Chemistry of Heterocyclic Compounds, Vol. 47, No. 11, February, 2012 (Russian Original Vol. 47, No. 11, November, 2011)

STUDIES OF BENZOXAZINES

16*. SYNTHESIS AND REACTIVITY OF 2,4-SUBSTITUTED 4*H*-3,1-BENZOXAZINES

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A novel method has been developed for preparation of substituted 4H-3,1-benzoxazines via formation of tetrafluoroborates. The substitution of halogen in 2-(α-haloalkyl)-4,4-diphenyl-4H-3,1-benzoxazines by NH and SH nucleophiles was performed. The effect of electrophilic substitution in the annelated aromatic ring in a series of 2,4-substituted 4H-3,1-benzoxazines has been studied.

Keywords: 2-aminopyridines, 4*H*-3,1-benzoxazines, mass spectroscopic fragmentation, nucleophilic and electrophilic substitution, synthesis.

o-Acylaminobenzyl alcohols which undergo heterocyclization in acid medium are usually used as starting materials in the synthesis of 4*H*-3,1-benzoxazines [2, 3]. The mechanism of benzoxazine heterocycle formation assumes generation in the starting aromatic substrate of a carbenium center in the *ortho* position to the NHC(R)=O group, the oxygen atom of which can show nucleophilic properties [4].

We have developed synthetic methods for the synthesis of 2,4-substituted 4*H*-3,1-benzoxazines *via* acylation of tertiary *o*-aminophenylcarbinols using carboxylic acids, their anhydrides, or acid chlorides in the presence of mineral or Lewis acids through formation of the corresponding chlorides [5], perchlorates [6], or hexahaloantimonates [7]. In this reaction the acylation of aminocarbinols and heterocyclization occur in sequence [5-8]. The 4*H*-3,1-benzoxazines and their salts obtained by us reveal compounds showing hypnosedative activity [9], plant growth regulator properties [10], and antidotal activity [11-14].

Extending investigations in this field we have studied the reaction of *o*-aminophenyldiethyl-(diphenyl)carbinols **1a,b** with the α-haloalkanyl or furanyl acid chlorides or bromides **2a-g** in the presence of boron trifluoride etherate. As a result we have prepared the 4*H*-3,1-benzoxazine tetrafluoroborates **3a-g** (Scheme 1) which were separated from the reaction medium by precipitation with ether. Thanks to their thermal stability and explosion resistance the tetrafluoroborates are preferred to perchlorates for further use [15].

The products **3a-e,g** were obtained as crystals in 60-75% yields (Table 1) and the salt **3f** as a viscous, oily liquid. IR spectra of the salts **3a-g** show absorption bands at 2750-2220 cm^{-1} due to the presence of the quaternary N^+H group nitrogen, $OCNH^+$ stretching bands at 1670-1640 cm^{-1}, and for the BF_4^- anion at 1120-990 cm^{-1}.

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*For Communication 15, see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1691-1701, November, 2011. Original article submitted October 26, 2010; revision submitted November 7, 2011.

TABLE 1. Characteristics of the 4*H*-3,1-Benzoxazinium Tetrafluoroborates **3a-g**

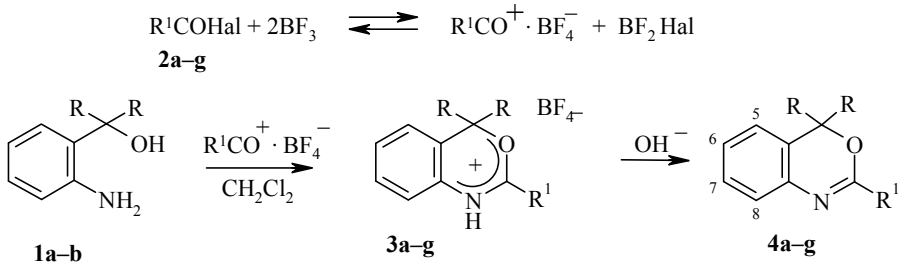
Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	IR spectrum, ν, см$^{-1}$			Yield, %
		C	H	N	Hal		N^+H	$OCNH^+$	BF_4^-	
3a	$C_{21}H_{17}BClF_4NO$	59.35 / 59.82	3.82 / 4.06	3.70 / 3.32	26.62 / 26.43	195-197	2230	1670	1100-1000	75
3b	$C_{21}H_{16}BCl_2F_4NO$	54.95 / 55.30	3.72 / 3.54	3.15 / 3.07	32.41 / 32.21	180-183	2350	1640	1110-1020	73
3c	$C_{23}H_{21}BBrF_4NO$	55.52 / 55.91	4.48 / 4.28	2.61 / 2.83	31.85 / 31.55	177	2750	1650	1120-1010	65
3d	$C_{24}H_{18}BF_4NO_2$	65.10 / 65.63	4.42 / 4.10	2.95 / 3.19	17.80 / 17.30	170	2220	1640	1120-1010	70
3e	$C_{24}H_{18}BF_4NO_2$	65.71 / 65.63	3.90 / 4.13	3.50 / 3.19	17.10 / 17.30	149	2235	1640	1100-990	72
3f	$C_{16}H_{17}BF_4N_2O_4$	49.35 / 49.51	4.10 / 4.41	7.51 / 7.22	19.84 / 19.58	—*	2710	1650*[2]	1100-1020	55
3g	$C_{24}H_{17}BF_4N_2O_4$	59.80 / 59.53	3.27 / 3.54	5.51 / 5.79	15.90 / 15.69	142-144	2720	1660*[3]	1120-1020	60

