REACTION OF QUINOXALINE WITH BENZOPYRIDINES IN ACETIC ANHYDRIDES IN THE PRESENCE OF Zn DUST*

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UDC 547.863.1'831.3.07:543.422

The reaction between quinoxaline and benzopyridine in acetic anhydride in the presence of zinc dust gives a quinoxaline anion and a benzopyridine N-acetyl radical, which recombine to give the previously unknown N-acetyl dihydrobenzopyridine derivative of 1,2-dihydroquinoxaline. Under these conditions, quinoxaline alone gives 1,4-diacetyl-1,4-dihydroquinoxaline and 1-acetyl-2-(1,2-dihydroquinoxalyl-2)-1,2-dihydroquinoxaline.

In inert solvents, pyridines and their benzo- and dibenzo-analogs are reduced to anions by active metals; this reaction is used in organic chemistry not only for the preparation of symmetrical bisheterocyclics, but also for the direct introduction of hetero-groups into organic compounds [2, 3]. In acetic anhydride, the reduction of these heterocycles generally leads to the formation of N-acetyl radicals as a result of the single-electron reduction of the intermediately formed N-acetyl heteroaromatic cations. These radicals either recombine to give the N,N-diacetyltetrahydropyridiles and their benzo-analogs [4-6], or are reduced to the anions, which in acid medium combine with a proton to give N-acetyldihydroheterocyclic compounds [6, 7]. The use of N-acetyl heteroaromatic radicals to introduce a heterocyclic group into indole and dialkylaniline molecules has also been reported [6, 8]. Sterically hindered heteroaromatic compounds which are basic (for example, benzo[h]quinoline [6]) or slightly basic (for example, pyrazine [9]) are reduced to the anion by zinc in acetic anhydride; intermediate N-acetyl cations are not formed in the presence of zinc.

The behavior of quinoxaline under analogous conditions was studied, since this reaction is not generally known.

Quinoxaline was reduced with zinc in acetic anhydride in an argon atmosphere at a temperature of 60-70°C, conditions slightly different from those given in [9]. Two compounds were obtained: 1,4-diacetyl-1,4-dihydroquinoxaline (I) and 1'-acetyl-2'-(1,2-dihydroquinoxalyl-2)-1'2'-dihydroquinoxaline (II) in the ratio of 1:8. In the IR spectrum of compound I, the amide carbonyl group absorbs at 1660 and the C=C double bond at 1615 cm^{-1}. In the NMR spectrum there is a chemical shift due to protons of the CH_3CO group (δ 2.51 ppm), and the multiplet corresponding to the aromatic protons (6.60-7.65 ppm) in the downfield region is readily distinguishable from an independent multiplet due to the two methine protons (6.60-7.00 ppm); this is consistent with the 1,4-dihydroquinoxaline structure. In the mass spectrum of compound I there are peaks from the molecular ion (M^+) 216,† the fission ion $[M - COCH_3]^+$, and a pseudomolecular quinoxaline ion (130), the decay of which has been studied [10].

The IR spectrum of compound II contains, in addition to the carbonyl group absorption at 1660 cm^{-1}, a broad moderately intense band at 3200-3400 cm^{-1}, which we attributed to the stretching vibrations of the NH group (associated hydrogen bond). The molecular weight of compound II, determined by mass spectrometry, is 304, which corresponds with the empirical formula $C_{18}H_{16}N_4O$, for which there are four possible structures IIa-d (see following page).

Of the three isomeric structures IIa-c, the most probable structure is IIb, since 2-substituted 1,4-dihydroquinoxalines of type IIa are known to rearrange to the thermodynamically more stable 2-substituted 3,4-dihydroquinoxalines of type IIc [11]. Formation of a compound

*Previous communication, [1].
†Values for ions correspond to m/z.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 967-973, July, 1985. Original article submitted June 18, 1984.

