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2-CARBETHOXYMETHYL-4H-3,1-BENZOXAZIN-4-ONE 6.* SYNTHESIS OF SOME NEW 3-ACYLAMINO-4-OXAQUINAZOLIN-2-YL-ACETIC ACID BENZYL-AMIDES AS POSSIBLE ANTICONVULSANTS

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Alternative ways of synthesizing 3-amino-4-oxoquinazolin-2-yl-acetic and propionic acid benzylamides and their acyl derivatives were investigated. The conditions of conversion of the synthesized 2-substituted 3-aminoquinazolin-4-ones into the corresponding 2-hydroxypyrazolo-3-R-[5,1-b]quinazolin-9(1H)-ones were determined. The findings of a study of the anticonvulsant properties of the synthesized compounds are reported.

A significant number of potential anticonvulsant drugs have now been found in almost all classes of organic compounds, both synthetic [2, 3] and isolated from plants [4]. However, the attempt to create an "ideal" anticonvulsant which satisfies such requirements as low toxicity, lack of pronounced side effects, and others [5] is an effective stimulus for most chemists and pharmacologists to conduct further studies in this area.

The published papers on creation of highly effective anticonvulsants based on 3-aminoquinazolin-4-one derivatives [6-9] were of interest to us with respect to the study of 2-carbethoxymethyl-3-aminoquinazolin-4(3H)one, which we described previously [10, 11].

As a result of generalizing the studies in [12-14] and analyzing the published data [2-4], we concluded that for substances to exhibit anticonvulsant properties, they must have a C_6H_5—CH(R)—NHCOCH— group of atoms in their structure. For this reason, we investigated 3-amino-4-oxoquinazolin-2-yl-carboxylic acid benzyl amides I and their N-acyl derivatives II.

The starting 3-amino-4-oxoquinazolin-2-yl-carboxylic acid benzylamides I can be synthesized by amidation of previously synthesized ethyl esters III (A) or hydrazinolysis of benzoxazinones IV, prepared by treatment of 2-carboxymalonanilic acid benzylamides V with N,N′-dicyclohexylcarbodiimide (B). The experimental data show that Method B can be used to synthesize 3-aminoquinazolinones I with higher yields (on conversion to the initial anthranilic acid) and for this reason it can be recommended as a preparative method. A significant drawback of Method A is the necessity of rigorously respecting the equimolar ratios of reagents in the VI → III stage (due to possible hydrazinolysis of the ethoxycarbonyl group) and consequently the necessity of separation of benzoxazinones VI. In addition, careful monitoring of the temperature is necessary in the amidation stage (III → I), since esters III are cyclized into pyrazoles VII at 80°C [11, 15]. Benzylamides I are cyclized into the corresponding 2-hydroxypyrazolo-3R-[5,1-*b*]quinazolin-9(1H)-ones (VII) with separation of benzylamine in much more rigorous conditions (heating to 250°C), while hydrazinolysis of benzoxazinones IV can be conducted without their preliminary separation from the reaction mixture.

It should be noted that intramolecular cyclodehydration of amides V by N,N′-dicyclohexylcarbodiimide probably takes place according to a mechanism similar to the one for 2-carboxymalonanilic acid ethyl ester VIIIa, i.e., with the participation of the carboxyl hydroxyl group and proton of the arylamide function [16].

*See [1] for Communication 5.

