AZIRIDINYL KETONES AND THEIR HETERO ANALOGS

4.* ACIDOLYSIS OF 1,1a-DIHYDROAZIRINO[1,2-a]QUINOXALINES

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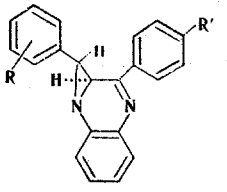
UDC 547.717'863.19

The isomerization of 1,2-diaryl-1,1a-dihydroazirino[1,2-a]quinozalines into 3-aryl-2-benzylquinoxalines under the action of acids is considered. The structures of the compounds synthesized have been confirmed by IR and PMR spectroscopy. It has been shown that the center of protonation in the azirinoquinoxalines and the model 1,2-dihydro-2,3-diphenylquinoxaline is the nitrogen atom of the azomethine group.

In our preceding communication [1, 2] we have described the synthesis and some properties of 1,2-diaryl-1,1a-dihydroazirino[1,2-a]quinoxalines (I). In developing these investigations, we set ourselves the task of studying the behavior of compounds (I) in acid media.

There is a number of communications [3-5] in the literature relating to the acid-catalyzed transformations of bicyclic aziridine systems, which also include compounds (I). Thus, Heine and Henzel [3] obtained 2-(4-nitrobenzyl)-3-phenylquinoxaline as the product of the transformation of the quinoxaline (Id). A different direction of the reaction was observed for 1,2-fused-ring aziridine bicyclic systems [4], for which expansion of the ring through cleavage of the three-membered ring was observed. At the same time, the aziridine-containing 2,3-linked bicyclic systems possess increased stability to acid hydrolysis [5].

In the present work we took as objects of investigation compounds with the general formula:



I a-j

I a R=H, R′=NO_2; b R=*p*-NO_2, R′=H; c R=*m*-NO_2, R′=Br; d R=*p*-NO_2, R′=H; e R=*p*-NO_2, R′=CH_3; f R=*p*-NO_2, R′=OCH_3; g R=*p*-NO_2, R′=Cl; h R=*p*-NO_2, R′=Br; i R=*p*-NO_2, R′=C_6H_4; j R=*p*-NO_2, R′=NO_2

In order to study their behavior in an acid medium, we used a number of solvents with different polarities (benzene, ether, acetone, methanol) and acids with anions having different nucleophilicities (HCl, HBr, HI, $HClO_4$, HBF_4, CF_3COOH). The experimental material obtained showed that even under mild conditions (HCl, aprotic solvent) compounds (I) isomerize into quinoxaline derivatives.

Attempts to isolate salts of compounds (Ia-j), as was done previously [6] under similar conditions for the 1,4-diazabicyclo[4,1,0]hept-4-enes (II) proved unsuccessful. In the previous paper [6] it was observed in a discussion of the mechanism of the acid cleavage of compounds (II) that the primary center of protonation is the nitrogen atom of the azomethine group. An analogous initial stage of acidolysis may be assumed for the quinoxalines (Ia-j) studied. This hypothesis is all the more justified since, according to the literature [7],

*For communication 3, see [2].

A. M. Gorkii Kharkov State University, Kharkov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 544-549, April, 1980. Original article submitted July 30, 1979.

 0009-3122/80/1604-0424$07.50

TABLE 1. PMR Spectra of the Azirinoquinoxalines (Ic-g, i, j) and of the Model Compounds (II), (V), and (VI)* (δ, ppm)

Compound	Solvent	H_A	H_B	J_{AB}	o-	m-	o'-	m'-	CH_3
Ic	$CDCl_3$	3,44	3,30	3,0		7,43—8,18			
Id	$CDCl_3$	3,49	3,03	3,0	7,54	8,25	7,97	7,30	
	CF_3CO_2H	6,30	5,98	7,4	7,61	8,25	8,00	7,61	
Ie	$CDCl_3$	3,50	3,03	2,8	7,55	8,26	7,82	7,26	2,34
	$CDCl_3+CCl_3CO_2H$†	3,56	3,36	2,8	7,60	8,29	7,87	7,29	2,44
	CF_3COOH	6,28	5,91	7,4	7,58	8,27	8,08	7,56	2,58
If	$CDCl_3$	3,46	3,00	2,8	7,53	8,26	7,91	6,96	3,83
Ig	$CDCl_3$	3,41	3,01	3,0	7,50	8,23	7,83	7,33	
Ii	$CDCl_3$	3,53	3,04	3,0		8,25	7,93		
Ij	$CDCl_3$	3,48	3,08	3,0	7,54	8,26	8,30	8,03	
II	$CDCl_3$	3,55	3,02	2,3	7,52	8,16	7,76	7,38	
V	$CDCl_3$	3,58	3,46	3,0	7,53	8,18	8,05	7,48	2,66
VI	$CDCl_3$	3,62	2,62	1,7	7,49	8,15	7,88	7,47	1,61; 1,60
	$CDCl_3+CCl_3CO_2H$	3,82	3,02	1,7	7,56	8,18	7,98	7,56	1,77; 1,75
	CF_3COOH	4,34	3,57	4,0	7,63	8,18	8,04	7,63	1,93; 1,96

