INVESTIGATION OF HETEROCYCLES CONTAINING NITROGEN OR SULFUR. 48.* DERIVATIVES OF 1-MORPHOLINOOXALYL-1,2-DIHYDROTHIAZOLO-[5,4-b]PYRIDINE, THEIR STRUCTURE, AND REACTIONS

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*The structures of the products of reactions of 1-N-morpholinooxalyl-1,2-dihydrothiazolo-[5,4-b]pyridine have been studied by IR, NMR, UV, and mass spectroscopy. Geometric (*cis–anti*) and rotational (about the CO–N amide bond) isomers of 1-N-morpholinooxalyl-2-propionyl-5-chloro-1,2-dihydrothiazolo-[5,4-b]pyridine oxime have been observed and studied. Treatment of 1-N-morpholinooxalyl-2-propionyl-5-chloro-1,2-dihydrothiazolo-[5,4-b]pyridine with ethanolic alkali gave 2-propionyl-5-chlorothiazolo-[5,4-b]pyridine, while treatment with concentrated H_2SO_4 gave 1,2-dioxo-ethylidene-7-chloroxazolidino[3,2-f]pyrido[2,3-b]1,4-thiazine.*

It was reported in the previous paper [1] that reaction of 1,2-dioxo-3a-alkyl-4,7-dichloroxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines with saturated cyclic amines was accompanied by opening of the oxazolidine and reduced thiazine rings to give 1-N-oxalamide derivatives of 1,2-dihydrothiazolo[5,4-b]pyridine.

Some reactions of one compound from this series — 1-N-(morpholinooxalyl)-2-propionyl-5-chloro-1,2-dihydrothiazolo-5,4-b]pyridine (I) — have been studied in the present work. Oxime (II) (Table 1) was obtained by the reaction of compound I with hydroxylamine hydrochloride. Its structure was confirmed by a hydroxyl absorption at 3400 cm^{-1} in the IR spectrum. In comparison with that of I [1], the mass spectrum of oxime II contains a molecular ion at larger mass number (M^+ 384) and peaks for the ions $[M - H_2O]^+$ (366), $[M - H_2O - CO - NC_4H_8O]^+$ (morpholino) (252), which indicated the presence of hydroxyl groups. The most intense peaks in the spectrum of oxime II, as in the spectrum of compound I [1], belonged to the N-morpholinocarbonyl cation (114) and the product of elimination of C_2H_4O from it (70) which showed that the morpholinocarbonyl groups was retained in II.**

A peculiarity of the 23°C ^1H and ^{13}C NMR spectra of oxime II is the presence of four sets of signals. As the temperature was increased pairs of signals broadened and coalesced so that above 90°C the spectrum had a double set of signals. It is natural to assume that the quadruple set of signals at room temperature arose from the *syn and anti* isomers of oxime II, each of which exists as two amide conformers. Since it is known that the activation energy for *syn–anti* isomerism is generally higher than that for amide isomerism, then the double set of signals observed at T > 80-90°C for compound evidently corresponds to a mixture of the *syn* and *anti* isomers. This suggestion is confirmed by the observation that the largest differences in ^1H and ^{13}C chemical shifts were for the oxime fragment and groups spatially close to it. The content of the geometric isomers was 23 and 77% from the intensities of the pairs of signals (see Table 3).

* For Communication 47 see [1].

**Here and below the mass number of chlorine-containing ions corresponds to those containing the ^{35}Cl isotope.

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TABLE 1. Characteristics of Compounds II-IV

