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REACTION OF THE FISCHER BASE WITH NITRO- AND BROMO-SUBSTITUTED o-HYDROXYCINNAMALDEHYDES

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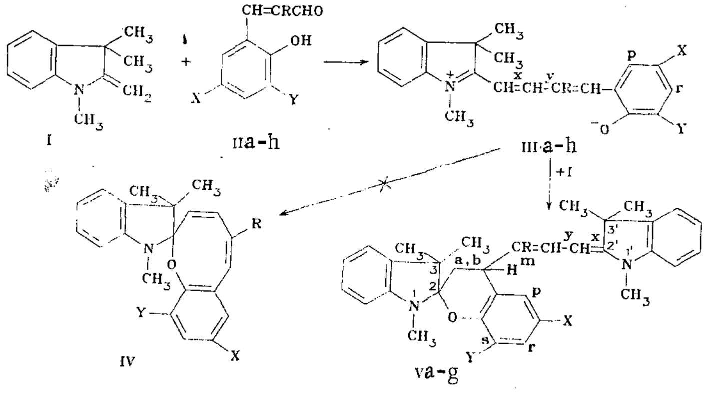
The Fischer base reacts with α-ethyl-5-nitro-, 5-bromo-, and 3,5-dibromo-2-hydroxycinnamaldehydes to give bisindoline spirochromans, with 3-bromo-5-nitro-2-hydroxycinnamaldehyde to give a mixture of a spirochroman and a monoindoline merocyanine, and with 3,5-dinitro-2-hydroxycinnamaldehyde to give only a merocyanine. The monoindoline merocyanines obtained do not display a tendency to undergo intramolecular cyclization to give spiro-2H-oxocines.

It is well known that the first attempt [1] to obtain new photochromic compounds, viz., indoline spiro-2H-oxocines (IV), by the reaction of the Fischer base (I) with o-hydroxycinnamaldehydes (IIa, b) was unsuccessful. It was recently shown [2] that the indicated reaction proceeds through a step involving the formation of merocyanine structure III; however, instead of the desired spirocyclization to give an eight-membered ring (IV), the next step involves the addition of a second molecule of the methylene base, as a consequence of which the final products are bisindoline spirochromans V, which do not have photochromic properties.



a X=Y=R=H; b $X=NO_2$, Y=R=H; c $X=NO_2$, Y=H, $R=CH_3$; d $X=NO_2$, Y=H, $R=C_2H_5$; e X=Y=Br, R=H; f X=Br, Y=R=H; g $X=NO_2$, Y=Br, R=H; h $X=Y=NO_2$, R=H

In the present research we continued our study of the reaction of the Fischer base with various substituted o-hydroxycinnamaldehydes in order to search for conditions under which the formation of spiro-2H-oxocines becomes possible. It is known that the formation of "di-

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condensed" chromans of the V type is hindered by the presence of electron-acceptor substituents in the aromatic ring of the o-hydroxy aldehyde [3-5]. Thus under conditions in which a mixture of a spiropyran and a bisindoline spirochroman is formed from salicylaldehyde and the Fischer base, only a monoindoline compound is obtained from nitrosalicylaldehydes [3]. However, in the case of o-hydroxycinnamaldehyde the introduction of one nitro group (IIb) is not sufficient to prevent the addition of a second molecule of the methylene base [1]. A spirochroman (Vc) is also obtained in the reaction of the Fischer base with α-methyl-5-nitro-2-hydroxycinnamaldehyde [2].

Our research has shown that the formation of bisindoline spirodihydropyrans (Vd-f) also occurs in the reaction of the Fischer base with α-ethyl-5-nitro-2-hydroxycinnamaldehyde, as well as with bromo-substituted o-hydroxycinnamaldehydes, viz., 5-bromo- and 3,5-dibromo-2-hydroxycinnamaldehyde. The results of the reaction of the Fischer base with 3,5-dinitro- and 3-bromo-5-nitro-2-hydroxycinnamaldehyde (IIh, g) proved to be more interesting. In the first case the product was a black crystalline substance, which, like the analogous products of the condensation of indoline bases with dinitrosalicylaldehyde [6], was the open form, viz., merocyanine IIIh, which does not display a tendency to undergo intramolecular cyclization.