* Viscous oil.

*[2] Other bands in the IR spectrum at 1525, 1330 (NO_2).

*[3] Other bands in the IR spectrum at 1510, 1340 (NO_2).

Scheme 1



1a, 3f, 4f R = Et; **1b, 3a–e,g, 4a–e,g** R = Ph; **2–4 a** $R^1 = CH_2Cl$, **b** $R^1 = CHCl_2$, **c** $R^1 = CH(Br)CH_2CH_3$, **d** R^1 = 2-furyl, **e** R^1 = 3-furyl, **f,g** R^1 = 5-nitro-2-furyl; **2a,b,d–g** Hal = Cl, **c** Hal = Br

The bases **4a-g** were prepared by deprotonation of the corresponding salts **3a-g** using 5% alkali solution.

Constants and spectroscopic parameters for the 4*H*-3,1-benzoxazines **4a,c,d,g** agree with literature data [6-8]. The spectroscopic properties and elemental analytical data for the novel compounds **4b,e,f** are given in Tables 2 and 3.

In the 4*H*-3,1-benzoxazines the heterocycle is annelated to the benzene ring and conjugatively bonded to it *via* the azomethine bond therefore the C=N bond of the heterocycle shows little reactivity [6]. The literature for 4*H*-3,1-benzoxazines records the occurrence of both opening of the heterocycle and also its transformation. The first relates to hydrolysis to give a substituted *o*-hydroxymethylanilide [16] and the second to the formation of 3,4-dihydroquinazolines [17-19] and 1,4-dihydro-2*H*-3,1-benzoxazines [20] through the action of nucleophiles and reducing agents. In the system $NaNH_2$–NH_3 the heterocycle in 2,4-diphenyl-4*H*-3,1-benzoxazine undergoes ring contraction through an intermediate indole-2,3-oxide anion *via* an intramolecular Wittig rearrangement to form 3-hydroxy-2,3-diphenylindole [20].

TABLE 2. Physicochemical Characteristics of 4*H*-3,1-Benzoxazines **4b**,**e,f**,**h-n**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	R_f*	Yield, %
		C	H	N			
4b	$C_{21}H_{15}Cl_2NO$	68.35 / 68.49	4.17 / 4.11	3.49 / 3.80	165-166	0.85	85.0
4e	$C_{24}H_{17}NO_2$	82.20 / 82.03	4.71 / 4.88	3.62 / 3.99	208	0.80	70.0
4f	$C_{16}H_{16}N_2O_4$	63.82 / 63.99	5.52 / 5.33	9.14 / 9.33	117-119	0.28	55.0
4h	$C_{25}H_{25}NOS$	77.61 / 77.48	6.40 / 6.50	3.56 / 3.62	76-78	0.87	50.0
4i	$C_{25}H_{26}N_2O$	81.32 / 81.05	7.11 / 7.07	7.43 / 7.56	61-63	0.16	72.5
4j	$C_{26}H_{26}N_2O$	81.82 / 81.64	6.65 / 6.80	7.42 / 7.33	161-162	0.35	85.6
4k	$C_{25}H_{26}N_2O$	81.25 / 81.05	7.32 / 7.07	7.28 / 7.56	92-94	0.29	75.0
4l	$C_{28}H_{30}N_2O$	81.67 / 81.91	7.55 / 7.37	6.52 / 6.82	112-114	0.15	82.0
4m	$C_{27}H_{22}N_2O$	83.32 / 83.05	5.25 / 5.68	7.02 / 7.17	135-138	0.25	51.0
4n	$C_{28}H_{24}N_2O$	83.44 / 83.14	5.63 / 5.98	6.70 / 6.93	83-85	0.22	55.0

