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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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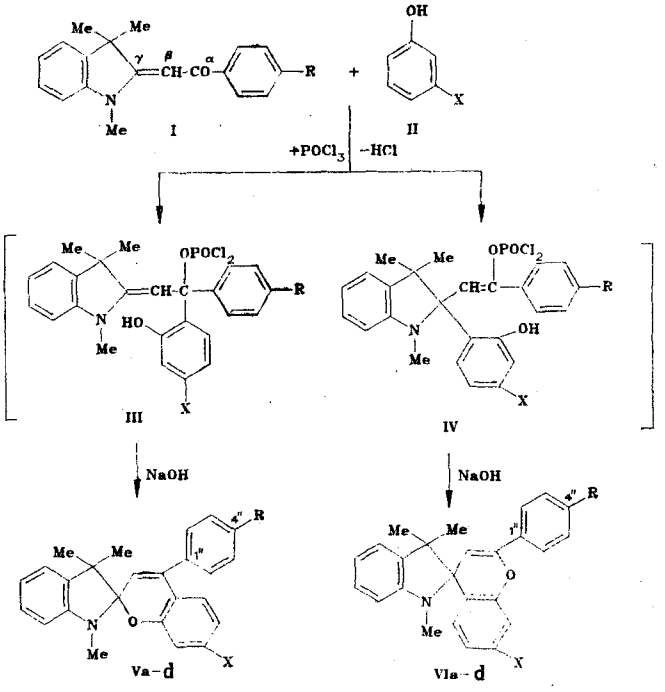
TABLE 1. Indoline 2H- and 4H-Spirochromenes

Compound	R	X	mp, °C	Found				Empirical formula	Calculated				Yield, %
				C, %	H, %	N, %	M*		C, %	H, %	N, %	M*	
Va	H	$N(C_2H_5)_2$	140—142 [1]				424	$C_{29}H_{32}N_2O$				424	34
Vb	H	OH	81—83	81,3	6,3	3,6	369	$C_{25}H_{23}NO_2$	81,3	6,3	3,8	369	11
Vc	OCH_3	OH	92—84	78,4	6,5	3,5	399	$C_{26}H_{25}NO_3$	78,2	6,3	3,5	399	3
VIa	H	$N(C_2H_5)_2$	180—182	82,3	7,5	6,6	424	$C_{29}H_{32}N_2O$	82,0	7,6	6,6	424	19
VIb	H	OH	193—195	81,6	6,4	3,7	369	$C_{25}H_{23}NO_2$	81,3	6,3	3,8	369	40
VIc	OCH_3	OH	194—195	77,9	6,5	3,5	399	$C_{26}H_{25}NO_3$	78,2	6,3	3,5	399	40

*Mass spectrometrically on an MX-1303 instrument.

nonequivalent C-methyl groups (~1.2 and 1.3 ppm) and the N-methyl group (~2.8 ppm) of the indoline fragment, as well as the singlet of the 3'-H proton (~5.3-5.5 ppm). Close values of the chemical shifts of the corresponding protons were observed earlier in the spectra of other spiro-2H-pyrans [2]. In the spectra of isomeric compounds VI, one of the signals of the C-methyl groups, as well as the signal of $N-CH_3$, were displaced into a stronger-field region (Table 2), which agrees with the structure of the spiro-4H-pyran compound VI. However, for a final confirmation of the structure of VI we considered it necessary to use the ^{13}C NMR method with complete and partial suppression of the interaction with protons.



