5-AMINO-2-ISOXAZOLINES

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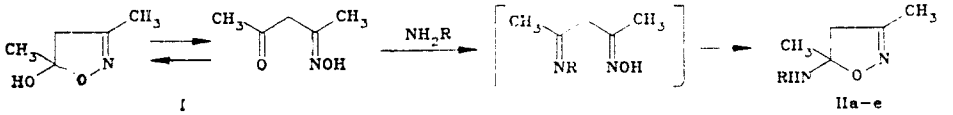
The corresponding previously unknown 5-amino-2-isoxazolines were obtained by the action of ammonia and primary amines on acetylacetone monoxime and on 3,4,4-trimethyl-5-methylene-2-isoxazoline. Their structure was confirmed by NRM spectroscopy.

β-Dioximes and β-hydrazonooximes [2, 3] are well known. Recently the first representatives of β-iminooximes were described which were obtained by the action of hydroxylamine on β-diimines [4]. Subsequently the same authors showed that compounds of this class have a 5-amino-2-isoxazoline structure [5], and like other 2-isoxazolines [6], find application as three-carbon synthones, in particular for the preparation of 1,3-aminoimines and 1,3-aminoalcohols. In this connection, we investigated the possibilities of a simpler method for the preparation of these compounds, i.e., by the action of amines on the readily available β-monooximes. We examined this reaction using acetylacetone as the subject.

It was found that the reaction does not proceed, even on prolonged boiling in toluene with distilling out of water, while on addition of acidic catalysts ($CaCl_2$, CF_3COOH), monoxime I is rapidly aromatized into 3,5-dimethylisoxazole, which was identified by PMR and TLC by comparison with an authentic sample

The reaction can be carried out successfully under solid phase synthesis conditions [7] on aluminum oxide (see Experimental). As a result, the corresponding 5-amino-2-isoxazolines IIa-f are formed in high yields (Table 1).



I IIa–e

This reaction cannot be extended to the benzoylacetone and benzoylacetaldehyde. In the first case, the reaction either entirely fails to proceed, or by using more rigorous conditions, 3-methyl-5-phenylisoxazole is formed, while in the second case the formation of a complex unidentified mixture is observed. Thus, this reaction can possibly be recommended for monooximes of aliphatic β-ketoaldehydes and sterically nonhindered β-diketones.

The compounds IIa-f obtained are fairly stable, except for 5-amino-2-isoxazoline IIa, which is extremely easily hydrogenated to monooxime I. This would imply in principle the possibility of its use for synthetic purposes in reactions with alcohols and amines, but this unfortunately was not the case.

Another path found for the preparation of 5-amino-2-isoxazolines is the action of amines on 3,4,4-trimethyl-5-methylene-2-isoxazoline (III), which, as known, adds phenylhdyrazine [3].

The action of aromatic amines as well as hydrazines on compound III causes the corresponding compounds IVa-e to be formed.

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TABLE 1. Properties of Compounds IIa-f and IVa-e

