SYNTHESIS AND STUDY OF SPIRO[(INDANE-1,3-DIONE)-2,3'-AZIR-1'-INES] AND THEIR CLEAVAGE PRODUCTS

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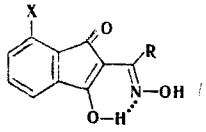
Spiro[(indane-1,3-dione)-2,3'(2'-substituted 1'-azirines)] were obtained by intramolecular cyclization of 2-acylindane-1,3-dione oximes. Their structures and properties were investigated, and it was established that the C—N and C—C single bonds are cleaved during opening of the three-membered ring.

In a previous paper we briefly reported the splitting out of water from 2-acylindane-1,3-dione oximes under the influence of acylating agents, and, on the basis of the IR spectra, we proposed a spiro[(indane-1,3-dione)-2,3'-alkyl(aryl)azir-1'ine] structure for the reaction products [1].

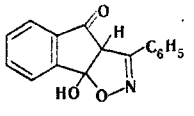
The subject of the present paper is the development of methods for the synthesis of these spiroazirines, the accurate establishment of their structure, and the study of some of their chemical properties. Intramolecular cyclization to give a compound containing one water molecule less than the starting oximine occurs when 2-acylindane-1,3-dione oximes Ia-d and II are treated with acylating reagents or the Beckmann mixture.

The configuration of the oxime is of no importance in the reaction, inasmuch as both oximes Ia-d, which exist in the trans form relative to the indanedione ring, and benzoylindanedione oxime II, which exists in the cyclic cis form, undergo cyclization.

Spiro[(indane-1, 3-dione)-2,3'-azir-1'-ine] (III) and isoxazole (IV) structures are more likely for the cyclization products.



I



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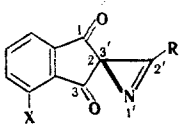
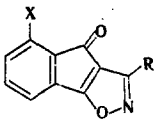


III a-e



IV

I a X=H, R=CH_3; b X=H, R=C_2H_5; c X=H, R=C_3H_7; d X=NO_2, R=CH_3; III a X=H, R=CH_3; b X=H, R=C_2H_5; c X=H, R=C_3H_7; d X=H, R=C_6H_5; e X=NO_2, R=CH_3

The shift of the absorption band of the C=N group in the IR spectra of the compounds to the higher frequencies (1770-1810 cm^{-1}) (see [1]; see Table 2 for the spectrum of IIIc) that are characteristic for azirines [2] confirms structure III. In addition, the dipole moments determined experimentally for the cyclization products are close to the values calculated from vector diagrams for structures IIIa-d (Table 1).

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TABLE 1. Data from the Determination of the Dipole Moments

Compound	α_{av}	β_{av}	P_{tot}	MR_d	μ, D		
					exptl., ± 0.07	vectorially for III	vectorially for IV
IIIa	8,1775	0,8484	292,564	48,421	3,40	3,5	2,1
IIIb	8,4312	0,4901	313,524	53,068	3,52	3,5	2,5
IIIc	7,9139	0,3824	299,718	57,743	3,39	3,5	2,5
IIId	9,9647	0,9489	364,636	68,127	3,75	3,5	2,5

TABLE 2. IR Spectra of the Products*

Compound	Medium	ν, cm⁻¹	
		6 μ	3 μ
IIIc	$C_2H_4Cl_2$	1805(14), 1748(30), 1710(77), 1600(25)	—
Va[11]	$C_2H_4Cl_2$	1760(21), 1722(52), 1705(35), 1680(32), 1645(73), 1600(36), 1532(55)	3445, 3375
Vb(K)	Nujol	1758(61), 1725(91), 1690(41), 1640(83), 1595(46), 1530(78)	3300
Vb	$C_2H_4Cl_2$	1757(17), 1720(46), 1705(29), 1675(27), 1640(63), 1600(30), 1530(43)	3445, 3375
Vc(E)	Nujol	1695(42), 1628(70), 1595(60), 1545(52)	3285
Vc	$C_2H_4Cl_2$	1720(40), 1690(34), 1675(28), 1640(68), 1600(35), 1530(42)	3445, 3375
Vd(K)	Nujol	1758(54), 1722(92), 1630(84), 1600(52), 1578(44), 1535(83)	3300
Vd	$C_2H_4Cl_2$ $C=3\cdot10^{-2}$ M d=0,276mm	1755(21), 1718(55), 1700(30), 1655(45), 1638(65), 1595(35), 1575(22), 1535(48)	3450, 3390

*The spectra were recorded with a UR-10 spectrometer with NaCl and LiF prisms, and the solution concentrations were $5\cdot10^{-2}$ M; d = 0.164 mm (6μ), and d = 1.01 mm (3μ); the percent absorption is given in parentheses.