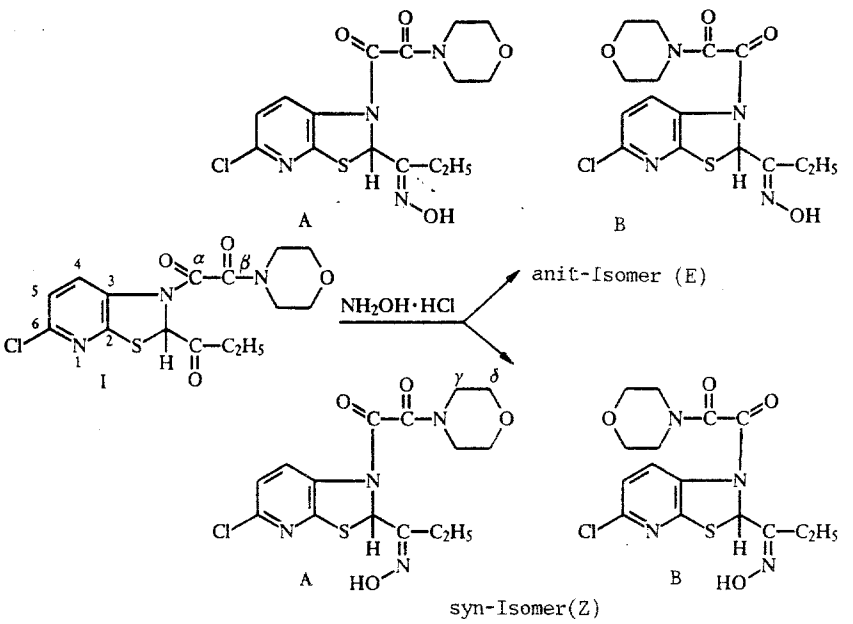
Compound	Molecular formula	mp,	R_f	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (lg ε)	Yield, %
				C=O	OH		
II	$C_{15}H_{17}ClN_4O_4S$	188...190	0,6	1630...1650*	3400	228 (4,28), 268 (3,84), 323 (4,04)	60
III	$C_9H_7ClN_2OS$	143...145	0,9	1720	—	222 (4,12), 258 (3,95), 287 (3,93), 312 (3,99	67
IV	$C_{11}H_7ClN_2O_3S$	148...150	0,6	1740*,1820**	—	232 (4,08), 305 (3,92)	79

*For N–CO.

**For COO.

Doubling of the signals of each of the geometric isomers at room temperature is explained by amide isomerism of the oxime II, analogous to that observed previously for the starting material I [1]. Thus the oxime II in solution at room temperature exists as two geometric isomers (*syn* and *anti***), each of which is found as two amide rotamers (A and B) (scheme 1).***

Scheme 1



The configurations of the geometric isomers of oxime II were established by analysis of the geminal and vicinal spin–spin coupling constants $^{15}N^1H$ and $^{15}N^{13}C$. In spectra of oxime II labeled with ^{15}N the value of the vicinal coupling constant $^3J_{^{15}N^1H}$ for the predominant isomer was 2.8 Hz while that for the minor isomer was zero (Table 3) which, according to literature data [2, 3], indicates that the major isomer has the *anti* and the minor isomer the *syn* configuration. The same conclusion was drawn from examination of the geminal and vicinal coupling constants for the carbon atoms of the CH and C_2H_4 fragments: in the predominant (*anti*) isomer $^2J_{^{15}N,CH}$ is maximal (11.5 Hz), whereas $^2J_{^{15}N,CH_2}$ and $^3J_{^{15}N,CH_3}$ for the ethyl unit are close to zero. The reverse situation holds for the minor (*syn*-) isomer: $^2J_{^{15}N,CH} \sim 0$, $^2J_{^{15}N,CH_2} \sim 7.5$ Hz and $^3J_{^{15}N,CH_3} \sim 3.0$ Hz (Table 4) which is in excellent agreement with literature data [2, 3].

**The *anti* isomer is the compound in which the dihydrothiazolopyridine ring and the OH group are in *anti* orientation relative to the C=N bond of the oxime unit.

*** Numbering of the carbon atoms in oxime II is analogous to that used for the starting compound I [1]. However, names used in the text conform to the normal nomenclature rules for organic compounds.