V, VI a R=H, X=$N(C_2H_5)_2$; b R=H, X=OH; c R=OCH_3, X=OH; d R=OCH_3, X=$N(C_2H_5)_2$

In the ^{13}C NMR spectra of compounds Va and VIa, c (Table 3), three signals of the carbon atoms of the C- and N-methyl groups of the indoline fragment (~20-30 ppm), the signal of the quaternary $C_{(3)}$ atom (~50 ppm), and the signals of the N-ethyl group (~44 and 12 ppm) and OCH_3 (~55 ppm) are observed. The signals of the remaining carbon atoms lie in the region of 73-160 ppm. The most important characteristic distinguishing the structure of VI from V is the chemical shift of the spiro atom. The value δ ~ 73 ppm (VIa, c) and the multiplicity of the signal correspond to the quaternary sp^3-hybridized carbon atom bonded to one heteroatom (nitrogen) [3]. In the analogous spectrum of spiro-2H-pyran (Va), just as in the spectra of other compounds of this class [4], the signal of the corresponding spiro-carbon atom, this time bonded to two heteroatoms (oxygen and nitrogen), lies in a weaker-field region (~104 ppm). Thus, the value of δ of the spiro-atom of compounds VIa and c is evidence of their 4H-chromene structure. Compounds VIa and c are also characterized by the signal of the $C_{(2')}$ carbon atom bonded to an oxygen atom and therefore shifted into a weaker field (~150 ppm).

It is known that 2H-spirochromenes of the type of V exhibit thermochromic properties. Analogous properties are also possessed by the first synthesized 4H-spirochromenes (VIa-d): when heated on silufol they acquire a yellow-green color.

TABLE 2. PMR Spectra of Indoline Spirochromenes

Compound	δ, ppm*						
	3,3-$(CH_3)_2$	1-CH_3	3′-H	7′-X	4-C_6H_4R		
					2″-H	3″-H	R
Va	1,37, 1,20	2,78	5,33	3,26, 1,09	7,38 (5H)		
Vb	1,34, 1,19	2,76	5,46	4,95	7,36 (5H)		
Vc	1,32, 1,19	2,75	5,44	4,85	7,33	6,93	3,48
Vd	1,35, 1,19	2,77	5,29	3,25, 1,09	7,35	6,90	3,83
VIa	1,23, 0,92	2,56	5,45	3,29, 1,15	7,38—7,77 (5H)		
VIb	1,24, 0,92	2,59	5,51	4,75	7,36—7,76 (5H)		
VIc	1,23, 0,92	2,57	5,37	4,85	7,62	6,88	3,81
VId	1,23, 0,95	2,58	5,34	3,30, 1,15	7,64	6,86	3,80

*SSIC of the vicinal protons of the N-ethyl groups in compounds Va, VIa) 7.0; Vd) 6.8; VId) 6.9 Hz. Vc) $J_{2''3''} = 8.6$; Vd) $J_{2''3''} = 8.0$; VIc, d) $J_{2''3''} = 9.0$ Hz.

Our investigation showed that not only m-diethylaminophenol [1] but also resorcinol enter into the reaction with acyl derivatives of the Fischer base in the presence of phosphorus oxychloride. In this case, together with the 2H-chromene spiro-compound, the 4H-spirochromene isomeric to it is almost always formed.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Varian CFT-20 spectrophotometer (80 MHz). The chemical shifts were measured relative to tetramethylsilane as the internal standard. The IR spectra were recorded in liquid petrolatum on a UR-20 instrument. The R_f values were determined on plates with a fixed layer of Silufol UV-254 silica gel (eluent chloroform).

1,3,3-Trimethyl-4′-phenyl-7′-diethylaminospiro(indoline-2,2′-[2H]chromene) (Va) and 1,3,3-Trimethyl-2′-phenyl-7′-diethylaminospiro(indoline-2,4′-[4H]chromene) (VIa). To a solution of 2.77 g (10 mmoles) 1,3,3-trimethyl-2-phenacylidenindoline (mp 138-139°C) [5] in 50 ml of 1,4-dioxane, cooled to 0°C, 3.06 g (20 mmoles) phosphorus oxychloride was added dropwise, and then 2.16 g (13 mmoles) diethylaminophenol was added in portions. The mixture was exposed at 60°C for 6 h, after which it was poured out into 100 ml of water with ice, neutralized with a 10% solution of sodium hydroxide, extracted with chloroform (3 × 50 ml), dried with sodium sulfate, the solvent evaporated, and the residue crystallized from acetone. Yield of compound VIa 0.8 g. The mother liquor was evaporated and the residue recrystallized from acetone. Yield 1.44 g of compound Va. IR spectrum of the spirochromene VIa: 1665 cm^{-1} (C=C).