		R	R_f	T °C	5-CH_3, 3H	3-CH, 3H	4-H (2H) or 4-CH_3 (6H)	NH s 1H**	R	Yield, %
IIa	$C_5H_{10}N_2O$	H	0,27 (1)	Oil	1,52	1,95	2,78	—	—	50
IIб	$C_6H_{12}N_2O$	CH_3	0,35 (1)	Oil	1,56	1,93	2,87	2,51	2,33 (s, 3H)	60
IIв	$C_9H_{18}N_2O$	$(CH_2)_3CH_3$	0,35 (2)	Oil	1,65	1,98	2,81	2,63	0,83 (t, 3H); 1,41 (m, 4H); 2,55 (m, 2H)	65
IIг	$C_7H_{14}N_2O_2$	$(CH_2)_2OH$	0,42 (1)	38...40	1,60	2,00	2,85	—	2,87 (m, 2H); 3,75 (m, 2H)	55
IIд	$C_{11}H_{14}N_2O$	C_6H_5	0,52 (2)	78...79	1,63	1,95	2,60 and 18 (18, AB-system)	4,63	6,91...7,50 (m, 5H)	40
IIe	$C_{12}H_{16}N_2O$	$CH_2C_6H_5$	0,49 (2)	Oil	1,52	1,88	2,68	2,30	3,53 and 3,77 (2H, 14, AB system); 7,25...7,31 (m, 5H)	75
IVa	$C_{13}H_{18}N_2O$	C_6H_5	0,85 (3)	80...82	1,36	1,75	0,95; 1,20	4,75	6,65...7,14 (m, 5H)	60
IVб	$C_{14}H_{20}N_2O$	4-$CH_3C_6H_4$	0,80 (3)	90...93	1,82	2,12	0,97; 1,09	5,01	1,31 (s, 3H); 6,61...7,16 (4H)	65
IVв	$C_{13}H_{17}N_3O_3$	4-NO_2—C_6H_4	0,76 (3)	130...131	1,55	1,84	1,03; 1,15	4,75	6,65...8,02 (m, 4H)	45
IVг	$C_9H_{17}N_3O_2$	$NHCOCH_3$	0,52 (2)	Oil	1,24	1,62	0,79; 0,96	—	1,82 (s, 3H)	84
IVд	$C_{14}H_{19}N_3O_2$	$NHCOC_6H_5$	0,67 (2)	94...96	1,28	1,73	0,92; 1,01	—***	7,20...7,78 (m, 5H)	87

*The PMR spectra of compounds IIa-f, IVb, c, e were recorded in $CDCl_3$, of compound IVa in $(CD_3)_2CO$. The PMR spectrum of compound IVd was obtained in C_5D_5N at 100°C; at lower temperatures the spectrum is complex due to restrained amide rotation.

**For compounds IIa, d and IVd – was not observed.

***4.48 (d, 1H, J = 4 Hz); 8.48 ppm (d, 1H, J = 4 Hz).

TABLE 2. ^{13}C NMR Spectra of Compounds IIa-f and IVa

	$C_{(3)}$, s	$C_{(4)}$, t	$C_{(5)}$, s	5-CH_3, q	3-CH_3, q	R
II	154,4	41,6	98,2	24,6	15,2	—
II	153,8	45,4	98,0	25,4	13,0	27,6 q
II*	153,7	46,1	97,9	25,9	13,2 q	13,5 q ($2CH_3$); 20,0 t 32,4 t 40,9 t ($3CH_2$)
II	154,5	46,5	97,8	25,7	13,2	43,5 t and 61,2 t
II	155,7	45,4	95,7	27,3	13,4	117,0 ... 142,9
II	154,2	46,2	98,1	26,0	13,3	126,6 ... 141,0
IV	164,4	53,7	98,3	10,2; 21.1	17,2; 17,5;	121,3 ... 143,7

*The spectrum of compound IIf was obtained in DMSO-D_6.

All the derivatives II and IV obtained exist exclusively in cyclic form in both polar and nonpolar solvents, similarly as 5-hydrazino-2-isoquinazolines [2]. In the case of compounds IIa-f, this follows from the position of the $C_{(5)}$ atom signal in the ^{13}C NMR specta at 96-98 ppm (Table 2) and from other data of the PMR and ^{13}C NMR spectra (see Tables 1 and 2). In the PMR spectra of 5-amino- and 5-hydrazino-2-isoxazolines IVa-e a nonequivalency of all four methyl groups is also observed.

Thus, 5-amino-2-isoxazolines like most products of the condensation of hydroxylamine and hydrazines with 1,3-dioxo compounds – monoximes [8], mono-, bishydrazones and hydrazonooximes [9], show a tendency to take the cyclic 2-azoline form.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-497 (100 MHz) spectrometer, and the ^{13}C NMR spectra on a Tesla BS-497 spectrometer (20.41 MHz) in a pulse regime with a Fourier transducer. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates or on silica gel (100/160) in the systems ether–methanol 5:1 (system 1), ether–hexane 7:3 (system 2), chloroform–hexane–methanol 6:4:1 (system 3).

For compounds IIa-f and IVa-e, satisfactory elemental analysis data were obtained for the contents of C, H, and N.