TABLE 2. Mass Spectra of Compounds II-V

Compound	m/z (I_{rel})*
II	384 (0,5), 366 (6), 297 (13), 252 (6), 242 (69), 226 (5), 198 (3), 197 (3), 196 (8), 171 (5), 170 (7), 115 (7), 114 (89), 89(9), 70(100), 42(35)
III	226 (1), 198 (50), 197 (28), 170 (26), 169(16), 135 (4), 83 (5), 64 (10), 57 (100)
IV	285 (4), 284 (33), 283 (12), 282 (85), 212 (35), 211 (29), 210 (100), 209 (40), 186 (4), 184 (7), 183 (4), 182 (5), 174 (4), 173 (3), 157 (5), 155 (4), 135 (4), 79 (7), 72 (9), 71 (16), 70 (7), 64 (14), 53 (9), 51 (7), 45 (16), 44 (9)

* Molecular ions and ions with $I_{rel} \geq 3\%$ (^{35}Cl) are cited.

TABLE 3. Chemical Shifts (ppm) and Coupling Constants (J, Hz) in the ^1H NMR Spectra of the Geometric Isomers of Oxime II in DMSO-D_6

T,°C	Amide content	Isomer content	Chemical shift, ppm*				$^3J_{N,CH}$*2	$\Delta G^{\neq}_{C-N}$, kkal. mol^{-1}
			CH s	4-H d	5-H d	OH s		
Anti-isomer								
23	A	64	6,67	8,29	7,30	11,27	2,7	19,1±0,3
	B	13	6,81	7,32	7,28	11,06	2,9	17,9±0,3
90	—	77	6,66	8,30	7,26	10,96	*3	—
Syn-isomer								
23	A	14	6,85	8,17	7,31	11,50	~0	18,3±0,3
	B	9	6,98	7,32	7,28	11,56	~0	17,6±0,3
90	—	23	6,94	8,30	7,28	11,25	*3	—

* Chemical shifts of the remaining protons: 0.9-1.10 ($\underline{CH_3}CH_2$), 2.00-2.55 ($CH_3\underline{CH_2}$), 3.20-3.80 ppm (γ,γ'-CH_2, δ,δ'-CH_2).

2* $^2J_{^{15}N,CH}$ ~ 1 Hz.

3* The CH signal is considerably broadened because of exchange processes ($I_{1/2h} > {}^3J_{^{15}N,OH}$.

The assignment of the NMR signals to the *syn* and *anti* isomers on the basis of the $^{15}N^1H$ and $^{15}N^{13}C$ coupling constants is in agreement with the considerably higher field signal for the methyne carbon in the minor isomer ($\Delta\delta\ ^{13}C_{CH\ c\text{-}a}$ = −7.2 ppm) and the reverse situation for the methylene carbon of the ethyl group ($\Delta\delta\ ^{13}C_{CH_2\ c\text{-}a}$ = 3.9 ppm)(the *γ-gauche* effect in oximes [4]).

The large energetic advantage of the *anti* isomer over the *syn* isomer which follows from the predominance of the former in the solutions studied (Table 3) may be explained by the large steric hindrance in molecules of the syn-isomer arising from the large volume of the EtHC=NOH group in the latter which results from free rotation around the HC–C=N) bond. Such steric interaction should be considerable in the amide conformer A in which the morpholinooxalyl and alkyloxime groups are close. Conversion to the other amide conformer B should be still less favorable since it should contain strong steric interaction between the morpholinooxalyl group and the pyridine ring which, as noted before [1], even causes some distortion of the latter. In agreement with this the ratio of the *syn* and *anti* forms in solution is about 1:3 (Table 3).

This conclusion is in excellent agreement with data on the ratio of the amide conformers A and B in each of the *syn* and *anti* isomers. It is seen from data on the relative intensities of the CH proton signals of the amide conformers that while the ratio A/B in the *anti* isomer is 5:1 (ΔG = 0.97 kcal·mole^{-1})* in the *syn* isomer it is 1.5:1 (ΔG = 0.36 kcal·mole^{-1}), i.e., the difference in energy of the amide conformers is decreased because of the large steric interaction between the morpholinooxalyl fragment and the alkyloxime group.

* The difference in values of ΔG ($\Delta G = -RT\ln C_B/C_A$) and ΔG^* for the A → B and B → A processes (Table 3) is a result of the relatively low precision of determination of ΔG^* (~ 0.3 kcal·mole^{-1}) by the method based on the coalescence temperature for the signals [5].

