4-HYDROXY-2-QUINOLONES. 16.* CONDENSATION OF N-R-SUBSTITUTED AMIDES OF 2-CARBOXY-MALONANILIC ACID WITH o-PHENYLENEDIAMINE

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The reaction of N-R-substituted amides of 2-carboxymalonanilic acid with the equimolar amount of o-phenylenediamine was studied under conditions of thermolysis. It was established that the main products of this reaction are the corresponding amides of benzimidazolyl-2-acetic acid and 1H-2-oxo-3-(benzimidazolyl-2)-4-hydroxyquinoline. Mechanisms of the indicated chemical conversions are discussed. The data on the study of the anticonvulsive activity of the compounds synthesized are presented.

It is known that the simplest method for the synthesis of benzimidazoles is the fusion of the corresponding carboxylic acids with o-phenylenediamines [2]. There is repeated mention in the literature of the ambiguous behavior of derivatives of anthranilic acid [3, 4] and malonic acid [2, 5] in such reactions; this is probably associated with the ease of formation of different cyclic structures from them.

Starting from this, it seemed interesting to investigate the character of the reaction of N-R-substituted amides of 2-carboxymalonanilic acid (Ia-j) with o-phenylenediamine (II) under conditions of thermolysis.

It was shown by the experiments performed (Table 1) that the main products of this reaction are amides of benzimidazolyl-2-acetic acid (IIIa, b, d-j) and 1H-2-oxo-3-(benzimidazolyl-2)-4-hydroxyquinoline (IV). In some cases, methylene-bis-2,2′-benzimidazole (V) was isolated.

The isolation of these compounds leads one to believe that the reaction of o-phenylenediamine and the amides (I) can occur by two paths the first of which (the path A) involves the initial formation of the corresponding amides of 4-oxo-3,1-benzoxazin-2-ylacetic acid (VI) which react further with o-phenylenediamine with the formation of the amides (III) (the properties of the last are presented in Table 2). The proposed mechanism for such a type of conversion was presented in the work [3].

The second path (the path B) involves the nucleophilic attack of the amides (I) by o-phenylenediamine at the carbonyl carbon atom of the alkylamide fragment leading to the dianilide (VII), which is converted via the compound (VIII) into the hydroxyquinolone (IV) (we previously presented the mechanism in the work [5]).

The structure of the amides (III) is confirmed by direct synthesis of the compound (IIIa) from the nitrile (IX).

Methylene-bis-2,2′-benzimidazole (V) was only isolated in the case of the methyl-, ethyl-, and hydroxyethylamides (Ia-c). Therefore, it seems most probable that it is formed as the result of the transamidation of the corresponding amides of benzimidazolyl-2-acetic acid (IIIa-c), i.e., it is one of the products of the reaction proceeding by the path A. In the contrary case (the path B), this compound could be found in all the experiments in which the hydroxyquinolone (IV) is formed.

The marked anticonvulsive activity of numerous derivatives of benzimidazole [2, 6] served as the theoretical reason for conducting pharmacological investigations of the substances which we synthesized. It was thereby established that neither the amides (III) nor the hydroxyquinolone (IV) exert noticeable influence on the course of the convulsive reaction induced by Corazol, whereas the anticonvulsive activity of methylene-bis-2,2′-benzimidazole (V) is not inferior to that of Chloracon [7].

*For Communication 15, see [1].

