Nitrogen Bridgehead Compounds. Part 85 [1]. Synthesis and Reactivity of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones

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Dedicated to the memory of Professor Roland K. Robins

3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** and its 1-methyl and 1-hydroxy derivatives **8** and **13** were prepared by different routes. The active methylene group of compound **3** was reacted with electrophilic reagents (bromine, phenyldiazonium chloride, nitrous acid, a Vielsmeier-Haack reagent, aromatic aldehydes and diethyl oxalate) to yield 1-substituted-3,4-dihydro[1*H*,6*H*]-1,4-oxazino[3,4-*b*]quinazo-lin-6-ones. The reactivity of 1-hydroxy and 1-bromo derivatives **13** and **15** were also investigated in some reactions. The 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones were characterized by means of uv, ^{1}H and ^{13}C nmr spectroscopy.

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A wide range of 2,3-condensed 4(3*H*)-quinazolinones occurs in different families of the plant kingdom and microorganisms and their representatives exhibit different pharmacological effects [2-5]. Among them some [1,4]oxazino[3,4-*b*]quinazolin-6-ones were obtained by the chemical transformations of fungus metabolites isolated from *Aspergillus clavatus* and *Aspergillus fumigatus* [6-8]. Only a few other papers deal with the investigation of the synthesis and the reactivity of this ring system [9-15].

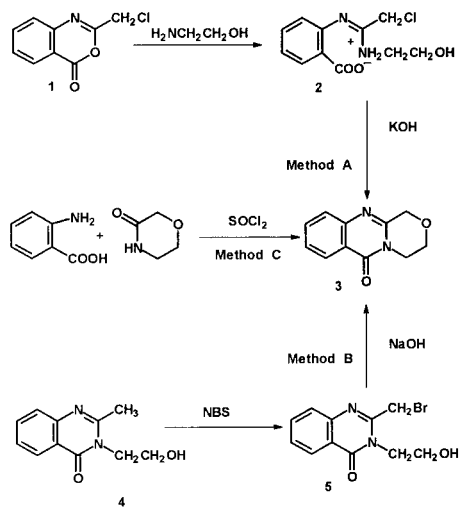
The present paper reports our results on the synthesis of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** and its 1-hydroxy **13** and 1-methyl derivatives **8**, and the reactivity of position 1 of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino-[3,4-*b*]quinazolin-6-one skeleton toward different electrophilic and nucleophilic reagents and the stereochemistry of the products.

Synthesis.

Earlier 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** was prepared by the oxidative cyclisation of *N*-(2-aminobenzyl)morpholine and the cyclocondensation of isatoic anhydride and 3-ethoxy-3,4-dehydromorpholine in 11% and 55% yields, respectively [9,11]. Compound **3** was obtained in moderate yield when 2-chloromethyl-3,1-benzoxazin-4-one **1**, prepared in the reaction of *N*-(chloroacetyl)anthranilic acid and acetic anhydride, was reacted with ethanolamine in water at room temperature, then the reaction mixture was treated with potassium hydroxide (Method A) (see Scheme 1).

A better yield was achieved when 2-bromomethyl-3-(2-hydroxyethyl)quinazolin-4-one **5**, obtained from 2-methyl-3-(2-hydroxyethyl)quinazolin-4-one **4** with NBS in chloroform under reflux for 3 hours in the presence of a catalytic amount of benzoyl peroxide, was cyclised by the treatment of 2.5% aqueous sodium hydroxide at room temperature (Method B).

Scheme 1

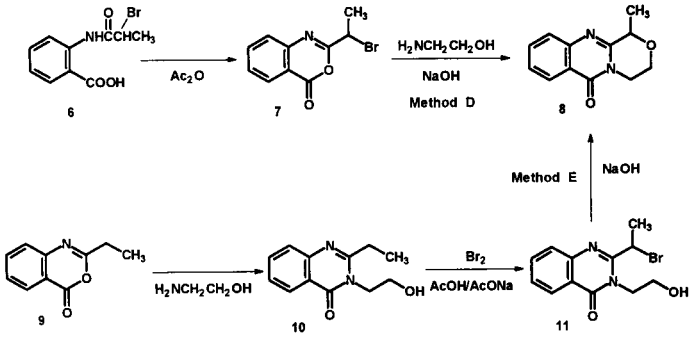


The application of Kametani's method [16] the reaction of 3-oxomorpholine and 2-sulfinylaminobenzoyl chloride [17] prepared *in situ* from anthranilic acid by thionyl chloride, gave compound **3** in 57% yield (Method C).