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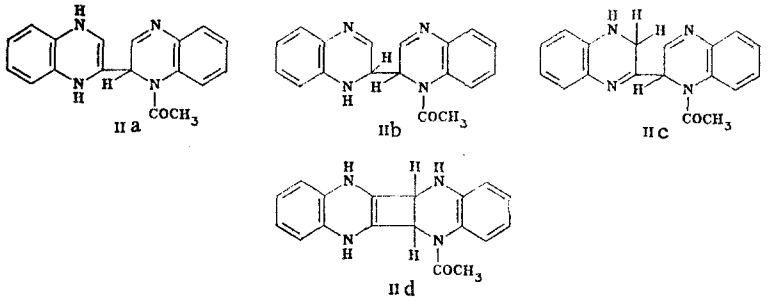
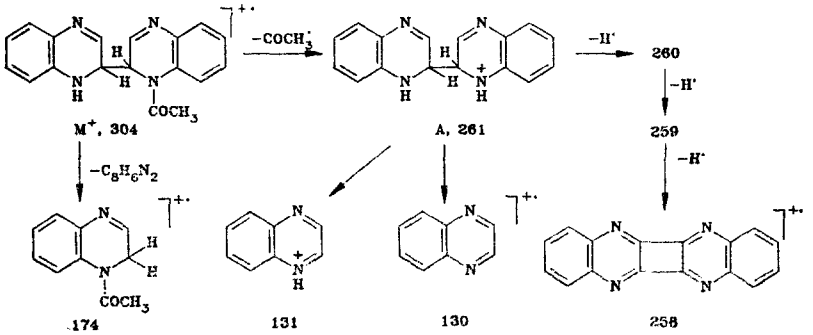
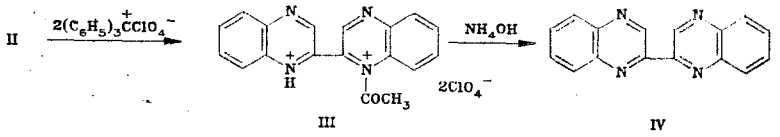


of structure IId is also possible, since both the neutral quinoxaline molecule [12] and its cation [13, 14] are known to lose nucleophiles from positions 2 and 3. However, confirmation for structure IIb is provided by the mass spectrum; the stability of M^+ to electron impact W_M is 0.13, which is about the same as for the majority of N-acyl derivatives of 1,2-dihydroheteroaromatic compounds [15]. The decay of M^+ can occur in two ways:



Cleavage of the labile amide bond in M^+ leads to the appearance in the mass spectrum of ion peaks at 43 and 261, corresponding to the acetyl cation and a cation of structure A. Cleavage of the internuclear bond in M^+ is accompanied by the migration of a hydrogen atom and leads to the formation of pseudomolecular ions of quinoxaline (130) and N-acetyl-1,2-dihydroquinoxaline (174). These fragments could also arise by the simultaneous cleavage of two internuclear bonds in the M^+ ion which arises from IId. However, the cation A undergoes subsequent dehydrogenation with the formation of fission ions with mass 260, 259, and 258, confirming that the structure IIb, not IId, is the correct one, since IId would show a five-stage dehydrogenation of the cation A. Structure IIb is also confirmed by the fragmentation pathway of the cation A in which the internuclear bond is broken with formation of a quinoxaline ion (130) and its protonated form (131); this is characteristic for all partially hydrogenated bisheterocyclics [10, 16]. Mass spectral data also show that structure IIb, rather than structure IIc, is the correct one (Table 1); there is a broad singlet from the NH group at 4.00 ppm and also a doublet from each of the single protons at the α-positions of both quinoxaline rings at 5.24 and 5.18 ppm. Compound IIc would give rise to a doublet corresponding to two α-protons from the quinoxaline rings.