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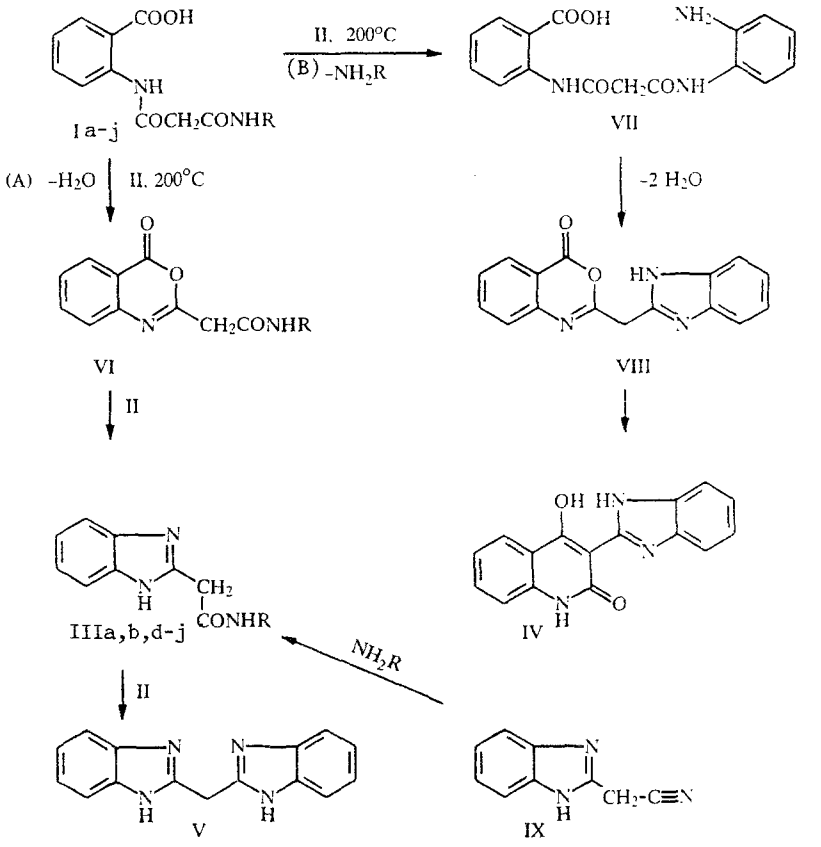
TABLE 1. Products of the Condensation of N-R-Substituted Amides of 2-Carboxymalonanilic Acid (Ia-j) with o-Phenylenediamine

Initial amide	R	Yields of reaction products, %			Initial amide	R	Yields of reaction products, %		
		III	IV	V			III	IV	V
Ia	CH_3	46	12	14	If	C_5H_{11}-*i*	73	11	0
Ib	C_2H_5	57	3	16	Ig	C_6H_{13}	76	7	0
Ic	$(CH_2)_2$-OH	0	18	33	Ih	C_7H_{15}	82	3	0
Id	C_3H_7-*i*	90	4	0	Ii	CH_2Ph	93	0	0
Ie	C_4H_9	35	58	0	Ij	(±)-$CH(CH_3)Ph$	85	0	0



EXPERIMENTAL

The IR spectra of the compounds synthesized were taken on the Specord M-80 instrument using tablets of KBr with the concentration of 1%. The PMR spectra were recorded on the Bruker WP-100 SY instrument (100 MHz) using DMSO-D_6 and TMS as the internal standard.

The data of the elemental analysis (C, H, and N) for the compounds (IIIa, b, d-j) correspond with the calculated data.

The N-R-substituted amides of 2-carboxymalonanilic acid (Ia-j) were obtained using the method which we developed previously [8]. The study of the anticonvulsive activity of the compounds synthesized was performed according to the method of the work [9].

General Method for the Isolation of N-R-Substituted Amides of Benzimidazolyl-2-acetic Acid (III). The mixture of 0.01 mole of the corresponding amide (I) and 1.08 g (0.01 mole) of o-phenylenediamine is maintained on a metallic bath at 200°C for 1 h. The mixture is cooled prior to the addition of 20 ml of water, the acidification with HCl to the pH 5, and the

TABLE 2. Characteristics of the N-R-Substituted Amides of Benzimidazolyl-2-acetic Acid