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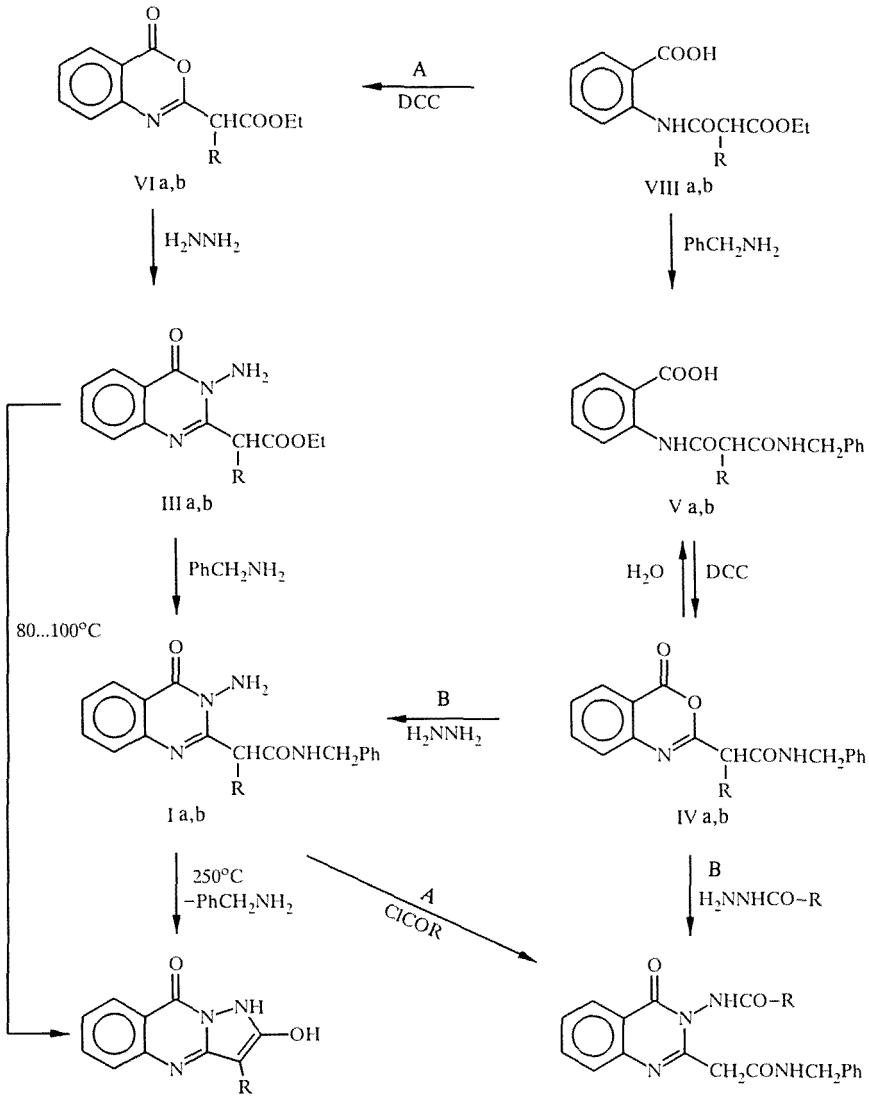
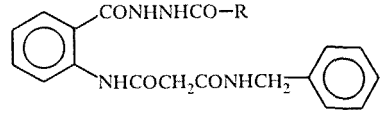
Scheme



I, III—VIII a R = H; b R = Me; II a R = Me, b R = Ph, c R = CH_2Ph, d R = *p*-MeC_6H_4, e R = *m*-$CH_3C_6H_4$, f R = *o*-FC_6H_4, g R = *m*-ClC_6H_4, h R = *o*-ClC_6H_4, i R = *o*-BrC_6H_4; j R = *p*-$NO_2C_6H_4$, k R = *m*-$NO_2C_6H_4$, ℓ R = 2,4-$(Cl_2)C_6H_3$

3-Acylamino-4-oxoquinazolin-2-yl-acetic acid benzylamides IIa-ℓ can also be obtained from benzoxazinones IV by acylation of intermediate 3-amino derivatives I (A, linear synthetic scheme) or direct reaction with the hydrazides of the corresponding acids (B, convergent synthesis scheme). Despite the undoubted advantages of convergent schemes of synthesis in most cases [17], the last method implies the use of extremely dry and also high-boiling solvents. Such requirements are on one hand due to the decrease in the nucleophilic properties of acylhydrazines in comparison to hydrazine; for this reason, the presence of water in the reaction mixture would enable hydrolysis of benzoxazinones IV. On the other hand, a high temperature is necessary to prevent formation of acyclic derivatives with the general formula:



In consideration of the above, preference should be given to the linear scheme, i.e., Method A, which allows synthesizing 3-acylamino-4-oxoquinazolin-2-yl-acetic acid benzylamides II with higher yields and lower costs. In addition, the strategic rule generally adopted in organic synthesis which requires assigning the most questionable and hazardous stages to

TABLE 1. Characteristics of 3-Acylamino-4-oxoquinazolin-2-yl-acetic Acid Benzylamides

