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CHEMICAL CONVERSIONS OF 8,18-DISUBSTITUTED DERIVATIVES OF 6,16-DIPHENYL-1,2,3,11,12,13-HEXAHYDRO-DIBENZO[*g,o*]-4,14-DIOXA-1,5,11,15-TETRA-AZACYCLOHEXADECINE-2,12-DIONES

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The chemical properties of 8,18-disubstituted 6,16-diphenyl-1,2,3,11,12,13-tetrahydrodibenzo[g,o]-4,14-dioxa-1,5,11,15-tetraazahexadecine-2,12-diones have been studied, including their interaction with N-nucleophiles (hydroxylamine, hydrazine, semicarbazide, and thiosemicarbazide), acidic and alkaline hydrolysis, and methylation. A hypothesis has been made from analysis of the mass spectral data of the thiosemicarbazide on the preferred existence of 6-substituted 4-phenylquinazoline-2-carbaldehydes in the gas phase as the linear tautomer.

Keywords: dibenzomacrocycle, N-nucleophile, thiosemicarbazone, quinazoline.

We previously reported the synthesis of 8,18-disubstituted 6,16-diphenyl-1,2,3,11,12,13-hexahydrodibenzo[*g,o*]-4,14-dioxa-1,5,11,15-tetraazacyclohexadecine-2,12-diones **1-3** from the *syn* isomers of 2-amino-5-substituted benzophenone oximes and also on their structure and antithrombotic activity [1]. While continuing investigations in this direction we have studied some chemical conversions of dibenzomacroheterocycles **1-3**. It turned out that, on interacting compounds **1-3** with various N-nucleophiles (hydroxylamine, hydrazine, semicarbazide, and thiosemicarbazide) in the presence of NaOH, the corresponding derivatives of 6-substituted 4-phenylquinazoline-2-carbaldehydes **4-6** may be obtained, *viz*. oximes **7-9**, hydrazones **10-12**, semicarbazones **13-15**, and thiosemicarbazones **16-18**.

Compounds **7-18** were also obtained by the alternate synthesis from the corresponding 6-substituted 4-phenylquinazoline-2-carbaldehydes **4-6** obtained in their turn by thermolysis of 7-substituted 3-hydroxy-5-phenyl-1,2-dihydro-3H-1,4-dibenzodiazepin-2-ones **19-21** [2] by the procedure of [3].

The study of the possibility of using macrocycles **1-3** is impeded by their extremely insignificant solubility in the overwhelming majority of organic solvents. The 1,11-dimethyl derivatives **22-24** possess much higher solubility in organic solvents. We obtained these compounds for the first time by methylating macrocycles **1-3** with dimethyl sulfate in the presence of NaOMe. Compounds **22-24** did not react with N-nucleophiles under the conditions described above.