The 1-methyl derivative **8** was synthesized by the reaction of ethanolamine and 2-(1-bromoethyl)-3,1-benzoxazin-4-one **7**, obtained from *N*-(2-bromopropionyl)anthranilic acid **6** by the treatment of acetic anhydride, in 23% yield (Method D) (see Scheme 2). The cyclisation of 2-(1-bromoethyl)-3-(2-hydroxyethyl)quinazolin-4-one **11** with 2.5% aqueous sodium hydroxide at ambient temperature gave 1-methyl derivative **8** in 43% yield (Method E). Quinazo-

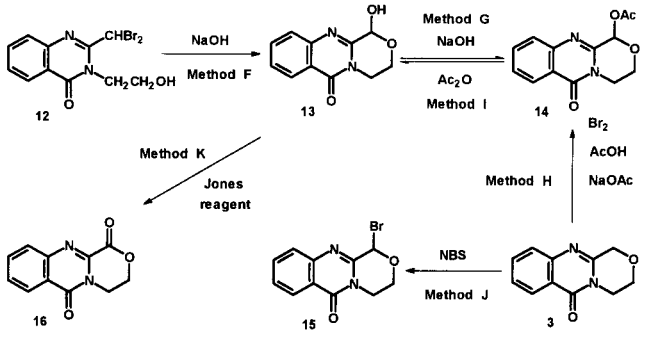
lin-4-one **11** was prepared from 2-ethyl-3,1-benzoxazin-4-one (**9**) *via* 2-ethyl-3-(2-hydroxyethyl)quinazolin-4-one **10** in two steps (see Scheme 2).

Scheme 2



The treatment of 2-methyl-3-(2-hydroxyethyl)quinazolin-4-one **4** with bromine in glacial acetic acid in the presence of sodium acetate afforded the 2-dibromomethyl derivative **12**, which was cyclised by the action of 2.5% aqueous sodium hydroxide at room temperature to give 1-hydroxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **13** (Method F) (see Scheme 3).

Scheme 3



Reactions at Position 1 of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino-[3,4-*b*]quinazolin-6-one **3**.

Similarly to the isosteric pyrido[2,1-*b*]quinazolin-6-one, 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** contains an active methylene group at position 1, which reacts easily with different electrophiles.

The bromination of compound **3** with bromine in acetic acid in the presence of sodium acetate gave the 1-acetoxy derivative **14** in moderate yield (Method H), instead of the desired 1-bromo derivative **15**, indicating that the compound **15** contains a very reactive bromine function (see Scheme 3).

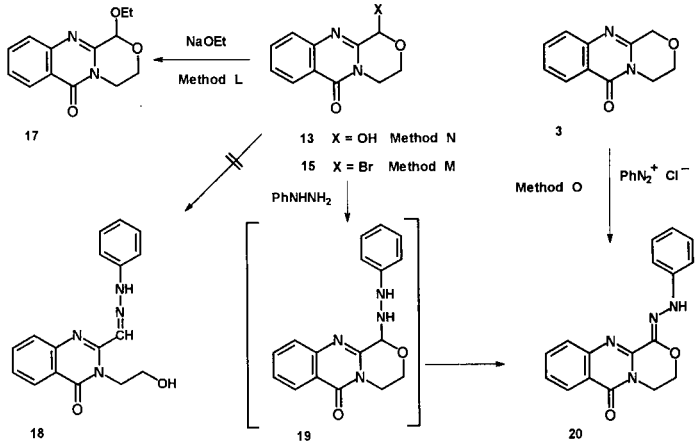
The [1,4]oxazino[3,4-*b*]quinazolin-6-one skeleton proved to be resistant under basic hydrolytic conditions, because hydrolysis of the acetoxy derivative in 2.5% aqueous sodium hydroxide gave the 1-hydroxy compound **13** in excellent yield (Method G). The acetylation of compound **13** with acetic anhydride in pyridine afforded 1-acetoxyoxazinoquinazolinone **14** in good yield (Method I).

When the bromination of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** was carried out with NBS in chloroform in the presence of a catalytic amount of benzoyl peroxide, the 1-bromo derivative **15** was obtained in 46% yield (Method J).

The oxidation of 1-hydroxyoxazinoquinazolin-6-one **13** with Jones reagent [18] afforded oxazinoquinazoline-1,6-dione **16** [10] in good yield (Method K).

The reaction of the 1-bromo derivative **15** and sodium ethoxide in ethanol at room temperature afforded 1-ethoxyoxazinoquinazoline **17** in high yield (Method L) (see Scheme 4).

Scheme 4



When the 1-bromo compound **15** (Method M) or the 1-hydroxy derivative (Method N) was reacted with phenylhydrazine in boiling ethanol, instead of the 1-phenylhydrazino **19** derivative or the ring opened derivative **18**, an oxidised product **20** could be isolated from the reaction mixture. The ring opened derivative **18** was prepared in the reaction of 2-dibromomethyl-3-(2-hydroxyethyl)quinazolin-4-one **12** and phenylhydrazine. Phenylhydrazono product **20** was identical to the compound obtained by diazonium coupling between 3,4-dihydro[1,4]oxazino[3,4-*b*]-quinazolone **3** and phenyldiazonium chloride (Method O). Because the phenylhydrazono derivative **20** was also obtained when the reaction of the 1-bromo compound **15** and phenylhydrazine was carried out in an inert atmosphere for its formation, an osazone-like mechanism is suggested which was justified for that of 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-arylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones in the reaction of 9-bromo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-bromo-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones, respectively, with arylhydrazines [19,22].

