SYNTHESIS AND MOLECULAR AND CRYSTAL STRUCTURE OF 3a-AZONIA(4-PHENYL-6-METHYL-4,9-DIHYDROQUINAZOLINO-[3a,9a]-3,10-DIHYDRO-1H-PYRAZINONE-2) BROMIDE

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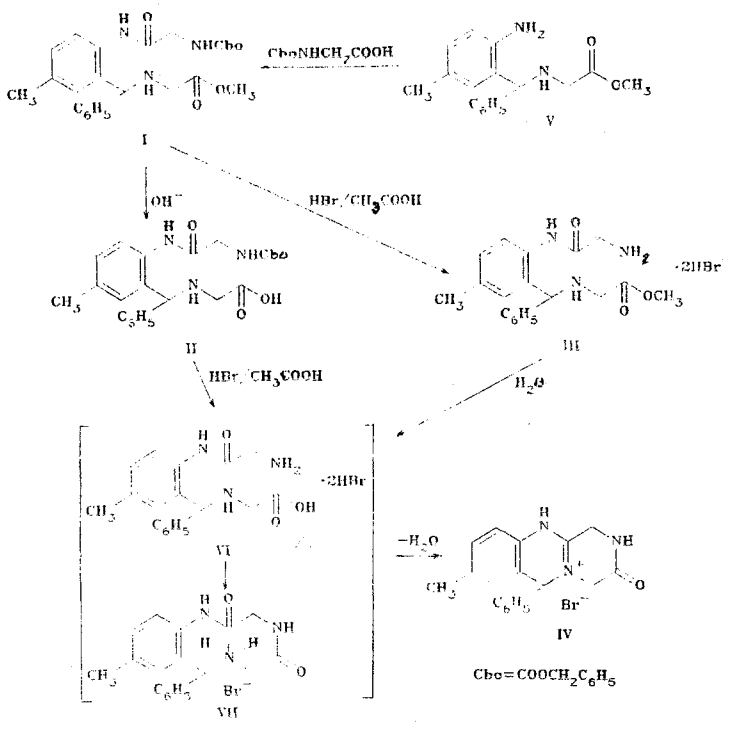
Under acid-catalyzed conditions of the action of hydrogen bromide in glacial acetic acid, N-[2-(N-carbobenzoxyglycyl)-amido-5-methylbenzhydryl]glycine is converted to a quinazolinopyrazinone derivative, which is also obtained from the dihydrobromide of the methyl ester of N-(2-glycylamido-5-methylbenzhydryl)glycine in the presence of water. The indicated compounds structurally represent ortho-substituted benzene derivatives, which is responsible for the specificity of their conversion under the conditions cited. The structure of quinazolinopyrazinone was established by x-ray crystallographic analysis.

We synthesized compounds I-III as intermediates in the synthesis of biologically active heteromeric peptides. In the course of an investigation of the chemical properties of the acid II and the ester III we obtained the heterocyclic compound IV with a quinazolinopyrazinone structure.



The reaction of the amino ester V with the chloride of carbobenzoxyglycine or its isobutylformate anhydride yields the ester I. Alkaline hydrolysis of the ester I produces the

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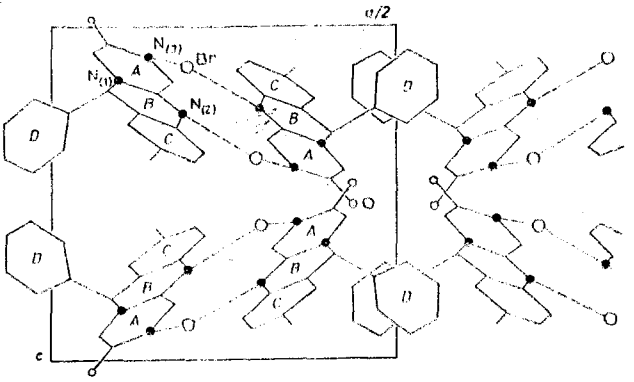

Fig. 1. Projection of the structure of 3a-azonia(4-phenyl-6-methyl-4,9-dihydroquinazolino[3a,9a]-3,10-dihydro-1H-pyrazinone-2) bromide onto the plane ac.

acid II. The quinazolinopyrazinone IV is formed under the action of hydrogen bromide in glacial acetic acid (HBr/CH_3COOH) on the acid II.

It is known that under the action of HBr/CH_3COOH, N-carbobenzoxyamino acids are converted to the corresponding amino acid hydrobromides [2]. In view of this it might have been expected that under the action of HBr/CH_3COOH on the acid II, the dihydrobromide of the acid VI would be obtained. However, the acid VI was not detected in the reaction medium.