Compound	Empirical formula	mp, °C (dioxane)	IR spectra $\nu_{C=O}$, cm^{-1}	PMR spectra (δ, ppm)*					Yield, %
				N—NH 1H, s	^{H} arom m	$\underline{H}CHCO$*2 1H, d	$HC\underline{H}CO$*2 1H, d	signals of protons of other functional groups	
IIa	$C_{19}H_{18}N_4O_3$	200...202	1680, 1672, 1656	11,12	8,20...7,25 (9H)	3,71	3,53	2,07 (3H, s, CH_3)	94
IIb	$C_{24}H_{20}N_4O_3$	208...210	1660, 1640, 1632	11,75	8,24...7,28 (14H)	3,80	3,64	–	97
IIc	$C_{25}H_{22}N_4O_3$	180...182	1675, 1648, 1630	11,40	8,20...7,22 (14H)	3,85	3,66	3,60 (2H, s, $COCH_2Ph$)	91
IId	$C_{25}H_{22}N_4O_3$	162...164	1689, 1657, 1641	11,65	8,27...7,24 (13H)	3,82	3,67	2,42 (3H, s, CH_3)	96
IIe	$C_{25}H_{22}N_4O_3$	232...234	1636, 1652, 1640	11,64	8,23...7,27 (13H)	3,86	3,63	2,41 (3H, s, CH_3)	97
IIf	$C_{24}H_{19}N_4O_3$	192...194	1692, 1664, 1644	11,60	8,25...7,24 (13H)	3,89	3,71	–	98
IIg	$C_{24}H_{19}N_4O_3$	244...246	1693, 1667, 1643	11,90	8,23...7,28 (13H)	3,90	3,68	–	89
IIh	$C_{24}H_{19}N_4O_3$	218...220	1696, 1680, 1652	11,81	8,28...7,20 (13H)	4,00	3,74	–	96
IIi	$C_{24}H_{19}N_4O_3$	216...218	1693, 1665, 1640	11,80	8,29...7,22 (13H)	4,02	3,75	–	86
IIj	$C_{24}H_{19}N_5O_5$	248...250	1698, 1664, 1638	12,11	8,45...7,24 (13H)	3,93	3,71	–	84
IIk	$C_{24}H_{19}N_5O_5$	220...222	1680, 1662, 1628	12,16	8,87...7,23 (13H)	3,91	3,78	–	81
IIl	$C_{19}H_{18}N_4O_3$	206...208	1687, 1660, 1633	11,87	8,50...7,30 (12H)	3,84	3,66	–	87

*8.64-8.89 (1H, t, J = 5.8 Hz, NH); 4.32-4.50 (2H, d, J = 5.8 Hz, CH_2).

*2J = 15.0 Hz.

the beginning of the synthesis scheme should not be neglected in this case [17]. In other words, the possible ambiguous behavior of benzoxazinones IV in the concluding stage of Method B again confirms the advantage of Method A.

In studying the anticonvulsant properties of amides IIa-*l* [13], an important anticonvulsant effect was observed in *o*-halogen-substituted derivatives IIh, i, which are not inferior to Chloracon in activity [18]. 3-(4-nitrobenzoylamino)-4-oxoquinazolin-2-yl-acetic acid benzylamide (IIj) has the most pronounced anticonvulsant action, greater than phenobarbital. The experimental data from pharmacological studies of compounds IIa-*l* are reported in [1].

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on a Specord M-80 in KBr pellets, concentration of 1%. The PMR spectra were recorded on a Bruker WP-100 SY in DMSO-D_6, TMS internal standard.

The data from elemental analysis for C, H, and N correspond to the calculations.

2-Carboxymalonanilic acid ethyl ester (VIIIa), 2-carbethoxymethyl-4H-3,1-benzoxazin-4-one (VIa), 2-carbethoxymethyl-3-aminoquinazolin-4(3H)-one (IIIa), 2-carboxymalonanilic (Va), 4-oxo-3,1-benzoxazin-2-yl-acetic (IVa), and 3-amino-4-oxoquinazolin-2-yl-acetic (Ia) acid benzylamides were prepared by previously described methods [11, 16].

α-(3-Amino-4-oxoquinazolin-2-yl)propionic acid benzylamide (Ib, $C_{18}H_{18}N_4O_2$). A. Here 18.1 g (0.11 mole) of methylmalonic acid monoethyl ester acid chloride [19] was added to a solution of 13.7 g (0.1 mole) of anthranilic acid and 14 ml (0.1 mole) of triethylamine in 100 ml of methylene chloride [19] and held (~20°C) for 8 h. Then 100 ml of water was added to the reaction mixture and carefully stirred. The organic layer was separated, dried with anhydrous $CaCl_2$, and the solvent was distilled off, yielding 24.1 g (91%) of dry ester VIIIb. Then 18.7 g (0.091 mole) of N,N'-dicyclohexylcarbodiimide was added to a solution of ester VIIIb in 100 ml of dry ether and boiled for 2 h. It was cooled, and the sediment was filtered off and washed on the filter with dry ether. The filtrate was concentrated dry in a vacuum and 21.5 g (87%) of benzoxazinone VIb was obtained; it was dissolved in 50 ml of methanol and 2.8 ml (0.087 mole) of hydrazine was added. After 5 h, 9.32 g (0.087 mole) of benzylamine was added to the reaction mixture and it was held in a water bath (50°C) for 15 h. The reaction mixture was poured into 200 ml of ice water and acidified to pH 5 with 10% HCl. The residue of 3-aminoquinazolinone Ib was filtered off, washed with water, and dried. After recrystallization from ethanol, colorless needles were obtained with mp = 200-202°C (in a sealed capillary). PMR spectrum: 8.44 (1H, t, NH); 8.15 (1H, d.d, 5-H); 7.84 (1H, t.d, 7-H); 7.68 (1H, d, 8-H); 7.52 (1H, t.d, 6-H); 7.29 (5H, s, Ph); 5.53 (2H, s, NH_2); 4.32 (3H, m, CH_2 + CH); 1.50 ppm (3H, d, CH_3). Yield of 19.1 g (59% on conversion to anthranilic acid).