Table 1

Physical and Analytical Data of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones **3, 8, 13-17** and **20-24**

Starting Compound	Product	Method	Mp °C	Yield %	Recrystallization solvent	Molecular Formula	Analyses Calcd. C	H	N	Found C	H	N
1	**3**	A	159-161 [a]	44.6	EtOH	$C_{11}H_{10}N_2O_2$	63.34	4.98	13.85	63.21	5.02	13.71
5	**3**	B	159-161	56.9	EtOH							
	3	C	158-160	84.0	EtOH							
7	**8**	D	158-160	23.0	EtOH	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.73	5.65	13.11
11	**8**	E	158-160	43.0	EtOH							
12	**13**	F	203-204	40.8	EtOH	$C_{11}H_{10}N_2O_3$	60.55	4.62	12.84	60.41	4.76	12.68
9	**13**	G	203-204	87.2	EtOH							
3	**14**	H	136-137	26.9	EtOAC	$C_{13}H_{12}N_2O_4$	60.00	4.65	10.76	59.85	4.73	10.58
13	**14**	I	138-139	73.0	EtOH-H_2O							
3	**15**	J	115-116	45.9	$CHCl_3$-Hexane	$C_{11}H_9BrN_2O_2$	47.00	3.23	9.97	47.16	3.27	9.81
13	**16**	K	217-219 [b]	72.2	MeOH	$C_{11}H_8N_2O_3$	61.11	3.73	12.96	61.14	3.78	13.12
15	**17**	L	121-123	83.0	EtOH	$C_{13}H_{14}N_2O_3$	63.40	5.73	11.38	63.27	5.79	11.52
15	**20**	M	212-214	68.9	EtOH	$C_{17}H_{14}N_4O_2$	66.66	4.61	18.29	66.47	4.47	18.54
13	**20**	N	212-214	76.4	EtOH							
3	**20**	O	210-211	69.0	EtOH							
3	**21**	P	287-290	50.2	EtOH	$C_{11}H_9N_3O_3$	57.14	3.92	18.17	57.39	4.05	17.94
3	**22a**	R	157-158	86.0	EtOH	$C_{18}H_{14}N_2O_2$	74.47	4.86	9.65	74.16	4.93	9.80
3	**22b**	R	180	71.8	EtOH	$C_{16}H_{12}N_2O_3$	68.57	4.32	9.99	68.31	4.27	10.03
3	**23**	S	179-182	68.0	DMF	$C_{14}H_{15}N_3O_2$	65.36	5.88	16.33	65.12	5.96	16.08
3	**24**	T	203-205	78.0	DMF	$C_{15}H_{14}N_2O_5$	59.60	4.67	9.27	59.42	4.71	9.33

[a] Lit mp 147° [9], mp 152° [11]. [b] Lit mp 219° [10].

Table 2

UV Data of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones **3, 8, 13, 14, 16, 17** and **20-24** in 96% Ethanol

Compound No.	λ max	(ε)								
3	316	(1660)	305	(2050)	279	(41000)	225	(12300)		
8	318	(2800)	305	(3400)	276	(7000)	268	(7200)	226	(23030)
13	316	(3100)	303	(3980)	276	(8200)	270	(8190)	226	(26330)
14	316	(2600)	303	(3040)	280	(6070)	271	(6050)	226	(19090)
16	302	(8100)	228	(19650)						
17	316	(2050)	304	(2670)	278	(5340)	260	(5340)	226	(17240)
20	390	(19700)	301 [i]	(6960)	294	(7430)	246 [i]	(15080)	228	(20700)
21	356	(27500)	343	(28800)	229	(20500)	217	(22400)		
22a	356 [i]	(24700)	346	(25600)	254 [i]	(7980)	228	(16500)		
22b	370	(31000)	252	(10530)	226 [i]	(18200)				
23	384	(33800)	276	(6420)	265	(6420)	226	(20000)		
24	376	(10000)	279	(4200)	225	(14800)				

[i] = Inflexion.

Table 3

^{1}H NMR Data of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones **3, 8, 13, 14, 16, 17** and **20-24** in DMSO-d_6

Compound No.	H-1 H_2-1	H_{eq}-3	H-3	H_{ax}-3	H_{eq}-4	H_2-4	H_{ax}-4	H-7	H-8	H-9	H-10	Others
3	4.70 s	–	4.10 t	–	–	3.91 t	–	8,.11	7.49 t	7.80 t	7.57 d	
8	4.78 q	4,20 m		3.95 m	4.07 m	–	3.82 m	8.12 d	7.50 t	7.81 t	7.61 d	1.60 d (Me), $^3J_1$, Me = 6.6 Hz
13	5.68 d	4.35 m		– 4.05 m	–		3.83 m	8.15 d	7.56 t	7.85 t	7.67 d	7.57 d (OH), $^3J_1$, OH = 1.6 Hz
14	6.69 s	–	–	– 4.22 m	–	–	3.83 m	8.17 d	7.57 t	7.86 t	7.69 d	2.17 s (COMe)
16	–	–	4.75 t	–	–	4.33 t	–	8.20 d	7.70 t	7.95 t	7.88 d	
17	5.56 s	4.27 m	–	– 4.12 m	–	–	3.88 m	8.18 d	7.60 t	7.89 t	7.72 d	3.88 qd and 3.74 qd (OCH_2) 1.26 t (Me)
20	–	–	4.64 t	–	–	4.36 t	–	8.20 d	7.58 t	7.89 t	7.81 d	9.91 s (NH), 7.35-7.27 and 6.85 (Ph)
21	–	–	4.50 t	–	–	4.25 t	–	8.15 d	7.57 t	7.85 t	7.70 d	11.09 s (OH)
22a	–	–	4.48 t	–	–	4.24 t	–	8.15 d	7.53 t	7.87 t	7.73 d	7.21 (=CH), 7.82, 7.40 and 7.29 (Ph)
22b	–	–	4.54 t	–	–	4.29 t	–	8.18 d	7.56 t	7.88 t	7.74 d	7.21 s (=CH-), 6.69 (H-4') 6.93 (H-3'), 7.80 (H-5')
23	–	–	4.79 t	–	–	4.38 t	–	8.27 d	7.79 t	8.00 t	7.98 d	7.25 (=CH), 2.54 s (2 x Me)
24	–	–	4.12 t	–	–	3.99 t	–	8.04 d	7.39 t	7.77 t	7.59 d	4.25 q (OCH_2), 1.27 t (Me) and 13.4 s (N(11)H)

