RING-CHAIN ISOMERISM OF 1,3,3-TRIMETHYL-2-FORMYLMETHYLENE-INDOLINE (FISCHER ALDEHYDE) OXIME AND ASSOCIATED REACTIONS

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The compound 1,3,3-trimethyl-2-formylmethyleneindoline oxime is synthesized for the first time. Using the polynuclear resonance method it is shown that the oxime exists as two isomers, one of which has a cyclic structure. A number of reactions are carried out involving the carbocyclic and oxime parts of the molecule.

Ring-chain isomerism in the spirochromene derivatives of 1,3,3-trialkyl-2-methyleneindoline (Fischer base) gives rise to the wide range of photochromic, thermochromic, halochromic, and solvatochromic properties that they exhibit [1, 2]. Studies have been made of ring-chain isomerism in Fischer base derivatives containing phenol, thiophenol, amide, and amine group substituents [1-4]. The ability of 1,3,3-trialkyl-2-methyleneindolines having an oxime group to demonstrate ring-chain isomerism has not been investigated [5]. Moreover, no information exists on the Fischer aldehyde oxime.

When aldehyde I reacts with hydroxylamine hydrochloride, the Fischer aldehyde oxime is formed. This proved to be capable of existing in two forms: the cyclic (compound II) and acyclic (compound III) isomers.

The characteristic hydroxyl group absorption band (2500-3600 cm^{-1}) is absent from the IR spectrum of compound II. The PMR spectrum shows a CH_2 group signal which, as a result of diastereotopicity, appears as two doublets (system AB: δ_A = 2.98; δ_B = 3.16 ppm; J_{AB} = 20 Hz). Each component of these doublets is cleaved by the neighboring CH=N group with coupling constant of 2 Hz. The CH=N proton signal overlaps the aromatic proton signals. The chemical shifts of the geminal methyl group protons appear as two singlets at 1.21 and 1.32 ppm. These methyl groups also appear as two signals in the ^{13}C NMR spectrum (27.3 and 28.1 ppm). Both these facts indicate that the molecule's asymmetry center is located nearby. The most significant pointer, however, is the chemical shift of the $C_{(2)}$ atom (111 ppm), which concords with data for similar spiro compounds [5]. The structure of compound II is also substantiated by a PMR spectrum taken in the presence of a Lanthanide Shift Reagent (LSR), in this case $Eu(fod)_3$. The LSR would be expected to produce the largest weak field shift for the CH=N proton group signal, since the europium chelate coordination in this compound should occur at the nitrogen atom of the dihydroisoxazole cycle [6]. Indeed, in PMR spectra taken with varying LSR concentrations the biggest displacement into the weak field region is observed for the CH=N proton signal, which exhibits a specific Lanthanide Induced Shift (LIS) of 5.1 ppm. Extrapolation of this shift to zero LSR concentration indicates that its original position in the spectrum is 7.0 ppm. The CH_2 group proton signals also experience an appreciable induced shift (specific LIS of 3.0 and 3.4 ppm). The specific LIS for the $C_{(3)}$—$(CH_3)_2$ group is 1.1 ppm and that for the N—CH_3 group 1.5 ppm.

The spectral data given above suggest that the molecule has a chiral center and a relatively stable dihydroisoxazole cycle. This enabled us to carry out selective bromination and azo coupling at position 5 of the carbocyclic ring of compound II. Similar electrophilic substitution reactions for the indoline series spiro compounds have been described in [7]. The structures of compounds IV and V are corroborated by PMR spectra.

In the PMR spectra of compounds IV and V the geminal methyl and CH_2 group signals relating to chemical shift and type of cleavage are similar to those described above for compound II. When bromine and p-nitrophenyldiazo groups are introduced into the carbocyclic ring, the 5-H proton signal disappears (in compound II it is seen at 6.83 ppm), and the 7-H proton appears as a strong field doublet at 6.36 ppm ($J_{6,7}$ = 8.0 Hz) for compound IV and 6.64 ppm ($J_{6,7}$ = 8.2 Hz) for compound V. The cyclic structure of the azo dye is also suggested by the fact that when it is dissolved in mineral acids, the absorption maximum in the UV spectrum changes from 435 to 595 nm (a batochromic shift of 160 nm). This is undoubtedly due to the fact that the isoxazole ring opens up and the oxime group is drawn into the overall chromophore system. It is known that halochromic shifts for similar dyes do not exceed 30 nm [8].