However, the condensation of the Fischer base with 3-bromo-5-nitro-2-hydroxycinnamaldehyde (IIg) at an equimolar reagent ratio led to the formation of a mixture of two substances, viz., a dark-orange substance and a greenish-black substance. The former was found to be bisindoline spirochroman Vg, and the latter was identified as merocyanine IIIg, which, like IIIh, was not converted to a cyclic isomer. When a twofold excess of the Fischer base as compared with 3-bromo-5-nitro-2-hydroxycinnamaldehyde was used in the reaction, the only product was spirochroman Vg. A similar observation was also previously made in a series of substituted salicylaldehydes [7-9].

The characteristics of the synthesized compounds are presented in Table 1, and the PMR spectra are presented in Table 2. In the PMR spectra of merocyanines IIIg,h the C-methyl groups give one signal at ~1.7 ppm, whereas the signals of the N-methyl groups are observed at ~4.0 ppm. Such a weak-field position of the $N-CH_3$ signals is characteristic for merocyanines of the indoline series and constitutes evidence for significant localization of the positive charge on the nitrogen atom, and the equivalence of the C-methyl groups indicates coplanarity of these compounds [10]. The spectrum of dinitro-substituted merocyanine IIIh contains a doublet of the H^x proton at 7.18 ppm with spin–spin coupling constant (SSCC) J_{xy} = 14.5 Hz. The value of this constant constitutes evidence for a trans orientation of the H^x and H^y protons. As a consequence of the low solubility of merocyanine IIIg, we were unable to assign the signals of the aromatic protons and the protons of the diene fragment in the spectrum of this compound.

Thus our research showed that the open forms of spiro-2H-oxocines can be obtained when strong electron-acceptor substituents are present in the o-hydroxycinnamaldehyde molecule; however, they do not display a tendency to undergo intramolecular nucleophilic cyclization. This can evidently be explained by the significant decrease in the electron density on the oxygen atom under the influence of electron-acceptor groups.

EXPERIMENTAL

The PMR spectra of IIIg,h in $(CD_3)_2SO$ and V in $CDCl_3$ were recorded with a Varian XL-100A-12 spectrometer (100 MHz); the chemical shifts were measured relative to tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The molecular masses were measured with Varian MAT-112 (Vd) and MAT-311A (IIIh,g) mass spectrometers.

1,3,3-Trimethyl-4'-[3-(1,3,3-trimethylindolin-2-ylidene)-1-ethyl-1-propenyl]-6'-nitroindoline-2-spiro-2'-chroman (Vd). A 0.28-g (1.62 mmole) sample of the Fischer base was added to a solution of 0.42 g (1.89 mmole) of α-ethyl-5-nitro-2-hydroxycinnamaldehyde in 15 ml of absolute alcohol, and the mixture was allowed to stand at room temperature for 2 days. The resulting precipitate was separated to give 0.32 g of the product, which was crystallized from benzene–ethanol to give orange crystals. IR spectrum: 1648 (C=C): 963 ($C_{spiro}-O$); 1520, 1345 cm^{-1} (NO_2). Found and calculated: M 549.