5-Amino-2-isoxazolines (IIa-f). A 5-g portion (43 mmoles) of acetylacetone monoxime (I) [10] deposited on 50 g of Al_2O_3 (160-250 μm), preliminarily held for 5 h at 250°C, was mixed together with 43 mmoles of amine IIIc-f (for IIIa, b on 150 g Al_2O_3 – by blowing dry ammonia and methylamine through aluminum oxide), and the mixture was allowed to stand for 24 h. The mixture was extracted with 3 × 150 ml of chloroform (for IIa, b, d – methanol). The solvent was evaporated under vacuum, and the residue was chromatographed on a column (2.5 × 30 cm) with silica gel (100/160) in systems 1 and 2.

3,4,4,5-Tetramethyl-5-phenylamino-2-isoxazoline (IVa). A 2.5-g portion (20 mmoles) of compound III [3] and 1.8 g (20 mmoles) of aniline were heated for 24 h at 60°C in 5 ml of chloroform (for IVd, e – in 50 ml of DMSO) with the addition of 5 drops of CF_3COOH. After the evaporation of the solvent under vacuum the residue was recrystallized from hexane.

Compounds IVb-e were obtained in a similar way.

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HETEROCYCLIC RING CLEAVAGE IN 20-ISOXAZOLINYL STEROIDS UPON TREATMENT WITH BASE

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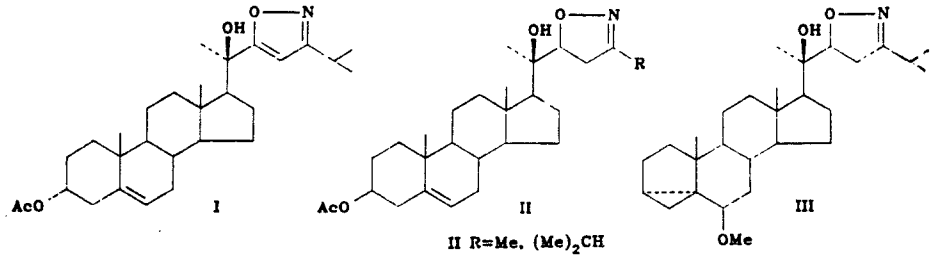
Heterocyclic ring cleavage in 20-isoxazolinyl steroids upon treatment with base has been studied. Treatment with sodium dimsyl (dimethylsulfoxide anion) has been found to result in cleavage of the isoxazoline ring and formation of an α,β-unsaturated ketoxime. The structures of the resulting products are discussed.

Continuing our studies of the synthesis of bifunctional compounds via heterocyclic ring cleavage in isoxazolines and isoxazoles [1], which are adducts formed from ntiriloxides and various unsaturated systems, and pursuant to the goal of preparing on this basis different natural products and related biologically active compounds, it was of great interest to us to examine the feasibility of this approach for the design and construction of polyfunctional steroidal side chains; the problem of stereoselective synthesis of steroidal side chains is an urgent and complex problem in contemporary steroid chemistry.

Toward this goal, we have recently synthesized 20-isoxazolyl- (I) [2] and 20-isoxazolinylsteroids (II and III) [3] via reactions of steroidal acetylenes and olefins, respectively, with nitriloxides.



In studying the catalytic hydrogenation of derivatives of I-III on a variety of catalysts (Pd, Pt, Raney Ni), we have found that there are substantial differences in the properties of these compounds. Isoxazoles I, for instance, readily undergo reductive cleavage along the N–O bond under standard conditions, leading to the corresponding enamino ketones in 100% yield [2]. Isoxazolines II and III, on the other hand, are completely stable with respect to reductive cleavage, which has prompted us to explore alternate pathways for unlocking the inherent functionality in the isoxazoline ring.

Cleavage of 2-isoxazolines II and III upon treatment with base would be of special interest. However, it was found that neither butyllithium nor alkali metal alkoxides led to the desired results. In contrast, use of the dimethylsulfoxide anion [4] as the base, prepared from DMSO upon treatment with sodium hydride, led to the formation of α,β-unsaturated ketoximes IV and VI.

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