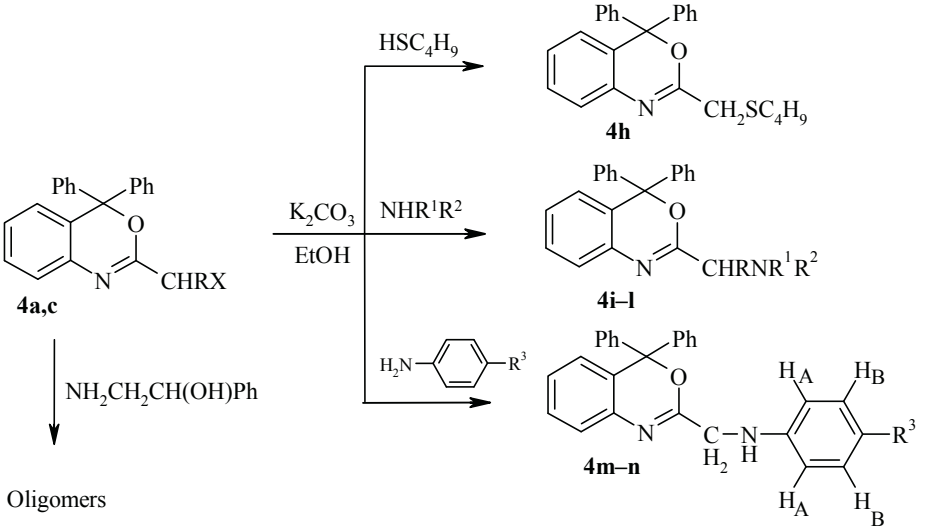
Eluents: benzene–acetone, 4:1 (compound **4b**); benzene–ether, 4:1 (compounds **4e,h-k**), and benzene (compounds **4f,l-n**).

TABLE 3. Spectroscopic Characteristics of 4*H*-3,1-Benzoxazines **4b**,**e**,**f**,**h-n**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
4b	1610 (C=N)	6.72 (1H, d, $^3J_{7,8}$ = 6.5, H-8); 7.00 (1H, s, $CHCl_2$); 7.22 (10H, m, H 2Ph); 7.35 (2H, m, H-5,7); 7.47 (1H, dd, $^3J_{6,5}$ = 6.5, $^3J_{6,7}$ = 7.0, H-6)
4e	1625 (C=N)	6.82 (1H, m, H-4'); 6.95 (4H, m, H Ar); 7.00-7.20 (10H, m, H 2Ph); 7.34 (1H, dd, $^3J_{4',5'}$ = 1.9, $^4J_{2',5'}$ = 1.5, H-5'); 7.90-7.95 (1H, m, H-2′)
4f	1620 (C=N); 1550, 1330 (NO_2)	0.80 (3H, t, ^3J = 7.0, CH_3); 1.05 (3H, t, ^3J = 7.0, CH_3); 1.65, 1.80, 2.05 and 2.23 (in all 4H, four q, ^3J = 7.0, $2CH_2$); 6.70-6.90 (4H, m, H Ar); 7.11 (1H, d, H-3'); 7.30 (1H, d, $^3J_{3',4'}$ = 3.0, H-4')
4h	1625 (C=N)	0.95-1.15 (7H, m, $(CH_2)_2CH_3$); 2.20 (2H, t, ^3J = 6.0, SCH_2Pr); 3.26 (2H, s, CH_2S); 6.67-6.77 (4H, m, H Ar); 7.00-7.25 (10H, m, H 2Ph)
4i	1620 (C=N)	1.00 (6H, t, ^3J = 6.5, $2CH_3$); 2.52 (4H, к, ^3J = 6.5, $N(CH_2)_2$); 3.23 (2H, s, NCH_2); 6.56-6.64 (4H, m, H Ar); 7.01-7.20 (10H, m, H 2Ph)
4j	1640 (C=N)	1.33-1.39 (6H, m, $(CH_2)_3$ piperidine); 2.27 (4H, t, ^3J = 5.0, $N(CH_2)_2$ piperidine); 3.12 (2H, s, CH_2); 6.65-7.10 (4H, m, H Ar); 7.15-7.45 (10H, m, H 2Ph)
4k	1615 (C=N); 3300 (NH)	0.98 (9H, s, $C(CH_3)_3$); 2.50 (1H, br. s, NH); 3.38 (2H, s, CH_2); 6.50-6.80 (4H, m, H Ar); 7.00-7.30 (10H, m, H 2Ph)
4l	1630 (C=N)	0.65 (3H, t, ^3J = 6.0, CH_3); 1.30-1.60 (6H, m, $(CH_2)_3$ piperidine); 1.60-1.80 (2H, m, CH_2); 2.45-2.60 (4H, m, $N(CH_2)_2$ piperidine); 3.10 (1H, t, ^3J = 6.5, CH); 6.63 (1H, d, $^3J_{7,8}$ = 7.0, H-8); 7.00-7.20 (3H, m, H-7,6,5); 7.25-7.40 (10H, m, H 2Ph)
4m	1620 (C=N); 3410 (NH)	3.92 (2H, d, ^3J = 5.5, CH_2); 5.20 (1H, br. s, NH); 6.45-7.00 (9H, m, H Ar, H NPh); 7.10-7.45 (10H, m, H 2Ph)
4n	1620 (C=N); 3400 (NH)	2.68 (3H, s, CH_3); 3.95 (1H, br. s, NH); 4.23 (2H, s, CH_2); 6.45 (2H, d, $^3J_{AB}$ = 8.0, H Ar); 6.80 (2H, d, $^3J_{AB}$ = 8.0, H Ar); 6.90-7.10 (4H, m, H Ar); 7.15-7.40 (10H, m, H 2Ph)

