2-CARBETHOXYMETHYL-4H-3,1-BENZOXAZIN-4-ONE. 4.* REACTION WITH ANILINES

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In a solution of DMF, 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one reacts with primarily aromatic amines basically with the formation of the corresponding 2-carbethoxymethyl-3-arylquinazolin-4(3H)-ones. Possible mechanisms of these chemical transformations are reported and discussed.

The reaction of 2-substituted 4H-3,1-benzoxazin-4-ones (acylanthranils) with primary aromatic amines passes through the stage of opening of the benzoxazine ring [2-4]. Either N-acylanthranilic acid anilides or inner amidine salts can form as a function of the substituent in position 2 of this ring and the amine used [3, 4]. Both types of compounds can easily be converted by cyclodehydration into the corresponding 2-R-3-arylquinazolin-4(3H)-ones [2-7], of interest as physiologically active substances with a broad spectrum of action [8-11].

Continuing our research on the chemical properties of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one (I), the present communication concerns the study of its behavior in reactions with primary aromatic amines (II).

It was found that boiling benzoxazinone I with an equimolar amount of the corresponding amine II in dry dimethylformamide medium basically yields 2-carbethoxymethyl-3-arylquinazolin-4(3H)-ones (III), whose properties are reported in Table 1. N-Ethoxymalonylanthranilic acid anilides (IV) were also formed in a small amount, demonstrated by the data from the PMR spectra of the reaction mixture (from 3-5% in the case of amines IIa, d-e to 15% for amine IIb).

It follows from the results obtained that all amines II attack benzoxazinone I preferentially at the carbon atom of the C=N, and not the C=O, group, probably due to the elevated stability of bipolar intermediate compounds V formed in attack by amines II at the imine carbon atom. As shown in [4], decyclization of these intermediates into compounds of type VI with migration of the negative charge from the nitrogen to the oxygen atom is more favorable than decyclization of the bipolar intermediate compounds VII into products of type VIII with migration of the negative charge from the more electronegative oxygen to the nitrogen atom on attack at the carbonyl carbon atom of benzoxazinone I by amines II. Reversal of the direction of the attack is slightly more pronounced only in the case of amine IIb, perhaps due to the steric hindrances created by the *o*-methyl substituent. A proton migrates from one nitrogen atom to another in intermediates VIII, finally with formation of anilides IV. The inner amidine salts VI are easily cyclodehydrated into quinazolones III in the conditions of synthesis.

TABLE 1. Characteristics of 2-Carbethoxymethyl-3-arylquinazolin-4(3H)-ones (IIIa-e)

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm					Yield, %
			H_{arom}, m	CH_2 (2H, S)	COOEt*		R (3H, S, Me)	
					CH_2	CH_3		
IIIa	$C_{18}H_{16}N_2O_3$	156...158	7,09...8,33(9H)	3,61	4,09	1,21	—	80
IIIb	$C_{19}H_{18}N_2O_3$	169...170	7,11...8,16(8H)	3,54	3,97	1,09	2,07	72
IIIc	$C_{19}H_{18}N_2O_3$	178...179	7,06...8,30(8H)	3,60	4,10	1,19	2,43	74
IIId	$C_{18}H_{15}ClN_2O_3$	182...184	7,23...8,20(8H)	3,61	3,98	1,07	—	79
IIIe	$C_{18}H_{15}BrN_2O_3$	190...192	7,26...8,21(8H)	3,63	3,97	1,08	—	78

*SSCC = 7.0 Hz.

*See [1] for Communication [3].