TABLE 4. ^{13}C NMR Spectral Characteristics of the Geometric Isomers of Oxime II in DMSO-D_6 at 90°C

Chemical shifts, ppm													Coupling constants		
CH	$\underline{CH_2}$-CH_3	CH_2-$\underline{CH_3}$	$C_{(2)}$*	$C_{(3)}$*	$C_{(4)}$*	$C_{(5)}$	$C_{(6)}$	C=NOH*	OC_α	OC_β	γ-CH_2 γ'-CH_2	δ-CH_2 δ'-CH_2	*2	*3	*4
Anti-isomer															
64,4	18,2	9,80	~152	~133	~126	119,7	145,6	~156	162,8	160,2	41,4; 45,9	65,2; 65,4	11,5	~0	~0
Syn-isomer															
57,2	22,1	10,2	~152	~133	~126	120,0	145,2	~156	162,8	160,2	41,2; 46,0	65,2; 65,4	~0	~7,5	~3

* Coalesced signals.

*2 $^2J_{^{15}NCH}$.

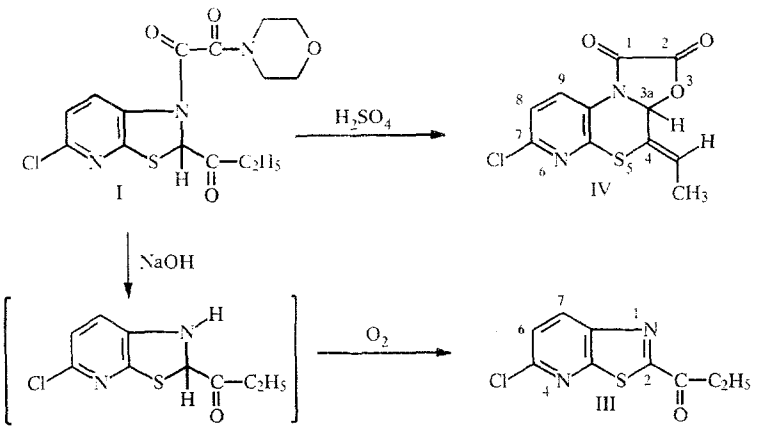
*3 $^2J_{^{15}N,CH_2}$.

*4 $^2J_{^{15}N,CH_3}$.

The reaction of amide I with alcoholic base (0.1 M NaOH) gave compound III, the IR spectrum of which contained a C=O band at 1696 cm^{-1}. Its mass spectrum had a molecular ion at mass number 226 (1 Cl) but peaks for the ions $[CO - NC_4H_8O]^+$ (114) and $[CONHCH=CH_2]^+$ (70), which were the most intense peaks for compounds I and II, were absent. The basic fragmentation of compound III is associated with elimination of a propionyl group or its fragments: $[M - C_2H_4]^+$ (198), $[M - C_2H_5]^+$ (197), $[M - COC_2H_5]^+$ (169), and $[COC_2H_5]^+$ (57) (Table 2).

The ^1H NMR spectrum of compound III in DMSO-D_6 solution contains two doublets for pyridine ring protons (δ 8.72 and 7.82 ppm, $^3J_{HH}$ = 8.6 Hz) and ethyl group signals at 1.17 (CH_3, t) and 3.25 ppm (CH_2, qu). The spectroscopic data coupled with elemental analysis indicate unambiguously that compound III is 2-propionyl-5-chlorothiazolo[5,4-b]pyridine. Hence in alkaline medium hydrolysis of the N_{ring}–CO amide bond is accompanied aromatization of the thiazoline ring, apparently by oxidative dehydrogenation by atmospheric oxygen in the basic medium, analogous to that described for derivatives of dihydrobenzthiazole [6].

Scheme 2



An interesting reaction was observed when amide I was boiled with concentrated H_2SO_4 to give compound IV. The IR spectrum of IV contained C=O bands at 1740 and 1820 cm^{-1}, permitting the suggestion that IV contained a five-membered oxazolidine ring (we had observed analogous bands previously for tricyclic compounds with oxazolidine rings [7]).