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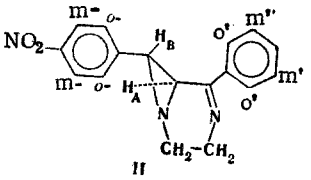
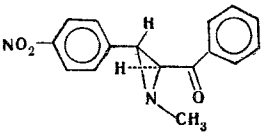
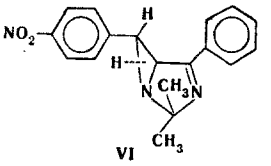


II



V



VI

†Acid : base ratio 1 : 1.

for the nonplanar molecules of 2,3-dihydro-1H-1,5-benzodiazepines protonation takes place at the nitrogen atom of the C=N bond. The results of a quantum-mechanical calculation (by the PPP method) of the ground state of the molecule of 1,2-dihydro-2,3-diphenylquinoxaline (III) — a compound modeling the azirinoquinoxalines — are also in harmony with this. The π-electron density distribution shows that the greatest negative charge (−0.201e) is concentrated on the azomethine nitrogen atom. An experimental confirmation of this conclusion was obtained in an investigation of the hydrochloride of the quinoxaline (III).

In the IR spectra of the free base and its salt the frequencies of absorption of the stretching vibrations of the N—H group proved to be close (~3400 cm^{-1}), while on salt-formation the band of the stretching vibrations of the C=N group shifted by 12 cm^{-1} in the direction of higher frequencies. The ν_{N-H} absorption in solutions of dihydroquinoxaline in CCl_4 with various additions of CF_3COOH was also checked. The value of ν_{N-H} remained constant at all concentrations of acid up to a fivefold molar excess (at a higher concentration of acid the assignment of the absorption of the N—H groups becomes difficult). In our opinion, the results of IR spectroscopy unambiguously confirm an iminium substructure of the salt and indicate the absence of diprotonation processes. A study of the UV spectra of compound (III) led to a similar conclusion. In an acid medium (CH_3OH + HCl) a solution of this compound acquires a coloration, and a new band with λ_{max} 474 nm arising in the spectrum is practically insensitive to an increase in the acidity of the medium. It is interesting to note that the same value of λ_{max} is predicted by the calculation of the spectrum of the imimium structure.

The center of protonation in compounds (Ia-j) can be determined by using the PMR method. In the spectra recorded in $CDCl_3$ (Table 1) the signals of the protons of the arizidine ring form a AB quartet (J = 2.7-3.0 Hz), the doublet in stronger fields being assigned to the H_B proton. This is shown by a broadening of the signals of this doublet through long-range spin—spin coupling with the protons of the aromatic ring attached to the aziridine ring.

The PMR spectra of compounds (Id, e) and of the model compound (VI), measured in CF_3COOH, showed that protonation appreciably changes both the chemical shifts and the SSCCs of the protons of the aziridine ring, but it does not change the multiplicities of the signals. In protonated ethyleneimines, the interaction of the N^+—H and CH protons appears fairly clearly [8], and therefore in our case the aziridine nitrogen atom is not the center of protonation. Protonation takes place at the nitrogen atom of the azomethine group, and the signals of the protons of the aziridine ring are shifted downfield. The H_B proton, more remote from the center of protonation, undergoes the greater shifts, just as in the case of

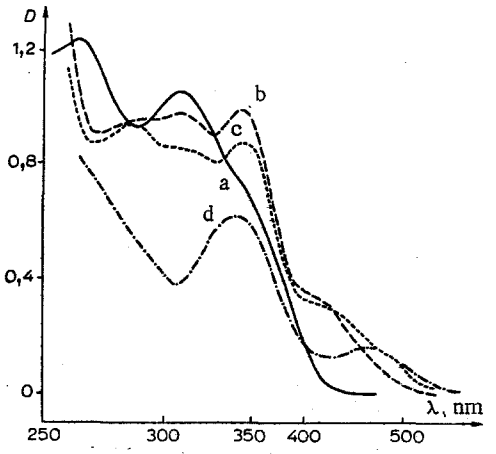


Fig. 1. UV spectrum of compound (Ie): a) in $CHCl_3$; b) in 0.01 M CCl_3CO_2H solution; c) in 0.01 M CF_3CO_2H solution in $CHCl_3$; d) in a saturated solution of CCl_3CO_2H in $CHCl_3$ + HCl (gaseous).

conjugated system. In other words, a condensed aziridine ring behaves similarly to a double bond conjugated with an azomethine group. In actual fact, the replacement of the azomethine group by a stronger acceptor — a carbonyl group [compare compounds (II) and (V)] — shows an analogous effect.

