2-CARBETHOXY-4H-3,1-BENZOXAZIN-4-ONE.
1. SYNTHESIS AND REACTION MECHANISM OF FORMATION

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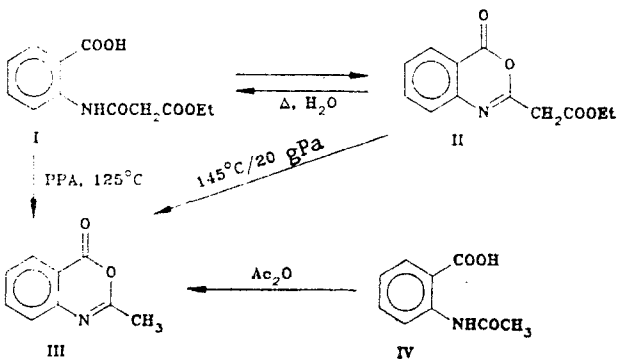
The possibility was examined of using various condensing agents in the intramolecular cyclization reaction of ethyl ester of 2-carbomalonanilic acid into 2-carboethoxymethyl-4H-3,1-benzoxazin-4-one. It was found that the optimal reagent is dicyclohexylcarbodiimide. By using NMR spectroscopy and deutero-exchange it was shown that the cyclization proceeds with the participation of the hydroxyl group of the carboxyl and a proton of the amide function.

In recent years extensive investigations have been carried out in the field of quinazolone compounds in order to obtain highly effective drugs. In this category, 2,3-disubstituted derivatives of 4-quinazolone are of great interest, since compounds among them have been discovered with soporific [1, 2], antispasmodic [3-5], fungicidal [6], antimicrobial [4, 7], hypotensive [8], and other types of activity.

The main method for the preparation of compounds of this series is heating 2-substituted benzoxazin-4-ones (acylanthranils) with amines [9].

We endeavored to develop a method for the preparation of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one (II), which may possibly find wide application in the biosynthesis of biologically active compounds. It is known that 2-substituted 4H-3,1-benzoxazin-4-ones are obtained by an intramolecular cyclization of N-acylanthranilic acids. Thus, thionyl chloride [10], acetic anhydride [11], or acetic anhydride in admixture with anhydrous sodium acetate [12], polyphosphoric acid (PPA) [13], acid chlorides of aromatic carboxylic acids [14], triphenyl phosphite in a pyridine medium [15] may be used as condensing agents. Moreover, acylanthranils can be obtained by thermal cyclodehydration of N-acylanthranilic acids [16], and also by heating mixed anhydrides of acetic and N-acylanthranilic acids [17]. However, on heating the ethyl ester of 2-carboxymalonanilic acid I in PPA the expected acylanthranil II is not formed. It can be assumed that under these conditions the ester group decomposes, with subsequent decarboxylation and cyclization of the N-acylanthranilic acid IV formed into acetylanthranil III, the structure of which was proved by a countersynthesis, carried out by a known method [9].



I II III IV

The use of triphenyl phosphite as the condensing agent involves prolonged heating in an inert gas current and distillation of the reaction mixture at reduced pressure in order to separate the desired end product. Moreover, attempts to purify the acylanthranil II at reduced pressure did not produce a positive result because this compound decomposes fairly readily with the formation of acetylanthranil III.

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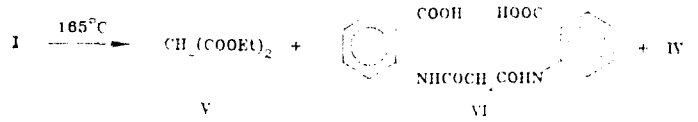
TABLE 1. Physicochemical Characteristics of Compounds I, II, VI

Compound	Mp, °C	R_f**	IR spectrum, cm^{-1}	PMR spectrum, σ, ppm (DMSO-D_6)	Yield, % (method)
I	104...106	0,63	1611 ($\nu_{C=C}$), 1678, 1693, 1754 ($\nu_{C=O}$), 2500...2650 (ν_{COOH})	1,21 (3H, t, CH_3); 3,59 (2H, s, $COCH_2CO$); 4,14 (2H, q, CH_2CH_3); 8,4...7,2 (4H, m, H_{arom}); 11,24 (1H, s, NH); 13,64 (1H, s, COOH)	92
II	62...64	0,54	1014 (ν^{s}_{C-O-C}), 1227 (ν^{as}_{C-O-C}), 1613 ($\nu_{C=C}$), 1651 ($\nu_{C=N}$), 1733, 1757 ($\nu_{C=O}$)	1,22 (3H, t, CH_3); 3,60 (2H, c, CH_2COOEt); 4,16 (2H, q, CH_2CH_3); 8,4...7,2 (4H, m, H_{arom})	94 (A), 56 (B), 71 (C), 73 (D), 64 (E)
VI	240 244 (d.)	—	1670 ($\nu_{C=O}$), 2400...2660 (ν_{COOH})	3,69 (2H, s, $COCH_2CO$); 8,5... 7,2 (8H, m, H_{arom}); 11,33 (2H, s, 2NH)	20

*Compound I was recrystallized from toluene, VI from dioxane.
**Eluent: hexane—isopropanol, 8:3.