One of the targets of our work was to study the chemical activity of substituted 4*H*-3,1-benzoxazines. Introduction into their structures of novel functional groups in nucleophilic and electrophilic reactions can lead to preparation of novel compounds with potential biological activity [3].

Scheme 2



4 i–k R = H, **i** $R^1 = R^2$ = Et, **j** $R^1 + R^2 = (CH_2)_5$, **k** R^1 = H, R^2 = *t*-Bu, **l** R = Et, $R^1 + R^2 = (CH_2)_5$, **m** R^3 = H, **n** R^3 = Me, **a** X = Cl, **b** X = Br

The reaction of 2-(1-haloalkyl)-4*H*-3,1-benzoxazines **4a,c** with mercaptan and with amines yields the corresponding sulphur- and nitrogen-containing compounds **4h-n** with retention of the benzoxazine system (Scheme 2 and Tables 2 and 3). This reaction is carried out by refluxing in absolute alcohol with a 1.5-fold excess of the nucleophilic reagent in the presence of K_2CO_3 [21].

It should be noted that the substitution reaction of the chlorine in benzoxazine **4a** for the butylmercaptan residue under the conditions described in method [21] forms the product **4h** in the course of 18-20 h. Compound **4a** under these conditions reacts with diethylamine, piperidine, and *tert*-butylamine and also the benzoxazine **4c** reacts with piperidine (6-7 h) forming the corresponding aminoalkyl-substituted benzoxazines **4i-l** (Table 2). Reaction occurs for benzoxazine **4a** with aniline and 4-methylaniline but not with the weaker nucleophile 4-nitroaniline. Reaction with α-phenylethanolamine is accompanied by formation of resinous materials, probably through dehydration and then polymerization of the reaction product.

The products **4k,m,n** contain a $–CH_2–NH–$ fragment and their ^{1}H NMR spectra might be expected to show a vicinal coupling constant for this fragment. However, because the ^{14}N atomic nucleus has spin number 1 and thus possesses a quadrupole moment [22], the N–H proton signals are broadened. However, in the spectrum of 4,4-diphenyl-2-(phenylaminomethyl)-4*H*-3,1-benzoxazine (**4m**) a doublet splitting of ^3J = 5.5 Hz is observed for the protons of the methylene group.

The spectrum of compound **4n** shows characteristic signals for aromatic substituent protons as an A_2B_2 system with $^3J_{AB}$ = 8.0 Hz. The chemical shift of the methine proton of the side chain in the spectrum of 2-dichloromethyl-4,4-diphenyl-4*H*-3,1-benzoxazine (**4b**) to low field can be explained by the deshielding effect of the substituent. The furan protons in the ^{1}H NMR spectra of compounds **4e,f** show a normal dependence [23]. The furan ring H-2' and H-5' proton signals' shift to low field in the spectrum of the 4,4-diphenyl-2-(3-furyl)-4*H*-3,1-benzoxazine (**4e**) when compared with the H-4' signal is related to the electron-acceptor effect of the furan ring oxygen atom (Table 3).

The IR spectra of benzoxazines **4b,e,f,h-n** show stretching bands for a conjugated azomethine group at 1640-1610 cm^{-1} (Table 3) which also confirms their structure.

