SYNTHESIS OF 3,4-DIHYDROISOXAZOLES — DERIVATIVES OF ω-CARBONYL-SUBSTITUTED 1,3,3-TRIMETHYL-2-METHYLENEINDOLINES AND THEIR CHEMICAL REACTIONS

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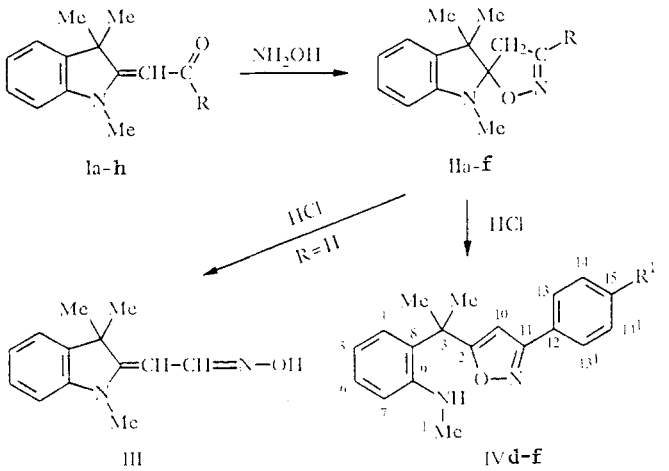
Stable spiro compounds containing a dihydroisoxazole ring are formed by the reaction of ω-carbonyl-substituted 2-methyleneindolines with hydroxylamine. These compounds are converted in acid media into isoxazoles with scission of the indoline unit.

In a previous paper [1] we showed that the dihydroisoxazole IIa was formed by the reaction of ω-formyl-2-methyleneindoline Ia with hydroxylamine. The present work is concerned with the synthesis of similar dihydroisoxazoles from ω-carbonyl-substituted 2-methyleneindolines and the study of their chemical reactions.

The carbonyl-substituted 2-methyleneindolines Ib-c were prepared by the reaction of 1,3,3-trimethyl-2-methyleneindoline with chlorides and anhydrides of carboxylic acids [2, 3] in the presence of base. Compounds Ib-f reacted with hydroxylamine in basic media to give the dihydroisoxazoles IIb-f (Table 1). This reaction did not occur with strong acceptor substituents (Ig, Ih). The cyclic structure of compounds IIb-f was established by ^1H and ^{13}C NMR spectroscopy: In the ^1H NMR spectrum the CH_2 group signal appeared as two doublets (AB system) in the 2.8-3.5 ppm region (J = 18.0-18.6 Hz) (Table 2); in the ^{13}C NMR spectra the chemical shift of $C_{(2)}$ at 112-115 ppm (Table 3) is most characteristic and is in agreement with literature values [4].



I, IIa) R = H; b) R = Me; c) R = CH_2Cl; d) R = C_6H_4OMe-p; e) R = Ph; f) R = $C_6H_4NO_2$-p; g) R = CCl_3; h) R = CF_3; IVd) R^1 = OMe; e) R^1 = H; f) R^1 = NO_2

We have previously established [1] that instantaneous scission of the dihydroisoxazole ring to form the oxime III occurred when compound IIa was dissolved in a mineral acid.

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Molecular formula	Tmp., °C	Solvent	Yield, %
Ic	$C_{14}H_{16}ClNO$	111...113	Hexane	78
Ig	$C_{14}H_{14}Cl_3NO$	87...89	Petroleum ether	43
IIb	$C_{14}H_{18}N_2O$	159...161	Isopropanol	57
IIc	$C_{14}H_{17}ClN_2O$	82...83	Hexane	31
IId	$C_{20}H_{22}N_2O_2$	157...158	Isopropanol	82
IIe	$C_{19}H_{20}N_2O$	118...119	Isopropanol	73
IIf	$C_{19}H_{19}N_3O_3$	173...175	Ethanol	48
IVd	$C_{20}H_{22}N_2O_2$	105...107	Washed w. methanol	85
IVe	$C_{19}H_{20}N_2O$	96...98	Washed w. methanol	75
IVf	$C_{19}H_{19}N_3O_3$	164...165	Washed w. methanol	90

A similar reaction was not observed with compounds IIb-f, which are analogs of IIa, but with a substituent on the carbon atom of the C=N group. The dihydroisoxazole IIb was recovered unchanged after dissolution in concentrated HCl. Under similar conditions compound IIc hydrolyzed to the initial carbonyl-substituted indoline Ic. The 3-arylisoxazoles IVd-f were obtained in quantitative yield on treatment of the dihydroisoxazoles IId-f with hydrochloric acid. In this case scission of the indoline ring occurs rather than the dihydroisoxazole ring. We isolated the similar 3-unsubstituted isoxazole IVa as a by-product (less than 10%) in the synthesis of the dihydroisoxazole IIa.