Table 4

^{13}C NMR Data of 3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones **3, 8, 13, 14, 16, 17** and **20-24** in DMSO-d_6

Compound No.	C-1	C-3	C-4	C-6	C-6a	C-7	C-8	C-9	C-10	C-10a	C-11a	Other
3	66.9	63.6	41.2	160.7	120.3	126.1	126.2	134.6	126.5	147.0	151.7	
8	72.5	62.1	41.9	160.8	120.1	126.1	126.6	134.6	126.9	147.0	155.3	19.5 (CH_3)
13	89.7	56.4	40.7	160.6	120.6	126.2	127.1	134.7	127.1	147.0	151.7	
14	89.2	59.2	40.2	160.3	120.8	126.3	127.3	134.9	127.7	146.7	148.1	21.0 (CH_3), 169.4 (-CO)
16	156.4	64.8	38.6	158.5	120.9	125.6	128.0	134.3	128.4	145.5	140.3	
17	94.9	56.8	40.5	160.5	120.8	126.3	127.3	134.9	127.5	146.8	149.5	15.3 (CH_3), 63.6 (OCH_2)
20	142.5	64.3	40.5	160.0	120.2	126.3	126.8	134.8	127.8	147.7	145.0	113.2, 119.7, 129.1, 135.7, (Ph)
21	142.3	64.2	40.3	159.7	120.8	126.3	127.5	134.8	127.8	147.2	146.1	
22a	144.3	63.9	40.6	160.1	119.9	126.3	127.4	134.7	127.8	147.2	146.0	111.1 (-CH=), 126.8, 128.7, 129.8 (Ph)
22b	142.5	64.1	40.6	160.1	120.0	126.3	126.7	134.8	127.4	147.4	145.5	112.7 (-CH=), 143.2 (C-5'), 150.4 (C-2'), 100.7 (C-3'), 112.4 (C-4)
23	149.1	63.2	41.7	161.7	118.2	123.4	125.9	134.0	126.6	130.3	148.9	125.9 (=C-), 42.7 (2 xCH_3)
24	158.6	63.0	41.4	158.6	119.5	119.7	125.3	135.7	127.1	145.5	140.1	14.2 (CH_3), 61.2 (OCH_2), 164.3 (CO), 164.9 (CO)

Table 5

^{13}C Substituent Chemical Shift (SCS) for Substituent in Position 1 at Compounds **8, 13, 14** and **17** [a]

Compound	Substituent	α	γ	δ
8	1-Me	5.9	-1.5	0.7
13	1-OH	21.8	-7.2	-0.5
14	1-OAc	21.3	-4.4	-1.0
17	1-OEt	28.0	-6.8	-0.7

[a] Calculated by subtracting the C-1 chemical shift for compound **3** from the C-1 chemical shift for compounds **8, 13, 14** and **17**.

Similar to the active 9-methylene group of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [23-29] the active methylene group of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]-quinazolin-6-one **3** also reacted smoothly with aromatic aldehydes under fusion conditions, with sodium nitrite in acetic acid at 0-5°, with the Vielsmeier-Haack reagent (a mixture of phosphoryl chloride and dimethylformamide) at 60°, and with diethyl oxalate in ethanol in the presence of sodium ethylate under reflux to give the appropriate 1-substituted derivatives **21-25** in good yields (see Table 1).

Spectroscopic Studies.

The uv, ^1H and ^{13}C nmr data on 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones are compiled in Tables 2-5.

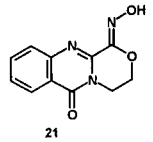
The unsubstituted oxazinoquinazolin-6-one **3** has two equally populated but rapidly interconverting half-chair forms, which is indicated by the time-averaged signals for the methylene protons at positions 3 and 4 in ^1H nmr spectra.

Introduction of a substituent into position 1 (compounds **8, 13, 14** and **17**) resulted in the predominance of one of the two half-chair conformers. Unambiguous assignment of 1-C, 3-C, 4-C, 7-C, 8-C, 9-C, 10-C and H-1, H-3, H-4, H-7, H-8, H-9, H-10 carbons and protons, respectively, was based on two dimensional heteronuclear chemical shift correlation experiments.