The thermal cyclodehydration and also heating of the mixed anhydrides of acetic and N-acylanthranilic acid cannot be used for the synthesis of acylanthranil II because of the high thermolability of the malonic acid derivatives. Thus, as a result of heating ester I at a temperature of 165°C, a mixture of products is formed from which diethyl malonate (V), di-2-carboxyaniline of malonic acid (VI) and N-acetylanthranilic acid (IV) can be isolated and identified by chromatography.



V VI

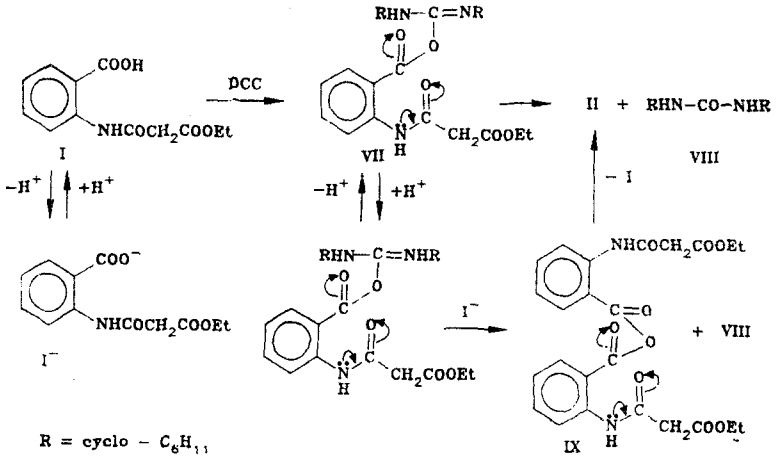
The ring closure by means of thionyl chloride, benzoyl chloride, and also acetic anhydride or acetic anhydride in admixture with anhydrous sodium acetate is fully acceptable from the point of view of yields of the end product II. Nevertheless, these condensing agents are, as known, used for the qualitative detection of malonic acid derivatives [18], which leads to heavy contamination of acylanthranil II obtained by the side reaction products.

In this connection, the condensation of ester I in the presence of dicyclohexylcarbodiimide (DCHC), which was not previously used for the preparation of benzoxazin-4-ones, is of interest.

It was found that in a medium of a dry diethyl ether in the presence of DCHC, the ethyl ester I readily condenses into benzoxazin-4-one II in a high yield (see Table 1).

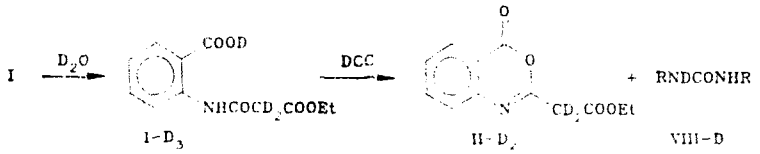
Considering the presence in the structure of the starting ester I of three groupings (carboxylic carbimide and the active methylene group) which may participate in the cyclodehydration, it was of interest to study the mechanism of this reaction.

According to [19], the reaction of ethyl ester of 2-carboxymalonanilic acid I with DCHC will lead first to the formation of O-acylisourea VII, and then either an intramolecular substitution of the isourea residue by the carbonyl oxygen of the neighboring amide function may occur, which leads to the desired acylanthranil II, or the formation may take place of the symmetric anhydride IX with the subsequent splitting off of a molecule of the starting ester I and closure of the benzoxazine ring [14].



However, it is known that the 2-carboxyphenylamide group has a pronounced enolizing effect [20]. The thus-formed enol form of ester I can also enter into the reaction with DCHC with the participation of the methylene group proton, forming the acylanthranil II.

The exact reaction mechanism could be established by means of deutero exchange from the NMR spectroscopy data. The results of the investigation have shown that protons of the carboxylic and the active methylene group enter into the deutero exchange.