In the ^1H NMR spectra of compounds IVa, d-f (Table 2) the NH group signal (3.25-3.86 ppm) appears as a poorly resolved quartet in deuterochloroform and acetonitrile which is extinguished on addition of deuteromethanol. The $N-CH_3$ group appears as a doublet (J = 5.15 Hz) in the 2.5-2.7 ppm region in acetonitrile (compounds IVa, e). On irradiating the NH signal and when the spectrum is recorded in $CDCl_3$ solution the $N-CH_3$ doublet for compound IVa is converted to a singlet. The presence of the isoxazole ring in compounds IV is confirmed by the two doublets at 5.94 and 8.40 ppm (J = 1.8 Hz) (4-H and 3-H for IVa) or the singlet for the 4-H proton at 6.2-6.3 ppm in the ^1H NMR spectrum. The C_{11}, C_{10}, and C_2 carbon atoms of the isoxazole ring in compounds IVa, e, f appear at 151-163, 98-100, and 179-181 ppm respectively in the ^{13}C NMR spectra. Literature data for the ^1H and ^{13}C NMR spectra are cited in papers [5, 6].

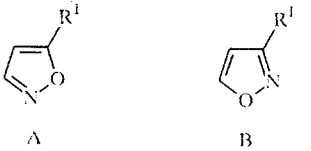
The structure of the isoxazole IVa was confirmed by recording the ^1H NMR spectrum in the presence of the lanthanide shift reagent Eu(fod)$_3$. The following values for the lanthanide induced shifts were obtained: H_6 1.0; H_5 2.0; H_7 2.1; $N-CH_3$ 2.6; H_4 2.9; C_3-CH_3 4.0; NH 8.5; H_{10} 9.4; H_{11} 24.5. The large shift values for the isoxazole ring protons shows that, as expected [7], complex formation occurs at the isoxazole nitrogen atom. It is interesting that addition of the lanthanide shift reagent causes narrowing of the NH and $N-CH_3$ signals, which is an unusual occurrence.

Heating compounds IVd-f at 150°C for 2 h leads to their partial conversion to the dihydroisoxazoles IId-f. The rate of conversion of an isoxazole to the corresponding dihydroisoxazole increases as the electron acceptor power of the substituent increases in the series OCH_3, H, NO_2. The content of the dihydroisoxazoles IId-f in the reaction mixtures was 40, 60, and 70%. This represents the thermodynamic equilibrium since further heating of the reaction mixture (6-8 h) did not cause changes in the ratio of compounds IV and II in the reaction mixture. Appearance of signals for the isoxazole IVe when the dihydroisoxazole IIe is heated also indicates a thermodynamic equilibrium:

$$\text{IIe} \longrightarrow \text{II-IV} \xleftarrow{150^\circ\text{C, 2 h}} \text{IVe (d-f)}$$

The isoxazole to dihydroisoxazole ratios in the reaction mixtures were estimated from integration of the ^1H NMR spectral curves.

It is known that isoxazoles are formed when β-carbonyl-substituted enamines react with hydroxylamine [8-10]. The formation of dihydroisoxazoles as intermediates was postulated in the last paper [10]. The structures of the isoxazoles were not established unambiguously: structure A was written in papers [8, 9] and structure B in [10].



A B

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds IIb-f and IVa, d-f (δ, ppm)