The characteristic γ-gauche values of SCS with **13, 14** and **17** suggest the pseudoaxial orientation of the hydroxyl, acetoxy and ethoxy group in the dominant conformation, which may be a consequence of a stereoelectronic effect developed between the occupied $\pi_{C=N}$ and the antibonding σ^*_{C-O} orbitals. The 1-methyl derivative **8** has almost equal populations of conformers with a pseudoequatorial or a pseudoaxial methyl group. An earlier similar situation was found for 9-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [30].

It is interesting while the 2-carbo analogue 6-phenylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one exists as a 45:55 mixture of *E* and *Z* geometric isomers in DMSO-d_6, (δ_{NH} 9.90 ppm for *E* isomer and 14.60 ppm for *Z* isomer) [18], the phenylhydrazono derivative **20** is present almost exclusively as the *E* isomer (δ_{NH} 9.90 ppm).

It is very likely that the other compounds, **21-23,** containing an exo-double bond at position 1, are also present as *E* isomers, while 1-oxalyl derivative **24** is present in 6*H*,11*H* tautomeric form [22].



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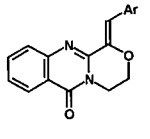
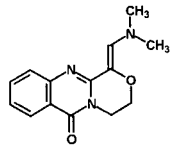
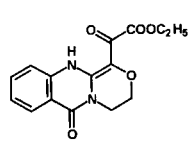


22a Ar = Ph

22b Ar = 2-furyl



23



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EXPERIMENTAL

Melting points are uncorrected. Yields were not optimized. The uv spectra were recorded on a Unicam SP-800 spectrophotometer, the ir spectra were recorded for potassium bromide pellets with a Zeiss UR-20 spectrophotometer. The ^1H and ^{13}C nmr spectra were measured on a Bruker AC 400 spectrometer at 400.132 MHz and 100.614 MHz, respectively. Chemical shifts are given on the δ scale, and TMS was used as the internal standard.

2-Chloromethyl-3,1-benzoxazin-4-one (**1**).

A solution of *N*-(2-chloroacetyl)anthranilic acid [31] (2.13 g, 10 mmoles) in acetic anhydride (8 ml) was heated under reflux while the acetic acid formed was distilled off. When the temperature of the vapor reached 140° the reaction mixture was evaporated *in vacuo* to dryness. The oily residue was dissolved in chloroform, and the soluion was decolorized with active charcoal and filtered. The filtrate was diluted with hexane. The precipitated crystals were collected by filtration. The crude crystals were recrystallized from a mixture of chloroform and hexane to give 2-chloromethyl-3,1-benzoxazin-4-one (**1**) (1.75 g, 89%, mp 87-88°); ^1H-nmr (deuteriochloroform): 4.42 (2H, s, C*H*$_2$-Cl), 7.5-8.5 (3H, m, Ar-*H*-6,7,8), 8.25 (1H, d, Ar-*H*-5).

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.18; H, 3.11; N, 7.03.

3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**3**).

Method A.

To a suspension of 2-chloromethyl-3,1-benzoxazin-4-one **1** (1.96 g, 10 mmoles) in water (10 ml) ethanolamine (0.61 g, 10 mmoles) was added and the reaction mixture was extensively stirred at ambient temperature for 1.5 hours. Then a solution of potassium hydroxide (1.7 g in 4 ml of water) was added to the reaction mixture, which gradually became clear, and after 15 minutes stirring, new crystals started to precipitate. The reaction mixture was allowed to stand overnight in the refrigerator. The product **3** was filtered off, washed with ethanol, and it was recrystallized from ethanol. The yield and melting point are given in Table 1.

Method B.

2-Bromomethyl-3-(2'-hydroxyethyl)quinazolin-4-one **5** (2.89 g, 10 mmoles) was stirred in 2.5% aqueous sodium hydroxide solution (24 ml) at ambient temperature for 1 hour. The crystalline product was filtered off, washed with water and recrystallized from ethanol to give compound **3** (see Table 1).

Method C.

Anthranilic acid (1.3 g, 10 mmoles) and thionyl chloride (7 g) were reacted in boiling benzene (20 ml) under nitrogen for 2 hours. The reaction mixture was evaporated *in vacuo* to dryness and the residue was dissolved in chloroform (20 ml). To the solution in chloroform 3-oxomorpholine (1.01 g, 10 mmoles) was added. The reaction mixture was allowed to stand at room temperature overnight and then it was treated with 10% aqueous sodium hydroxide solution (10 ml). The organic phases were separated, washed with 10% aqueous sodium hydroxide then with water. The dried (sodium sulfate) organic layer was evaporated *in vacuo* to dryness and the residue was crystallized from ethanol to give compound **3** (see Table 1).

2-Bromomethyl-3-(2-hydroxyethyl)quinazolin-4-one (**5**).

