CONDENSED DERIVATIVES OF BENZAZOLES.

1. SYNTHESIS OF 6- AND 5-SUBSTITUTED BENZIMIDAZO[2,1-b]QUINAZOLIN-12-ONES

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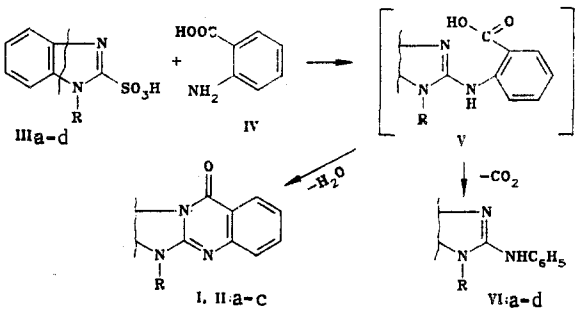
6(5)H-Benzimidazo[2,1-b]quinazolin-12-one was obtained in high yield by condensation of benzimidazole-2-sulfonic acid with anthranilic acid. Methods for the introduction of substituents selectively into the 5 and 6 positions of this heterocycle were developed.

The activity of the immunosuppressant azathioprine, which is used in medical practice, is inferior to that of 6(5)H-benzimidazo[2,1-b]quinazolin-12-one (I) and its derivatives (II) [1], which are obtained in low yields by condensation of 2-chlorobenzimidazoles with anthranilic acid [2].

For the synthesis of the indicated compounds we used benzimidazole-2-sulfonic acids IIIa-d instead of 2-chlorobenzimidazoles; this made it possible to significantly increase the yields of I and IIa-c. The starting sulfonic acids IIIa-d were obtained by oxidation of 2-mercaptobenzimidazoles with Perhydrol in aqueous alkali solution [3]; 78% hdyrogen peroxide in acetic acid has been previously used for this purpose [4].

Our investigation of the reaction of benzimidazole-2-sulfonic acids with anthranilic acid (IV) showed that nucleophilic substitution of the sulfo group by a residue of amino acid IV and the subsequent condensation of the intermediately formed 2-(o-carboxyphenylamino)benzimidazoles (V) proceeds quite smoothly in the case of a gradual increase in the temperature of the reaction mixture from 140°C to 160°C in the course of 2-3 h [3]. The synthesis of I and IIa-c by a method similar to that in [5] at 170-180°C leads to the development in the reaction mixture of, in addition to I and IIa-c, appreciable amounts of 2-phenylaminobenzimidazoles VIa-d. Moreover, in the reaction of benzimidazole-2-sulfonic acids IIIa-d with p-aminobenzoic acid under similar conditions VIa-d are also formed unexpectedly. Compounds VIa, b were previously obtained by the reaction of sulfonic acids IIIa, b with aniline [5].



I R=H; II a R=CH_3, b R=C_2H_5, c R=$CH_2C_6H_5$; III, VI a R=H, b R=CH_3, c R=C_2H_5, d R=$CH_2C_6H_5$

Since o- and p-aminobenzoic acids are stable under the reaction conditions, it is apparent that amino compounds VI are formed only as a result of decarboxylation of the less stable o- and p-carboxyphenylaminobenzimidazoles. Compounds VIc, d were found to be identical to the 2-phenylamino derivatives of benzimidazole that we obtained by condensation of sulfonic acids IIIc, d with aniline by a method similar to that in [5]. Compounds I and IIa-c are formed in good yields without admixed amines VIa-d in the reaction of sulfonic acids IIIa-d with methyl anthranilate.