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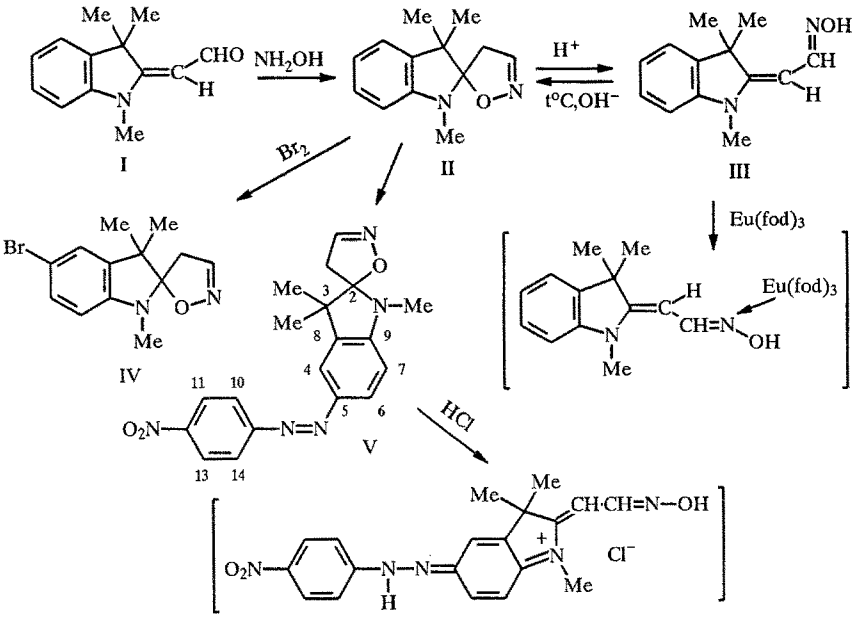


When dissolved in acids, the dihydroisoxazole ring immediately opens up. Dihydroisoxazole II is converted into the linear oxime III, which is borne out by the PMR spectrum of compound II taken in trifluoroacetic acid. The CH_2 group signal is absent, the geminal methyl group signals appear as a singlet at 1.71 ppm, and the signals for the α- and β-protons are seen at 4.22 and 8.29 ppm. Linear oxime III can be isolated by dissolving compound II in mineral acids and then neutralizing with ammonia at a temperature of up to 10°C. If the solution heats up spontaneously to 70°C on neutralization, compound III changes into the initial dihydraoxazole II.

The structure of compound III is substantiated by x-ray diffraction, the geometrical parameters of the molecule having the normal values. Intermolecular hydrogen bonds of the type N...H—O (N...H 1.94 Å, H—O 0.91 Å, N...O 2.77 Å, hydrogen atom angle 152.5°) link the molecules into infinite chains.

Compound III's structure in solution is similar to that in crystalline form, which is borne out by PMR spectral data in $CDCl_3$: the CH= and CH=N group protons appear as doublets at 5.79 and 7.71 ppm, $J_{\alpha,\beta}$ = 10.8 Hz; the OH group proton appears as a broad signal in a position typical of oximes (8.55 ppm); and the geminal methyl group signals are seen at 1.59 ppm. By comparing the chemical shifts of these methyl groups and the N—CH_3 groups with the chemical shifts of compounds VI and VIII described below, and with those of other 2-methylene-substituted indolines [9, 10], it can be inferred that the linear oxime is an E-isomer. However, on the strength of the PMR spectrum recorded in the presence of the LSR, compound III in solution can be ascribed a Z-configuration. The LIS for the N—CH_3 group (6.0 ppm) is considerably larger than the LIS for the geminal methyl groups (1.4 ppm); for the aromatic protons the biggest shift in the presence of the LSR is experienced by the 7-H proton signal (3.0 ppm), while the LIS of the 4-H, 5-H, and 6-H protons is 0.7 ppm. Since the most likely coordination of the LSR in this case occurs at the nitrogen atom of the oxime group, these data suggest that compound III exists as a Z-isomer. The specific LISs for the α- and β-protons (24.2 and 13.8 ppm, respectively) indicate that oxime III has the *anti* form. The transition energy of the *syn, anti*- and E, Z-isomers in compounds of this type are usually small, so it may be assumed that the configuration of compound III changes as a result of $Eu(fod)_3$ coordination.