A solution of 2-methyl-3-(2-hydroxyethyl)quinazolin-4-one **4** [32] (2.04 g, 10 mmoles) in chloroform was reacted with *N*-bromosuccinimide (1.78 g, 10 mmoles) in the presence of a catalytic amount of benzoyl peroxide at reflux temperature for 1.5 hours. The reaction mixture was cooled to room temperature and it was washed with water and after drying over sodium sulfate the organic phase was evaporated *in vacuo* to dryness. The residue was crystallized from a mixture of ethyl acetate and hexane to give compound **5** (1.21 g, 43%, mp 163-165°); uv (ethanol): λ max (log ϵ) 317 (3.65), 304 (3.82), 284 (4.00), 227 (4.39); ^1H-nmr (deuteriochloroform): 4.05 (2H, m, N-C*H*$_2$), 4.47 (2H, m, C*H*$_2$O), 4.71 (2H, s, C*H*$_2$-Br), 7.3-7.9 (3H, m, Ar-*H*-6,7,8), 8.16 (1H, d, J = 8 Hz, Ar-*H*-5).

Anal. Calcd. for $C_{11}H_{11}BrN_2O$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.47; H, 4.01; N, 9.73.

N-(2-Bromopropionyl)anthranilic Acid (**6**).

To a stirred solution of anthranilic acid (13.7 g, 100 mmoles) in dimethylformamide (30 ml) 2-bromopropionyl bromide (21.6 g, 100 mmoles) was dropwise added at 0°. Then the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was treated with ice water (220 ml) and the precipitated crystals were filtered off, washed with water and dried to give compound **6** (22.3 g, 82%, mp 176-177°).

Anal. Calcd. for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; N, 5.15. Found: C, 43.98; H, 3.78; N, 5.45.

2-(1-Bromoethyl)-3,1-benzoxazin-4-one (**7**).

N-(2-Bromopropionyl)anthranilic acid (**6**) (2.72 g, 10 mmoles) was reacted with acetic anhydride (8 ml) under reflux while the acetic acid formed was distilled off. When the temperature of the vapor reached 140° the reaction mixture was evaporated *in vacuo* to dryness. The oily residue gradually became solid. It was recrystallized from a mixture of chloroform and hexane to give compound **7** (2.39 g, 94%, mp 103-106°).

Anal. Calcd. for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.08; H, 3.23; N, 5.64.

2-Ethyl-3-(2-hydroxyethyl)quinazolin-4-one (**10**).

N-Propionylanthranilic acid (1.93 g, 10 mmoles) was dissolved in acetic anhydride (7 ml) by gently heating. The solution was refluxed at 140° while the acetic acid formed was distilled off. Then the reaction mixture was concentrated *in vacuo* to dryness and the formed 2-ethyl-3,1-benzoxazin-4-one **9** was treated with ethanolamine (2.5 ml) and the mixture was stirred on an oil bath between 145-150° for 3 hours. After cooling to ambient temperature 50% aqueous acetic acid (5 ml) was added to the reaction mixture, which was allowed to crystallize. The crystals were filtered off, washed with water, and dried to give compound **10** (0.92 g, 52%, mp 143-145°); ^1H-nmr (deuteriochloroform): 1.37 (3H, t, J = 7 Hz, 2-CH$_2$C*H*$_3$), 2.98 (2H, q, J = 7 Hz, 2-C*H*$_2$), 4.01 (2H, t, J = 5 Hz, NC*H*$_2$), 4.31 (2H, t, J = 5 Hz, C*H*$_2$O), 7.31-7.90 (3H, m, Ar-*H*-7,8,9), 8.15 (1H, d, J = 8 Hz, Ar-*H*-5).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.17; H, 6.44; N, 12.90.

2-(1-Bromoethyl)-3-(2-hydroxyethyl)quinazolin-4-one (**11**).

To a solution of 2-ethyl-3-(2-hydroxyethyl)quinazolin-4-one **10** (2.18 g, 10 mmoles) and sodium acetate (0.82 g, 10 mmoles) in acetic acid (20 ml) a solution of bromine (1.6 g, 10 mmoles) in acetic acid (10 ml) was added dropwise at room temperature. The reaction mixture was stirred for 4 hours, then it was diluted with

water (100 ml). The precipitated crystals were filtered off, washed with water, and recrystallized from ethanol to give compound **11** (2.84 g, 95%, mp 100-102°); ^{1}H-nmr (deuteriochloroform): 2.01 (3H, d, -C*H*$_3$), 4.10 (2H, m, NC*H*$_2$), 4.20-4.80 (2H, m, C*H*$_2$O), 5.48 (1H, q, 2-C*H*-Br), 7.30-7.90 (3H, m, Ar-*H*-6,7,8), 8.21 (1H, d, Ar-*H*-5).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$: C, 49.50; H, 4.41; N, 9.43. Found: C, 49.52; H, 4.41; N, 9.29.

1-Methyl-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**8**).

Method D.

To a solution of 2-(1-bromoethyl)-3,1-benzoxazin-4-one **7** (2.54 g, 10 mmoles) in dioxane (5 ml) a solution of ethanolamine (0.61 g, 10 mmoles) was added, and the reaction mixture was stirred at room temperature for 0.5 hour. After addition of 40% aqueous sodium hydroxide (1 ml) to the reaction mixture, the organic part of the reaction mixture was distilled off *in vacuo*. From the aqueous residue the precipitated crystals were filtered off, washed with water and recrystallized from ethanol to give compound **8** (see Table 1).