B. Here 3.52 g (0.11 mole) of hydrazine was added to a solution of 24.7 g (0.1 mole) of α-(4-oxo-3,1-benzoxazin-2-yl)propionic acid benzylamide (IVb) in 50 ml of methanol and held for 5 h at room temperature. The reaction mixture was then treated with the method described above. Yield of 31.9 g (99% or 69% on conversion to anthranilic acid).

A mixed sample with 3-aminoquinazolinone Ib prepared by Method A did not depress the melting point; the PMR spectra were identical.

3-Benzoylamino-4-oxoquinazolin-2-yl-acetic Acid Benzylamide (IIb). A. Here 1.55 g (0.011 mole) of benzoyl chloride was added to a mixture of 3.08 g (0.01 mole) of 3-aminoquinazolinone Ia and 1.4 ml (0.01 mole) of triethylamine in 15 ml of dioxane and held at room temperature for 10 h. Then 100 ml of water was added. The sediment of amide IIb was filtered off, washed with water, and dried. Yield of 4.00 g (97%).

The other 3-acylamino-4-oxoquinazolin-2-yl-acetic acid benzylamides (see Table 1) were prepared analogously.

B. A mixture of 2.94 g (0.01 mole) of benzoxazinone IVa and 1.92 g (0.01 mole) of benzoylhydrazine in 15 ml of dry DMF was boiled for 1 h. The reaction mixture was cooled and treated with the method described above. Yield of 3.34 g (81%).

A mixed sample with amide IIb prepared by Method A did not depress the melting point; the PMR and IR spectra were identical.

α-(4-Oxo-3,1-benzoxazin-2-yl)propionic Acid Benzylamide (Ib, $C_{18}H_{16}N_2O_3$). Here 2.06 g (0.01 mole) of N,N'-dicyclohexylcarbodiimide was added to a solution of 3.26 g (0.01 mole) of amide Vb in 70 ml of dry methylene chloride and boiled for 2 h. It was cooled and the sediment was filtered off. The filtrate was evaporated dry in a vacuum. Colorless crystals with mp = 147-149°C (methanol). Yield of 3.02 g (98%). PMR spectrum: 8.78 (1H, t, NH); 8.14 (1H, d.d, 5-H); 7.92 (1H, t.d, 7-H); 7.66 (2H, t, 6,8-H); 7.30 (5H, s, Ph); 4.33 (2H, d, CH_2); 3.83 (1H, q, CH); 1.48 ppm (3H, d, CH_3).

Methylmalonic Acid 2-carboxyanilide Benzylamide (Vb, $C_{18}H_{18}N_2O_4$). Here 2.35 g (0.022 mole) of benzylamine was added to a solution of 2.65 g (0.01 mole) of ethyl ester VIIIb in 10 ml of methanol and boiled with a reflux condenser for 10 h. It was cooled, 100 ml of water was added, and it was acidified to pH 4 with 10% HCl. The precipitated sediment of amide Vb was filtered off, washed with water, and dried. Colorless prisms with mp = 199-201°C (ethanol). Yield of 2.54 g (78%). PMR spectrum: 13.65 (1H, br. s, COOH); 11.39 (1H, s, NH—Ar); 8.72 (1H, t, J = 5.52 Hz, **NH—CH_2); 8.56 (1H**, d, J = 8.00 Hz, 3-H); 8.03 (1H, d.d, J = 7.93; 1.84 Hz, 6-H); 7.61 (1H, t.d, J = 8.00; 2.00 Hz, 5-H); 7.28 (5H, s, Ph); 7.17 (1H, t.d, J = 7.98; 2.00 Hz, 4-H); 4.34 (2H, d, J = 5.52 Hz, NCH_2); 3.54 (1H, q, CH); 1.40 ppm (3H, d, CH_3).

2-Hydroxypyrazolo-3-methyl[5,1-*b*]quinazolin-9(1H)-one (VIIb, $C_{11}H_9N_3O_2$). Here 3.22 g (0.01 mole) of 3-aminoquinazolinone Ib was held in a metal bath at 250°C for 10 min. It was cooled and the sediment was pulverized with 20 m of ethanol and filtered. Mp > 275°C (DMF). Yield of 2.06 g (96%). PMR spectrum: 11.61 (1H, s, NH); 11.11 (1H, br. s, OH); 8.09 (1H, d.d, J = 7.92, 1.20 Hz, 8-H); 7.69 (1H, t.d, J = 7.98 and 2.00 Hz, 6-H); 7.38 (1H, d, J = 8.00 Hz, 5-H); 7.20 (1H, t, J = 7.00 Hz, 7-H); 1.95 ppm (3H, s, CH_3).

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