CHEMISTRY OF HETEROCYCLIC QUINONEIMINES.

9.* REACTION OF BENZO[a]PHENOXAZIN-9-ONE WITH C-NUCLEOPHILES

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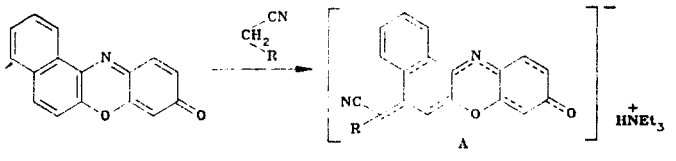
Selective replacement of the hydrogen atom in the 5 position of the aromatic fragment of the substrate by the residue of a C-nucleophile, which is accompanied by rearrangement of the benzoquinoid structure to a naphthoquinoid structure, occurs in the reaction of benzo[a]phenoxazin-9-one with cyanoacetic acid derivatives under conditions of activation of the reagent.

The 1,4-addition of CH acids to quinones is well known as a convenient method for the synthesis of various annealated heterocycles [2]. At the same time, the synthetic possibilities of nucleophilic alkylation have not been studied in the heterocyclic quinoneimine series. Reports regarding the alkylation of such quinoneimines by radicals generated from carboxylic acids have been recently published [3, 4]. The formation of methylidene derivatives was observed in the case of nucleophilic substitution of a hydrogen atom in N-alkylphenazinium and phenothiazinium cations [5, 6].

It has been shown [7, 8] that the reaction of benzo[a]phenoxazin-9-one (I) with N- and S-nucleophiles under conditions of acidic activation may take place at two electrophilic centers — the 5 and 10 positions. The formation of the final products in this case occurs as a result of simultaneous activated aromatic nucleophilic substitution and substitution of a hydrogen atom in the quinoneimine part, which includes primary 1,4-C=C—C=N addition. We have found that the selective reaction of benzo[a]phenoxazin-9-one with C-nucleophiles can be accomplished under conditions of activation of the reagent. At 20°C in solution in ethanol in the presence of triethylamine benzo[a]phenoxazin-9-one reacts smoothly with malonodinitrile and cyanoacetic acid ester and amide to give II-IV. Cationic activation of the substrate under these conditions is not effective. β-Dicarbonyl compounds (acetylacetone, acetoacetic ester, etc.) are inert with respect to the substrate under mild conditions. Under severe conditions and when stronger bases (alkali metal alkoxides, alkalis) are used the reactions with C-nucleophiles proceed with the formation of a complex mixture of unidentified compounds and are accompanied by destruction of benzo[2]phenoxazin-9-one due to nucleophilic attack at the central heteroring.

The products of the reaction of I with malonodinitrile and cyanoacetic acid ester and amide are red and have pronounced acidic properties, readily dissolving in aqueous solutions of various bases with the formation of blue-green anions A. On the basis of the results of elementary analysis and spectral data the structures of 5-alkyl derivatives were assigned to II-IV, as well as to their acetyl derivatives V-VII, which are formed in the acylation of hydroxy derivatives II-IV with acetic anhydride at 20°C:



A

*See [1] for Communication 8.

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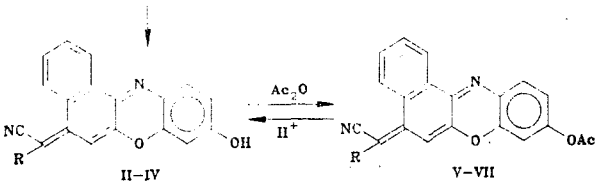

II–IV V–VII

II, V R=CN; III, VI R=COC_2H_5; IV, VII R=$CONH_2$

Acetylation made it possible to overcome the difficulties (see below) that arise in establishing the structures of hydroxy derivatives II-IV.