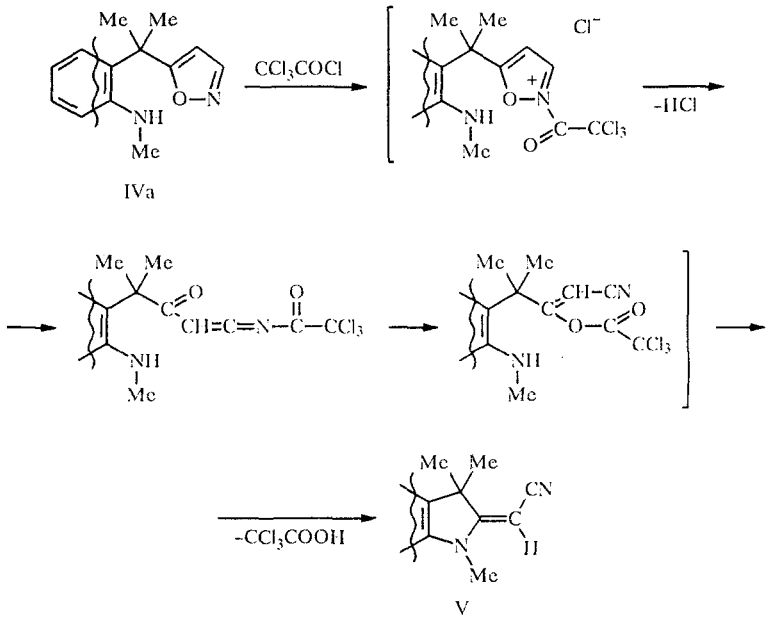
Compound	Solvent	3-$(CH_3)_2$, s	N-CH_3, s	4-H(sox, J, Hz)	7-H, d	Other protons
IIb	$CDCl_3$	1,19; 1,33	2,65	2,82; 3,12 (18,6)	6,50 (6,8)	2,04 (3H, s 3-CH_3 Isox); 6,79 (1H, d.d 5-H); 7,02...7,16 (2H, m 4-H, 6-H)
	CF_3COOD	1,69	4,13	–	–	2,44 (3H, s 3-CH_3 Isox); 7,73...7,74 (4H, m, Ar)
IIc	$CDCl_3$	1,22; 1,34	2,68	3,07; 3,22 (18,6)	6,52 (8,0)	4,30; 4,42 (2H, d.d $-CH_2Cl$, J = 12,2 Hz 7,05...7,25 (3H, m Ar)
IId	$CDCl_3$	1,30; 1,41	2,71	3,29; 3,51 (18,0)	6,45 (7,6)	3,86 (3H, s OCH_3); 6,84 (1H, d.d, 5-H); 6,97 (1H, d, 4-H); 7,07...7,26 (3H, m 6-H, *m*, *m*-H); 7,67 (2H, d, *o*, *o*-H)
IIe	$CDCl_3$	1,29; 1,39	2,69	3,30; 3,53 (18,2)	6,54 (7,8)	6,84 (1H, dd 5-H); 7,08...7,78 (7H, m Ar)
	CF_3COOD	1,51	4,03	–	–	7,50...7,61 (10H, m Ar)
IIf	$CDCl_3$	1,24; 1,33	2,62	3,25; 3,47 (18,0)	6,49 (7,6)	6,83 (1H, d.d 5-H); 7,03...7,21 (2H, m 4-H, 6-H); 7,85 (2H, d, *m*, *m*-H); 8,23 (2H, d, *o*, *o*-H)
IVa	$CDCl_3$	1.75	2.65	5,94, d (1,8)	6,63	3,23 (1H, m, NH); 6,77 (1H, d.d 5-H); 7,22 (1H, d.d 6-H); 8,41 (1H, d, 3-H Isox, J = 1,8
	CD_3CN	1.63	2.53 (J = 5.15 Hz)	5,80, d (1,8)	6,54	3,41 (1H, m, NH); 6,71 (1H, d.d 5-H); 6,97 (1H, d.d 6-H); 7,28 (1H, d, 4-H); 8,16 (1H, d, 3-H Isox, J = 1,8 Hz)
IVd	$CDCl_3$	1.79	2.69	6,21	6,69	3,86 (1H, m, NH); 6,81...7,72 (7H, m, Ar)
IVe	$CDCl_3$	1,80	2.69	6,27	6,66	3,51 (1H, m, NH); 6,80 (1H, d.d, 5-H); 7,37...7,80 (7H, m Ar)
	CD_3CN	1.75	2.62 (J = 5.0 Hz)	6,76	6,63	3,64 (1H, m, NH); 6,74 (1H, d.d, 5-H); 7,20 (1H, d.d 6-H); 7,38 (1H, d, 4-H); 7,46...7,85 (5H, m Ar)
IVf	$CDCl_3$	1,82	2.70	6,34	6,68 (8)	3,30 (1H, m, NH); 6,81 (1H, d.d 5-H); 7,27 (1H, dd, 6-H); 7,37 (1H, d, 4-H); 7,97 (2H, d, *o*, *o*-H); 8,28 (2H, d, *m*, *m*-H)