Basic hydrolysis of compound II gave the 2,2'-biquinoxaline IV described in [17, 18]. Aromatization of compound II using triphenylmethylperchlorate gave the perchlorate of 1'-acetyl-2'-(1,2-dihydroquinoxalyl-2)quinoxaline III, which was hydrolyzed with ammonia to give the biquinoxaline IV, added confirmation that the structure IIb is the correct one.



To identify the 2,2-biquinoxaline IV, we prepared it by an alternate method involving the reduction of the quinoxaline with an active metal (Na, Al, Mg) in tetrahydrofuran in the presence of mercuric chloride.*

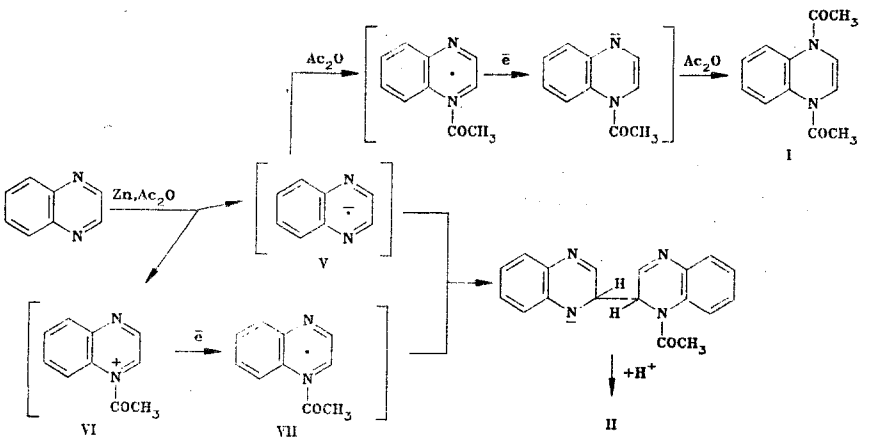
*B. V. Geras'kov helped to develop this method for the preparation of 2,2-biquinoxaline.

TABLE 1. NMR and Mass-Spectral Data for Compounds I, II, VIII, and IX

Compound	NMR spectrum, δ, ppm	Mass spectrum, m/z (intensity of peaks as % of maximum)
I	2,51 (6H, s, CH_3CO); 6,6—7,0 (2H, m, CH=CH); 7,0—7,5 (4H, m, arom.)	**216*** (2), 174 (37), 173 (21), 131 (95), 104 (3), 103 (5), 77 (13), 76 (10), 51 (3), 50 (3), 43 (100)
II	2,30 (3H, s, CH_3CO); 5,18 (1H, d, J=2,6 Hz, H-2′); 5,24 (1H, d, J=3 Hz, H-2); 7,70 (2H, d, J=3 Hz, CH=N); 6,8—7,6 (8H, m, arom.); 4,00 (1H, broad s, NH)	**304** (2), 261 (5), 260 (3), 259 (5), 258 (4), 174 (10), 133 (34), 132 (67), 131 (100), 130 (23), 129 (13), 108 (25), 107 (11), 104 (22), 103 (30), 102 (24), 78 (15), 77 (59), 76 (48), 75 (19), 51 (50), 44 (28), 43 (88)
VIII	2,28 (3H, s, CH_3CO); 5,16 (1H, d, J=2,8 Hz, H-2′); 5,20 (1H, d, J=3 Hz, H-2); 6,7—7,6 (8H, m arom.); 7,65 (1H, d, CH=N); 6,20—6,45 (2H, qu, J=6 Hz, CH=CH); 4,0 (1H, broad s, NH)	**303** (4), 302 (2), 261 (2), 260 (2), 259 (4), 258 (3), 175 (5), 174 (6), 173 (5), 172 (15), 133 (8), 132 (16), 131 (51), 130 (100), 129 (36), 128 (10), 104 (6), 103 (13), 102 (12), 101 (5), 98 (5), 78 (4), 77 (16), 76 (15), 75 (8), 69 (24)
IX	2,25 (3H, s, CH_3CO); 6,8—7,9 (8H, m, arom.); 5,24 (1H, d, H-2); 5,00 (1H, d, H-1′); 7,72 (1H, d, CH=N); 6,20—6,45 (2H, qu, J=7 Hz, CH=CH); 3,95 (1H, broad s, NH)	**303** (2), 302 (3), 261 (2), 260 (2), 259 (5), 258 (2), 175 (4), 174 (6), 173 (7), 172 (35), 133 (8), 132 (20), 131 (59), 130 (100), 129 (44), 128 (10), 103 (18), 102 (19), 101 (5), 98 (4), 77 (12), 76 (20), 75 (11), 74 (7), 73 (15), 69 (9), 68 (4), 60 (18)