The tendency of the indane-1,3-dione derivatives to undergo closing to three-membered rings is already well known [3, 4]. On acylation the oxygen atom of the oxime group is converted to the oxonium form [5], and this facilitates splitting out of the proton in the 2 position. The formation of azirines as intermediates also occurs during Neber rearrangement of the oximes, but stable azirines are formed in this case only in individual cases [6]. The spiroindanedioneazirines (III) obtained in this research, which are stabilized by two adjacent carbonyl groups, are characterized by special stability as compared with most of the other azirines [7]; azirines III can be stored in the crystalline form for a long time without appreciable decomposition.

It is known [2, 8] that unsaturated groupings (amide and ester) in the azirine ring lower the electron density of the C=N bond. The electron-acceptor effect of carbonyl groups in III has a pronounced effect on the electron density distribution in the three-membered ring, and, in our opinion, is the reason for deactivation of the C=N bond with respect to the addition of bromine, benzoyl chloride, and hydrogen.

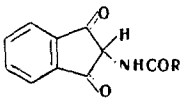
Opening of the three-membered ring with cleavage of the C–N and C–C single bonds is characteristic for azirines III. The C–N bond undergoes reductive cleavage during the reduction of azirine IIIa in acidic media with hydrogen iodide in chloroform, but the C=N double bond is retained, and, 2-acetylindane-1,3-dione imine (VI) is formed. The latter splits out ammonia on alkaline hydrolysis to give 2-acetylindane-1,3-dione. Imine VI is a known compound [9], but little study has been devoted to it. We have established that imine VI is quite inert (it is not reduced by sodium hydrosulfide and does not form a 2-bromo derivative), and it therefore is the final product of the reduction of azirine IIIa under the given conditions. The reduction of imine VI itself apparently requires more severe conditions.

TABLE 3. Spiro[(indane-1,3-dione)-2,3'-(2'-substituted)azir-1'-ines]

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, %, and synthetic method			
			C	H	N	C	H	N	a	b	c	d
IIIa	164—166	$C_{11}H_7NO_2$	71,3	3,7	7,5	71,3	3,8	7,6	81	65	79	55
IIIb	124—125	$C_{12}H_9NO_2$	72,3	4,5	6,9	72,3	4,5	7,0	80	—	70	52
IIIc	83—84	$C_{13}H_{11}NO_2$	73,4	5,3	6,1	73,2	5,2	6,6	81	—	—	—
IIId	179—180	$C_{16}H_9NO_2$	77,8	3,5	5,5	77,8	3,6	5,8	87	48	—	—
IIIe	138—140 (155—160)	$C_{11}H_6N_2O_4$	57,3	2,6	12,2	57,4	2,6	12,2	—	72	99	—

*The melting points were determined with a Böetius apparatus.

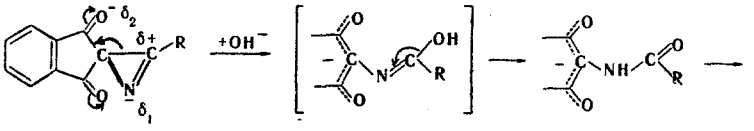
The three-membered ring of azirines III is especially sensitive to nucleophilic reagents. The C–C bond of the three-membered ring of IIIa-d is cleaved in alkaline media (in aqueous sodium hydroxide solution) to give 2-acylaminoindane-1,3-diones (Va-d) (we also obtained Va by another method [10]). Indanediones Vb, d, like VA [11], in the crystalline form may exist in both a keto (K) and a bright-red enol (E) form, but Vc was obtained only in the enol form. An equilibrium between both forms, as attested to by their IR spectra (see Table 2 and [11]), is established in solutions of indanediones Va-d.