The mass spectrum has a group of intense peaks of the molecular ion $[M]^+$ (282, 1 Cl). Fragmentation of the molecular ion is highly selective ($S_{1/2}$ = 2) with the loss of 72 mass units which is characteristic of compounds containing the oxazolidine ring [7, 8]. The absence of peaks with ionic masses of 114 and 70 indicates that the N-morpholinocarbonyl unit is not present in compound IV.

The UV spectrum contains two maxima [λ_{max} (logε): 232 (4.08) and 305 nm (3.90)] which are close in position and intensity to those observed in derivatives containing the oxazolidinopyridothiazine ring system [242 (4.04) and 295 nm (3.90)] [7].

The ^{1}H NMR spectrum of compound IV in DMSO-D_6 contains pyridine ring proton signals (8.53 d and 7.46 ppm d, $^3J_{HH}$ = 8.6 Hz) plus three signals assigned to an all fragment of the type $H_y-C-C=C(H_x)CH_3$ basis of chemical shifts and multiplicities. The doublet at 1.85 ppm (3H) ($^3J_{CH_3,H_x}$ = 7 Hz), the components of which are further split into doublets ($^5J_{CH_3},H_y$ = 1.6 Hz), corresponds to the methyl group. The signals at 6.35 ppm (1 H, qu), the components of which also show additional splitting ($^3J_{H_x,CH_3}$ = 7 Hz, $^4J_{HX,Hy}$ = 1.6 Hz), and 6.37 ppm (1 H, qu, $^4J_{H_y,H_x}$ = $^5J_{H_y,CH_x}$ = 1.6 Hz) belong to the protons H_x and H_y respectively. Combination of all the spectral results indicate that compound IV is 1,2-dioxo-4-ethylidene-7-chloroxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine.

Thus while reaction of dichloroxazolidinopyridothiazines with saturated cyclic amines led to ring opening of the oxazolidine ring and ring closure with conversion of a thiazine ring to a thiazolidine ring [1], treatment of the product formed with concentrated sulfuric acid caused reformation of the initial oxazolidinopyridothiazine tricyclic system (scheme 2).

EXPERIMENTAL

The IR spectra (Nujol mulls) were recorded with a Perkin-Elmer 599 instrument, UV spectra (ethanol solutions) with a Perkin-Elmer 575 spectrophotometer and ^{1}H NMR spectra with a Varian XL-200 spectrometer with TMS as internal standard. Electron impact mass spectra were obtained with a Varian MAT-112 spectrometer with direct insertion of samples into the ion source and an electron ionizing energy of 70 eV. Purity of compounds was confirmed by TLC on Silufol UV-254 strips with benzene–ethyl acetate eluent and UV development.

Characteristic of the compounds synthesized are cited in the tables. Compounds were crystallized from ethanol.

Elemental analysis results for C, H, N, Cl and S for compounds II-IV agreed with calculated values.

1-N-(Morpholinooxalyl)-2-(α-hydroximinopropyl)-5-chloro-[5,4 b]pyridine (II). A mixture of compound I (0.5 g, 1.5 mmole) and hydroxylamine hydrochloride (0.18 g, 2.6 mmole) in ethanol (10 cm^3) and pyridine (5 cm^3) was stirred at 78°C for 3 h. The reaction mixture was then filtered, the filtrate was evaporated to dryness and added to water. The precipitate of compound II was filtered off, washed with water and dried.

2-Propionyl-5-chlorothiazolo[5,4-b]pyridine (III). A mixture of compound I (0.5 g, 1.5 mmole) and NaOH (10 cm^3, 0.1 M in ethanol) was stirred at 78°C for 3h. The precipitate of compound III was filtered off, washed with water and dried.

1,2-Dioxo-4-ethylidene-7-chloroxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine (IV). A mixture of compound I (0.5 g, 1.5 mmole) and concentrated sulfuric acid (3 cm^3) was boiled for 0.5 h. The reaction mixture was poured into water. The precipitate of compound IV was filtered off, washed with water and dried.

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