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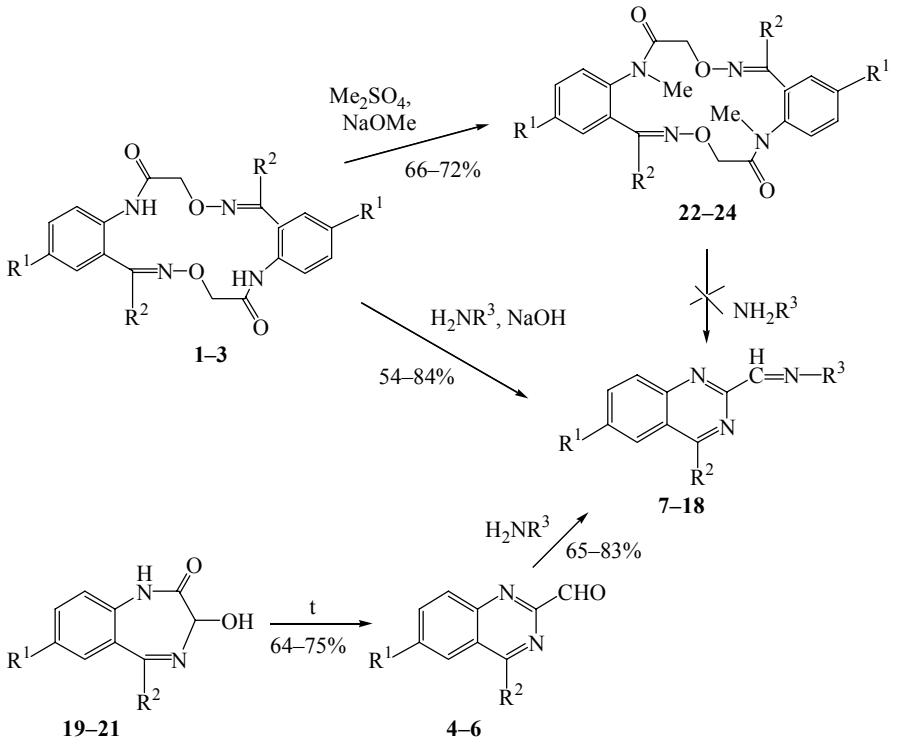
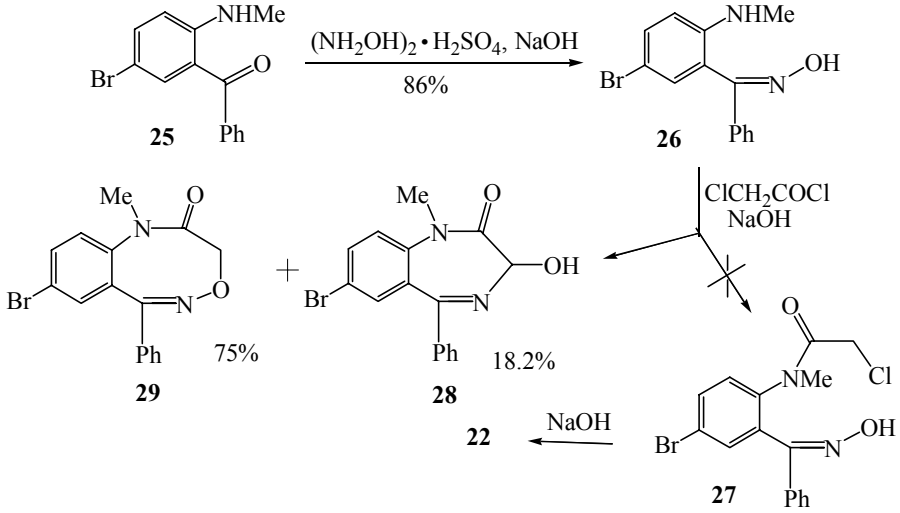


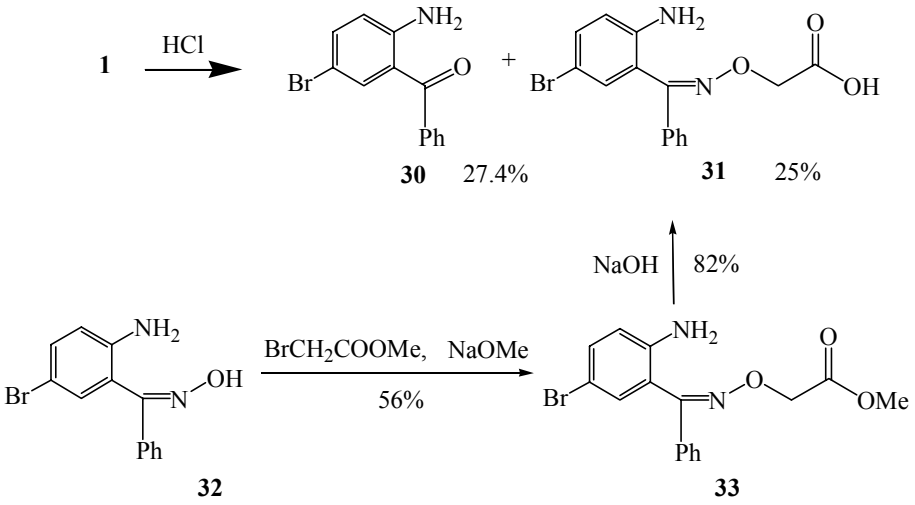
1, **4**, **7**, **10**, **13**, **16**, **19**, **22** R^1 = Br, R^2 = Ph; **2**, **5**, **8**, **11**, **14**, **17**, **20**, **23** R^1 = Br, R^2 = *o*-ClC_6H_4;
3, **6**, **9**, **12**, **15**, **18**, **21**, **24** R^1 = Me, R^2 = Ph; **7-9** R^3 = OH, **10-12** R^3 = NH_2,
13-15 R^3 = $NHCONH_2$, **16-18** R^3 = $NHCSNH_2$