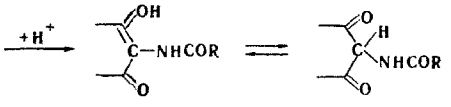
V

V a R = CH_3, b R = C_2H_5, c R = C_3H_7, d R = C_6H_5

We proposed the following scheme for the mechanism of the cleavage of the $C_{(2,3')}$–$C_{(2')}$ bond with alkali:



III A



V

Owing to conjugation of the azirine ring with the carbonyl groups, the positive center of the molecule is the $C_{(2')}$ carbon atom, to which the attacking OH^- anion adds with simultaneous cleavage of the most polarized $C_{(2,3')}$–$C_{(2')}$ bond to give reactive anion A, which is stabilized in the amide form; acylamidoindanedione V is formed by acidification.

EXPERIMENTAL

The dipole moments were determined in dioxane solutions at 25 ± 0.1° with a Dipole apparatus by the method described in [12]. The following bond moments and group moments [13, 14] were used in the calculation of the dipole moments: μ_{C-N} = 0.45 D, $\mu_{C=N}$ = 1.4 D, $\mu_{C=O}$ = 2.4 D, μ_{CH_3} = + 0.37 D, and $\mu_{indane\text{-}1,3\text{-}dione}$ = 2.72 D.

Spiro[indane-1,3-dione)-2,3'-(2'-alkyl(aryl)azir-1'-ines)] (IIIa-e). A) Dry hydrogen chloride was bubbled into a heated (on a water bath) suspension of 0.01 mole of Ia-c or II in 15 ml of glacial acetic acid and 5 ml of acetic anhydride until the solid had dissolved (~ 15 min). The solution was then diluted with water to a volume of 100 ml and allowed to stand in a refrigerator for 2 h. The resulting precipitate was removed by filtration and

recrystallized from ethanol or benzene to give IIIa-d (Table 3).

B) A mixture of 1 g (0.005 mole) of Ia, 2, 5 ml of acetic anhydride, and one drop of pyridine was heated on a water bath, after which it was cooled, and the resulting crystals were removed by filtration and washed with acetic acid and ethanol to give IIIa.

Azirine IIId (the reaction time was 5 min) was similarly obtained from II, and azirine IIIe was similarly obtained from Id (by dilution of the reaction mixture with water) (Table 3).

C) A solution of 0.95 g (0.005 mole) of p-toluenesulfonyl chloride in 5 ml of acetone was added dropwise to a stirred suspension of 0.005 mole of Ia, b, d in 10 ml of dry acetone, after which the flask was cooled with ice water, and a solution of 1 ml [0.76 g (0.0075 mole)] of triethylamine in 5 ml of acetone was added dropwise with stirring. Stirring was continued for 1 h, after which the solution was diluted with 100 ml of water, and the aqueous mixture was allowed to stand for 30 min. The resulting precipitate was removed by filtration to give IIIa, b, e (Table 3).

D) A 0.4-ml (0.0056 mole) sample of acetyl chloride was added to 0.005 mole of oxime Ia, b in 10 ml of dry acetone, after which the mixture was cooled, and a solution of 1.4 ml [1 g (0.010 mole)] of triethylamine in 5 ml of acetone was added with stirring. The yellow oxime dissolved, and colorless crystals of the triethylamine salt precipitated. The salt was separated, the filtrate was diluted with water, and the resulting precipitate was removed by filtration to give azirines IIIa, b (Table 3).

