donor substituents into these positions can change the photochromic properties of the molecule we synthesized several series of indolinospirochromenes that contain methoxy and methyl groups in the 4-7 positions. Indolinospirochromenes (I-VI) were obtained by the reaction of substituted 1,3,3-trimethyl-2-methyleneindolines (X) with substituted salicylaldehydes.



I B $R^1=R^4=OCH_3$; II E $R^3=R^4=OCH_3$; III D $R^2=R^3=OCH_3$; IV A $R^1-R^3=OCH_3$; V C $R^1=CH_3$, $R^4=OCH_3$; VI F $R^1=R^2=R^3=R^4=CH_3$; I—VI a $R^5=NO_2$; b $R^5=NO_2$, $R^6=OCH_3$; c $R^5=NO_2$, $R^6=Br$; d $R^5=R^6=NO_2$; e $R^6=NO_2$, f $R^5=OCH_3$, $R^6=NO_2$. not indicated $R^i=H$

The methods for the synthesis of the indolenines VIII that are necessary for the preparation of substituted 2-methyleneindolines X differed depending of the position of the substituents. Thus for the preparation of 4,6-dimethoxy- (VIIIA), 4,7-dimethoxy- (VIIIB), and

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0009-3122/82/1809-0937$07.50