SYNTHESIS, STEREOCHEMISTRY, AND ISOMERIC TRANSFORMATIONS OF 4-ARYL-5-AROYL-2-METHYLTHIO-2-IMIDAZOLINES

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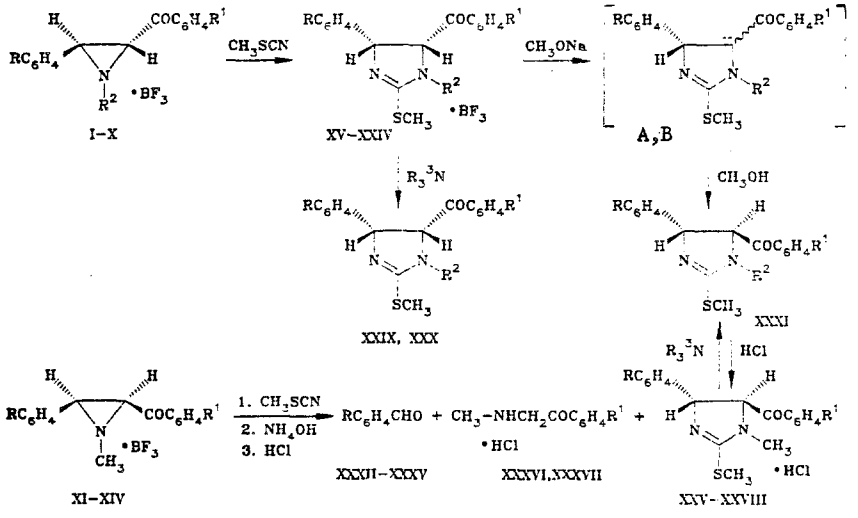
The corresponding 4-aryl-5-aroyl-2-methylthio-2-imidazolines were obtained by the reaction of complexes of cis- and trans-3-aroylaziridines and boron trifluoride with methyl thiocyanate. It is shown on the basis of spectral data that the aziridine ring is opened regiospecifically at the $C_{(2)}$ atom and stereospecifically with inversion of the configuration.

It has been previously established [1] that complexes of cis- and trans-2-aryl-3-aroylaziridines with boron trifluoride from salts of 2-imidazolines on heating with acetonitrile. We assumed that 3-aroylaziridine borotrifluorides should also react with methyl thiocyanate to give 2-methylthio-2-imidazolines, which in a number of cases have high biological activity]2-4] and serve as convenient intermediates in the synthesis of 2-amino-2-imidazolines [5].

In fact, cis-4-aryl-5-aroyl-2-methylthio-2-imidazolines XV-XXIV were obtained in 60-75% yields from trans-2-aryl-3-aroylaziridine borotrifluorides I-X on heating in an inert atmosphere with methyl thiocyanate (Table 1). According to the PMR spectra of the reaction mixtures, only one 2-imidazoline isomer is formed. The change in the relative reactivities of the salts of 3-aroylaziridines in the order p-CH_3 > H > p-Cl ≈ p-Br > m-NO_2 makes it possible to assume that nucleophilic attack by methyl thiocyanate is directed to the $C_{(2)}$ atom of the aziridine ring as in the case of acetone [6] and acetonitrile [1].

As shown in [1, 6], only ω-(N-methylamino)acetophenones and substituted benzaldehydes and no products of addition of acetone to the aziridines are formed from cis-3-aroylaziridine borotrifluorides and acetone, while trans-2-imidazolines are nevertheless obtained with acetonitrile.



We have observed that, as in the case of acetonitrile, trans-4-aryl-5-aroyl-1-methyl-2-methylthio-2-imidazoline salts XXV-XXVIII (35-40% yields) (Table 1) and side products — aminoacetophenones XXXVI and XXXVII and substituted benzaldehydes XXXII-XXXV — are formed

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TABLE 1. 4-Aryl-5-aroyl-2-methylthio-2-imidazolines