1,3,3-Trimethyl-4'-[3-(1,3,3-trimethylindolin-2-ylidene)-1-propenyl]-6',8'-dibromoindoline-2-spiro-2'-chroman (Ve). This compound was obtained by condensation of 0.45 g (1.47 mmole) of 3,5-dibromo-2-hydroxycinnamaldehyde with 0.26 g (1.50 mmole) of the Fischer base in 17 ml of absolute alcohol at room temperature for 6 days. Workup gave 0.35 g of the product,

TABLE 1. Indoline Spirochromans (V) and Merocyanines (III)

Compound	X	Y	R	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
					C	H	Br	N		C	H	Br	N	
Vd	NO_2	H	C_2H_5	190—191	76,8	7,2	—	7,7	$C_{35}H_{39}N_3O_3$	76,5	7,2	—	7,6	72
Ve	Br	Br	H	161—163	62,0	5,6	24,8	4,5	$C_{33}H_{34}Br_2N_2O$	62,5	5,4	25,2	4,4	37
Vf	Br	H	H	172—174	71,1	6,4	14,7	5,2	$C_{33}H_{35}BrN_2O$	71,3	6,4	14,4	5,1	47
Vg	NO_2	Br	H	147—159 (dec.)	66,1	6,1	13,7	7,4	$C_{33}H_{34}BrN_3O_3$	66,0	5,7	13,3	7,0	36*
IIIh	NO_2	NO_2	H	—†	64,5	4,9	—	10,8	$C_{21}H_{19}N_3O_5$	64,1	4,9	—	10,7	69
IIIg	NO_2	Br	H	242—244	60,1	4,9	18,4	6,9	$C_{21}H_{19}BrN_2O_2$	59,0	4,5	18,7	6,7	14

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*In the case of an equimolar reagent ratio. The yield of Vg was 38% in the case of a twofold excess of the Fischer base.

†Charred without melting.

TABLE 2. PMR Spectra of Spirochromans (V) and Merocyanines (III)

Compound	δ, ppm										J, Hz						
	$3\text{-}CH_3$	$1\text{-}CH_3$	$3'\text{-}CH_3$	$1'\text{-}CH_3$	R	H_x	$H_{a,b}$	H_m	H_p	H_r	xy	am (trans)	bm (cis)	ab (gem)	mR	Ry	pr
Vd*	1,28, 1,28	2,87	1,52, 1,58	3,13	1,18, 1,99	5,34	2,37	3,85	8,04	8,00	11,9	9,0	9,0	—	—	—	2,7
Ve	1,29, 1,27	2,83	1,60, 1,64	3,10	5,25	5,29	2,35 2,14	3,75	—	8,48	11,6	13,2	5,6	13,8	8,6	14,5	2,0
Vf	1,29, 1,29	2,82	1,60, 1,64	3,10	5,29	5,30	2,32, 2,14	3,73	—	—	11,4	12,5	5,6	13,8	8,8	14,5	—
Vg	1,32, 1,27	2,87	1,60, 1,65	3,11	5,28	5,31	2,43, 2,17	3,80	8,12	8,28	11,5	12,8	5,6	14,0	9,0	14,0	2,8
IIIg	1,76	3,94	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IIIh	1,72	3,96	—	—	—	7,18	—	—	8,25	8,50	14,5	—	—	—	—	—	3,0

$*J_{rs} = 8.9$, $J_{CH_2,CH_3} = 7.4$ Hz.

which was crystallized from benzene—ethanol to give yellow crystals. IR spectrum: 1648 (C=C) and 978 cm^{-1} (C_{spiro}—O).

1,3,3-Trimethyl-4'-[3-(1,3,3-trimethylindolin-2-ylidene)-1-propenyl]-6'-bromoindoline-2-spiro-2'-chroman (Vf). This compound was obtained by condensation of 0.35 g (1.54 mmole) of 5-bromo-2-hydroxycinnamaldehyde with 0.27 g (1.56 mmole) of the Fischer base in 15 ml of absolute alcohol at room temperature for 24 h. Workup gave 0.41 g of the product, which was crystallized from benzene—ethanol to give light-yellow crystals. IR spectrum: 1652 (C=C) and 970 cm^{-1} (C_{spiro}—O).