Under analogous conditions the ester I is converted to the dihydrobromide of the ester III, which is stable in HBr/CH_3COOH solution and in anhydrous solvents. In the presence of water the ester III is converted to the quinazolinopyrazinone IV. When the amount of water is increased, for example, from 0.01 mole to 0.1 mole with respect to a solution of 0.002 mole of the ester III in methanol, the rate of conversion of the ester III to the quinazolinopyrazinone IV increases by a factor of 5-6. Consequently, the indicated conversion proceeds through a step of hydrolysis of the ester III to the acid VI. We were unable to confirm the step of hydrolysis under the conditions cited directly, since in the preceding case the acid VI was not detected in the reaction medium. The step limiting the conversion of the acid II and the ester III to the quinazolinopyrazinone IV in the first case is the N-decarbobenzoxylation of the acid II, and in the second the step of hydrolysis of the ester group of the ester III, as evidenced by its stability in anhydrous medium. Consequently, in both cases the conversion should proceed through a step of formation of the acid VI. Cyclization of the acid VI may begin with the formation of an amide bond – the intermediate compound VII, which is indirectly indicated by the absence of formation of a quinazoline ring in the ester III in anhydrous medium. The hydrobromide VII, losing water, is converted to the bromide IV. We did not confirm the steps of formation of the acid VI and the hydrobromide VII experimentally on account of the high rate of the cyclization process under the conditions cited. The formation of the quinazolinopyrazinone IV under these conditions is determined by the structure of compounds II and III (orthosubstituted benzene derivatives), as a result of which the functional groups capable of interaction are in a favorable position for this.

In the IR spectra of the ester I, the acid II, the ester III, and the quinazolinopyrazinone IV, the characteristic absorption bands at 1690, 1710, 1690, 1695 cm^{-1}, respectively, belong to the C=O of amide groups; those at 1740 (I), 1750 cm^{-1} (III) belong to C=O of the ester groups; the band at 1635 cm^{-1} (II) belongs to the C=O of the carboxyl group; the band at 1665 cm^{-1} (IV) belongs to the $C{=}N^+$ group.

Colorless crystals of the quinazolinopyrazinone IV have a prismatic habitus. The crystals are monoclinic with parameters of the unit cell a = 24.192 (4), b = 13.678 (3), c = 10.748 (2) Å, γ = 104.2 (1)°. ρ (calc.) = 1.433 g/cm^3 at Z = 8, composition $C_{18}H_{18}N_3BrO$, space group B2/b.

The crystal was constructed from organic cations and bromide anions, intermolecularly bonded by hydrogen bonds (Fig. 1) . The numeration of the atoms in the cation, the interatomic distances, and valence angles are cited in Fig. 2.

The organic cation consists of three condensed six-membered rings A, B, and C and a phenyl substituent D in the B ring (Fig. 1). The carbon atoms $C_{(14)}$, $C_{(16)}$ and $C_{(18)}$ are in sp^3-hybridization, the rest in sp^2. The protons are localized at the $N_{(2)}$ and $N_{(3)}$ atoms. The C