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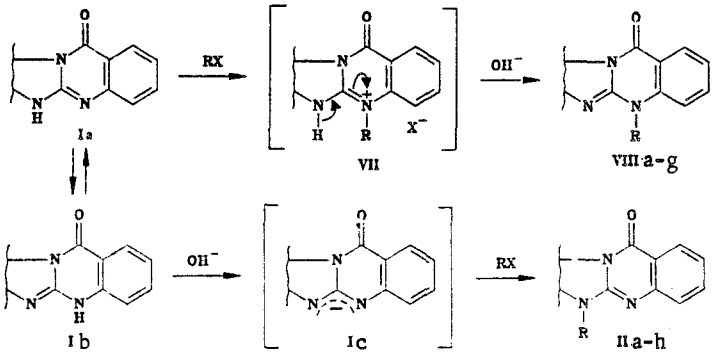
It is known that, in addition to 6-alkylbenzimidazo[2,1-b]quinazolin-12-one (II), 5-methylbenzimidazo[2,1-b]quinazolin-12-one (VIIIa) was also obtained by condensation of 2-chlorobenzimidazole with methyl N-methylanthranilate [2]. Our attempts to realize the condensation of benzimidazole-2-sulfonic acid IIIa with N-methyl- or N-phenylanthranilic acids or their methyl esters were unsuccessful. The indicated acids are readily decarboxylated under the reaction conditions, whereas their esters, on the other hand, react with sulfonic acid IIIa to give thermally stable sulfammonium salts, which undergo destruction with resinification only on heating above 230°C. The synthesis of 5-methyl derivative VIIIa was accomplished by methylation of I with methyl iodide by refluxing in solution in DMF. The initially formed salt VII was treated, without isolation from the reaction mixture, with sodium carbonate solution or ammonium hydroxide, and VIIIa was obtained in high yield. In addition, the isomeric 6-methyl derivative IIa was also formed in high yield in the alkylation of I with methyl iodide in an alkaline medium under interphase-catalysis conditions.



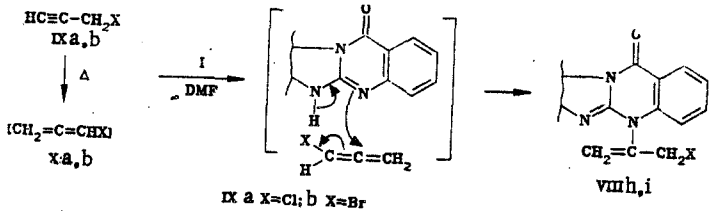
II, VIII a R=CH_3, b R=C_2H_5, c R=$CH_2C_6H_5$, d R=p-C_3H_7, e R=p-C_4H_9, f R=CH_2CH=CH_2, g R=CH_2CBr=CH_2; II h R=$CH_2C{\equiv}CH$

By alkylation of I with the corresponding alkyl halides with variation of the reaction conditions we obtained a number of previously unknown 6- and 5-alkyl derivatives IId, f-h and VIIIb-g, as well as IIb, c, e, which were described in [2].

Thus I is alkylated in the 5 position in a neutral medium, whereas it is alkylated in the 6 position in an alkaline medium. The tautomerism of I has not been studied [2]; however, one should take into account the possibility of the existence of its 6H (Ia) and 5H (Ib) tautomers, as well as mesomeric anion Ic. Our data from quantum-chemical calculations of tautomers Ia, b by the Pariser–Parr–Pople (PPP) method with the aid of the method in [6] show that the charge of the tertiary $N_{(5)}$ atom (–0.3692) of Ia is somewhat higher than the charge of the $N_{(6)}$ atom (–0.3200) of Ib. The charges on the N atoms of anion Ic – $N_{(5)}$ (–0.5982) and $N_{(6)}$ (–0.6230) differ only slightly. Consequently, the selective alkylation of I in the 6 position in an alkaline medium is evidently due to specific solvation of the mesomeric anion Ic under interphase-catalysis conditions.