Attempts to synthesize dibenzomacroheterocycle **22** by another method from 5-bromo-2-methylaminobenzophenone (**25**) were not successful. On acylating the *syn* isomer of 5-bromo-2-methylaminobenzophenone oxime (**26**) with chloroacetyl chloride under Schotten–Baumann conditions a mixture was formed of 7-bromo-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**28**), described in [4], and a compound, which from data of IR spectroscopy, mass spectrometry, and elemental analysis, was assigned the structure 8-bromo-1-methyl-6-phenyl-1,3-dihydro-2H-4,1,5-benzoxadiazocin-2-one (**29**). The corresponding 2-chloroacetamido oxime derivative **27**, by the cyclization of which in the presence of NaOH we hoped to obtain macrocycle **22** analogously to that described in [1], was not isolated from the reaction mixture.

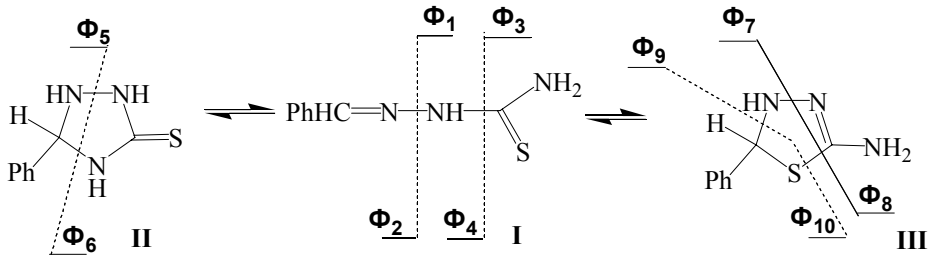


The mechanism of the conversion of dibenzomacroheterocycles **1-3** into **7-18** by the action of N-nucleophiles is not studied specially in the present work. It possibly contains the following stages: 1) transition of the dibenzoheterocycle into 3-hydroxybenzodiazepine in alkaline medium analogously to that described for the rearrangement of benzoxadiazocine into 3-hydroxybenzodiazepine [5], and 2) interaction of the latter with N-nucleophiles, as in [6], leading to the formation of quinazoline-2-carbaldehyde derivatives.

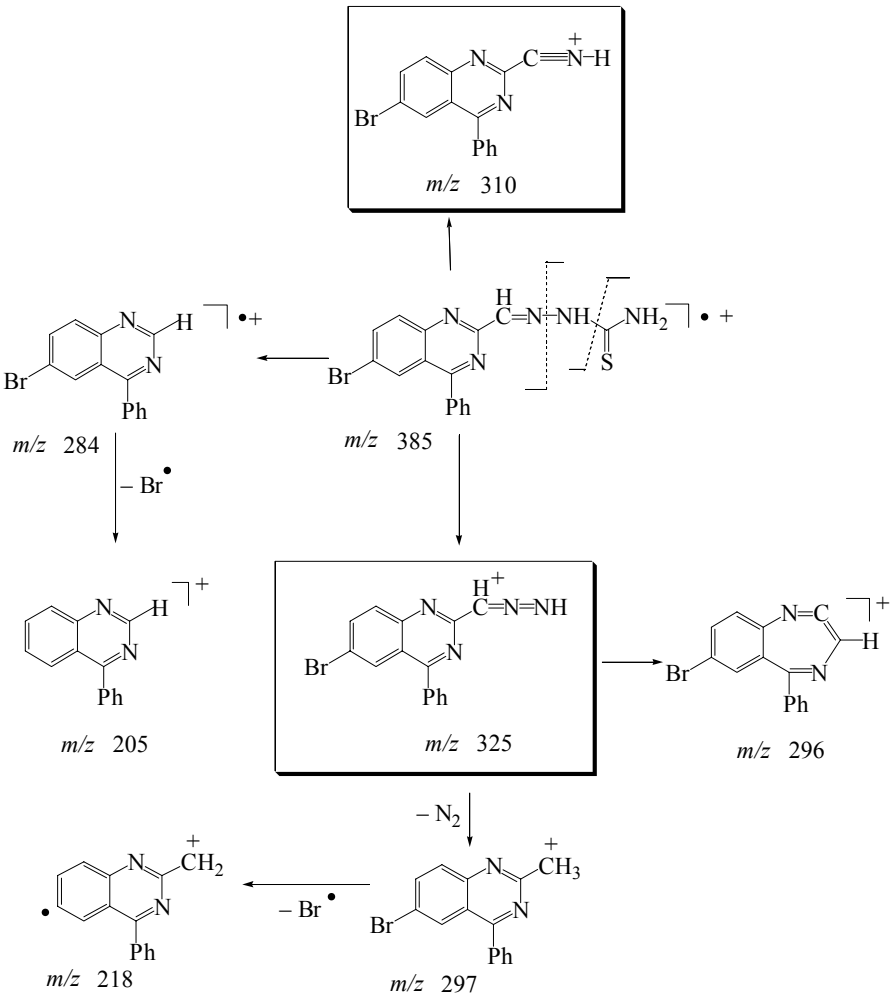
Using 8,18-dibromo-6,16-diphenyl-1,2,3,11,12,13-hexahydrodibenzo[*g,o*]-4,14-dioxa-1,5,11,15-tetra-azacyclohexadecine-2,12-dione (**1**) as example we established that alkaline hydrolysis of the dibenzomacroheterocycles leads to the formation of 5-substituted 2-aminobenzophenones and a series of resinous compounds. Study of the acid hydrolysis of dibenzomacroheterocycle **1** showed that, in addition to 2-amino-5-bromobenzophenone (**30**), the *syn* isomer of N-(2-amino-5-bromophenylmethylene)iminooxyacetic acid (**31**) is formed. Evidently on hydrolysis of compound **1** fission of the amide bond occurs first, which, as described for the alkaline hydrolysis of benzodiazepin-2-ones [7], leads to the formation of compound **31**. Hydrolytic fission of the azomethine bond then occurs as a result of which aminobenzophenone **30** is obtained. With the aim of confirming the structure of compound **31** we proposed an independent alternate route of synthesis, consisting of the interaction of the *syn* isomer of 2-amino-5-bromobenzophenone oxime (**32**) with monobromoacetic acid methyl ester in the presence of NaOMe with subsequent saponification of the resulting O-alkylation product **33** with the formation of compound **31**.