The introduction of an electron-acceptor substituent into the 5 position of the substrate molecule with simultaneous rearrangement of the benzoquinoid system to a naphthoquinoid system leads to a slight shift of λ_{max} in the electronic spectra of derivatives II-IV and to a somewhat stronger shift for the corresponding acetyl derivatives (see Table 1) relative to unsubstituted benzo[a]phenoxazin-9-one (λ_{max} 505 nm).

The PMR spectra of V-VII contain a characteristic multiplet of 8-H, 10-H, and 11-H protons at 6.7-7.6 ppm, a singlet of a 6-H proton at 8.0 ppm, and signals of the protons of the substituents and annealated benzo ring (see the experimental section); this makes it possible to determine unequivocally that the residues of C-nucleophiles are incorporated in the 5 position of the molecule. In the PMR spectra of the hydroxy derivatives one observes substantial broadening of the signals, indicating the presence of paramagnetic particles, the formation of which is evidently promoted by partial ionization of II-IV in solutions with the formation of anions that contain, in addition to a donor (phenoxide) fragment, a strongly acceptor quinoid fragment.

Absorption bands of a quinoid fragment at 1590-1650 cm^{-1}, two CN groups at 2205 and 2217 cm^{-1}, and of an OH group at 3450 cm^{-1}, which is absent in the case of the corresponding acetyl derivative V, are present in the IR spectrum of II, which can be regarded as a model. The absorption band of the C=O group of acetyl derivatives VI and VII is observed at 1770 cm^{-1}. The IR spectrum of IV contains absorption bands of an amide NH_2 group at 3200 and 3430 cm^{-1}, of a CN group at 2196 cm^{-1}, and of a quinoid fragment at 1590-1650 cm^{-1}, on which the absorption band of an amide carbonyl group that participates in conjugation with the quinoid fragment is superimposed. The absorption band of an OH group is found at 3520 cm^{-1}. Agreement with the proposed structures is also observed in the IR spectra of the remaining alkyl derivatives (see the experimental section).

The molecular masses of II-IV and the corresponding acetyl derivatives V-VII determined mass spectrometrically correspond to the calculated values, and the character of the fragmentation does not contradict the proposed structures.

Thus in the examined reactions of benzo[a]phenoxazin-9-one we observed the rarely encountered replacement of a hydrogen atom bonded to an aromatic ring under the influence of a C-nucleophile; the loss of aromatic character by the naphthalene fragment of the substrate molecule is compensated by aromatization of the benzoquinoid part. The selective formation of 5-alkyl derivatives in the reactions of benzo[a]phenoxazin-9-one with C-nucleophiles constitutes evidence for substantially greater electrophilicity of the para position with respect to the nitrogen atom in the aromatic fragment of the substrate as compared with the alternative reaction center in the quinoid fragment (the 10 position). A comparison of the reactivities of benzo[a]phenoxazin-9-one and nonannelated phenoxazin-9-one, for which attack

TABLE 1. 5-(R-Cyanomethylene)-9-hydroxy(acetoxy)-5H-benzo[a]-phenoxazines II-VII

Compound	mp, °C	λ_{max}, nm (lg ε)	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
II	>350	550 (4,52)	73,6	3,2	13,4	$C_{19}H_9N_3O_2$	73,3	2,9	13,5
III	278—280	544 (4,49)	66,9	4,0	7,7	$C_{21}H_{14}N_2O_4 \cdot H_2O$	67,0	4,2	7,4
IV	>350	496 (4,43)	69,3	3,7	13,4	$C_{19}H_{11}N_3O_3$	69,3	3,4	12,8
V	247—249	503 (4,47)	71,3	3,2	11,8	$C_{21}H_{11}N_3O_3$	71,4	3,1	11,9
VI	187—189	491 (4,44)	69,4	4,0	7,3	$C_{23}H_{16}N_2O_5$	69,0	4,0	7,0
VII	264—266	462 (4,37)	67,7	3,5	11,4	$C_{21}H_{13}N_3O_4$	67,9	3,5	11,3

at the quinoneimine center is preferred [9], indicates an increase in the electrophilicity of the atomatic fragment in the case of its type [a] annelation.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-acetone and d_6-methanol were recorded with a Bruker spectrometer (80.13 MHz) with tetramethylsilane as the internal standard. The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The electronic spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The mass spectra were recorded with a MAT-311A spectrometer; the ionizing-electron energy was 70 eV. Benzo[a]phenoxazin-9-one was obtained from β-naphthol and p-nitrosophenol by the method in [10].