Reaction of 2-chloromethyl-4,4-diphenyl-4*H*-3,1-benzoxazine (**4a**) with 2-amino-5-chloropyridine proceeds unexpectedly under conditions reported in method [21] to give the novel tetracyclic system 9-chloro-12,12-diphenyl-5,12-dihydropyrido[1',2':1,2]imidazo[4,5-*b*]quinoline [24].

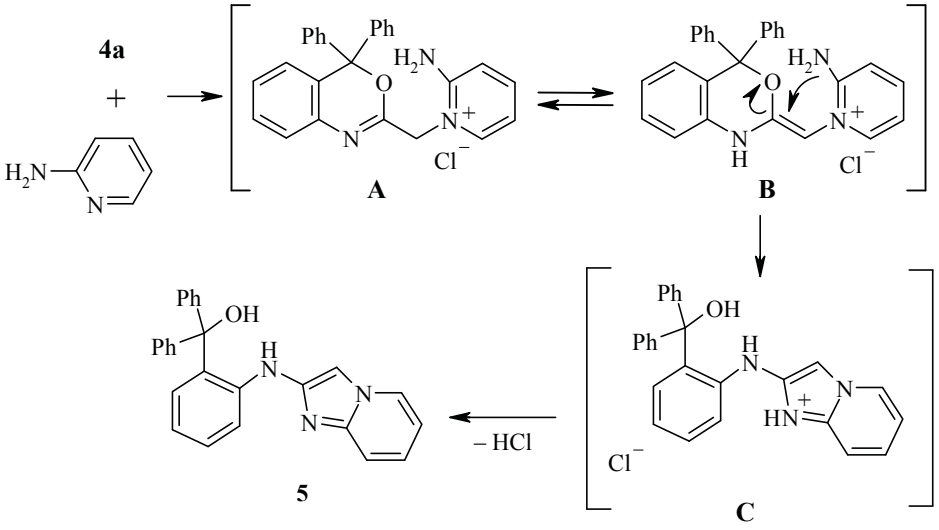
Reaction of benzoxazine **4a** with 2-aminopyridine proceeds differently. Analogous conditions gave colorless crystals of [2-(imidazo[1,2-*a*]pyridin-2-ylamino)phenyl]diphenylmethanol (**5**) whose structure was identified by spectroscopic methods. Both nitrogen atoms of the reagent take part in the reaction of benzoxazine **4a** with both 2-aminopyridine and 2-amino-5-chloropyridine. The reactions (~6 h) occur *via* the intermediate states **A**, **B**, and **C** with cleavage of the benzoxazine ring [24]. Formation of the product **5** occurs *via* deprotonation of the cation **C** (Scheme 3).

The IR spectrum of compound **5** (see Experimental) shows a band for the NH group stretching vibrations at 3310 cm^{-1}. The broad absorption at 3200-2850 cm^{-1} points to the presence in this compound of a hydroxyl group which takes part in formation of a chelate structure [25]. Position of the OH group proton signal in low field in the ^{1}H NMR spectrum indicates its participation in the formation of hydrogen bonds [26].

The structure of compound **5** was also supported by the mass spectroscopic data showing the presence of a molecular ion peak. Its initial fragmentation scheme involves loss of a water molecule to form ion $\mathbf{\Phi_1}$ (Scheme 4) which, with the presence of proton donors [27], points to the existence of a hydroxyl group in the studied structure. Ion $\mathbf{\Phi_1}$ then eliminates a hydrogen atom, a phenyl radical, or a radical of mass 117 a.u. which has a pyridoimidazole structure, to give cations $\mathbf{\Phi_2}$–$\mathbf{\Phi_4}$.