In accordance with the data of [8,9] molecules of the thiosemicarbazones of aromatic aldehydes in the gas phase may be found in a linear **I** or two cyclic forms, 1,2,4-triazoline-3-thione **II** or 1,3,4-thiadiazole **III**. For each of the tautomeric forms there is a characteristic distinct type of fragmentation under electron impact. According to the data of [9] the presence in the gas phase of the linear tautomer is confirmed by the presence of fragment ions formed by breaking C–N and N–N bonds.



A scheme for the proposed fragmentation of 6-bromo-4-phenylquinazoline-2-carbaldehyde thiosemicarbazide (**16**) is given below as an example. The presence in the mass spectrum of fragment ions with *m/z* 325 and 310 corresponding to fragments Φ_4 and Φ_2 and the absence of fragment ions characteristic of the cyclic tautomeric forms permits the assumption that thiosemicarbazone **16** is found in the linear form in the gas phase. The stability of the linear form, according to [8], may be explained by the effective linear π-*p*-π conjugation chain in it.



The fragmentation of thiosemicarbazones **17** and **18** is analogous to the above.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer in $CHCl_3$ solution. The UV spectra were obtained on a SF-56 spectrophotometer in ethyl alcohol at a concentration of 3×10^{-5} M at a cell thickness of 10 mm. The mass spectra were recorded on a MX-1321 mass spectrometer using direct insertion of samples into the ion source, the energy of the ionizing electrons was 70 eV, ionization chamber temperature was 150°C.

The characteristics of the compounds synthesized are given in Tables 1 and 2.