*Molecular ion designated as aliphatic type.

Thus, the reduction of quinoxaline with zinc in acetic anhydride (cf. pyrazine [9]) leads to the formation of the quinoxaline anion-radical V, which is partially acetylated (10%), reduced to the anion, and again acetylated to the 1,4-diacetyl derivative of 1,4-dihydroquinoxaline (I); the remaining 90% reacts with the N-acetyl quinoxaline cation VI or radical VII, also formed during the reaction, to give the dimer II:

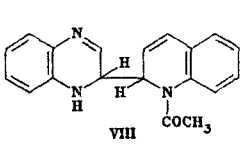


The proposed route for the formation of the dimer II is a typical method of introducing a hetero-group into a molecule [19], the only difference being that a nucleophilic reagent — the quinoxaline anion-radical — is also formed in the reaction mixture by a one-electron reduction of the π-deficient quinoxaline ring. This suggests that not only can "cross-linking" occur between a π-deficient and π-excessive heterocycle, but also between two different π-deficient heterocycles. For this reaction to occur, the π-deficient heterocyclic pairs should have considerably different basicities or reduction potentials. Thus, for a pair of 1,4-diazines, for example quinoxaline or pyrazine, with low pK_a values (0.3 and 0.6) and high half-wave reduction potentials ($E_{1/2}$ = −1.10 and −1.57 in DMFA [20] and −1.70 and −2.08 in CH_3CN [21]), and monoazines with higher basicities, for example pyridine, quinoline, and isoquinoline (pK_a = 5.2, 4.85, and 5.14) and more negative half-wave potentials ($E_{1/2}$ = −2.20, −1.60, and −1.64 in DMFA [20] and −2.62, −2.11, and −2.22 in CH_3CN [21]), the first step in the reaction in acetic anhydride in the presence of zinc will probably be the reduction of the diazine to the anion and the formation of the monoazine N-acetyl cation. The difference in the magnitude of $E_{1/2}$ is probably less important than the difference in basicities. The

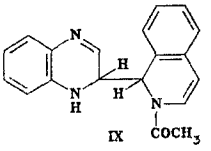
data indicate that quinoxaline–pyridine, quinoxaline–quinoline, and quinoxaline–isoquinoxaline should be suitable pairs for the preparation of mixed biheterocyclic compounds.

We have verified this hypothesis by carrying out the reaction using these pairs. The reduction of mixtures of heterocycles was carried out with zinc duct in acetic anhydride at 40-60°C in an atmosphere of argon. In the reaction with pyridine, only one product — compound I — was identified; no other products could be isolated from the reaction mixture. In the reaction with quinoline, together with compound I (8%), 1'-acetyl-2'-(1,2-dihydroquinoxalyl-2)-1',2'-dihydroquinoline (VIII) was obtained in 64% yield. In the reaction with isoquinoline, two products were obtained: the 1,4-diacetyl derivative I and the 2'-acetyl-1-(1,2-dihydroquinoxalyl-2)-1',2'-dihydroisoquinoline (IX) in yields of 10% and 50%, respectively.