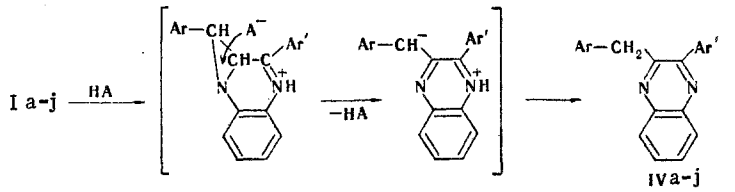
Protonation at the C=N group is also confirmed by the change in the chemical shifts of the protons of the benzene ring adjacent to the azomethine bond. These changes amount to about 0.3 ppm and are close to the changes observed in the protonation of benzophenones [9]. The changes in the shielding of the protons remote from the center of protonation of an aromatic ring (the o- and m- positions in Table 1) are insignificant.

It is characteristic that in the protonated molecules the vicinal constants J_{AB} sharply increase. A similar phenomenon is characteristic for aziridines having electron-accepting substituents on the nitrogen atom, and also for quaternary aziridinium salts [10]. In our case, probably, a considerable negative induction effect of the protonated C=N group is shown which is transmitted through the ortho-phenylene bridge. Consequently, in the case of protonation at the C=N group of compound (V), where such a "bridge" interaction is greatly weakened, the value of J_{AB} (trans) has a considerably smaller value.

The UV spectra of compounds (Ia-j) measured in $CHCl_3$ solutions with additions of CCl_3CO_2H, CF_3CO_2H, and HCl (Fig. 1) showed that solutions intermediate in acidity permit a form with a C=N···HA hydrogen bond to be recorded (λ_{max} ~ 410-420 nm); in the PMR spectra the H-bound form appears for compounds (Ie) and (V) in measurements in the $CDCl_3$ + CCl_3CO_2H system (Table 1). Protonation leads to the appearance in the UV spectrum of an absorption at 460 nm (Fig. 1, d). This nature of the UV spectra obtained in acid media is in harmony with the fact that the long-wave absorption band in the spectra of unprotonated compounds is determined by the transfer of charge from the aziridine nitrogen atom to the C=N group [2]. The increase in the electron-accepting properties of the latter on protonation should undoubtedly promote this process.

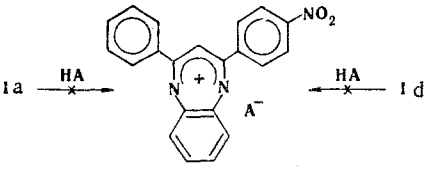
The electron-accepting influence of a protonated azomethine group on an aziridine ring should increase its sensitivity to nucleophilic attack by the anion of the corresponding acid, leading to the opening of the three-membered ring. In a series of experiments that we have performed on the acid conversion of compounds (Ia-j) (in acetone with catalytic amounts of acid at room temperature), a deepening of the color of the solutions was first observed, and then they gradually faded. In relation to their influence of the rate of change in the color of solutions, the acids can be arranged in the following sequence: HCl, HBr, HI. In the case of HCl, the process takes 30-40 min, while for HBr it already requires several tens of hours. This series corresponds to a decrease in the nucleophilicity of the halide anions in aprotic solvents (acetone) [11].

The isomerization of compounds (Ia-j) is determined completely by the energetically most favorable process — the aromatization of the bicyclic system — and can be represented by the following scheme.



IVa-j

It is interesting to note that in the case of compound (Ia-j) protonation does not lead to the cleavage of the 1,3-bond of the aziridine ring. Such ring-opening would lead to the formation of a 7-membered diazepine system the protonation of which would give a stable diazatropylium cation. If such a product were formed, then in the case of compounds (Ia) and (Id) we would obtain the same salt (VII),* which was not observed in the experiment.



VII

The structure of the 2-aryl-3-(nitrobenzyl)quinoxalines (IVa-j), the sole products of the acidolysis of the quinoxaline (I) is confirmed by the independent synthesis from α-diketones [compounds (IVd, e, h)] [6], and also by their IR and PMR spectra. The IR spectra show the frequencies of the vibrations of all the main structural elements of compounds (IVa-j). In particular, the methylene group is shown in the form of symmetrical (2852-2860 cm^{-1}) and asymmetrical (2923-2930 cm^{-1}) deformation vibrations. In the PMR spectra, the CH_2 group appears in the form of a singlet in the 4.45-4.57 ppm region and in addition to this a group of signals is observed in the 7.0-8.1 ppm region which is due to the protons of the aromatic ring.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr tablets in the 700-3600 cm^{-1} interval. The PMR spectra were measured on Tesla BS-487B and XL-100 instruments in CCl_4, $CDCl_3$, and CF_3COOH with TMS as internal standard.