Method E.

A suspension of 2-(1-bromoethyl)-3-(2-hydroxyethyl)quinazolin-4-one **11** (2.97 g, 10 mmoles) in 2.5% aqueous sodium hydroxide (24 ml) was stirred at ambient temperature for 1 hour. Then the precipitated crystals were filtered off, washed with water and recrystallized from ethanol to give compound **8** (see Table 1).

2-Dibromomethyl-3-(2-hydroxyethyl)quinazolin-4-one (**12**).

To a solution of 2-methyl-3-(2-hydroxyethyl)quinazolin-4-one **4** [32] (2.04 g, 10 mmoles) and sodium acetate (1.64 g, 20 mmoles) in acetic acid (20 ml) a solution of bromine (3.2 g, 20 mmoles) in acetic acid (4 ml) was dropwise added at 60° during a period of 15 minutes. After stirring the reaction mixture for 10 minutes at this temperature, it was cooled to room temperature and diluted with water (10 ml). The precipitated crystals were filtered off and recrystallized from ethanol to give compound **12** (2.75 g, 76.0%, mp 153-155°); ^{1}H-nmr (deuteriochloroform): 4.05 (2H, m, NC*H*$_2$), 4.53 (2H, m, NC*H*$_2$O), 7.13 (1H, s, CHBr$_2$), 7.37-7.90 (3H, m, Ar-*H*-6,7,8), 8.25 (1H, d, J = 8 Hz, Ar-H-5).

Anal. Calcd. for $C_{11}H_{10}Br_2N_2O_2$: C, 36.49; H, 2.78; N, 7.74. Found: C, 36.54; H, 2.85; N, 7.65.

1-Hydroxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**13**).

Method F.

A suspension of 2-dibromomethyl-3-(2-hydroxyethyl)quinazolin-4-one **12** (3.62 g, 10 mmoles) in 2.5% aqueous sodium hydroxide solution (48 ml) was stirred at ambient temperature for 1 hour. Then the reaction mixture was filtered and the *p*H of the filtrate was adjusted to 5-6 with acetic acid. The precipitated crystals were filtered off and recrystallized from ethanol to give compound **13** (see Table 1).

Method G.

A suspension of 1-acetoxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino-[3,4-*b*]quinazolin-6-one (**14**) (2.6 g, 10 mmoles) in a mixture of ethanol (10 ml) and 5% aqueous sodium hydroxide (20 ml) was heated while the reaction mixture became clear (about 1 hour). Then the ethanol was distilled off *in vacuo* and after cooling to ambient temperature the *p*H of the aqueous residue was adjusted to 5-6 with acetic acid. The precipitated crystals were filtered off, washed with water and recrystallized from ethanol to give compound **13** (see Table 1).

1-Acetoxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**14**).

Method H.

To a solution of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) and sodium acetate (1.62 g, 10 mmoles) in acetic acid (20 ml) bromine (1.6 g, 10 mmoles) was dropwise added at room temperature. After two-hour stirring the reaction mixture was heated on a water bath for 4 hours. Then the reaction mixture was poured into water (100 ml). The aqueous mixture was extracted with chloroform (3 x 20 ml). The combined organic phase was first extracted with saturated aqueous bicarbonate solution (2 x 20 ml), then with water (2 x 20 ml). The dried (sodium sulfate) chloroformic solution was evaporated *in vacuo* to dryness. The residue was crystallized from ethyl acetate to give compound **14** (see Table 1).

Method I.

To a solution of 1-hydroxy-3,4-dihydro[1,4]oxazino[3,4-*b*]quinazolin-6-one (**13**) (2.18 g, 10 mmoles) in pyridine (10 ml) a mixture of acetic anhydride (1.02 g, 10 mmoles) and pyridine (5 ml) was dropwise added at room temperature. Then the reaction mixture was stirred for 1 hour and it was diluted with water (50 ml). The reaction mixture was neutralized with 20% aqueous hydrochloric acid. The aqueous reaction mixture was extracted with chloroform (3 x 20 ml). The combined organic phase was washed with water, dried (sodium sulfate) and evaporated *in vacuo* to dryness. The residue was crystallized from aqueous ethanol to give compound **14** (see Table 1).

1-Bromo-3,4-dihydro[1,4]oxazino[3,4-*b*]quinazolin-6-one (**15**).

Method J.

A solution of 3,4-dihydro[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (1.78 g, 10 mmoles) and *N*-bromosuccinimide (1.78 g, 10 mmoles) in the presence of a catalytic amount of benzoyl peroxide in chloroform (40 ml) was refluxed for 3 hours. After cooling to room temperature the reaction mixture was extracted with water, then the dried (sodium sulfate) organic phase was evaporated *in vacuo* to dryness. The residue was purified by chromatography over silica gel column (eluent: ethyl acetate). The product **15** was crystallized from a mixture of chloroform-hexane (see Table 1).

3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazoline-1,6-dione (**16**).

Method K.