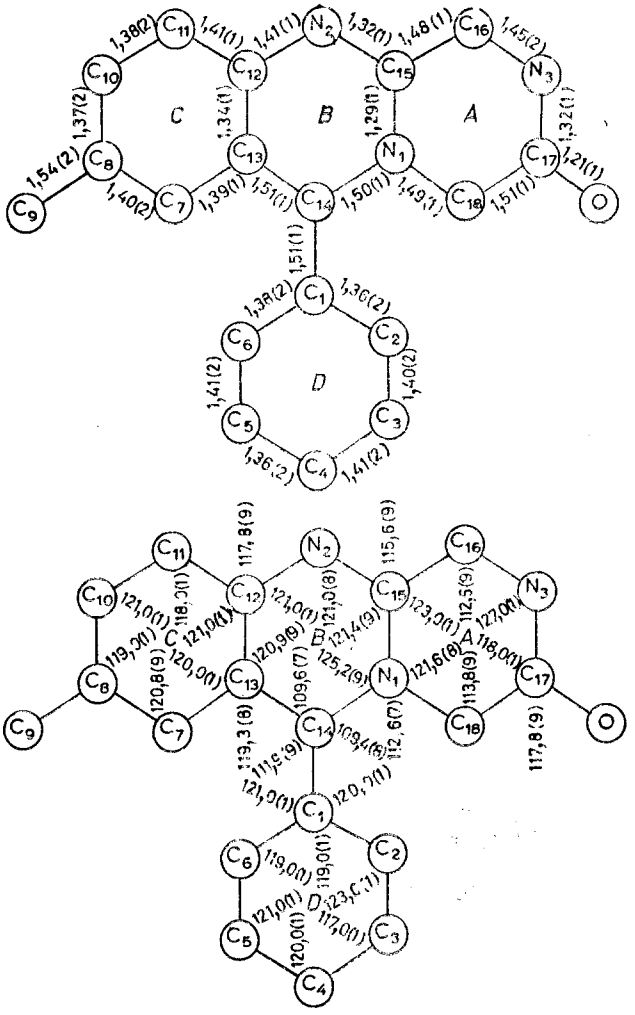

Fig. 2. Numeration of the atoms, interatomic distances, and valence angles in the cation of 3a-azonia(4-phenyl-6-methyl-4,9-dihydroquinazolino[3a,9a]-3,10-dihydro-1H-pyrazinone-2) bromide.

and D rings are flat with characteristic interatomic distances and valence angles (Fig. 2). In the C ring the average C-C distance is equal to 1.38 Å, the angle CCC 120°, the distance $C_{(8)}$—$C_{(9)}$ 1.54 Å; the $C_{(8)}$—$C_{(9)}$ bond is in the plane of the C ring. In the D ring the average C—C distance is equal to 1.38 Å, the internal angle 119.8°. The $C_{(14)}$ atom deviates from the plane D by 0.077 Å. The A and B rings have a flattened boat conformation. In both rings the atoms $C_{(16)}$ deviate to one side of the average plane by 0.106 Å, and $C_{(18)}$ by 0.146 (A), $C_{(14)}$ and $N_{(2)}$ (B) by 0.05 Å. In the amide group the C=O distance is equal to 1.21 Å, $C_{(17)}$—$N_{(3)}$—1.32, $C_{(17)}$—$C_{(18)}$ — 1.51, $N_{(3)}$—$C_{(16)}$ — 1.45 Å. The distances are typical of systems for which C^1=O is equal to 1.24 Å, C^1—N — 1.32, N—C^α — 1.47, C^1—C^α — 1.55 Å [3]. The pyramidization of the amide group noted, which is expressed in deviation of the $C_{(17)}$ atom from the average plane of the amide group by 0.018 Å, is observed.

In the B ring a substantial π-delocalization of the electron density is detected. The trigonal $N_{(1)}$ nitrogen atom has two single bonds to carbon (1.49 and 1.50 Å) and $N_{(1)}$—$C_{(15)}$, which is predominantly a double bond (1.29 Å), which permits the presence of a positive charge on the $N_{(1)}$ atom. The delocalization of the π-electrons affects the chain $N_{(1)}$—$C_{(15)}$—$N_{(2)}$, which in turn is manifested in a shortening of the $C_{(15)}$—$N_{(2)}$ bond to 1.32 Å. The $C_{(12)}$—$N_{(2)}$ bond (1.41 Å) is a single bond.

In the crystal the organic cations are bonded by hydrogen bonds through the bromide anions (Fig. 1). The NH groups of the $N_{(2)}$ and $N_{(3)}$ atoms are proton donors. The distance $N_{(2)}$—Br is equal to 3.24 Å, the hydrogen bond Br...H = 2.29, the bond $N_{(2)}$—H = 0.96 Å. The distance $N_{(3)}$—Br is equal to 3.39 Å, the hydrogen bond Br...H = 2.64, and the bond $N_{(3)}$—H =

TABLE 1. Coordinates of Nonhydrogen Atoms in the Structure of 3a-Azonia-(4-phenyl-6-methyl-4,9-dihydroquinazolino[3a,9a]-3,10-dihydro-1H-pyrazinone-2) Bromide