Compound*	R†	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IV	*p*-Cl	207	52,7	4,4	6,5	$C_{18}H_{17}ClN_2OS \cdot BF_3$	52,4	4,1	6,8	69
XVI	*p*-Br	207	47,4	3,6	6,0	$C_{18}H_{17}BrN_2OS \cdot BF_3$	47,2	3,7	6,1	73
XVII	*m*-NO_2	205	51,4	4,1	9,7	$C_{18}H_{17}N_3O_3S \cdot BF_3$	51,1	4,0	9,9	65
XVIII	*p*-CH_3	153	57,7	5,3	7,2	$C_{19}H_{20}N_2OS \cdot BF_3$	58,1	5,1	7,1	67
XIX	H	157	57,4	4,9	7,1	$C_{18}H_{18}N_2OS \cdot BF_3$	57,1	4,8	7,4	63
XX	H	202	52,3	4,3	6,5	$C_{18}H_{17}ClN_2OS \cdot BF_3$	52,4	4,1	6,8	71
XXI	H	203	47,5	3,8	5,8	$C_{18}H_{17}BrN_2OS \cdot BF_3$	47,2	3,7	6,1	70
XXII	H	179	55,7	4,2	7,6	$C_{17}H_{16}N_2OS \cdot BF_3$	56,0	4,4	7,7	61
XXIII	*p*-CH_3	163	56,7	4,9	7,1	$C_{18}H_{18}N_2OS \cdot BF_3$	57,1	4,8	7,4	63
XXIV	*p*-Cl	176	51,4	3,9	7,0	$C_{17}H_{15}ClN_2OS \cdot BF_3$	51,2	3,8	7,0	52
XXV	*p*-Cl	129	56,9	4,9	7,0	$C_{18}H_{17}ClN_2OS \cdot HCl$	56,6	4,5	7,3	41
XXVI	*p*-Br	128	50,3	4,1	6,7	$C_{18}H_{17}BrN_2OS \cdot HCl$	50,7	4,0	6,6	39
XXVII	*m*-NO_2	123	55,4	4,8	10,4	$C_{18}H_{17}N_3O_3S \cdot HCl$	55,1	4,3	10,7	37
XXVIII	H	178	50,9	4,3	6,3	$C_{18}H_{17}BrN_2OS \cdot HCl$	50,7	4,0	6,6	44
XXIX	*p*-Cl	151	62,9	4,6	8,0	$C_{18}H_{17}ClN_2OS$	62,7	4,9	8,1	93
XXX	*p*-Br	134	55,2	4,2	7,1	$C_{18}H_{17}BrN_2OS$	55,5	4,4	7,2	91
XXXI	*p*-Cl	—	62,4	4,7	7,9	$C_{18}H_{17}ClN_2OS$	62,7	4,9	8,1	81

*Compounds IV, XVI-XXIV, XXIX, and XXX have a cis configuration, while XXV-XXVIII and XXXI have a trans configuration. †IV, XVI-XIX, XXII-XXVII, XXIX-XXXI R^1 = H, XX R^1 = p-Cl, XXI, XXVIII R^1 = p-Br; IV, XVI-XXI, XXV-XXXI R^2 = CH_3, XXII-XXIV R^2 = H.

TABLE 2. Mass Spectra of 4-Aryl-5-benzoyl-2-methylthio-2-imidazolines

Compound	m/z (relative intensity, %)*
XIX	310 (10), 309 (3), 295 (4), 263 (8), 262 (39), 205 (100), 190 (23), 148 (24), 77 (47), 32 (30)
XVIII	324 (2), 323 (3), 277 (5), 276 (23), 219 (9), 218 (53), 105 (40), 149 (24), 91 (16), 77 (73), 49 (100)
XVI	388 (3), 387 (8), 341 (9), 340 (42), 283 (35), 282 (100), 267 (9), 105 (15), 131 (51), 77 (3)
XVII	355 (2), 354 (4), 340 (3), 307 (5), 250 (4), 135 (5), 105 (7), 86 (22), 77 (8), 32 (100)
XXII	296 (6), 295 (12), 294 (52), 281 (3), 249 (10), 191 (19), 105 (56), 77 (36), 66 (100), 47 (50), 49 (27)
XXVI	388 (5), 387 (13), 341 (6), 340 (28), 283 (67), 282 (100), 131 (47), 105 (9), 89 (5), 77 (7), 32 (23)

*The molecular ion and 10-11 of the most characteristic peaks are presented.

when cis-2-aryl-3-aroyl-1-methylaziridine borotrifluorides XI-XIV are heated with methyl thiocyanate at 90°C in an inert atmosphere. The mechanism of the formation of these compounds is apparently the same as in the case of acetone [6] and acetonitrile [1], since they were not detected in the case of prolonged heating at 90°C of 1-phenyl-2-methylamino-3-hydroxy-3-(p-bromophenyl)-1-propanone hydrochloride with methyl thiocyanate.