After the reaction of the deutero-substituted ester I-D_3 with DCHC, 2-carboxymethyl-4H-3,1-benzoxazin-4-one completely deuterated at the methylene group (II-D_2) and the monodeutero-substituted urea (VIII-D) were isolated, which indicates the realization of a mechanism involving a direct intramolecular substitution in the O-acylisourea VII, since the cyclodehydration with the participation of anhydride IX would lead to a dideutero-substituted urea VIII, while a preliminary enolization of acid I — to monodeutero-substituted acylanthranil II. It can be assumed that in the formation of 2-substituted benzoxazin-4-ones via reactions of N-acylanthranilic acids with dicyclohexyldiimide, the established mechanism is obviously general in character.

EXPERIMENTAL

The IR spectra of the synthesized compounds were run on a Specord IR-75 spectrophotometer in KBr tablets, the concentration of the compound was 1%. The PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) spectrometer, using TMS as internal standard. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates.

The elemental analysis data correspond to the calculated values.

Ethyl Ester of 2-Carboxymalonanilic Acid (I, $C_{12}H_{13}NO_5$). A solution of 16.6 g (0.11 mole) of ethoxymalonyl chloride in 20 ml of acetone was added with cooling and stirring to a solution of 13.7 g (0.1 mole) of anthranilic acid and 8.9 ml (0.11 mole) of pyridine in 50 ml of acetone, and the mixture was allowed to stand overnight. Then 200 ml of water was added, and the mixture was acidified with HCl to pH 4. The precipitate was filtered off, washed with water, and dried. Yield 23.1 g.

Deutero-substituted ethyl ester of 2-carboxymalonanilic acid (I-D_3) was obtained by double recrystallization of I from D_2O. PMR spectrum ($CDCl_3$): 1.32 (3H, t, CH_3), 8.7-7.2 (4H, m, H_{arom}), 4.27 (2H, q, CH_2CH_3), 11.38 ppm (1H, s, NH).

2-Carbethoxymethyl-4H-3,1-benzoxazin-4-one (II, $C_{12}H_{11}NO_4$). A. A solution of 10.3 g (0.05 mole) of DCHC in 50 ml of ether was added with stirring and cooling to a solution of 12.6 g (0.05 mole) of anilide I in 100 ml of anhydrous diethyl ether, and the mixture was allowed to stand overnight at room temperature. The precipitate (dicyclohexylurea) was filtered off and washed with ether. The filtrate was evaporated to a volume of 30 ml, and after adding 100 ml of hexane, was cooled. The precipitate that separated out was filtered off and dried. Yield 10.9 g.

B. A solution of 3.6 ml (0.05 mole) of $SOCl_2$ in 20 ml of ether was added with cooling to a solution of 12.6 g (0.05 mole) of anilide I and 14 ml (0.05 mole) of triethylamine in 50 ml of anhydrous diethyl ether, and the mixture was allowed to stand overnight. The ether was distilled off, and 100 ml of ice water was added to the residue. The precipitate was filtered off. Yield 6.51 g.

C. A solution of 12.6 g (0.05 mole) of anilide I in 80 ml of Ac_2O was boiled for 1 h. The excess of Ac_2O was distilled off at reduced pressure, and 100 ml of ether was added. The reaction mixture was shaken with carbon and filtered. The filtrate was treated according to method **A**. Yield 8.2 g.

D. A mixture of 12.6 g (0.05 mole) of anilide I, 100 ml of Ac_2O, and 10.0 g of anhydrous sodium acetate was boiled under a reflux condenser for 1 h 30 min. The reaction mixture was treated according to method **C**. Yield 8.4 g.

E. A 7.03 g portion (0.05 mole) of benzoyl chloride was added with cooling to a solution of 12.6 g (0.05 mole) of anilide I in 50 ml of pyridine. The mixture was stirred for 30 min at room temperature and poured into 300 ml of glacial acetic acid. The precipitate was filtered off and dried. Yield 7.41 g.

The identity of the products obtained was established according to the melting point of mixed samples.

Deutero-Substituted 2-Carboxymethyl-4H-3,1-benzoxazin-4-one (II-D_2). A solution of 2.06 g (0.01 mole) of DCHC in 20 ml of dry CCl_4 was added to a solution of 2.51 g (0.01 mole) of ester I-D_3 in 20 ml of dry CCl_4. The mixture was allowed to stand overnight at room temperature. The precipitate (a monodeuterated dicyclohexylurea VIII-D) was filtered off and washed with dry CCl_4. PMR spectrum ($CDCl_3$): 2.0-0.8 (20H, m, $10CH_2$), 3.48 (2H, m, 2CH); 4.06 ppm (1H, d, NH).

The filtrate was evaporated to a 5-ml volume and chromatographed on a column (adsorbent — silica gel L100/250) in a hexane—CCl_4 (2:1) system of solvents Benzooxazin-4-one II-D_2 was obtained. PMR spectrum ($CDCl_3$): 1.30 (3H, t, CH_3), 4.25 (2H, q, CH_2CH_3), 8.2-7.6 ppm (4H, m, H_{arom}).