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
Br	0,1950 (1)	0,1468 (1)	0,0967 (1)	$C_{(8)}$	0,3392 (5)	0,5973 (8)	0,142 (1)
$N_{(1)}$	0,3875 (3)	0,3090 (6)	0,3431 (8)	$C_{(9)}$	0,3513 (6)	0,2109 (8)	0,886 (1)
$N_{(2)}$	0,3070 (4)	0,2900 (6)	0,2259 (9)	$C_{(10)}$	0,2906 (5)	0,5311 (9)	0,100 (1)
$N_{(3)}$	0,3594 (5)	0,1068 (8)	0,405 (1)	$C_{(11)}$	0,2795 (5)	0,4290 (9)	0,126 (1)
O	0,4410 (3)	0,1234 (5)	0,5110 (8)	$C_{(12)}$	0,3195 (5)	0,3937 (8)	0,198 (1)
$C_{(1)}$	0,4663 (4)	0,4307 (7)	0,242 (1)	$C_{(13)}$	0,3674 (4)	0,4569 (7)	0,2389 (9)
$C_{(2)}$	0,5132 (5)	0,501 (1)	0,279 (1)	$C_{(14)}$	0,4110 (4)	0,4183 (7)	0,312 (1)
$C_{(3)}$	0,5646 (5)	0,521 (1)	0,213 (1)	$C_{(15)}$	0,3398 (4)	0,2534 (7)	0,302 (1)
$C_{(4)}$	0,5671 (5)	0,463 (1)	0,106 (2)	$C_{(16)}$	0,3179 (5)	0,1459 (9)	0,337 (1)
$C_{(5)}$	0,5203 (6)	0,392 (1)	0,068 (1)	$C_{(17)}$	0,4076 (5)	0,1594 (8)	0,454 (1)
$C_{(6)}$	0,4689 (5)	0,3750 (9)	0,136 (1)	$C_{(18)}$	0,4204 (4)	0,2729 (8)	0,443 (1)
$C_{(7)}$	0,3773 (5)	0,5597 (8)	0,214 (1)				

TABLE 2. Coordinates of the Hydrogen Atoms in the Structure of 3a-Azonia-(4-phenyl-6-methyl-4,9-dihydroquinazolino[3a,9a]-3,10-dihydro-1H-pyrazinone-2) Bromide

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
$H_{(1)}$	0,521 (5)	0,534 (9)	0,33 (1)	$H_{(8)}$	0,260 (6)	0,05 (1)	0,95 (1)
$H_{(2)}$	0,596 (5)	0,578 (8)	0,27 (1)	$H_{(9)}$	0,239 (4)	−0,128 (7)	0,89 (1)
$H_{(3)}$	0,610 (6)	0,49 (1)	0,07 (1)	$H_{(10)}$	0,275 (3)	0,246 (6)	0,187 (8)
$H_{(4)}$	0,513 (7)	0,34 (1)	−0,03 (1)	$H_{(11)}$	0,708 (6)	0,39 (1)	0,28 (1)
$H_{(5)}$	0,427 (5)	0,314 (8)	0,10 (1)	$H_{(12)}$	0,349 (5)	0,048 (8)	0,43 (1)
$H_{(6)}$	0,424 (3)	0,468 (5)	0,390 (8)	$H_{(13)}$	0,412 (3)	0,296 (6)	0,528 (8)
$H_{(7)}$	0,411 (4)	0,104 (6)	0,759 (8)	$H_{(14)}$	0,466 (3)	0,298 (6)	0,427 (8)

0.83 Å. The hydrogen bonds combine individual structural units into helical chains, directed along the b axis.

EXPERIMENTAL

The course of the reactions and the homogeneity of the compounds obtained were monitored by thin-layer chromatography on Silufol plates; R_f was determined in the system water–pyridine–acetic acid–ethyl acetate (6:8:11:75, system B), detected by 2 min exposure of the plate in an atmosphere of chlorine, followed by its spraying with an aqueous alcohol solution (1:1) of o-toluidine (2%) and KI (5%). The IR spectra were recorded on a Perkin-Elmer 325 spectrophotometer in KBr tablets.

X-ray crystallographic analysis was performed on a DAR-UMB diffractometer with controlling M-6000 computer, in MoK_α radiation (graphite monochromator), by the method of ω-Q/2Q scanning. In a recalculation of the intensities, the Lorentz factors and polarizations were introduced into the moduli of the structural amplitudes. The absorption was neglected. In the calculations we used 1335 reflections with $I \geq 3\sigma$. The structure was solved by the heavy atom method. The position of the bromine atom was found from the three-dimensional Paterson function. The synthesis of the electron density, constructed considering the signs determined according to the coordinates of the bromine atom, permitted localization of all the nonhydrogen atoms of the cation. The structure was refined in an anisotropic approximation for all the nonhydrogen atoms. The positions of the hydrogen atoms were determined from a differential Fourier synthesis. The concluding R-factor was equal to 0.050. The coordinates of the base atoms are cited in Tables 1 and 2.

Methyl Ester of N-[2-Carbobenzoxyglycyl)amido-5-methylbenzhydryl]-glycine (I). A. To a suspension of 4.18 g (20 mmoles) carbobenzoxyglycine in 20 ml of chloroform at −16°C we added 4.2 g (20 mmoles) of phosphorus pentachloride and mixed for 20 min. Then 5.68 g (20 mmoles) of the methyl ester of N-(2-amino-5-methylbenzhydryl)glycine (V) in 30 ml of chloroform was added, mixed for 1 h at −6 C, and evaporated under vacuum. To the residue we added 20 ml of water, a saturated solution of sodium bicarbonate to pH 7.8–8, and ethyl acetate until the precipitate dissolved (80–100 ml); the ethyl acetate solution was removed, washed with water, dehydrated with sodium sulfate, evaporated under vacuum, the residue crystallized

from methanol, and 8 g (85%) of the ester I was obtained. mp 116-117°C (from methanol). R_f 0.50 (acetone–hexane, 2:3). Found: C 68.3; H 6.1; N 8.9%. $C_{27}H_{29}N_3O_5$. Calculated: C 68.2; H 6.1; N 8.8%.