TABLE 1. 6-Substituted 4-Phenylquinazoline-2-carbaldehydes **4-6**, Their Oximes **7-9**, Hydrazones **10-12**, Semicarbazones **13-15**, Thiosemicarbazones **16-18**, and 1,11-Dimethyl-8,18-disubstituted 6,16-Diphenyl-1,2,3,11,12,13-hexahydrodibenzo[*g,o*]-4,14-dioxa-1,5,11,15-tetraazacyclohexadecine-2,12-diones **22-24**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	N	S		
4	$C_{15}H_9BrN_2O$	57.48 / 57.53	2.27 / 2.90	8.97 / 8.95	—	163-165	72
5	$C_{15}H_8BrClN_2O$	51.79 / 51.83	2.28 / 2.32	8.02 / 8.06	—	168-170	75
6	$C_{16}H_{12}N_2O$	77.36 / 77.40	4.90 / 4.87	11.32 / 11.28	—	164-165	64
7	$C_{15}H_{10}BrN_3O$	54.87 / 54.90	3.04 / 3.07	12.77 / 12.80	—	251-253	70 (A), 73 (B)
8	$C_{15}H_9BrClN_3O$	49.72 / 49.68	2.46 / 2.50	11.56 / 11.59	—	290-295	82 (A), 84 (B)
9	$C_{16}H_{13}N_3O$	73.02 / 72.99	4.95 / 4.98	15.99 / 15.96	—	228-230	65 (A), 67 (B)
10	$C_{15}H_{11}BrN_4$	55.02 / 55.06	3.42 / 3.39	17.17 / 17.12	—	173-175	75 (A), 65 (B)
11	$C_{15}H_{10}BrClN_4$	49.86 / 49.82	2.76 / 2.79	15.53 / 15.49	—	163-168	83 (A), 70 (B)
12	$C_{16}H_{14}N_4$	73.22 / 73.26	5.41 / 5.38	21.33 / 21.36	—	174-175	72 (A), 63 (B)
13	$C_{16}H_{12}BrN_5O$	51.89 / 51.91	3.29 / 3.27	18.89 / 18.92	—	212-215	68 (A), 56 (B)
14	$C_{16}H_{11}BrClN_5O$	47.52 / 47.49	2.78 / 2.74	17.35 / 17.31	—	220–223	70 (A), 62 (B)
15	$C_{17}H_{15}N_5O$	66.89 / 66.87	4.89 / 4.95	22.97 / 22.94	—	221-224	73 (A), 58 (B)
16	$C_{16}H_{12}BrN_5S$	49.72 / 49.75	3.18 / 3.13	18.15 / 18.13	8.27 / 8.30	222-224	69 (A), 54 (B)
17	$C_{16}H_{11}BrClN_5S$	45.65 / 45.68	2.59 / 2.64	16.70 / 16.65	7.63 / 7.62	223-225	74 (A), 58 (B)
18	$C_{17}H_{15}N_5S$	63.56 / 63.53	4.73 / 4.70	21.82 / 21.79	9.95 / 9.98	182-185	72 (A), 60 (B)
22	$C_{32}H_{26}Br_2N_4O_4$	55.65 / 55.67	3.77 / 3.80	8.13 / 8.12	—	385-390	66
23	$C_{32}H_{24}Br_2Cl_2N_4O_4$	50.59 / 50.62	3.21 / 3.19	7.40 / 7.38	—	387-391	72
24	$C_{34}H_{32}N_4O_4$	72.82 / 72.84	5.72 / 5.75	9.97 / 9.99	—	383-385	70

TABLE 2. Spectral Characteristics of Compounds **4-18** and **22-24**

Compound	IR spectrum, ν, cm^{-1}					UV spectrum, λ_{max}, nm (log ε)	M^+, *m/z*
	N–H	OH	C=O	C=N	C=S		
1	2	3	4	5	6	7	8
4	—	—	1725	1600	—	232 (4.44), 274 (3.71), 326 (3.54)	312
5	—	—	1725	1595	—	233 (4.53), 271 (3.62), 320 (3.50)	346
6	—	—	1730	1605	—	229 (4.37), 274 (3.59), 325 (3.56)	248

TABLE 2 (continued)

1	2	3	4	5	6	7	8
7	—	3545	—	1595	—	257 (4.50), 297 (4.03), 335 (3.70)	327
8	—	3560	—	1595	—	255 (4.59), 295 (4.10), 332 (3.66)	361
9	—	3565	—	1600	—	256 (4.51), 299 (3.80), 332 (3.65)	263
10	3285, 3435	—	—	1600	—	264 (4.25), 306 (4.41), 360 (3.69)	326
11	3295, 3440	—	—	1595	—	265 (4.28), 309 (4.48), 359 (3.80)	360
12	3280, 3425	—	—	1595	—	263 (4.16), 297 (4.25), 358 (3.57)	262
13	3315, 3380, 3440, 3495	—	1690	1600	—	265 (4.37), 302 (4.57), 361 (3.82)	369
14	3330, 3395, 3485, 3515	—	1700	1595	—	267 (4.34), 306 (4.57), 362 (3.78)	403
15	3335, 3400, 3455, 3520	—	1695	1575	—	255 (4.25), 292 (4.46), 359 (3.66)	305
16	3310, 3350, 3485	—	—	1595	1095	249 (4.24), 281 (4.26), 333 (4.53)	385
17	3315, 3355, 3490	—	—	1575	1090	231 (4.43), 277 (4.23), 335 (4.55)	419
18	3325, 3365, 3500	—	—	1580	1095	252 (4.24), 274 (4.25), 330 (4.50)	312
22	—	—	1660	1590	—	201 (4.65), 262 (4.21)	688
23	—	—	1655	1580	—	205 (4.68), 262 (4.25)	756
24	—	—	1655	1585	—	203 (4.67), 262 (4.24)	560