The structures of compounds VIII and IX were established on the basis of spectral data (Table 1), and confirmed by chemical reactions. The presence of the acetyl group in the monoazine rather than the quinoxaline ring was shown by the appearance in the mass spectrum of ion peaks at 131 and 172, arising from the cleavage of the internuclear bond in the first stage of the fragmentation of M^+ with mass 303. Further decay of M^+ for compounds VIII and IX was similar to that for compound II and other α-substituted N-acyl-1,2-dihydroquinolines and isoquinolines [15].

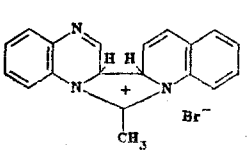


VIII

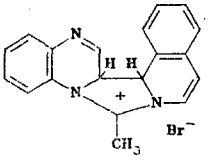


IX

The α–α-coupling in compounds VIII and IX was confirmed by intramolecular cyclodehydration; under the conditions described for the cyclodehydration of 2-acetyl-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline [5], refluxing compounds VIII and IX in concentrated HBr gave the imidazoline salts X and XI, respectively.



X



XI

In the infrared spectra of the salts X and XI, there are bands at 1540 and 1620 cm^{-1} corresponding to the stretching vibrations of the C=N and C=C bonds, but no bands attributable to CO and NH groups. The NMR spectra of compounds X and XI are identical: The three protons of the methyl group give rise to a singlet at 3.10 ppm, the methine proton of the pyrazine group appears as a doublet at 7.65 ppm (J ≈ 5 Hz), and the aromatic protons of the benzene ring appear as a multiplet at 6.70-7.60 ppm. The signals from the heterocyclic ring α-protons are shifted downfield in comparison with those of compounds VIII and IX, and occur in the same region as the signal from the monoazine CH–CH protons, which appear as a multiplet at 6.20-6.55 ppm.

Thus, using quinoxaline, we have shown that it is possible to introduce a hetero-group directly into a π-deficient heteroaromatic compound.

EXPERIMENTAL

Infrared spectra of the compounds in acetonitrile and in mineral oil were taken on a UR-20, NMR spectra on an XL-100 using $CDCl_3$ and trifluoroacetic acid as solvents and TMS as internal standard. Mass spectra were recorded on an MX-1303 spectrometer with direct introduction of the samples into the ion source at an ionization energy of 50 eV, electron emission current 1.5 mA, and temperatures close to the melting points of the compounds.

Data obtained for the first time are given in Table 2.

Reduction of Quinoxaline with Zinc in Acetic Anhydride. To a solution of 13 g (0.1 mole) of quinoxaline in 90 ml of acetic anhydride at 30-40°C in a current of dry argon, 50 g

TABLE 2. Physicochemical Data for Compounds

Compound	IR spectra, cm^{-1}	Mp, °C	R_f†	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N (Hal)		C	H	N (Hal)	
I	1615, 1660	250	0,81 (A)	66,5	5,8	13,1	$C_{12}H_{12}N_2O_2$	66,7	5,5	12,9	10
II	1660, 3240—3400	265—267	0,64 (A)	69,9	5,4	18,3	$C_{16}H_{16}N_4O$	71,0	5,7	18,4	87
III	1700, 3400	320	—	48,7	3,4	12,5 (16,9)	$C_{16}H_{14}Cl_2N_4O_5$	49,4	3,2	12,8 (16,3)	33
VIII	1660, 3350—3400	206—208	0,65 (B)	75,0	5,4	13,4	$C_{19}H_{17}N_3O$	75,2	5,6	13,8	64
IX	1660, 3350—3400	193—194	0,70 (B)	75,6	5,4	13,6	$C_{19}H_{17}N_3O$	75,2	5,6	13,8	50
X	1570, 1605	224—226	—	60,7	4,9	12,1 (22,0)	$C_{18}BrH_{16}N_3O_2$	61,0	4,5	11,8 (22,4)	15
XI	1540, 1620	296—299	—	61,4	4,8	12,5 (21,9)	$C_{18}H_{16}BrN_3O_2$	61,0	4,5	11,8 (22,4)	24