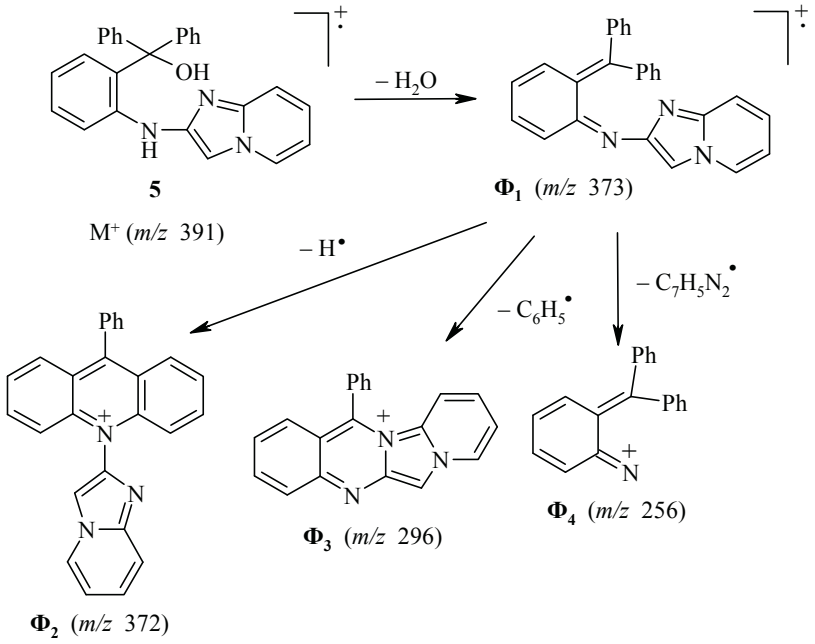
Reaction of the 2,4-substituted 4*H*-3,1-benzoxazines **4a,c-g** with electrophilic reagents has been studied using bromination of 4,4-diethyl(diphenyl)-2-(5-nitro-2-furyl)-4*H*-3,1-benzoxazines **4f,g** by bromine in acetic acid at room temperature [28] (Scheme 5) to give the corresponding 6,8-dibromo benzoxazines **6a,b** in 65% and 70% yield respectively. Their properties were identical to those reported by us previously [29] where

Scheme 3



these compounds were obtained as side products in the bromination of 4,4-diethyl(diphenyl)-2-(5-nitro-2-furyl)-1,2-dihydro-4*H*-3,1-benzoxazines. Compounds **4d,e** with unsubstituted furyl substituents in position 2 of the heterocycle undergo tarring during this reaction.

Scheme 4

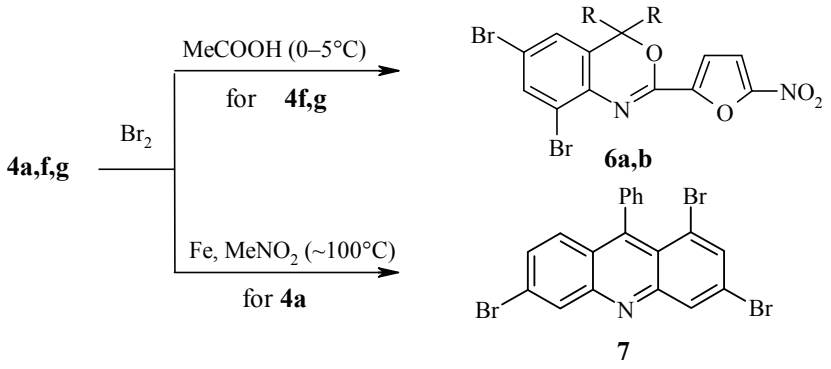


The 2-(1-haloalkyl)-4*H*-3,1-benzoxazines **4a,c** were not brominated under the conditions reported. Increasing the temperature of the reaction mixture to 70-80ºC causes destruction of the heterocycle with tarring.

The bromination of benzoxazine **4a** in refluxing nitromethane led to formation of the yellow colored compound **7** (Scheme 5) whose mass spectrum shows a specific group of molecular ion peaks (cluster): $[M]^+$, $[M+2]^+$, $[M+4]^+$, and $[M+6]^+$. The peaks intensity distribution is characteristic for ions containing three bromine atoms and is found to be in full agreement with additivity rules [30].

The IR spectrum of compound **7** contains characteristic absorption peaks for the stretching vibrations of conjugated =CH and C=C bonds and the aromatic nucleus [25, p. 87]. The ^{1}H NMR spectrum also confirms a presence of the aromatic protons and an absence of a signal for the methylene group protons. According to ^{1}H NMR, IR, and mass spectrometric data the product **7** obtained is 1,3,6-tribromo-9-phenylacridine.

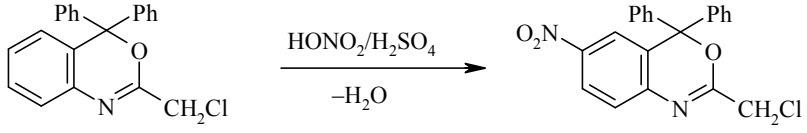
Scheme 5



6 a R = Et, **b** R = Ph

We have previously [5] reported the nitration of 2,4,4-trimethyl-4*H*-3,1-benzoxazinium chloride using a nitration mixture in the cold to give the mononitration product in up to 67% yield with retention of a heterocycle. Nitration of 2-chloromethyl-4,4-diphenyl-4*H*-3,1-benzoxazine (**4a**) under the same conditions gave a low (15-20%) yield of the corresponding product **8** but with much tarring (Scheme 6). It is possibly related to the C–H acidity of the methylene group ion in the starting benzoxazine **4a** which enables a 1,3-prototropic shift of the multiple bond to the exocyclic position and to subsequent oligomerization.