6-Bromo-4-phenylquinazoline-2-carbaldehyde (4). Compound **19** (0.1 g, 0.302 mmol) was heated at 194-196°C until gas evolution ceased. The melt was cooled to room temperature. The oil obtained was triturated with hexane. The resulting white solid was filtered off, dried, and recrystallized from hexane. Compound **4** (0.68 g, 72%) was obtained.

Compounds 5 and 6 were obtained analogously from compounds **20** and **21**.

6-Bromo-4-phenylquinazoline-2-carbaldehyde Oxime (7). A. Hydroxylamine sulfate (0.052 g, 0.319 mmol) was added to a solution of compound **4** (0.1 g, 0.319 mmol) in ethanol (20 ml) and the mixture stirred for 15 min. The precipitated white solid was filtered off, dried, washed with water, and recrystallized from ethanol. Yield of oxime **7** 0.074 g.

B. A solution of 2 N NaOH (0.32 ml) was added to a suspension of compound **1** (0.1 g, 0.151 mmol) and hydroxylamine sulfate (0.05 g, 0.302 mmol) in ethanol (11 ml) and the mixture boiled for 30 min. The reaction mixture was then poured into water, the precipitated amorphous white solid was filtered off, and recrystallized from ethanol. Yield of **7** 0.072 g.

Compounds 8-18 were obtained by the interaction of **1-3** and **4-6** with the appropriate nitrogenous bases by a procedure analogous to the above using hydroxylamine, hydrazine hydrate, and the hydrochlorides of semicarbazide and thiosemicarbazide as nucleophilic agent.

1,11-Dimethyl-8,18-dibromo-6,16-diphenyl-1,2,3,11,12,13-hexahydrodibenzo[*g*,*o*]-4,14-dioxa-1,5,11,15-tetraazacyclohexadecine-2,12-dione (22). Dimethyl sulfate (0.03 ml, 0.302 mmol) was added with stirring to a suspension of compound **1** (0.2 g, 0.302 mmol) and NaOMe (0.033 g, 0.604 mmol) in 1,4-dioxane (30 ml).

Stirring was continued for 2 h at room temperature, and the reaction mixture was poured into water, the precipitated white amorphous solid was filtered off, washed with water, dried, and crystallized from dioxane. Compound **22** (0.138 g) was obtained.

Compounds 23 and 24 were synthesized analogously.

***syn* Isomer of 5-Bromo-2-methylaminobenzophenone Oxime (26).** A solution of NaOH (1.38 g) in water (5 ml) was added to a mixture of compound **25** (10 g, 35 mmol) and hydroxylamine sulfate (2.83 g, 17 mmol) in ethanol (50 ml). The mixture was boiled for 6 h, poured into water, and acidified to pH ~7. The precipitated white clotted solid was filtered off, washed with water, dried, and recrystallized from a benzene–hexane mixture. The *syn* isomer of oxime **26** was obtained, yield 9.047 g (86%); mp 155-157°C. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3555 (O–H), 3430 (N–H), 1590 (C=N). UV spectrum, λ_{max}, nm (log ε): 250 (4.29), 319 (3.27). Mass spectrum, *m/z*: 304 $[M]^+$, 286 $[M\text{-}H_2O]^+$, 272 $[M\text{-}H_2NO]^+$, 271 $[M\text{-}H_2O\text{-}CH_3]^+$, 207 $[M\text{-}H_2O\text{-}Br]^+$, 193 $[M\text{-}H_2NO\text{-}Br]^+$. Found, %: C 55.12; H 4.31; N 9.21. $C_{14}H_{13}BrN_2O$. Calculated, %: C 55.10; H 4.29; N 9.18.