Since I is only slightly soluble in water and organic solvents, it is expedient to carry out its alkylation in the 6 position in a two-phase aqueous system (40-50% NaOH solution) in the presence of a polar aprotic solvent (DMSO or acetone or a mixture of them) and a catalyst —triethylbenzylammonium chloride. These conditions promote dissolving of I and the formation of mesomeric anion Ic. The alkylation of I in the 5 position is realized in a small amount of refluxing DMF; the resulting precipitate of hydrohalide VII, without isolation from the reaction mixture, was treated with a base.

The unique character of the properties of the amide system of I is also manifested in the fact that bases — 5-haloallyl derivatives VIIIh, i (X = Cl, Br) — were obtained instead of the hydrohalide of the corresponding propargylammonium salt VII when it was refluxed with propargyl halides IXa, b in DMF. Rearrangement of propargyl halides IXa, b to the corresponding allenes Xa, b evidently precedes the formation of VIIh, i since the characteristic absorption band of an allene at 1970 cm^{-1} appears in the IR spectrum of propargyl bromide after it is refluxed in DMF for 5 h. The combined polarizing action of DMF and the starting compound — cyclic amide I — evidently promotes the rearrangment of the propargyl halides to allenes. This is followed by nucleophilic attack on the β-C atom of allene X by the free electron pair of the $N_{(5)}$ atom of I.



IX a X=Cl; b X=Br

VIIIh, i

The structure of VIIIh, i are confirmed by data from the IR and PMR spectra. Thus, for example, the PMR spectrum of VIIIh [8.0 and 7.2 ppm (10H, m, aromatic and $=CH_2$ protons); 5.0 ppm (2H, s, CH_2)] differs from the PMR spectrum of 6-propargyl derivative IIh [7.3 (8H, aromatic protons), 4.9 (2H, s, CH_2); 2.2 ppm (1H, s, $\equiv CH$)] but is similar to the PMR spectrum of isomeric VIIIg, which was obtained by the reaction of I with 2,3-dibromopropene in DMF [8.0 and 7.2 (10H, m, aromatic and $=CH_2$ protons); 5.1 ppm (2H, s, CH_2)]. The absorption bands of the carbonyl group in the IR spectra of IIh and VIIIh are at 1690 cm^{-1}, as compared with 1695 cm^{-1} for VIIIg.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CF_3COOH were recorded with a Tesla BS-467 spectrometer [with hexamethyldisiloxane (HMDS) as the internal standard].

The constants of the compounds obtained are presented in Table 1.

Benzimidazole-2-sulfonic Acid (IIIa). A mixture of 59 g (0.5 mole) of benzimidazole and 16 g (0.5 mole) of powdered sulfur was heated until an exothermic reaction commenced (~160-170°C), after which the temperature of the mixture rose spontaneously to 240-260°C. Water (300 ml) and 30 g of sodium hydroxide were added to the cooled (to 80-100°C) melt, and the resulting alkaline solution of 2-mercaptobenzimidazole was filtered. The filtrate was added in small portions in the course of 2 h with stirring and cooling with ice to 180 ml of 30% hydrogen peroxide, and the mixture was allowed to stand overnight and then neutralized with concentrated HCl. The precipitated acid IIIa was removed by filtration and dried. The yield of the monohydrate of sulfonic acid IIIa, with mp 198°C (mp 200°C [4]), was 81.6 g (89%). Sulfonic acids IIIb-d were similarly obtained from the corresponding 1-alkylbenzimidazoles in 80-90% yields. Compounds IIIb, c were more conveniently obtained by alkylation of sulfonic acid IIIa with alkyl sulfates.