In the presence of trichloroacetyl chloride or phosphorus oxychloride in DMF oxime II dehydrates into nitrile VI. From PMR spectral data the resultant nitrile exists essentially as the E-isomer (Table 1) (see scheme in the middle of page 151).

This conclusion is based on the strong field shift (0.5 ppm) of signals for the geminal methyl groups in the E-isomer due to the anisotropic effect of the nitrile group. The isomer ratio is determined from the integral intensity of signals for these groups (10:1) [9, 10].

Formylcyanoindoline VII is formed by the action of a threefold excess of Vilsmeier reagent. Compounds VI and VII are mentioned in the German patent [11]. In the PMR spectrum of compound VII it is not possible to distinguish signals corresponding to the isomeric forms due to the low rotational barrier around the C=C bond. This is indicated by the broadening and very low intensity of the signals for the geminal methyl groups and the N—CH_3 group in the ^{13}C NMR spectrum (Table 2), and by the broadening of the aldehyde group proton signal in the PMR spectrum.

TABLE 1. Spectral Data for Compounds II-VIII

Compound	Solvent	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)					
			3-$(CH_3)_2$, s	N-CH_3, s	–CH, d [CH_2, d]	CH=N, d	H-7	aromatic and other protons
II	$CDCl_3$	1600 (–CH)	1,21; 1,32	2,64	[2,92; 3,16 (*J* = 20)]	—	6,51	6,83 (1H, dd 5-H); 7,10...7,40 (3H m, Ar, CH=N)
	CF_3COOD		1,71	3,67	4,22	8,29	7,26	7,37...7,77 (5H,m, Ar, OH)
III	$CDCl_3$		1,59	3,18	5,79 (*J* = 10,4)	7,71 (*J*=10,8)	6,79	6,91 (1H, dd 5-H); 7,14...7,26 (2H,m, Ar)
IV	$CDCl_3$	1600 (–CH)	1,19; 1,29	2,61	[2,88; 3,17]	—	6,36	7,14...7,25 (3H, m Ar, CH=N)
	CF_3COOD		1,65	3,57	4,19	8,25	7,09	7,52...7,85 (3H, m Ar, OH)
V	$CDCl_3$		1,29; 1,42	2,79	[3,02; 3,27 (*J* = 19,4)]	7,76 (*J*=2)	6,64 (*J*=8,2)	7,27 (2H,m, 10-H, 14-H); 7,88...7,99 (2H, m 4-H, 6-H)
E-VI	$CDCl_3$	2190 (C≡N)	1,59	3,04	4,04*	—	6,45	6,87...7,17 (3H, m Ar)
Z-VI			1,26	3,57	—	—	—	—
VII	$CDCl_3$	1650 (C=O), 2190 (C≡N)	1,64; 1,65	3,76	—	—	—	7,15...7,38 (4H, m Ar); 9,70 (1H, s CHO)
E-VIII	$CDCl_3$	1650 (C=O), 3470 (NH_2)	1,76	3,10	4,77*	—	6,66	6,93 (1H, dd 5-H); 5,04 (2H, broad, s, NH_2) 7,14...7,26 (2H, m Ar)
Z-VIII			1,34	3,56	—	—	—	—

*Singlet.