7-Bromo-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (28) and 8-Bromo-1-methyl-6-phenyl-1,3-dihydro-2H-4,1,5-benzoxadiazocin-2-one (29). Chloroacetyl chloride (2.66 ml, 33 mmol) and NaOH (2.64 g) in water (10 ml) were added alternately with stirring to a solution of the *syn* isomer of oxime **26** (10 g, 33 mmol) in 1,4-dioxane (10 ml) so that the medium remained neutral or weakly alkaline but the temperature did not rise above 5°C. The mixture was stirred for 2 h to 2 h 30 min, then poured into water. The precipitated solid was separated, washed with water, and dried. Fractional crystallization from a mixture of benzene–hexane gave compound **28** (0.994 g, 18%) and compound **29** (4.095 g, 75%). The properties of compound **28** are described in [4]. Compound **29** had mp 140-142°C. IR spectrum, ν, cm^{-1}: 1650 (C=O), 1585 (C=N). UV spectrum, λ_{max}, nm (log ε); 224 (4.45), 285 (3.52). Mass spectrum, *m/z*: 344 $[M]^+$, 314 $[M\text{-}CH_2O]^+$, 299 $[M\text{-}CH_2O\text{-}CH_3]^+$, 286 $[M\text{-}COCH_2O]^+$, 272 $[M\text{-}COCH_2ON]^+$, 207 $[M\text{-}COCH_2O\text{-}Br]^+$, 193 $[M\text{-}COCH_2ON\text{-}Br]^+$. Found, %: C 55.65; H 3.82; N 8.11. $C_{16}H_{13}BrN_2O_2$. Calculated, %: C 55.67; H 3.80; N 8.12.

***syn* Isomer of N-(2-Amino-5-bromodiphenylmethylene)iminooxyacetic Acid (31).** A solution of NaOH (0.84 g) in water (2 ml) was added to a solution of N-(2-amino-5-bromodiphenylmethylene)-iminooxyacetic acid methyl ester (*syn* isomer) (**33**) (5 g, 14 mmol) in 1,4-dioxane (15 ml). The suspension obtained was boiled for 30 min. The reaction mixture was poured into water, acidified to pH ~7, the precipitated white solid was filtered off, washed with water, dried, and recrystallized from a benzene–hexane mixture. Compound **31** (4 g, 82%) was obtained; mp 170-172°C. IR spectrum, ν, cm^{-1}: 3445 ($NH_{2\ antisym}$), 3340 ($NH_{2\ sym}$), 1725 (C=O), 1620 (C=N). UV spectrum, λ_{max}, nm (log ε): 246 (4.11), 318 (3.12). Mass spectrum, *m/z*: 348 $[M]^+$, 272 $[M\text{-}OHCH_2COOH]^+$, 257 $[M\text{-}NH_2OCH_2COOH]^+$, 193 $[M\text{-}OHCH_2COOH\text{-}Br]^+$, 178 $[M\text{-}NH_2OCH_2COOH\text{-}Br]^+$. Found, %: C 51.58; H 3.76; N 8.02. $C_{15}H_{13}BrN_2O_3$. Calculated, %: C 51.60; H 3.75; N 8.02.

The synthesis of compound **33** from **32** was described in [1].

Acid Hydrolysis of Macrocycle 1. Conc. hydrochloric acid (2 ml) was added to a solution of compound **1** (1 g, 2 mmol) in 1,4-dioxane (7 ml). The suspension obtained was boiled for 2 h. The reaction mixture was poured into water, the precipitated solid was filtered off, washed with water, dried, and dissolved in a benzene–hexane 1:1 mixture (10 ml). The insoluble solid was filtered off, recrystallized from benzene, and compound **31** (0.175 g, 25%) was obtained. The mother liquor was evaporated, the precipitated solid was filtered off, crystallized from hexane, and 2-amino-5-bromobenzophenone (**30**) (0.151 g, 27%), described previously in [10], was obtained.

Alkaline Hydrolysis of Macrocycle 1. A solution of NaOH (0.32 g) in water (2 ml) was added to a solution of compound **1** (1 g, 2 mmol) in 1,4-dioxane (5 ml). The suspension obtained was boiled for 5 h. The reaction mixture was poured into water, the precipitated solid was filtered off, washed with water, dried, and recrystallized from hexane. Compound **30** (0.817 g, 74%) was obtained.

Compounds 1-3, 19-21, and 25 were synthesized analogously to those described in [1,2,10].

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