The IR spectra of 2-imidazoline salts XV-XXVIII contain bands of aromatic C=C and C=N bonds of an imidazole ring (1500, 1605 cm^{-1}) and a CO group (1700 cm^{-1}). In the mass spectra of XV-XXVIII (Table 2) one observes $[M]^+$ and $[M - 1]^+$ peaks of low intensity, as well as peaks of $[M - 15]^+$, $[M - 47]^+$, and $[M - 48]^+$ ions, which correspond to the detachment of CH_3, SCH_3, and $SHCH_3$ from $[M]^+$, respectively. The peaks of $[M - 105]^+$ and $[M - 106]^+$ ions, which correspond to splitting out of ArCO and ArHCO from $[M]^+$, have high intensities. There are also a number of ions that are formed as a result of fragmentation of the imidazoline ring, particularly the $[M - 147]^+$ ion, which indicates that attack of the nucleophile is directed to the $C_{(2)}$ atom of the aziridine ring.

The vicinal constants in the PMR spectra of 2-methylthio-2-imidazoline salts XV-XXVIII (Table 3) constitute evidence [7] for a cis configuration of XV-XXIV (J = 11.8-12.0 Hz) and a trans configuration of XXV-XXVIII (J = 5.6-5.8 Hz). In order to confirm the structures

TABLE 3. PMR Spectra of 4-Aryl-5-aroyl-2-methylthio-2-imidazolines

Compound	δ, ppm					$J_{4,5}$, Hz
	S—CH_3	N—CH_3	4-H	5-H	H_{arom}	
XV	2,85	3,15	5,94	6,47	7,10...7,63	12,0
XVI	2,83	3,13	5,98	6,47	7,43...7,63	11,8
XVII	2,83	3,13	6,20	6,55	7,00...8,10	11,8
XVIII	2,87	3,13	5,93	6,43	6,73...8,13	11,8
XIX	2,71	3,17	6,00	6,43	7,00...7,57	11,8
XX	2,85	3,13	5,97	6,40	7,04...7,60	11,8
XXI	2,85	3,13	6,00	6,45	7,05...7,57	12,0
XXII	2,85	—	6,07	6,50	7,03...7,60	11,8
XXIII	2,83	—	6,02	6,47	6,76...7,60	11,8
XXIV	2,83	—	6,05	6,50	6,78...7,63	11,8
XXV	2,87	3,15	5,02	6,20	7,33...7,83	5,6
XXVI	2,88	3,17	5,03	6,20	7,37...7,83	5,6
XXVII	2,86	3,23	5,45	6,20	7,47...8,23	5,8
XXVIII	2,80	3,20	5,16	6,07	7,40...7,63	5,8
XXIX	2,42	2,78	5,43	5,70	6,83...7,63	11,0
XXX	2,40	2,73	5,33	5,63	6,73...7,63	11,0
XXI	2,53	2,70	4,40	4,75	6,93...7,63	7,0

and configurations of 2-methylthio-2-imidazolines XV-XXVIII we measured the Overhauser nuclear effect (ONE) (Table 4) in the case of the bases cis- (XXIX) and trans-5-benzoyl-1-methyl-2-methylthio-4-(p-chlorophenyl)-2-imidazoline (XXXI) (Table 1). The data obtained in the case of irradiation of the ortho protons of the phenyl ring confirm a cis configuration of XXIX and a trans configuration of XXXI in conformity with [7], whereas the data obtained in the case of irradiation of the protons of the CH_3N group indicate the direction of opening of the aziridine ring by methyl thiocyanate (Table 4).

Thus, as in the case of acetone and acetonitrile, the reaction of cis- and trans-2-aryl-3-aroylaziridine borotrifluorides with methyl thiocyanate is realized regiospecifically at the $C_{(2)}$ atom of the aziridine ring. In addition, the reaction is stereospecific: inversion of the configuration of the $C_{(2)}$ atom of the aziridine ring occurs, and trans-3-aroylaziridine borotrifluorides give cis-2-methylthio-2-imidazolines, while cis-3-aroylaziridine borotrifluorides give the corresponding trans isomers.