TABLE 1. 6- and 5-Substituted Benzimidazo[2,1-b]quinoxalin-12-ones IIa-h and VIIIa-i

Compound	R	Reaction time, h	T_{mp},* °C	IR spectrum, cm^{-1} ($\nu_{C=O}$)	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	N (Hal)		C	H	N (Hal)	
IIa	CH_3	1	271—273	1675	72,0	4,4	16,7	$C_{15}H_{11}N_3O$	72,3	4,4	16,9	92,1
IIb	C_2H_5	2	230—231	1680	72,8	4,8	15,8	$C_{16}H_{13}N_3O$	73,0	4,9	16,0	92,5
IIc	$CH_2C_6H_5$	3	218—219	1700	77,7	4,5	12,6	$C_{21}H_{15}N_3O$	77,6	4,6	12,9	87,3
IId	p-C_3H_7	4	202—203	1700	73,7	5,6	15,4	$C_{17}H_{15}N_3O$	73,6	5,4	15,2	98,5
IIe	p-C_4H_9	5	171—172	1695	73,8	5,6	14,3	$C_{18}H_{17}N_3O$	74,2	5,8	14,5	93,5
IIf	$CH_2CH=CH_2$	3	198—199	1690	74,1	4,6	15,5	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	91,2
IIg	$CH_2CBr=CH_2$	5	189—191	1685	57,2	3,7	12,0 (22,8)	$C_{17}H_{12}BrN_3O$	57,6	3,4	11,7 (22,6)	88,2
IIh	$CH_2C\equiv CH$	3	245—246	1690	74,5	4,0	15,6	$C_{17}H_{11}N_3O$	74,7	4,0	15,4	98,1
VIIIa	CH_3	1	273—274	1680	72,1	4,3	16,7	$C_{15}H_{11}N_3O$	72,3	4,4	16,9	88,7
VIIIb	C_2H_5	2	254—256	1680	72,7	4,7	15,8	$C_{16}H_{13}N_3O$	73,0	4,9	16,0	90,0
VIIIc	$CH_2C_6H_5$	2	209—210	1695	77,4	4,4	13,0	$C_{21}H_{15}N_3O$	77,6	4,6	12,9	87,7
VIIId	p-C_3H_7	6	193—194	1695	73,9	5,5	15,5	$C_{17}H_{15}N_3O$	73,6	5,4	15,2	96,4
VIIIe	p-C_4H_9	6	195—196	1690	73,9	5,7	14,4	$C_{18}H_{17}N_3O$	74,2	5,8	14,5	91,2
VIIIf	$CH_2CH=CH_2$	1	193—194	1687	74,5	4,8	15,6	$C_{17}H_{13}N_3O$	74,2	4,7	15,3	83,2
VIIIg	$CH_2CBr=CH_2$	4	194—196	1695	57,2	3,5	12,1 (22,2)	$C_{17}H_{12}BrN_3O$	57,6	3,4	11,7 (22,6)	83,5
VIIIh	$CH_2=C-CH_2Br$	6	196—198	1690	57,4	3,5	12,1 (22,3)	$C_{17}H_{12}BrN_3O$	57,6	3,4	11,7 (22,6)	85,7
VIIIi	$CH_2=C-CH_2Cl$	12	171—172	1690	69,0	4,0	11,8 (11,7)	$C_{17}H_{12}ClN_3O$	69,1	4,1	12,0 (12,0)	76,8

*The compounds were crystallized: IIa and VIIIg from dioxane, IIb from ethyl acetate, IIf and VIIIf from alcohol, IIg, VIIIc, and VIIIh from aqueous DMF, and the remaining compounds from DMF.

1-Methylbenzimidazole-2-sulfonic Acid (IIIb). A 21.6-g (0.1 mole) sample of the monohydrate of sulfonic acid IIIa, 20 ml of ethanol, and 15 ml of dimethyl sulfate (in portions with ice cooling) were added to a solution of 8 g (0.2 mole) of sodium hydroxide in 40 ml of water. After 1 h, the liberated sulfonic acid IIIb was removed by filtration, washed with water, and dried to give 22.4 g (87%) of a product with mp 328°C (mp 326-328°C [7]).

Sulfonic acid IIIc was similarly obtained using diethyl sulfate as the alkylating reagent. The yield was 86.3%.