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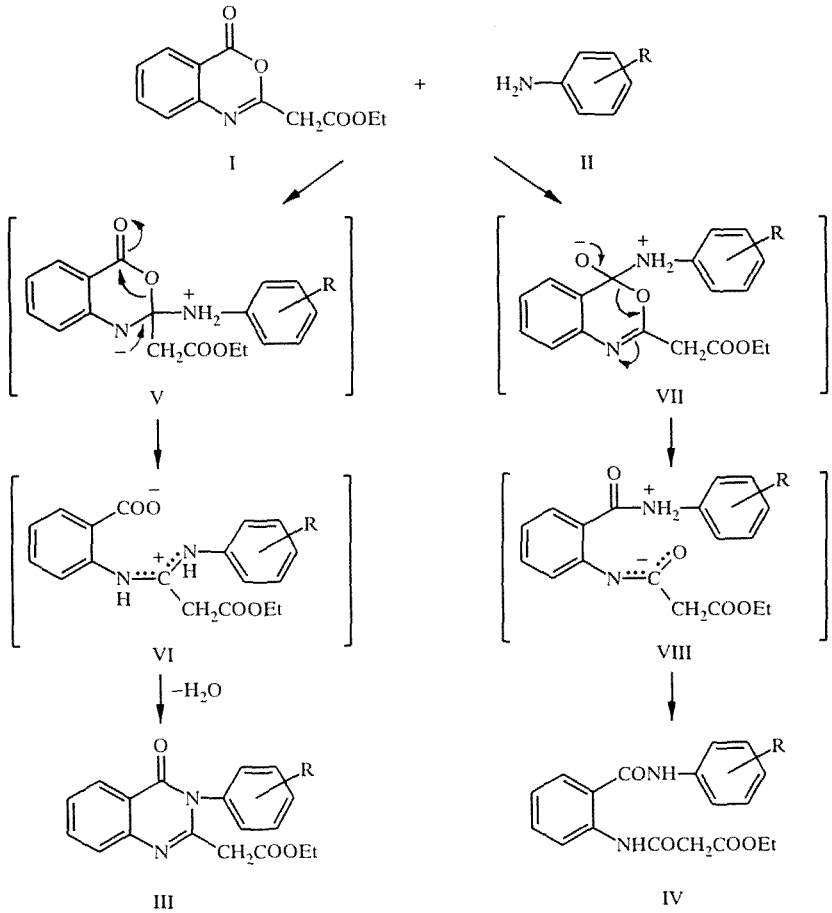
We previously found that acylanthranil I unexpectedly forms 1H-2-oxo-3-(benzimidazolyl-2)-4-hydroxyquinoline with an equimolar amount of *o*-phenylenediamine in conditions of pyrolysis [1]. It is interesting that this reaction takes place in solution by a totally different path. After the reaction of benzoxazinone I with *o*-phenylenediamine in dry diethyl ether, adduct IX is separated at room temperature with a quantitative yield, identified by PMR, IR, and mass spectroscopy as an inner

Scheme 1



II—VIII a R = H; b R = 2-CH_3; c R = 4-CH_3; d R = 4-Cl; e R = 4-Br

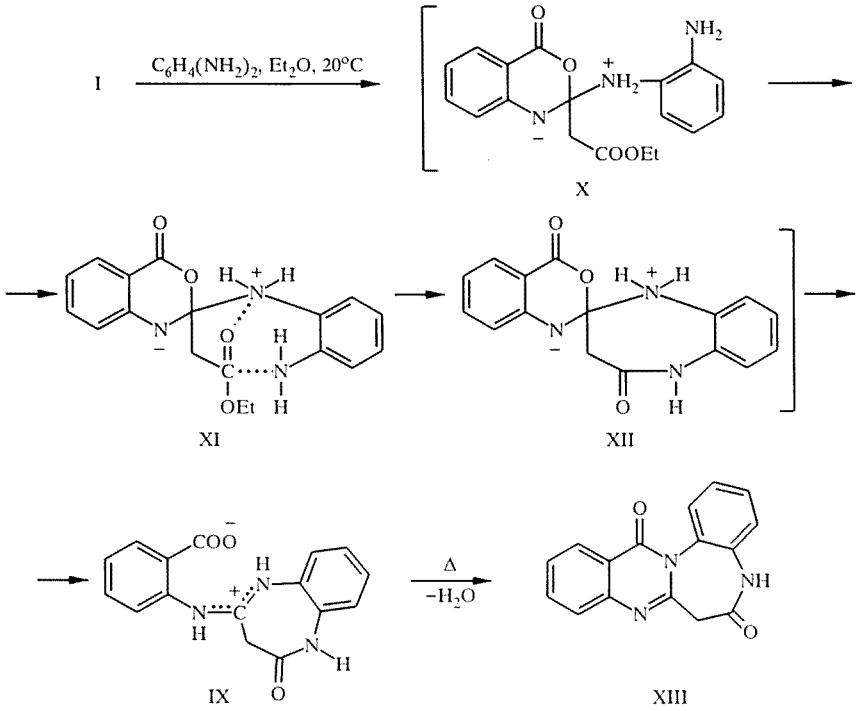
amidine salt. As a consequence, and in the given case, nucleophilic attack takes place at the imine carbon atom. The increase in the reactivity of the ethoxycarbonyl group of intermediate X formed, probably due to the formation of quasi-cyclic transition state XI, is accompanied by intramolecular amidation of the second amino group in *o*-phenylenediamine and yields product XII. Similar to intermediates of V, this bicyclic product is exposed, finally forming inner amidine salt IX, which is relatively stable and can easily be separated from the reaction mixture. On heating above the melting point, this salt is cyclized into 2-oxo-3H-1,5-benzodiazepino[4,5-*b*]quinazolin-9(1H)-one with a high yield.