To a solution of 1-hydroxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**13**) (2.18 g, 10 mmoles) in acetone (60 ml) Jones reagent [18] (7.5 ml) was dropwise added. The reaction mixture was stirred for 1 hour and 2-propanol (1 ml), then the solution of sodium acetate (1.5 g) in water (5 ml) was added to it. From the green precipitation the solution was decanted and decolourized with activated carbon. The filtered organic phase was evaporated *in vacuo* to dryness. The residue was recrystallized from methanol to give compound **16** (see Table 1).

1-Ethoxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**17**).

Method L.

To a solution of 1-bromo-3,4-dihydro[1,4]oxazino[3,4-*b*]quinazolin-6-one **15** (2.81 g, 10 mmoles) in ethanol a solution of sodium ethoxide (0.68 g, 10 mmoles) in ethanol (10 ml) was added dropwise. The precipitated sodium bromide was filtered off and the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from ethanol to give compound **17** (see Table 1).

2-(Phenylhydrazonomethyl)-3-(2-hydroxyethyl)quinazolin-4-one (**18**).

2-Dibromomethyl-3-(2-hydroxyethyl)quinazolin-4-one **12** (3.62 g, 10 mmoles) was reacted with phenylhydrazine (4.32 g, 40 mmoles) in boiling ethanol (35 ml) for 30 minutes. After cooling the precipitated crystals were filtered off and recrystallized from ethanol to give yellow compound **18** as a 1:3 mixture of *Z* and *E* geometric isomers (1.9 g, 62%, mp 214-219°); ^{1}H-nmr (DMSO-d_6): 11.12 (0.73 H, s, N*H*-*E*), 14.57 (0.27 H, s, N*H*-*Z*).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.05; H, 5.28; N, 18.37.

1-Phenylhydrazono-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**20**).

Method M.

1-Bromo-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **15** (2.81 g, 10 mmoles) was reacted with phenylhydrazine (4.32 g, 40 mmoles) in boiling ethanol (30 ml) for 6 hours. After cooling the precipitated yellow crystals were filtered off and recrystallized from ethanol to give compound **20** (see Table 1).

Method N.

1-Hydroxy-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **13** (2.18 g, 10 mmoles) was reacted with phenylhydrazine (4.32 g, 40 mmoles) in boiling ethanol (30 ml) for 6 hours. After cooling the precipitated yellow crystals were filtered off, washed with ethanol and recrystallized from ethanol to give compound **20** (see Table 1).

Method O.

To a chilled (0°) solution of phenyldiazonium chloride, prepared from aniline (0.93 g, 10 mmoles) in 1:1 diluted aqueous hydrochloric acid (5 ml) in water (10 ml) [33], a solution of sodium acetate (1.32 g) in acetic acid (5 ml) then 3,4-dihydro-1*H*,6*H*-[1,4]-oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) in acetic acid (8 ml) were gradually added at 0° and the reaction mixture was stirred for 3 hours at this temperature. Then the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was diluted with water and the precipitated yellow crystals were filtered off, washed with water and recrystallized from ethanol to give compound **20** (see Table 1).

1-Hydroxyimino-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**21**).

Method P.

To a solution of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) in acetic acid (20 ml) at 0-5° a solution of sodium nitrite (0.7 g, 10 mmoles) in water (4 ml) was dropwise added. The reaction mixture was stirred at 0° for 3 hours, then it was allowed to stand in the refrigerator overnight. The reaction mixture was diluted with water (100 ml) and the precipitated crystals were filtered off, washed with water, and boiled with ethanol to give compound **21** (see Table 1).

1-Arylidene-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-ones (**22**).

Method R.

A mixture of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) and the appropriate aromatic aldehyde (15 mmoles) was heated at 160° for 30 minutes under nitrogen. Then the reaction mixture was recrystallized from ethanol to give compound **22a** and **22b** (see Table 1). In the preparation of compound **22a**, benzaldehyde and that of compound **22b**, 2-furaldehyde were used as the aromatic aldehydes.

1-(*N*,*N*-Dimethylamino)methylene-3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one (**23**).

Method S.

To a solution of 3,4-dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) in dimethylformamide (10 ml), phosphoryl chloride (2 ml, 20 mmoles) was dropwise added, and the reaction mixture was stirred at 60° for 3 hours. After the mixture had cooled it was poured onto crushed ice (20 g) and the *p*H of the aqueous phase was adjusted to 7 with 10% sodium hydroxide. The precipitated yellow crystals were filtered off, washed with water and recrystallized from dimethylformamide to give compound **23** (see Table 1).

Ethyl α,6-dioxo-3,4-dihydro-6*H*,11*H*-[1,4]oxazino[3,4-*b*]quinazolin-1-acetate (**24**).

Method T.

3,4-Dihydro-1*H*,6*H*-[1,4]oxazino[3,4-*b*]quinazolin-6-one **3** (2.02 g, 10 mmoles) and ethyl oxalate (2.72 ml, 20 mmoles) were allowed to react in ethanol (20 ml) in the presence of sodium ethoxide (1.32 g, 20 mmoles) at 80° for 4 hours. After cooling to room temperature the precipitated crystals were filtered off, dissolved in water (50 ml) and acidified with 5% hydrochloric acid (15 ml). The precipitated crystals were filtered off, dried and recrystallized from dimethylformamide to give compound **24**.

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