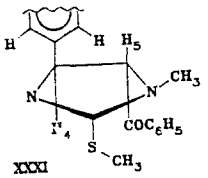
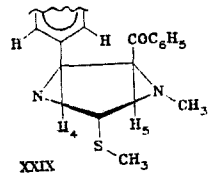
From complex salts of both cis- and trans-2-imidazolines XV-XXVIII by treatment with tertiary amines or ammonium hydroxide we isolated cis-2-imidazoline bases XXIX and XXX in the form of white crystals and trans base XXXI in the form of a viscous oil (Table 1). The assignment of the signals of the 4-H and 5-H protons in the PMR spectra of cis- and trans-2-imidazoline bases XXIX and XXXI (Table 3) was made on the basis of the ONE (Table 4), as well as deuterium-exchange experiments.

Treatment of cis-2-methylthio-2-imidazoline salts XV-XXIV with potassium or sodium hydroxide gives, instead of the cis bases, trans-2-imidazoline derivatives, which were isolated in the form of hydrochlorides and were identical to XXV-XXVIII obtained by the direct reaction of cis-3-aroylaziridine borotrifluorides with methyl thiocyanate. However, the alkalization of trans-2-imidazoline salts XXV-XXVIII with subsequent acidification with hydrogen chloride gives the unchanged starting compounds. As in the case of acetonitrile [1], the conversion of cis-2-methylthio-2-imidazolines to the trans isomers under the influence of bases probably proceeds with the detachment of the 5-H proton and the formation of cis carbanion A, as evidenced by deuterium-exchange experiments. Carbanion A then undergoes isomerization to the sterically more favorable trans carbanion B, which adds a proton and gives the trans base. However, in contrast to cis-2-methyl-2-imidazolines [1], the isomerization of cis-2-methylthio-2-imidazolines under the influence of bases proceeds more slowly. The process is easily followed by TLC and PMR; this is evidently explained by the high polarizability of the sulfur atom and, as a consequence, destabilization of anion A.

EXPERIMENTAL

The IR spectra of solutions in CCl_4 (0.1 mole/liter) or KBr pellets were recorded with UR-20 and IR-75 spectrometers. The PMR spectra of 5-10% solutions of the substances in CCl_4 and d_6-acetone were obtained with a Tesla BS-467 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The ONE data were measured using degassed 5-7% solutions

TABLE 4. Data on the Overhauser Nuclear Effect (ONE) of the Stereoisomers

Compound	Irradiated group	Chemical shift, ppm	Observed proton	ONE, %
 XXXI	*o*-HAr	7,05	5-H	20,5
	o-HAr	7,05	4-H	28,5
	N—CH_3	2,81	4-H	0
	N—CH_3	2,81	5-H	14
 XXIX	*o*-HAr	6,73	5-H	0
	o-HAr	6,73	4-H	28
	N—CH_3	2,77	4-H	0
	N—CH_3	2,77	5-H	18

of the compounds in CCl_4. The mass spectra were recorded with a Varian MAT-311 mass spectrometer at an ionizing voltage of 70 eV and an input-system temperature of 125-155°C. The stereoisomeric cis- and trans-3-aroylaziridines were obtained by the methods in [8, 9], respectively, whereas the cis- and trans-3-aroylaziridine borotrifluorides were obtained by the methods in [1, 6].

cis-4-Aryl-5-aroyl-2-methylthio-2-imidazoline Borotrifluorides XV-XXIV. A solution of 0.01 mole of the cis-2-aryl-3-aroylaziridine borotrifluoride in 10 ml (0.15 mole) of freshly fractionated methyl thiocyanate was purged with nitrogen (argon) and heated in an ampul for 0.5-1 h at 90°C. The ampul was then opened, and the contents were transferred to a flask and diluted with ether. The resulting crystals were removed by filtration, washed on the filter with ether, and recrystallized from acetonitrile–ether.

trans-4-Aryl-5-aroyl-1-methyl-2-methylthio-2-imidazoline Hydrochlorides XXV-XXVIII. A) A thoroughly dried (in a Fischer pistol) 0.01-mole sample of cis-3-benzoylaziridine borotrifluoride was dissolved in 10 ml (0.15 mole) of freshly fractionated methyl thiocyanate, and the solution was purged with nitrogen (argon) and heated in a sealed ampul for 2-3 h at 90°C. The ampul was then opened, and the contents were transferred to a flask and diluted with ether. An oil precipitated. The ether solution was evaporated, and the residue was dissolved in alcohol. The corresponding benzaldehydes were identified in the form of 2,4-dinitrophenylhydrazones. The oily precipitate was dissolved in chloroform, and the precipitated crystals of ω-(N-methylamino)acetophenone was removed by filtration, washed on the filter with ether, and air dried. The filtrate, which contained the 2-imidazoline borotrifluoride, was evaporated, the residue was diluted with 30-40 ml of dry ether, and saturated with gaseous ammonia until the precipitate dissolved. The ether solution was partially evaporated, and the concentrate was passed through a 2-3-cm layer of silica gel on a Schott filter. The silica gel was washed with dry ether, and dry hydrogen chloride was passed through it. The resulting precipitate was crystallized from acetone–ether.