*Compounds were purified by crystallization: I from DMFA, II from ethanol, III from acetonitrile, VIII and IX from carbon tetrachloride, X from isopropanol, XI from a mixture of ethanol and ether.
†Chromatographic mobility of the compounds was measured on Silufol 254 plates in chloroform—benzene—hexane—methanol, 30:6:1:1 (A) and chloroform—benzene—hexane, 30:6:1 (B); spots were visualized in iodine vapor.

of zinc dust was added over a period of 2 h. The temperature of the reaction mixture rose to 60°C; the mixture was vigorously stirred for 6 h, then cooled, filtered, and the precipitate washed on the filter with a small quantity of acetic anhydride and then with ice water. The material remaining was extracted with hot DMFA; on cooling, 2.1 g (10%) of a white precipitate of 1,4-diacetyl-1,4-dihydroquinoxaline separated out. The combined acetic anhydride filtrates were concentrated to half volume in vacuum, and poured onto ice to give 24 g (80%) of compound II.

Reaction of Quinoxaline with Quinoline in Acetic Anhydride in the Presence of Zinc. Using the above method, 13 g (0.1 mole) of quinoxaline and 13 g (0.1 mole) of quinoline in 100 ml of acetic anhydride in the presence of 15 g of zinc dust at 40-60°C in a current of argon gave 1.72 g (8%) of the diacetyl derivative of I and 19.4 g (64%) of the bisheterocycle VIII.

Analogously, 13 g (0.1 mole) of quinoxaline and 13 g (0.1 mole) of isoquinoline gave 2.1 g (10%) of compound I and 15 g (50%) of compound IX.

Using the same method, the reaction between quinoxaline and pyridine in acetic anhydride in the presence of zinc dust gave a 10% yield of compound I, together with some tarry material.

Perchlorate of 1'-Acetyl-2'-(1,2-dihydroquinoxalyl-2)quinoxaline (III). To 0.61 g (0.002 mole) of the dimer II in 10 ml of absolute acetonitrile was added portionwise 1.23 g (0.004 mole) of triphenylmethylperchlorate. The mixture was kept at 40°C for 10 min, and the red precipitate of the salt III which separated was recrystallized from acetonitrile to give 0.4 g of III (Table 2). The salt III was stable on keeping in a sealed tube for 5-6 days.

2,2-Biquinoxaline (IV). A. A solution of 3 g (0.01 mole) of the dimer II in 30 ml of 10% NaOH in aqueous ethanol was refluxed for 15 h, then cooled, and the precipitated 2,2-biquinoxaline IV recrystallized from DMFA to give 0.75 g (29%) with mp 272-274°C (literature value 274°C [17, 18]).

B. A solution of 0.4 g of the salt III in acetonitrile was poured into dilute aqueous ammonia, whereupon compound IV (0.34 g) precipitated out.

C. A solution of 32.5 g (0.25 mole) of quinoxaline in anhydrous tetrahydrofuran was refluxed for 8 h with 6.5 g (0.25 mole) of aluminum dust (or other active metal), and 1-2 g of mercuric chloride in an argon atmosphere. Nitrobenzene (50 ml) was added and the mixture filtered. The tetrahydrofuran was evaporated, the remainder of the solution refluxed in air for 4 h, the nitrobenzene distilled off in vacuum, and the dry residue recrystallized from DMFA to yield 41.6 g (65%) of the biquinoxaline IV with mp 274°C.

Cyclodehydration of Compounds VIII and IX (General Method). A solution of 1 g of the dimer VIII or IX in 20 ml of concentrated HBr was refluxed for 20 h, filtered, and the filtrate evaporated to dryness in vacuum. The residue was dissolved in water, and the solution filtered. The aqueous filtrate was evaporated to dryness, and the residue twice recrystallized from a mixture of ethanol and ether (3:2) to yield the salts X and XI (0.3-0.4 g) as bright green needles.

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