TABLE 2. ^{13}C NMR Spectra for Compounds I-VII

Compound	δ, ppm											
	N-CH_3	3-$(CH_3)_2$	$C_{(2)}$	$C_{(3)}$	–CH (CH_2)	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	other carbon atoms
I	30,0	29,4	174,1	47,7	99,2	122,9	122,2	128,5	100,4	139,7	143,9	186,9 (CHO)
II	19,1	27,3; 28,1	111,3	45,6	(35,3)	121,4	119,3	127,5	107,0	136,6	148,0	144,5 (CH=N)
III	29,6	29,0	164,0	46,2	84,1	122,1	121,0	128,4	107,1	139,4	—	145,3; 145,7 ($C_{(9)}$, CH=N)
VI	29,6	26,3	173,0	47,5	58,6	122,2	122,2	128,4	107,4	138,2	144,2	120,6 (CH=N)
VII	29,5	25,0	169,4	47,6	86,2	122,1	121,4	127,7	106,9	140,4	144,4	169,8 (C=O)

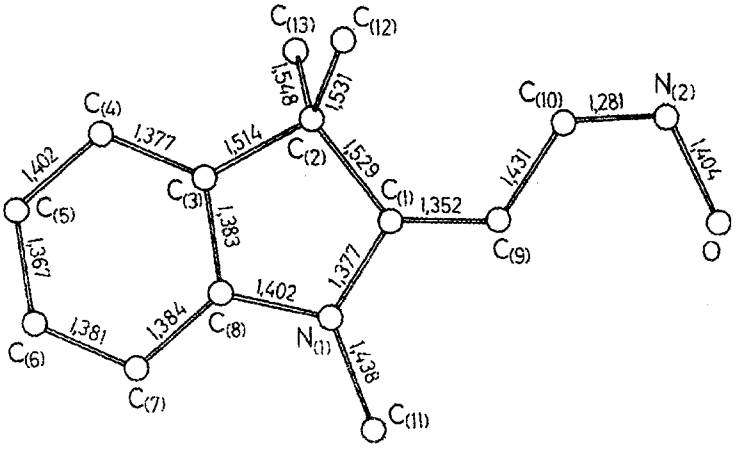
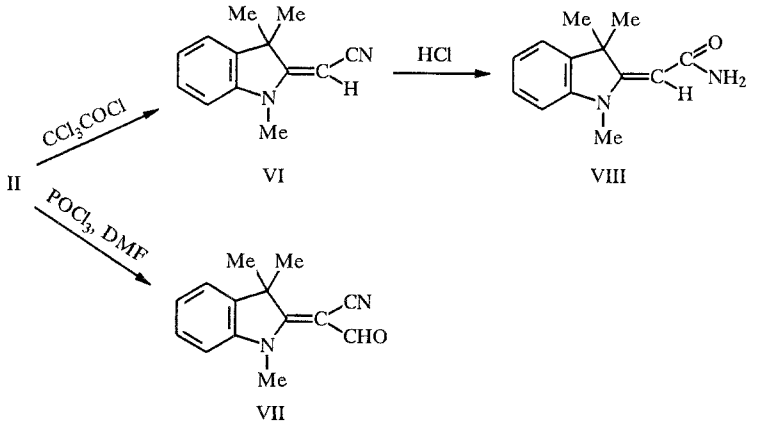


Diagram of molecule III showing atom numeration and bond lengths (errors are ±0.001-0.002 Å)



Heating of nitrile VI for a short period in hydrochloric acid yields amide VII, which also exists as the E-isomer (Table 1). We failed to hydrolyze nitrile VI or amide VIII to the acid under normal conditions, 1,3,3-trimethyl-2-methyleneindoline (Fischer aldehyde) being isolated as the hydrolysis product. The high lability of the C—C bond in compounds with 2-methyleneindoline groups has also been observed in a previous work [12]. Hydrolysis of compounds II and IV also produces 2-methyleneindolines. Using this information as a basis, we formulated a simple preparative method for introducing bromine into position 5 of the Fischer base by brominating oxime II and then hydrolyzing the product to 5-bromo-1,3,3-trimethyl-2-methyleneindoline.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument in KBr tablets, PMR and ^{13}C NMR spectra on Bruker—WP (100 MHz) and Varian (200 MHz) spectrometers in $CDCl_3$, CD_3OD, CD_3CN, and CF_3COOD (internal standard TMS). Lanthanide Shift Reagent — commercial $Eu(fod)_3$, NPO Reagent.