B) A solution of 0.02 mole of potassium hydroxide (or sodium hydroxide or a quaternary ammonium base) in 20 ml of ethanol was added to a solution of 0.01 mole of cis-4-aryl-5-benzoyl-1-methyl-2-methylthio-2-imidazoline borotrifluoride, and the mixture was allowed to stand at room temperature for 0.5 h. The ethanol was evaporated, the residue was dissolved in 40-50 ml of ether, and the solution was passed through a 2-3-cm layer of silica gel on a Schott filter. The ether solution was then saturated with dry hydrogen chloride, and the precipitated oil was crystallized from acetone–ether. The yield was 80-85%.

cis-4-Aryl-5-benzoyl-1-methyl-2-methylthio-2-imidazolines XXIX and XXX. A mixture of 0.01 mole of cis-4-aryl-5-benzoyl-1-methyl-2-methylthio-2-imidazoline borotrifluoride, 40-50 ml of ether, and 0.015 mole of triethylamine was shaken until the borotrifluoride crystals had dissolved, after which the solution was filtered through a 2-3-cm layer of silica gel on a Schott filter, and the ether was evaporated at reduced pressure. The residue was crystallized from acetone–hexane.

trans-5-Benzoyl-1-methyl-2-methylthio-4-(p-chlorophenyl)-2-imidazoline (XXXI). A solution of 0.02 mole of potassium hydroxide (or sodium hydroxide or a quaternary ammonium base) in 10 ml of ethanol was added to a solution of 0.01 mole of cis-5-benzoyl-1-methyl-2-methylthio-4-(p-chlorophenyl)-2-imidazoline borotrifluoride in 30 ml of ethanol, and the mixture was allowed to stand at room temperature for 0.5 h. The ethanol was evaporated at reduced pressure, the residue was dissolved in 40-50 ml of ether, the solution was passed through a 2-3-cm layer of silica gel on a Schott filter, and the ether was removed by distillation to dryness.

Deuterium Exchange of Stereoisomeric 5-Benzoyl-1-methyl-2-methylthio-4-(p-chlorophenyl)-2-imidazolines XXIX and XXXI. A 0.1-g sample of the 2-imidazoline, 1 ml of d_4-methanol, and 0.01 g of sodium methoxide were placed in a PMR ampul, and the mixture was allowed to stand at room temperature. According to the PMR data, 90% deuterium exchange of the 5-H proton occurs in the case of XXIX after 5 min, as compared with 90% deuterium exchange in the case of XXXI after 25 min.

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SYNTHESIS AND TAUTOMERISM OF 5,7-DIARYL-4,7(6,7)-DIHYDROTETRAZOLO[1,5a]PYRIMIDINES

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5,7-Diaryl-4,7(6,7)-dihydrotetrazolo[1,5-a]pyrimidines were synthesized by the cyclocondensation of 5-aminotetrazole with chalcones. The tautomerism of the compounds obtained is discussed.

Azolopyrimidine derivatives have attracted attention as a consequence of their potential physiological activity, but their dihydrogenated derivatives until recently [1] have remained virtually uninvestigated and have been examined only as intermediates in the synthesis of heteroaromatic systems [2].

The aim of the present research was to obtain and study the properties of aromatic substituted 4,7-dihydrotetrazolo[1,5-a]pyrimidines. We have previously reported [1] the synthesis of 4,7-dihydrotriazolo[1,5-a]pyrimidine derivatives by condensation of 3-amino-1,2,4-triazole with 1,3-diaryl-1-propen-3-ones (chalcones). The synthesis of the desired IIIa-h was accomplished by a similar method — by refluxing solutions of 5-aminotetrazole (I) and chalcones IIa-h in dimethylformamide (DMF):

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