Reduction of Spiro[(indane-1,3-dione)-2,3'-(2'-methyl-1'-azirine)] (IIIa). A mixture of 0.2 g of azirine IIIa, 5 ml of chloroform, and 3 ml of hydriodic acid (freshly distilled) was heated on a water bath for 30 min, after which it was cooled and diluted with 30 ml of chloroform. The mixture was washed with sodium thiosulfate solution, the organic layer was separated, the sulfur was removed by filtration, and the solution was dried over $MgSO_4$. Dry ethanol (1 ml) containing 0.3 g of hydrogen chloride was added to the dry solution, and the precipitated yellow salt of 2-acetylindane-1,3-dione imine was removed by filtration and suspended in 5 ml of water. The suspension was allowed to stand at room temperature for 1 h, after which the solid was removed by filtration to give 0.1 g (49.6%) of imine VI with mp 223-225° (from benzene). Found: C 70.4; H 4.8; N 7.4%. $C_{11}H_9NO_2$. Calculated: C 70.6; H 4.8; N 7.5%. The product did not depress the melting point of authentic 2-acetylindane-1,3-dione imine [9].

A mixture of 0.54 g of imine VI with 10 ml of 5% aqueous sodium hydroxide solution was heated to the boiling point, whereupon the substance dissolved with ammonia evolution. The yellow solution was acidified to give 0.45 g (83.3%) of 2-acetylindane-1,3-dione with mp 109-110° (from ethanol) (no melting-point depression was observed for a mixture of this product with authentic 2-acetylindane-1,3-dione).

2-Acylaminoindane-1,3-diones (Va-d) (Cleavage of Azirines III with Alkali). A red solution of 0.5 g of azirine IIIa in a mixture of 2 ml of ethanol and 3.5 ml of 10% aqueous sodium hydroxide at room temperature was diluted with 10 ml of water, after which the mixture was filtered, and the filtrate was acidified. The resulting precipitate was removed by filtration to give 0.32 g (58.4%) of 2-acetamidoindane-1,3-dione (Va) [10] with mp 221-222° (from alcohol). 2-Propionamidoindane-1,3-dione (Vb), with mp 192-193°, was similarly obtained in 32.5% yield from azirine IIIb. Found: C 66.2; H 4.9; N 6.3%. $C_{12}H_{11}NO_3$. Calculated: C 66.4;H 5.1; N 6.5%. Compounds Vc and Vd were obtained from the corresponding spiroazirines IIIc and IIId by heating the substances in a mixture of 5% sodium hydroxide and ethanol. 2-Butyramidoindane-1,3-dione (Vc), with mp 127-128°, was obtained in 67.3% yield. Found: C 67.3; H 5.8; N 5.9%. $C_{13}H_{13}NO_3$. Calculated: C 67.5; H 5.7; N 6.0%; 2-Benzamidoindane-1,3-dione (Vd), with mp 206-207° (from dioxane), was obtained in 75.6% yield. Found: C 72.5; H 3.9; N 5.3%. $C_{16}H_{11}NO_3$. Calculated: C 72.5; H 4.2; N 5.3%.

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RELATIVE STABILITIES OF THE TAUTOMERIC FORMS OF CONJUGATE ACIDS AND KINETICS OF DEUTERIUM EXCHANGE IN DERIVATIVES OF INDOLIZINE, PYRROLO[1,2-a]IMIDAZOLE, AND PYRROLO[1,2-a]BENZIMIDAZOLE

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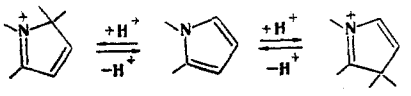
UDC 547.759.4'75'781'785.5:541.127'623

The effect of the temperature and the acidicity of the medium on the ratio of the two tautomeric forms of the conjugate acids of derivatives of indolizine, pyrrolo[1,2-a]imidazole, and pyrrolo[1,2-a]benzimidazole was investigated by PMR spectroscopy. The change in the ratio of the forms with time was studied under fixed reaction conditions. The position of the tautomeric equilibrium in a number of the investigated systems was established. A correspondence between the relative stabilities of the protonated forms and the rate constants for electrophilic deuterium exchange in the neutral molecules was observed.

A study of the protonation of indolizine (I) [1-3], pyrrolo[1,2-a]imidazole (II) [4], and pyrrolo[1,2-a]benzimidazole (III) [5] derivatives in trifluoroacetic acid showed that these systems are ambident bases capable of forming two tautomeric forms of conjugate acids.

The structure of the protonated forms corresponds to the addition of a proton to the carbon atom of the pyrrole ring in the α and β positions relative to the bridge nitrogen atom.



α-form β-form

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