5-(R-Cyanomethylene)-9-hydroxy-5H-benzo[a]phenoxazines II-IV. The nucleophilic reagent and triethylamine were added in portions with stirring at room temperature to a solution of 0.5 g (∿2 mmole) of benzo[a]phenoxazin-9-one in 50 ml of ethanol. A sufficient degree of conversion of the substrate was achieved when a twofold excess of the reagent was used and the process was carried out for 3-4 days (with monitoring by TLC). After this, the ethanol was removed by distillation, the residue was suspended in chloroform, and the suspension was filtered. The II-IV obtained were recrystallized from DMF–water (1:1).

5-Dicyanomethylene-9-hydroxy-5H-benzo[a]phenoxazine (II). The yield was 0.2 g (32%). IR spectrum: 1590, 1637 (quinoid fragment); 2205, 2217 (CN); 3450 cm^{-1} (broad) (OH). M^+ 311.

5-(Ethoxycarbonylcyanomethylene)-9-hydroxy-5H-benzo[a]phenoxazine (III). The yield was 0.3 g (41%). IR spectrum: 1588, 1640 (quinoid fragment); 1705 (C=O); 2202 (C≡N); 3280 cm^{-1} (broad) (OH). M^+ 358.

5-(Aminocarbonylcyanomethylene)-9-hydroxy-5H-benzo[a]phenoxazine (IV). The yield was 0.2 g (30%). IR spectrum: 1590 (quinoid fragment); 1650 (C=O); 2196 (C≡N); 3200, 3430 (broad, NH_2); 3520 cm^{-2} (broad) (OH). M 329.

5-(R-Cyanomethylene)-9-acetoxy-5H-benzo[a]phenoxazines V-VII. A 0.1-g sample of the corresponding hydroxy derivative II-IV was dissolved at room temperature with stirring in 10 ml of acetic anhydride, to which 0.1 g of sodium acetate had been previously added. After the hydroxy derivative had dissolved, the reaction mass was diluted with 100 ml of water, and the yellow-red precipitate of the corresponding 9-acetoxy derivative V-VII was removed by filtration. The yields were quantitative. The compounds were crystallized from acetone.

5-Dicyanomethylene-9-acetoxy-5H-benzo[a]phenoxazine (V). PMR spectrum: 2.3 (3H, s, CH_3), 7.0 (1H, s, 6-H), 7.25 (1H, dd, 10-H, $J_{10\,8}$ = 2, $J_{10\,11}$ = 8.5 Hz), 7.35 (1H, d, 8-H, $J_{8\,10}$ = 2 Hz), 7.9 (1H, d, 11-H, $J_{11\,10}$ = 8.5 Hz), 7.9-8.0 and 8.8-9.0 ppm (4H, 4H, m, 1-, 2-, 3- and 4-H). IR spectrum: 1590 (quinoid fragment); 1770 (C=O); 2205, 2216 cm^{-1} (C≡N). M^+ 353.

5-(Ethoxycarbonylcyanomethylene)-9-acetoxy-5H-benzo[a]phenoxazine (VI). PMR spectrum: 2.5 (3H, s, CH_3), 1.32 (3H, t, CH_3CH_2), 4.3 (2H, q, CH_2CH_3), 7.2 (1H, dd, 10-H, $J_{10\,11}$ = 8.5, $J_{10\,8}$ = 2 Hz), 7.3 (1H, d, 8-H, $J_{8\,10}$ = 2 Hz), 7.8 (1H, d, 11-H, $J_{11\,10}$ = 8.5 Hz), 7.8-8.0 and 8.8-9.0 (4H, m, 1-, 2-, 3-, and 4-H), 8.2 ppm (1H, s, 6-H). IR spectrum: 1593 (quinoid fragment), 1710 (C=O), 1770 (C-O), 2200 cm^{-1} (C≡N).