Elemental analysis data on C, H, Br, and N for compounds II-VIII was in line with calculated values.

X-Ray Diffraction Analysis (Table 3). Crystals of compound III (see diagram) are monoclinic, at 25°C: a = 9.140(2), b = 10.478(3), c = 12.571(3) Å, β = 92.20(2)°, V = 1203.1(9) Å^3, Z = 4, d_{calc} = 1.19 g/cm^3, space group $P2_1/n$. Nucleus parameters and intensities of 1602 independent reflections were measured at 25°C on a CAD4 automatic four-circle diffractometer (λ_{CuKCl}, graphite monochromator, scanning speed ratio $\omega:\theta$ = 1.2:1, $2\theta \leq 120°$). The structure was decoded by direct method using a MULTAN program and refined by full-matrix least squares in anisotropic approximation from 1520 reflections with $F^2 \geq 3\delta$. Calculated coordinates of H atoms (the hydroxyl hydrogen atom was identified from differential synthesis) at the latter stages of refinement were included in the calculation with fixed positional and thermal parameters B_{iso} = 5 Å^2. Final divergence factor values R = 0.056 and R_W = 0.091. All calculations were made on a PDP 11/23+ computer using SDP programs.

Spiro-1,3,3-Trimethylindoline-[2:3′]-3′,4′-dihydroisoxazole (II, $C_{13}H_{16}N_2O$). A mixture of 32.2 g (160 mmoles) of aldehyde I and 16.3 g (230 mmoles) of hydroxylamine hydrochloride were heated in 45 ml of pyridine and 90 ml of ethanol

TABLE 3. Coordinates of Nonhydrogen Atoms in Compound III Molecule

Atom	x	y	z	Atom	x	y	z
O	0,5216(2)	0,0341(2)	0,6235(4)	$C_{(6)}$	1,2876(2)	0,1604(2)	1,0269(2)
$N_{(1)}$	0,9334(2)	0,1312(1)	0,8759(1)	$C_{(7)}$	1,1376(2)	0,1683(2)	1,0110(2)
$N_{(2)}$	0,6437(2)	0,089(2)	0,5624(1)	$C_{(8)}$	1,0804(2)	0,1315(2)	0,9121(1)
$C_{(1)}$	0,9185(2)	0,0846(2)	0,7738(1)	$C_{(9)}$	0,7867(2)	0,0696(2)	0,7227(2)
$C_{(2)}$	1,0717(2)	0,0577(2)	0,7345(1)	$C_{(10)}$	0,7646(2)	0,0278(2)	0,6150(2)
$C_{(3)}$	1,1674(2)	0,0879(2)	0,8322(1)	$C_{(11)}$	0,8151(2)	0,1739(2)	0,9392(2)
$C_{(4)}$	1,1369(2)	0,0816(2)	0,8493(2)	$C_{(12)}$	1,0920(3)	-0,0817(2)	0,7015(2)
$C_{(5)}$	1,3763(2)	0,1192(2)	0,9489(2)	$C_{(13)}$	1,1117(2)	0,1499(2)	0,6439(2)

for 3 h on a boiling water bath. The reaction mixture was cooled, then 250 ml of water saturated with sodium chloride and 50 ml of ether were added. The organic layer was separated and dried with Na_2SO_4; the solvent was evaporated off and the remaining oil kept in vacuum for 1 h at 60°C. It was then crystallized from heptane. Mp 79-80°C. Yield 67%.

1,3,3-Trimethyl-2-methyleneiminohydroxindoline (III, $C_{13}H_{16}N_2O$). A sample of 1.1 g (5 mmoles) of compound II was warmed for 1 h at 40°C in 10 ml of conc. HCl. The mixture was then poured into 50 ml of water with ice, neutralized with ammonia at a solution temperature of no higher than 10°C to pH 7, extracted with chloroform and dried with Na_2SO_4. The solvent was evaporated and the residue crystallized from heptane. Mp 133-134°C. Yield 45%.