Compound	Empirical formula	mp, °C (ethanol)	IR spectra, cm^{-1} C=N, C=O	PMR spectra, δ, ppm*			
				NH (1H, s)	CH_2CO (2H, s)	CONH (1H)	R
IIIa	$C_{10}H_{11}N_3O$	195...200	1660, 1640	12,24	3,73	8,22q	2,63 (3H, d, CH_3)
IIIb	$C_{11}H_{13}N_3O$	234...236	1662, 1635	12,25	3,71	8,23 t	3,13 (2H, q, CH_2CH_3); 1,04 (3H, t, CH_3)
IIId	$C_{12}H_{15}N_3O$	244...245	1657, 1625	12,21	3,70	8,16 d	3,82 (1H, m, NHCH); 1,07 (6H, d. CH_3)
IIIe	$C_{13}H_{17}N_3O$	212...214	1665, 1645	12,24	3,72	8,23 t	3,09 (2H, q, $NHCH_2$); 1,37 (4H, m, $CH_2(CH_2)_2$); 0,87 (3H, t, CH_3)
IIIf	$C_{14}H_{19}N_3O$	168...170	1667, 1630	12,25	3,74	8,20 t	3,12 (2H, q, $NHCH_2$); 1,58 (1H, m, $CH(CH_3)_2$); 1,32 (2H, q, $NHCH_2CH_2$); 0,86 (6H, d, CH_3)
IIIg	$C_{15}H_{21}N_3O$	186...188	1659, 1630	12,26	3,73	8,26 t	3,07 (2H, q, $NHCH_2$); 1,24 (8H, s, $CH_2(CH_2)_4$); 0,85 (3H, t, CH_3)
IIIh	$C_{16}H_{23}N_3O$	180...182	1667, 1630	12,26	3,71	8,23 t	3,08 (2H, q, $NHCH_2$); 1,22 (10H, s, $CH_2(CH_2)_5$); 0,84 (3H, t, CH_3)
IIIi	$C_{16}H_{15}N_3O$	208...210	1660, 1628	12,28	3,82	8,75 t	7,30 (5H, s, Ph); 4,32 (2H, d, CH_2-Ph)
IIIj	$C_{17}H_{17}N_3O$	204...206	1663, 1631	12,25	3,80	8,76 d	7,32 (5H, m, Ph); 4,95 (1H, q, NHCH); 1,38 (3H, d, CH_3)

*The signals of the aromatic protons of benzimidazole have the form of two characteristic multiplets of the AA'BB' spin system at 7.48-7.50 ppm (2H) and 7.11-7.13 ppm (2H).

careful stirring and filtration. Methylene-bis-2,2'-benzimidazole (V) is isolated from the filtrate after neutralization with the solution of NaOH. The residue on the filter [the mixture of the amide (III) and the hydroxyquinolone (IV)] is treated with hot ethyl alcohol and is filtered. The filtrate is cooled in an ice bath, and the separated residue of the corresponding amide (III) is filtered off and dried. The hydroxyquinolone (IV), which was insoluble in the alcohol, is recrystallized from DMF. The known methylene-bis-2,2'-benzimidazole (V) and the hydroxyquinolone (IV) were identified from the melting temperature of mixed samples including known samples, as well as by the data of the IR and PMR spectra [5].

Benzimidazolyl-2-acetic Methylamide (IIIa) ($C_{10}H_{11}N_3O$). The mixture of 1.57 g (0.01 mole) of 2-cyanomethylbenzimidazole (IX) [2] and 10 ml of the 20% aqueous solution of methylamine is maintained in an autoclave at 100°C for 4 h. The mixture is cooled, and the excess of the methylamine is distilled off in vacuo; the residue is acidified with HCl to pH 7. The separated residue of (IVa) is filtered off, washed with cold water, and dried. The yield is 1.13 g (60%).

The mixed test with the sample obtained by the condensation of o-phenylenediamine with 2-carboxymalonanilic methylamide (Ia) does not give a depression of the melting temperature.

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