Scheme 6



The IR spectrum of compound **8** has strong absorption peaks for the stretching vibrations of the azomethine bond and the nitro group. From the ^{1}H NMR spectrum, in which the vicinal aromatic protons H-8 and H-7 show doublet signals and the H-5 proton appears as a singlet, it follows that the heterocycle orients the nitronium to position 6 of the annelated aromatic ring of benzoxazine **4a** to give 2-chloromethyl-4,4-diphenyl-6-nitro-4*H*-3,1-benzoxazine (**8**).

The experimental data obtained shows that the course of nucleophilic substitution of the halogen in 2-(α-haloalkyl)-4*H*-3,1-benzoxazines by aliphatic and aromatic amines occurs as expected with retention of a heterocycle. In the case of α-aminopyridines the reaction occurs with participation of the pyridine nitrogen and opening of the oxazine ring to give the substituted 2-aminophenylmethanol. Electrophilic substitution in the annelated aromatic ring of benzoxazines depends on the substituent structure in the 2 position of the heterocycle.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument at room temperature using vaseline oil. ^{1}H NMR spectra were taken on a Bruker DRX-500 instrument (500 MHz) using DMSO-d_6 (compound **4b**),

Tesla 60 (60 MHz) using CCl_4 (compound **4e**), $CDCl_3$ (compounds **4h-j**), or $(CD_3)_2CO$ (compounds **4k,m,n**), or on Bruker AC-200 (200 MHz) using $CDCl_3$ (compounds **4f,l**). TMS was used as internal standard. Mass spectra were recorded on a Varian CH-6 instrument with direct introduction, ionization chamber temperature 50-180ºC, and ionization energy 70 eV. TLC was performed on Silufol UV-254 plates and revealed using iodine vapor.

The substituted *o*-aminobenzyl alcohols **1a,b** were synthesized from methyl anthranilate using the method [31].

2-(1-Bromopropyl)-4,4-diphenyl-4*H*-3,1-benzoxazinium Tetrafluoroborate (3c). *o*-Aminophenyldiphenylcarbinol (**1b**) (2.75 g, 10 mmol) was added portionwise with stirring to a mixture of α-bromobutyric acid bromide (4.56 g, 20 mmol) and boron trifluoride etherate (2.84 g, 20 mmol) in methylene chloride (10 ml) cooled to 0ºC. The mixture became blue-green in color and a mild warming effect was observed. After 30 min the mixture was heated to the solvent reflux temperature and stirred for 3 h. The reaction mixture was cooled and the salt **3c** was precipitated by addition of absolute ether. The precipitated crystals were filtered off, washed with ether, and dried in air. Yield 3.2 g (65%).

The salts **3a,b,d-g** were prepared similarly using the corresponding acid chlorides.

2-(1-Bromopropyl)-4,4-diphenyl-4*H*-3,1-benzoxazine (4c). A mixture of the salt **3c** (0.89 g, 1.8 mmol) in 5% aqueous KOH solution (10 ml) was stirred on a boiling water bath for 10 min. The organic fraction was extracted with ether and dried over anhydrous Na_2SO_4. Solvent was distilled off and the precipitate formed was recrystallized from a 1:1 mixture of petroleum ether and carbon tetrachloride. Yield 0.54 g (80%). Benzoxazine **4c** properties agreed with those in the literature [8].

Benzoxazines 4a,b,d-g were prepared similarly.

2-Diethylaminomethyl-4,4-diphenyl-4*H*-3,1-benzoxazine (4i). A mixture of benzoxazine **4a** (0.6 g, 1.8 mmol), diethylamine (0.31 ml, 3 mmol), and K_2CO_3 (0.3 g) in absolute alcohol (7 ml) was heated with stirring on a boiling water bath to the solvent reflux temperature and refluxed for 6 h. At the end of the reaction (TLC monitoring) the mixture was cooled and the precipitate was filtered off. The filtrate was evaporated and the crude product obtained was recrystallized from alcohol. Yield 0.48 g.

Benzoxazines 4h,j-n, 5 were prepared similarly. The synthesis of 2-butylsulfanylmethyl-4,4-diphenyl-4*H*-3,1-benzoxazine (**4h**) took 20 h.