Spiro-1,3,3-trimethyl-5-bromoindoline[2:3′]-3′,4′-dihydroisoxazole (IV, $C_{13}H_{15}BrN_2O$). To 7 g (30 mmoles) of oxime II in 40 ml of chloroform with vigorous stirring was added dropwise 5.1 g (30 mmoles) of bromine in 30 ml of chloroform. The mixture was warmed for 2 h at 60°C (the precipitate appeared after 1 h). After cooling 500 ml of water and 210 g of soda were added. The reaction mixture was stirred until the precipitate dissolved, then the organic layer was separated and dried with Na_2SO_4. The solvent was driven off and the residue crystallized from heptane. Mp 100-101°C. Yield 83%.

Spiro-1,3,3-trimethyl-5-p-nitrodiazophenylindoline-[2:3′]-3′,4′-dihydroisoxazole (V, $C_{19}H_{19}N_5O_3$). A sample of 1 g (4.6 mmoles) of compound II was dissolved in 20 ml of acetone; to this was added 0.39 g (4.6 mmoles) of pyridine and then in small portions 1.18 g (5 mmoles) of p-nitrodiazophenyl fluoboride. After 30 min the reaction mixture was poured into 200 ml of water and the resultant precipitate was extracted with chloroform. This was dried with Na_2SO_4 and the solvent was then evaporated. The precipitate was washed with hot hexane and crystallized from isopropyl alcohol. Mp 177-178°C. λ_{max} 435 nm. Yield 32%.

1,3,3-Trimethyl-2-cyanomethyleneindoline (VI, $C_{13}H_{14}N_2$). A. To a mixture of 30 g (140 mmoles) of oxime II, 38 ml (280 mmoles) of triethylamine, and 100 ml of methylene chloride at 0°C was added dropwise 25 g (140 mmoles) of trichloroacetyl chloride in 50 ml of methylene chloride. The reaction mixture was stirred at room temperature for 1 h and the methylene chloride was evaporated. Then 200 ml of ether were added and triethylamine hydrochloride was filtered off. The ethereal layer was washed with water and dried with Na_2SO_4. After the solvent had been evaporated, the residue was crystallized from heptane. Mp 108-110°C. Yield 75%.

B. To 50 ml of DMF at −10°C were added dropwise 1.85 g (20 mmoles) of phosphorus oxychloride; this was kept at 15 min at 0°C, then for 2 h on a boiling water bath. The cooled reaction mixture was then poured into water with ice, neutralized with sodium acetate, extracted with chloroform, and dried with Na_2SO_4. After the solvent had been evaporated, the residue was crystallized from heptane. Mp 108-110°C. Yield 55%.

1,3,3-Trimethyl-2-formylcyanomethyleneindoline (VII, $C_{14}H_{14}N_2O$). To 2.53 g (17 mmoles) of oxime II in 35 ml of DMF at −30°C were added dropwise 4.71 ml (51 mmoles) of phosphorus oxychloride. The mixture was kept at 0°C for 1 h, then heated on a boiling water bath for 6 h. After that the mixture was treated as in procedure **B** for compound VI. Mp 152-153°C. Yield 25%.

1,3,3-Trimethyl-2-methyleneacetamidoindoline (VIII, $C_{13}H_{16}N_2O$). A Sample of 1 g (5 mmoles) of nitrile VI in 10 ml of conc. HCl was warmed on a water bath for 1 h at 40°C. The mixture was poured into water and neutralized with ammonia while cooling. The resultant precipitate was filtered off. After drying with Na_2SO_4, it was crystallized from xylene. Mp 170-171°C. Yield 93%.

Hydrolysis of Compounds II, IV, VI, and VIII to 2-Methyleneindoline (Compound IV to 1,3,3-Trimethyl-5-bromoethyleneindoline). A solution of 5 mmoles of compounds II (IV, VI, and VIII) in 10 ml of HCl was heated for 6 h on a boiling water bath. The mixture was then cooled, poured into water, and neutralized with ammonia. It was extracted with benzene and dried with Na_2SO_4, and after the solvent had been evaporated, the residue was kept in high vacuum for 1 h; quantitative

yield. The structure of the hydrolysis products was substantiated by comparing the PMR spectra obtained by the present authors with those quoted in [13].

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