2,3-Diphenyl-1,2-dihydroquinoxaline (mp 148°C) was obtained with a yield of 46% by Fischer's method [12].

2-(4-Nitrophenyl)-1-phenyl-1,1a-dihydroazirino[1,2-a]quinoxaline (Ia). The substance was obtained by a method described previously [1] with a yield of 58%, and consisted of small bright yellow acicular crystals with mp 136-137°C (decomp.), which acquired a greenish-brown coloration in the light. IR spectrum (KBr), cm^{-1}: 1612 (C=N) 1521, 1345 (NO_2). Found: N 12.4%. $C_{21}H_{15}N_3O_2$. Calculated: N 12.3%.

2-Benzyl-3-(4-nitrophenyl)quinoxaline (IVa). Compound (Ia) (1.50 g) was dissolved in boiling acetone, and then 0.5 ml of concentrated HCl was added, whereupon the solution acquired a dark red coloration. After five minutes' boiling the acetone was distilled off in a rotary evaporator. The residual oil crystallized after the addition of 5 ml of cold methanol. This gave 1.37 g (91%) of the quinoxaline (IVa). When it was crystallized from methanol, it formed silky white crystals with mp 167°C (according to the literature [13], mp 167°C). IR spectrum (KBr), cm^{-1}: 2932, 2853, 1457 (CH_2), 1523, 1349 (NO_2). PMR spectrum (in $CDCl_3$), ppm: 4.50 (2 H, s, CH_2).

The following previously undescribed quinoxalines (IVb, c, e, f) were obtained with high yields. 2-(2-Nitrobenzyl)-3-phenylquinoxaline (IVb) mp 70-71°C. IR spectrum (KBr), cm^{-1}: 2924, 2858, 1460 (CH_2), 1542, 1350 (NO_2). PMR spectrum (CCl_4), ppm: 4.73 (2 H, s, CH_2).

*The diazatropylium hydrochloride (VII), forming dark violet crystals with decomp. mp 195°C, has been synthesized by the reaction of p-nitrodibenzoylmethane with o-phenylenediamine.

Found: N 12.5%. $C_{21}H_{15}N_3O_2$. Calculated: N 12.3%. 3-(4-Bromophenyl)-2-(2-nitrobenzyl)-quinoxaline (IVc): mp 153°C. IR spectrum (KBr), cm^{-1}: 2922, 2863, 1444 (CH_2), 1548, 1350 (NO_2). PMR spectrum ($CDCl_3$), ppm: 4.74 (2 H, s, CH_2). Found: N 9.9%. $C_{21}H_{14}BrN_3O_2$. Calculated: N 10.0%. 2-(4-Nitrobenzyl)-3-(4-tolyl)quinoxaline (IVe): mp 165-167°C. IR spectrum (KBr), cm^{-1}: 2923, 2853 (CH_2), 1522, 1349 (NO_2). PMR spectrum ($CDCl_3$), ppm: 4.48 (2 H, s, CH_2), 2.43 (3 H, s, CH_3). Found: N 12.0%. $C_{22}H_{17}N_3O_2$. Calculated: N 11.8%. 3-(4-Anisyl)-2-(4-nitrophenyl)quinoxaline (IVf): mp 157°C. IR spectrum (KBr), cm^{-1}: 2930, 2855 (CH_2), 1528, 1349 (NO_2). PMR spectrum ($CDCl_3$), ppm: 4.57 (2 H, s, CH_2), 3.91 (3 H, s, OCH_3). Found: N 11.1%, $C_{22}H_{17}N_3O_3$. Calculated: N 11.3%.

4-(4-Nitrophenyl)-2-phenyl-3H-1,5-benzodiazepine (VII). A mixture of 4.44 g (0.02 mole) of p-nitrodibenzoylmethane and 2.16 g (0.02 mole) of o-phenylenediamine in 100 ml of methanol was boiled in the presence of 10 ml of concentrated HCl for 1 h. The hot reaction mixture was filtered through a glass filter (1.05 g of unchanged diketone was recovered), and the filtrate was treated with 40 ml of ether and was left at 0°C for a day. The violet diazepine salt was filtered off and crystallized from a mixture of methanol and ether. This gave 3.7 g (82%) of black-violet crystals of the hydrochloride of (VII) with mp 194-195°C (decomp.). The salt was dissolved in ethanol and ammonia was added until the initial coloration had disappeared, whereupon a yellow crystalline precipitate of the benzodiazepine (VII) separated out with mp 288-291°C. IR spectrum (KBr), cm^{-1}: 1609 (C=N), 1523, 1346 (NO_2). Found: N 12.5% $C_{21}H_{15}N_3O_2$. Calculated: N 12.3%.

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