Reaction of 1-R-Benzimidazole-2-sulfonic Acids IIIa-d with p-Aminobenzoic Acid. A mixture of 0.01 mole of sulfonic acid IIIa-d with 1.4 g (0.01 mole) of p-aminobenzoic acid was maintained at 160-170°C for 3 h until sulfur dioxide evolution ceased, after which it was cooled and treated with 10 ml of 10% HCl. The precipitate was removed by filtration and suspended in water, and the suspension was neutralized with ammonia and filtered again. The yield of amino compound VIa, with mp 192°C (from alcohol) (mp 192-194°C [5]), was 68.1%. Compound VIb was similarly obtained in 77% yield and had mp 201°C (from alcohol) (mp 201-202°C [5]).

1-Ethyl-2-phenylaminobenzimidazole (VIc). This compound was similarly obtained by the reaction of sulfonic acid IIIc with p-aminobenzoic acid or with aniline. The colorless crystals, with mp 220-221°C, were obtained in 66-68% yield. Found: C 73.5; H 9.8; N 17.3%. $C_{15}H_{15}N_3$. Calculated: C 73.2; H 10.0; N 17.0%.

1-Benzyl-2-phenylaminobenzimidazole (VId). This compound was similarly obtained. The colorless crystals, with mp 238°C (from alcohol), were obtained in 70% yield. Found: C 80.1; H 5.4; N 13.9%. $C_{20}H_{17}N_3$. Calculated: C 80.3: H 5.6: N 14.1%.

6(5)H-Benzimidazo[2,1-b]quinazolin-12-one (I). A mixture of 4.2 g (0.02 mole) of the monohydrate of benzimidazole-2-sulfonic acid IIIa and 2.8 g (0.02 mole) of anthranilic acid was heated at 140-150°C until sulfur dioxide evolution was complete (~3 h), after which the melt was cooled and treated with 10% HCl. The precipitate was removed by filtration, washed with ammonium hydroxide, and dried to give 3.4 g (72%) of colorless crystals with mp 358°C (from DMF). IR spectrum: 1670 (C=O), 3390 cm^{-1} (associated NH groups). Found: C 71.2; H 3.9; N 17.6%. $C_{14}H_9H_3O$. Calculated: C 71.5; H 3.8; N 17.9%.

Compounds IIa-c. These compounds were similarly obtained in 75-77% yields.

6-Substituted Benzimidazo[2,1-b]quinazolin-12(6H)-ones (IIa-h). A 4.7-g (0.02 mole) sample of I, 0.01 g of triethylbenzylammonium chloride, 15 ml of acetone, and 2 ml [4.3 g (0.03 mole)] of methyl iodide were added to a solution of 3 g (0.02 mole) of sodium hydroxide in 3 ml of water, and the mixture was stirred for 45 min. It was then diluted with an equal volume of water, and the precipitated IIa was removed by filtration to give 4.5 g (92.1%) of colorless crystals (from DMF) with mp 271-273°C (mp 273-274°C [2]). No melting-point depression was observed for a mixture of this product with IIa obtained by the method described above. PMR spectrum of IIa: 7.8 and 7.7 (8H, m, aromatic protons); 3.7 ppm (3H, s, NCH_3).

Compounds IIb, c, f, h. These compounds were similarly obtained. Compounds IId, e, g were obtained by heating to 50°C.

5-Substituted Benzimidazo[2,1-b]quinazolin-12(5H)-ones (VIIIa-g). A solution of 2.35 g (0.01 mole) of I in 10 ml of DMF was refluxed with 1.3 ml (0.02 mole) of methyl iodide for 30-40 min, after which the mixture was cooled, and the precipitate was removed by filtration and suspended in 20 ml of water. The suspension was treated with 5 ml of concentrated ammonium hydroxide, and the colorless crystals, which were only slightly soluble in chloroform were removed by filtration. The yield of VIIIa, with mp 273-274°C (from DMF) (mp 273-275°C [2]), was 2.2 g (88.7%). PMR spectrum: 8.1 and 7.3 (8H, m, aromatic protons); 3.8 ppm (3H, s, NCH_3).