2-Methyl-4H-3,1-benzoxazin-4-one (III, $C_9H_7NO_2$). A. A 12.6 g portion (0.05 mole) of anilide I was heated in 35 g of PPa for 1 h. The reaction mixture was cooled and poured onto ice. The precipitate was filtered off, washed with ice water, and dried. Mp 81-82°C (heptane). Yield 7.2 g (89%).

B. A 12.6 g portion (0.05 mole) of anilide I in 80 ml of Ac_2O was boiled for 1 h. The excess Ac_2O was distilled off and the residue was distilled under reduced pressure. Bp 145°C (20 gPa), mp 81-82°C (heptane). Yield 4.1 g (51%). A mixed sample with acetylanthranil obtained according to [9] does not give a depression of the melting point.

Pyrolysis of Ethyl Ester of 2-Carboxymalonanilic Acid (I). A 2.51 g portion (0.01 mole) of anilide I was heated at 165°C for 1 h. It was then cooled, and 20 ml of anhydrous diethyl ether was added; the precipitate was filtered off, washed with ether, and dried. Yield 0.69 g of diamide VI. A mixed sample with a compound obtained according to [21] does not give a depression of the melting point.

The filtrate was evaporated to 5 ml and was partitioned on a chromatographic column (adsorbent — silica gel L100/250) in a hexane—chloroform—acetone (10:5:3) system of solvents to yield 0.31 g of malonic ester V and 0.16 g of N-acetylanthranilic acid IV.

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2-CARBETHOXY-4H-3,1-BENZOXAZIN-4-ONE. 2.* HYDRAZINOLYSIS

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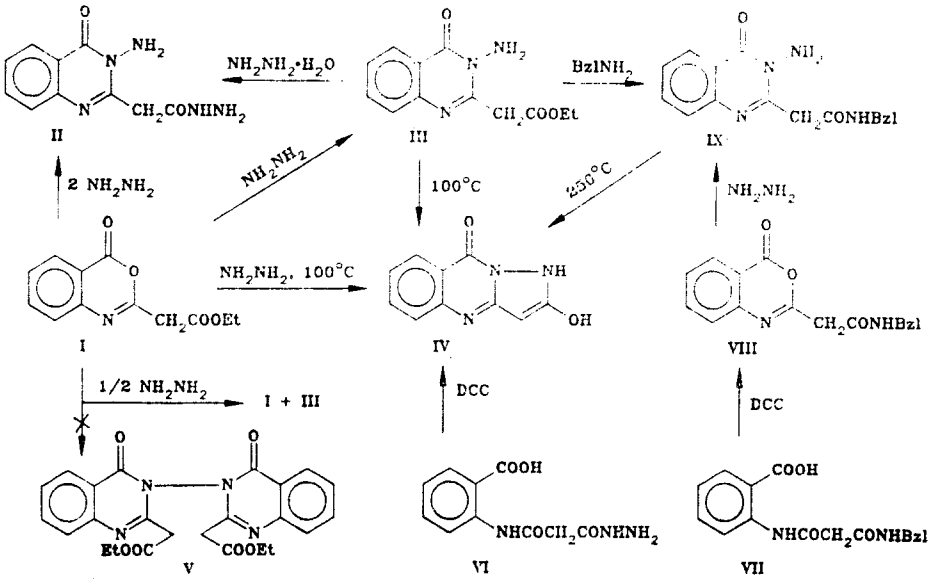
3-Amino-2-carboxymethylquinazolin-4(3H)-one was obtained by hydrazinolysis of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one. Its transformations into 2-hydroxypyrazolo[5,1-b]quinazolin-9(1H)-one and 3-amino-2-hydrazido-(orbenzylamido)carbonylmethylquinazoline-4(3H)-ones were studied.

The present investigation is addressed to the clarification of the reaction of 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one (I) [1] with hydrazine. With diethyl malonate the anthranilic acid hydrazide forms 2-hydroxypyrazolo[5,1-b]quinazolin-9(1H)-one (IV) [2], which is used in color photography, and 3-amino-2-carbethoxymethylquinazolin-4(3H)-one (III). 3-Aminoquinazolones, which comprise compounds with high antispasmodic [4, 5], hypoglycemic [6], and sedative [7] activity can also be obtained by the reaction of 2-substituted 4H-3,1-benzoxazin-4-ones (acylanthranils) with hydrazine [7].



Acylanthranil I reacts readily with hydrazine in an equimolar ratio in methanol at room temperature. As a result, 3-aminoquinazolinone III was obtained in 91% yield [8]. Increase in the temperature to 100°C is accompanied

*For Communication 1, see [1].

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