1,3,3-Trimethyl-4'-[3-(1,3,3-trimethylindolin-2-ylidene)-1-propenyl]-6'-nitro-8'-bromoindoline-2-spiro-2'-chroman (Vg). This compound was obtained by condensation of 1.0 g (5.77 mmole) of the Fischer base with 0.60 g (2.21 mmole) of 3-bromo-5-nitro-2-hydroxycinnamaldehyde in 125 ml of absolute alcohol at room temperature for 4.5 days. Workup gave 0.50 g of the product in the form of dark-orange crystals. IR spectrum: 1648 (C=C); 985 (C_{spiro}—O); 1520, 1345 cm^{-1} (NO_2).

1,3,3-Trimethyl-2-[4-(2-oxido-3,5-dinitrophenyl)-1,3-butadienyl]-indoleninium (IIIh). This compound was obtained by condensation of 0.90 g (3.77 mmole) of 3,5-dinitro-2-hydroxycinnamaldehyde with 0.69 g (3.98 mmole) of the Fisher base in 25 ml of absolute alcohol at room temperature for 2 days. Workup gave 1.03 g of black crystals. IR spectrum: 1520 and 1340 cm^{-1} (NO_2). Found and calculated: M 393.

1,3,3-Trimethyl-2-[4-(2-oxido-3-bromo-5-nitrophenyl)-1,3-butadienyl]-indoleninium (IIIg). A solution of 0.32 g (1.84 mmole) of the Fischer base in 7 ml of absolute alcohol was added to a solution of 0.50 g (1.84 mmole) of 3-bromo-5-nitro-2-hydroxycinnamaldehyde in 44 ml of absolute alcohol, and the mixture was allowed to stand at room temperature for 12 h. The precipitated mixture of merocyanine IIIg and spirochroman Vg was removed by filtration and separated by crystallization from benzene—ethanol, in which the merocyanine was virtually insoluble. The mother liquor remaining after separation of the mixture of the merocyanine and the spirochroman was evaporated to half its original volume, and the concentrate was allowed to stand for 3 days for completion of the reaction. The resulting greenish-black precipitate of merocyanine IIIg was separated and washed with alcohol. Workup gave 0.20 g of spirochroman Vg and 0.11 g of merocyanine IIIg. IR spectrum of the merocyanine: 1520 and 1340 cm^{-1} (NO_2). Found and calculated: M 426 (for ^{79}Br).

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CRYSTAL AND MOLECULAR STRUCTURE OF 2-CHLORO-1-METHYL-4-PHENYL-α-CARBOLINE HYDROCHLORIDE

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A compound with the composition $C_{18}H_{16}Cl_2ON_2$ was subjected to an x-ray diffraction study. All of the rings in the molecule are planar. Both of the six-membered rings of the carboline system are inclined slightly and identically with respect to the central pyrrole ring, forming angles of 3° with it and 6° with one another. The phenyl ring is turned at an angle of 52.7° relative to the average plane of the carboline system.

2-Chloro-α-carbolines have cytotoxic properties [1, 2]. Their biological activity depends only slightly on the size and position of the alkyl substituents in the pyridine ring and parameters such as the coefficient of distribution and the basicity constant. However, 1- and 4-aryl derivatives do not display cytotoxic properties.

α-Carbolines form complexes with DNA [3], and this may be the reason for their biological activity. It might be assumed that intercalation of the planar heterocyclic chromophore into the space between parallel layers of the bases in the DNA double helix occurs in these complexes [4]. The biological inertness of aryl derivatives may be a consequence of the nonplanarity of their molecules: Rotation of the benzene ring relative to the plane of the heteroring may create hindrance to intercalation. In order to evaluate the degree of deviation from planarity we subjected crystals of 2-chloro-1-methyl-4-phenyl-α-carboline hydrochloride (I) [5] grown from solution in isopropyl alcohol to x-ray diffraction analysis (see following page).

The molecule as a whole is nonplanar. Its noncoplanarity is determined primarily by the phenyl substituent, which forms an angle of 51° with the pyridine ring and an angle of 52.7° with the average plane of the carboline system. The latter is approximately planar.

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