1,3,3-Trimethyl-4′-phenyl-7′-hydroxyspiro(indoline-2,2′-[2H]chromene) (Vb) and 1,3,3-Trimethyl-2′-phenyl-7′-hydroxyspiro(indoline-2,4′-[4H]chromen) (VIb). To a solution of 2.08 g (7.5 mmoles) 1,3,3-trimethyl-2-phenacylidenindoline [5] in 25 ml of 1,2-dichloroethane, cooled to 0°C, 3.45 g (22.5 mmoles) of phosphorus oxychloride was added dropwise, and then 1.08 g (9.8 mmoles) of resorcinol was added in portions. The mixture was exposed at 60°C for 6 h, after which it was poured out into 50 ml of water with ice and neutralized with a 10% sodium hydroxide solution. The organic layer was removed, dried with sodium sulfate, and the solvent evaporated. The residue was passed through a column with silica gel, eluting with chloroform. We obtained 1.12 g of compound VIb (R_f 0.22) and 0.3 g of compound Vb (R_f 0.18). IR spectrum of the spirochromene VIb: 1650 (C=C), 3540 cm^{-1} (OH).

1,3,3-Trimethyl-4′-p-methoxyphenyl-7′-hydroxyspiro(indoline-2,2′-[2H]chromene) (Vc) and 1,3,3-Trimethyl-2′-p-methoxyphenyl-7′-hydroxyspiro(indoline-2,4′-[4H]chromene) (VIc). Produced analogously to compounds Vb and VIb from 6.15 g (20 mmoles) of 1,3,3-trimethyl-2-p-methoxyphenacylindenindoline [1], 2.86 g (26 mmoles) resorcinol, and 9.2 g (60 mmoles) phosphorus oxychloride. Yield of the spirochromene VIc 3.23 g (R_f 0.18), and of the spirochromene Vc 0.3 g (R_f 0.14). IR spectrum of the spirochromene VIc: (C=C), 3390 cm^{-1} (OH).

1,3,3-Trimethyl-4′-p-methoxyphenyl-7′-diethylaminospiro(indoline-2,2′-[2H]chromene) (Vd) and 1,3,3-Trimethyl-2′-p-methoxyphenyl-7′-diethylaminospiro(indoline-2,4′-[4H]chromene) (VId). Produced analogously to compounds Va and VIa from 1.5 g (4.9 mmoles) of 1,3,3-trimethyl-2-p-methoxyphenacylidenindoline, 1.22 g (9.8 mmoles) m-diethylaminophenol, and 1.21 g (7.8 mmoles)

TABLE 3. Chemical Shifts of the ^{13}C Nuclei of Compounds Va, VIa, and VIc

Carbon atom*	Va	VIa	VI
1-CH_3	29,1	30,2	30,2
3,3-$(CH_3)_2$	20,4	24,2	24,0
CH_2†	26,7	25,4	25,4
	44,1	44,2	
CH_3†	12,7	12,6	
OCH_3			55,3
2	104,3	72,8	72,7
3	51,4	50,2	50,3
7	103,4	105,3	105,3
7a	149,3	150,8	150,7
3a	137,1	137,6	137,2
2′	104,3	151,0	150,6
3′	97,8	98,7	98,6
4′	141,8	72,8	72,7
5′	128,1	118,8	117,8
6′	112,8	107,7	110,7
7′	148,5	148,1	153,0
8′	116,6	100,5	113,0
8′a	156,3	153,5	155,4
4′a	108,4	107,3	113,0
1″	139,0	134,3	126,4
4″	127,5	121,4	160,2

*Chemical shifts of the remaining carbon atoms for compound Va: $C_{(4)}$ 128.5; $C_{(5)}$ 121.8; $C_{(6)}$ 117.6; $C_{(2'')}$ 128.7; $C_{(3'')}$ 128.2; $C_{(5'')}$ 128.3; $C_{(6'')}$ 125.0; for compound VIa: $C_{(4)}$ 127.6; $C_{(5)}$ 127.5; $C_{(6)}$ 126.4; for compound VIc: $C_{(4)}$ 128.5; $C_{(5)}$ 127.7; $C_{(6)}$ 121.9.
†For X=N$(C_2H_5)_2$.

of phosphorus oxychloride. Crystallized from aqueous ethanol, yielding 0.87 g of a mixture of the isomers Vd and VId in a 1:4 ratio (according to the integral curve of the ^1H NMR spectrum).

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