TABLE 3. ^{13}C NMR Spectra of Compounds IIb, c, e, f and IVa, e, f (δ, ppm)*

Compound	N-CH_3	3-$(CH_3)_2$	$C_{(2)}$	$C_{(3)}$	CH_2 ($C_{(10)}$)	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	Other carbon atoms
IIb	19,4	27,5; 28,4	112,6	45,8	38,9	121,3	119,3	127,6	107,2	136,7	148,2	153,6 ($C_{(11)}$), 13,5 (CH_3–$C_{(11)}$)
IIc	–	33,4; 34,2	115,1	46,5	38,8	121,7	120,0	128,1	107,6	136,7	148,2	153,5 ($C_{(11)}$); 41,9 (CH_2Cl)
IIe	19,4	27,7; 28,4	113,7	45,9	35,1	121,4	119,5	127,6	107,2	136,7	148,1	126,4; 128,8; 129,7; 130,0; 154,8 ($C_{(11)}$)
IIf	19,6	28,7; 27,9	115,5	46,5	34,6	121,7	120,1	128,1	107,6	–	–	127,3; 124,4; 136,09; 136,7; 148,07; 148,68; 153,5 ($C_{(11)}$)
IVa	31,2	27,8	179,6	39,2	(99,8)	126,4	120,1	129,1	112,1	147,5	150,7	151,2 ($C_{(11)}$)
IVe	30,9	27,4	180,0	39,1	(98,1)	125,9	116,9	130,0	111,6	–	–	126,7; 128,5; 128,6; 128,9; 129,1; 147,0; 162,6 ($C_{(11)}$)
IVf	30,9	27,4	181,3	39,2	(98,3)	125,9	117,1	128,7	111,7	146,8	148,6	124,1 ($C_{(13,13')}$); 127,6 ($C_{(14',14)}$); 128,2 ($C_{(12)}$); 135,0 ($C_{(15)}$); 160,8 ($C_{(11)}$)

*The carbon atom numbering corresponds to that in the reaction scheme.

Subsequent literature data [11] show that the reaction may occur in two directions via A or B. In our case a strict choice between structures A and B in favor of B thanks to the conversion of the dihydroisoxazoles IId-f into the isoxazoles IVd-f and the thermal conversion of the latter into the dihydroisoxazoles IId-f. The isoxazole IVa was converted into the nitrile V [12] by trichloroacetyl chloride which also indicates that structure B is preferable. This conversion probably occurs as follows in agreement with literature data [13].



EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3CN, and CF_3COOD solution with TMS as internal standard on a Varian instrument (200 MHz). The lanthanide shift reagent $Eu(fod)_3$ was manufactured by NPO "Reactive".

Elemental analysis results for compounds Ic, g, IIb-f, and IVd-f agreed with calculated values.

1,3,3-Trimethyl-2-methylene-ω-chloromethylacylindoline (Ic). Triethylamine (7 ml) and monochloroacetyl chloride (5.65 g, 5 mmoles) in benzene (10 ml) were added to 1,3,3-trimethyl-2-methyleneindoline (8.65 g, 5 mmoles) in benzene (10 ml). The reaction mixture was heated for 1 h at 60-80°C and the product was precipitated with hexane after removal of triethylammonium chloride.

1,3,3-Trimethyl-2-methylene-ω-chloromethylacylindoline (Ig) was prepared analogously to Ic.

Spiro-1',3',3'-trimethylindoline-(2':5)-3-methyl-4,5-dihydroisoxazole (IIb). A mixture of compound Ib (17.2 g, 8 mmoles), and hydroxylamine hydrochloride (8.3 g, 12 mmoles) in pyridine (20 ml) and ethanol (45 ml) was heated for 3 h on a boiling water bath. Water saturated with sodium chloride (150 ml) and ether (50 ml) were added to the cooled reaction mixture. The organic layer was separated, the solvent evaporated and the product crystallized from isopropanol.

Spiro-1',3',3'-trimethylindoline-(2':5)-3-chloromethyl-4,5-dihydroisoxazole (IIc), spiro-1',3',3'-trimethylindoline-(2':5)-3-p-methoxyphenyl-4,5-dihydroisoxazole (IId), spiro-1',3',3'-trimethylindoline-(2':5)-3-phenyl-4,5-dihydroisoxazole (IIe), spiro-1',3',3'-trimethylindoline-(2':5)-3-p-nitrophenyl-4,5-dihydroisoxazole (IIf) were made analogously to IIb by the method described above.

3-p-Methoxyphenyl-5-(1-methyl-1-o-methylaminophenylethyl)isoxazole (IVd); 3-Phenyl-5-(1-methyl-1-o-methylaminophenylethyl)isoxazole (IVe); 3-p-Nitrophenyl-5-(1-methyl-1-o-methylaminophenylethyl)isoxazole (IVf). Compound IId (e,f) (5 mmoles) was dissolved in concentrated HCl (10 ml) and kept at 20°C for 1 h, then poured over ice and neutralized with ammonia to pH 7 at 20-25°C. The precipitate obtained was washed with water and methanol.

5-(1-Methyl-1-o-methylaminophenylethyl)isoxazole (IVa) was obtained in 7% yield by fractional crystallization from heptane during the synthesis of compound IIa [1].

Thermal Reactions of Compounds IId-f, IVd-f. A compound (1 g) was heated at 150°C for 2 h. The reaction mixture was analyzed via the integrated curves from the ^1H NMR spectra.

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