Compounds VIIId-g. These compounds were similarly obtained using 0.015 mole of the corresponding alkyl bromide per 0.01 mole of I. Ethyl iodide was used to obtain VIIIb, and benzyl chloride was used to obtain VIIIc.

5-(3-Bromo-1-propen-2-yl)benzimidazo[2,1-b]quinazolin-12(5H)-one (VIIIh). A solution of 0.47 g (20 mmole) of I and 0.3 ml (30 mmole) of propargyl bromide in 2 ml of DMF was refluxed for 6 h, after which it was cooled, and the precipitate was removed by filtration. Colorless crystals (from DMF) were obtained.

Compound VIIIi. This compound was similarly obtained (see Table 1).

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4- AND 5-HYDROXYLAMINOTHIAZOLIDINE-2-THIONES. REARRANGEMENT OF THE CARBAMOYL DERIVATIVES TO 4- AND 5-UREIDOTHIAZOLIDIN-2-ONES

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The carbamoylation of 4- and 5-hydroxyaminothiazolidine-2-thiones by methyl and 3,4-dichlorophenyl isocyanates leads to the corresponding hydroxyureas, which rearrange to 4- and 5-ureidothiazolidin-2-ones on heating in the presence of a base. Under these conditions, the hydroxyurea based on 5-hydroxylaminothiazolidin-2-one is converted to 5-ureidooxazolidin-2-one.

In the continuation of work on the study of the properties of 4- and 5-hydroxylaminothiazolidine-2-thiones [1, 2], we investigated their reaction with isocyanates, as well as some conversions of the carbamoyl derivatives obtained.

The treatment of the hydroxylamines (Ia, c) and (IIa-c) with methyl and 3,4-dichlorophenyl isocyanates is accompanied by the formation of the corresponding N-monocarbamoyl derivatives — the hydroxyureas (III) and (IV). The structure of the hydroxyureas (III) and (IV) is confirmed by the presence of the band of the carbonyl absorption in the region of 1640-1695 cm^{-1} and the amide-II band at 1500-1545 cm^{-1} in the IR spectra (KBr), and by the appearance of the signals of the protons of the NH group in the region of 7.0-9.5 ppm and the OH group in the region of 9.0-10.0 ppm in the PMR spectra. Moreover, the presence of the hydroxyurea fragment in the compounds (III) and (IV) is confirmed by the positive reaction with an alcoholic solution of ferric chloride. In the carbamoylation of the sterically hindered hydroxylamine (Ib) ($R^1 = R^2 = CH_3$), the corresponding carbamoyl derivatives are not successfully isolated.

The hydroxyureas (III) and (IV) are stable to the action of acids. The heating of the hydroxyurea (IIIa) and (IVa-c) in the presence of sodium ethoxide or NaOH leads to the formation of the compounds (V) and (VI), which contain one sulfur atom less than the initial hydroxyureas according to the data of the elemental analysis. The IR spectra of the compounds (V) and (VI) are characterized by the presence of the absorption bands of two carbonyl groups in the regions of 1625-1670 and 1700-1752 cm^{-1}; this indicates the substitution of the thione group by the carbonyl group in the compounds (III) and (IV).

Moreover, the compounds (V) and (VI) do not give a qualitative reaction with ferric chloride solution; their PMR spectra lack the signal of the N-OH group which is characteristic of the initial hydroxyureas. In the case of compounds (VIb, c), the broad singlet of the proton of one more NH group appears in the region of 5.9-7.2 ppm. In the case of the compounds (V) and (VIa), two doublets are observed in the regions of 5.3-5.5 and 6.7-7.3 ppm ($J = 10$ Hz); these pertain to the protons of the CHNH group. On the basis of these data,

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