5-(Aminocarbonylcyanomethylene)-9-acetoxy-5H-benzo[a]phenoxazine (VII). PMR spectrum: 2.3 (3H, s, CH_3), 7.08 (1H, dd, 10-H, $J_{10\,11}$ = 8.5, $J_{10\,8}$ = 2 Hz), 7.12 (1H, d, 8-H, $J_{8\,10}$ = 2 Hz), 7.65 (1H, d, 11-H, $J_{11\,10}$ = 8.5 Hz), 7.7-7.9 and 8.8-9.0 ppm (4H, m, 1-, 2-, 3-, and 4-H). IR spectrum: 1590, 1623 (quinoid fragment); 1650 (C=O; 1770 (C=O); 2186 (C≡N); 3200, 3400 cm^{-1} (broad) (NH_2).

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CONFORMATIONAL MAPS OF MEDIUM-SIZED RINGS

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A graphical method of quantitative conformational analysis of medium-sized rings that unites earlier concepts is proposed. This method was used to obtain conformational maps of 6-8-membered rings that make it possible to unequivocally determine the conformations of real rings and to show all possible pathways of conformational transitions without depiction of the individual conformations. This approach made it possible to ascertain previously unknown conformations and pathways of conformational transitions.

In the investigation of the conformational properties of cyclic molecules one must know, first, the most probable ring conformations and, second, the possible pathways of conformational transitions. Appreciable progress has been made in the description of the conformations of medium-sized rings. At the same time, the reflection of the possible conformational transitions is almost always fraught with certain difficulties.

A general method for the qualitative description of the symmetrical conformations of medium-sized rings was proposed in the sixties by Hendrickson [1, 2]. Within the framework of this approach any symmetrical conformation can be characterized completely by a symbol that contains a horizontal line that represents a symmetry element (an axis or plane) and a set of signs of the intracyclic dihedral angles (+, 0, and −) that surround this line in the sequence that exists in the real ring.

Real molecules are usually distorted to a greater or lesser extent relative to ideal — symmetrical — conformations. For the quantitative description of these distortions in the case of five-membered rings (subsequently indicated as 5-rings) Kilpatrick developed the concept of folding coordinates (FC) 40 years ago [3]. A similar approach was subsequently used also for 6-rings [4, 5], and Cremer and Pople generalized this method for N-rings in 1975 [6]. The introduction of FC makes it possible to decrease the number of parameters necessary for the description of the form of the ring to N − 3.

Despite all of the advantages of FC, this method has not yet been widely used. In most studies the authors, as before, use the signs of the dihedral angles or simply projections of the rings to determine the conformations of medium-sized rings. This often leads to various misunderstandings. In our opinion, one of the reasons for this is the lack of visual descriptiveness when FC are used. As a result of this, the concept of FC is extremely abstract.

In this paper we present conformational maps of medium-sized (N = 6-8) rings that make it possible to solve, in part, the problems mentioned above.

Folding Coordinates

According to Cremer and Pople [6], for any N-ring one can select a plane in such a way that the deviations of the atoms from it (z_j) satisfy the equation (1)

$$z_j = (2/N)^{1/2} \sum_{m=2}^{M} q_m \cos\left[\psi_m + 2\pi m(j-1)/N\right] + \delta_{N,2(M+1)}(-1)^{j-1}N^{-1/2}q_{N/2}, \quad (1)$$

where N = (N − 1)/2 if N is odd or M = (N/2) − 1 if N is even, j = 1, 2, ..., N. q_m are the folding amplitudes, ψ_m are the phase angles that describe the various forms of folding, δ = 1 if N is even, and δ = 0 if N is odd. One can calculate N − 3 folding coordinates using

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