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY (10 MHz), with DMSO-D_6 solvent and TMS as internal standard. The IR spectrum of salt IX was made on a Specord M-80 and the mass spectrum of this compound was recorded on a Finnigan MAT-461 B mass spectrometer with an ionization energy of 70 eV in ballistic heating of the sample.

The data from elemental analysis of synthesized compounds IIIa-e and XIII for C, H, and N corresponded to the calculated data.

Scheme 2



Overall Method of Preparation of 2-carbethoxymethyl-3-arylquinazolin-4(3H)-ones (III). A solution of 2.33 g (0.01 mole) of benzoxazinone I and 0.01 mole of the corresponding aniline II in 5 ml of dry DMF was boiled with a reflux condenser for 5 h. The solvent was vacuum distilled and the residue was carefully pulverized with 15 ml of diethyl ether. The sediment of product III was filtered off and recrystallized from dioxane.

2-(2′-Carboxyphenylamino)-3,4,5-trihydro-1,5-benzdiazepin-4(1H)-one (IX, $C_{16}H_{13}N_3O_3$). A solution of 1.08 g (0.01 mole) of *o*-phenylenediamine in 10 ml of dry diethyl ether was added to a solution of 2.33 g (0.01 mole) of benzoxazinone I in 15 ml of dry diethyl ether and stirred for 30 min at room temperature. The separated sediment of salt IX was filtered off, washed with diethyl ether, and dried. Yield of 2.95 g (quant.). After recrystallization from DMF, light yellow crystals were obtained, mp = 223-224°C. PMR spectrum: 10.41 (1H, s, CONH); 8.86 (1H, d, J = 8.0 Hz, 3′-H); 8.02 (1H, d.d, J = 8.0 and 2.0 Hz, 6′-H); 7.60 (1H, t.d, J = 8.0 and 2.0 Hz, 5′-H); 7.27-7.02 (5H, m, H_{arom}); 3.89 (2H, br. s, NH × 2); 3.15 (2H, s, CH_2). IR spectrum (ν, cm^{-1}, KBr): 3025, 1680, 1565, 1520, 1435, 1400, 1220, 730. Mass spectrum, *m/z*: 295 (M^+), 277 (M^+-H_2O, basic peak).

2-Oxo-3H-1,5-benzodiazepino[4,5-*b*]quinazolin-9(1H)-one (XIII, $C_{16}H_{11}N_3O_2$). Here 2.95 g (0.01 mole) of salt IX was held in a metallic bath at 250°C for 30 min. It was cooled to room temperature and the residue was pulverized with 10 ml of ethanol. The sediment of quinazolone XIII was filtered off and dried. Yield of 2.43 g (88%). After recrystallization from DMF, colorless crystals were obtained, mp = 266°C (sublim.). PMR spectrum: 10.49 (1H, s, NH); 8.17 (1H, d.d, J = 8.2 and 1.5 Hz, 8-H); 7.91 (1H, t. d, J = 7.5 and 2.0 Hz, 6-H); 7.77-7.21 (6H, m, H_{arom}); 3.82 (2H, s, CH_2).

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