B. To a solution of 2.09 g (10 mmoles) carbobenzoxyglycine in 15 ml dimethylformamide and 1.4 ml (10 mmoles) triethylamine at −10°C, 1.36 g (10 mmoles) of isobutyl chloroformate was added, mixed for 5 min, and a solution of 2.8 g (10 mmoles) of the ester V in 20 ml of ethyl acetate was added. The solution was mixed at 0°C for 1 h, at 20°C for 30 min, evaporated under vacuum, the residue dissolved in 50 ml of ethyl acetate, the solution washed successively with a 1% HCl solution to pH 6 and a 5% $NaHCO_3$ solution to pH 7.5, with water, and then the ester I was isolated as described in method A. Yield 3.2 g (68%).

N-[2-(N-Carbobenzoxyglycyl)amido-5-methylbenzhydryl]glycine (II). To a solution of 4.75g (10 mmoles) of the ester I in 5 ml of dioxane and 5 ml of methanol over a period of 20 min, 5 ml of a 2 N sodium hydroxide solution (10 mmoles) was added, mixed for 1 h, and evaporated under vacuum. The residue was dissolved in water, acidified with citric acid, the precipitate formed was removed, washed with water, dried, crystallized from methanol, and 3.3 g (71%) of the acid II was obtained. mp 169-170°C (methanol). R_f 0.23 (system B). Found: C 67.8; H 5.9; N 9.2%. $C_{26}H_{27}N_3O_5$. Calculated: C 67.7; H 5.9; N 9.1%.

Dihydrobromide of the Methyl Ester of N-(2-Glycylamido-5-methyl-benzhydryl)glycine (III). To 2.37 g (5 mmoles) of the ester I we added 20 ml of a 15-20% solution of hydrogen bromide in glacial acetic acid, then mixed at 20-23°C for 30 min. To the solution we added 100-120 ml of absolute ether; the precipitate formed was removed and washed with 50 ml of absolute ether. The precipitate was exposed for three days in a vacuum desiccator over sodium hydroxide and phosphoric anhydride, and 2.3 g (91%) of the ester III was obtained. mp 170-173°C. R_f 0.21 (system B). Found: C 45.6; H 5.1; Br 32.0; N 8.4%. $C_{19}H_{23}N_3O_8 \cdot 2HBr$. Calculated: C 45.3; H 5.0; Br 31.7; N 8.4%. The ester III was stable in a solution of anhydrous alcohols and could be stored for a long time under a layer of absolute diethyl ether.

3α-Azonia(4-phenyl-6-methyl-4,9-dihydroquinazolino[3α,9α]-3,10-dihydro-1H-pyrazinone-2) bromide (IV). A. To 2.3 g (5 mmoles) of the acid II we added 20 ml of a 15-20% solution of hydrogen bromide in glacial acetic acid, then mixed at 20-23°C for 30 min. Then 80-100 ml of absolute ether was added to the solution, the precipitate formed was removed, dissolved in 80% aqueous ethanol, the solution neutralized with 2 N sodium hydroxide, and ethyl acetate added until separation of the layers of liquid. The precipitate formed was removed, washed with 10-15 ml of water, recrystallized from 80% aqueous methanol, and 1.7 g (93%) quinazolinopyrazinone IV was obtained. mp 309-310°C (aqueous methanol). R_f 0.36 (system B). Found: C 58.2; H 4.9; Br 21.2; N 11.4%. $C_{18}H_{18}BrN_3O$. Calculated: C 58.1; H 4.9; Br 21.5; N 11.3%.

B. We dissolved 1 g (2 mmoles) of the ester III in 15 ml of 80% aqueous methanol, containing 1 ml of 20% hydrobromic acid. After 5-6 h (the time was determined according to the absence of the ester III in the mixture by the method of thin-layer chromatography), the solution was neutralized with 2 N sodium hydroxide, treated further as described in method A, and 0.66 g (89%) of the quinazolinopyrazinone IV was obtained; it was identical with a sample produced by method A according to the data of the melting point, R_f, IR spectra, and elementary analysis.

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