2-(1-Piperidinopropyl)-4,4-diphenyl-4*H*-3,1-benzoxazine (4l) was prepared similarly to compound **4i** by substituting the bromine in benzoxazine **4c** with a piperidine residue.

2-[(Imidazo[1,2-*a*]pyridin-2-ylamino)phenyl]diphenylmethanol (5) of weight 0.39 g was purified by column chromatography using L 40/100 grade silica gel sorbent and benzene–acetone (1:2) as eluent. Column diameter 3 cm, layer thickness 10 cm. The fraction with R_f 0.83 was separated. Yield 0.17 g (45%); mp 207-209ºC. IR spectrum, ν, cm^{-1}: 3310 (NH); 3200-2850 (OH); 1540 (C=N). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.45 (1H, d, $^3J_{3',4'}$ = 6.5, H-3'); 6.65 (1H, m, H-7); 6.75 (1H, m, H-6); 7.05-7.30 (14H, m, H 2Ph, H-4',5',6', NH); 7.45 (1H, s, H-3); 7.63 (1H, d, $^3J_{7,8}$ = 5.0, H-8); 8.25 (1H, d, $^3J_{5,6}$ = 4.5, H-5); 8.57 (1H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 391 $[M]^+$ (14), 373 (65), 372 (75), 296 (60), 256 (100), 187 (38), 148 (47), 118 (40), 105 (48), 78 (71), 77 (75). Found, %: C 79.25; H 5.72; N 10.33. $C_{26}H_{21}N_3O$. Calculated, %: C 79.77; H 5.41; N 10.73.

1,3,6-Tribromo-9-phenylacridine (7). A mixture of 2-chloromethyl-4*H*-3,1-benzoxazine (**4a**) (1.03 g, 3 mmol) and powdered reduced iron (0.5 g) in nitromethane (5 ml) was heated with stirring to the solvent reflux temperature. Bromine (2.88 g, 0.9 ml, 18 mmol) was added gradually at this time and the reaction mixture was stirred for 1.5 h under these conditions. At the end of the reaction (TLC monitoring) the inorganic fraction was filtered off. Solvent was evaporated from the filtrate and the residue was then treated with aqueous $Na_2S_2O_3$ solution, recrystallized from alcohol, and dried. Yield 0.37 g (25%), R_f 0.75 (benzene); mp 220ºC. IR spectrum, ν, cm^{-1}: 3070, 1580, 1570 (C=CH ar); 1610 (C=N).^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 7.25-7.90 (8H, m, Ph, H-4,5,8); 7.90-8.40 (2H, m, H-2,7). Mass spectrum, *m/z* (I_{rel}, %): 495 $[M+6]^+$ (13), 493 $[M+4]^+$ (42), 491 $[M+2]^+$ (40), 489 $[M]^+$ (13), 413 (30), 253 (55), 251 (31), 126 (100), 112 (40), 100 (17), 87 (10). Found, %: C 46.75; H 2.34; N 2.70; Br 48.56. $C_{19}H_{10}Br_3N$. Calculated, %: C 46.38; H 2.05; N 2.85; Br 48.72.

2-Chloromethyl-6-nitro-4,4-diphenyl-4*H*-3,1-benzoxazine (8). A nitrating mixture (prepared earlier from HNO_3 (2.1 ml, d = 1.5) and H_2SO_4 (3 ml, d = 1.84) with cooling in an ice salt bath) was added gradually over 30 min to a solution of the benzoxazine **4a** (1.03 g, 3 mmol) (again with cooling). The mixture was allowed to stand at room temperature for 24 h, poured into crushed ice, and neutralized with sodium bicarbonate solution. The precipitate formed in the weakly alkaline medium was filtered off, washed with water, and dried in air. The product obtained was chromatographed on a column (neutral alumina sorbent, benzene eluent) collecting the fraction with R_f 0.29. Yield 0.2 g (18%); mp 137-139ºC (benzene). IR spectrum, ν, cm^{-1}: 3160, 1590, 1570 (C=CH ar); 1620 (C=N); 1490, 1330 (NO_2). ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm (J, Hz): 4.32 (2H, d, CH_2); 7.20-7.70 (10H, m, 2 Ph); 8.05 (1H, d, $^3J_{8,7}$ = 8.7, H-8); 8.22 (1H, d, $^3J_{7,8}$ = 8.7, H-7); 8.27 (1H, s, H-5). Found, %: C 66.71; H 3.85; Cl 9.45; N 7.28. $C_{21}H_{15}ClN_2O_3$. Calculated, %: C 66.58; H 3.99; Cl 9.36; N 7.40.

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