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Studies on 1,3-Benzoxazines. VI.[1] Formation of Quinazolines and 4*H*-3,1-Benzoxazines by the Reaction of 4-Chloro-2*H*-1,3-benzoxazines with Aminoacetophenone, Aminobenzophenone and Aminobenzyl Alcohol Derivatives

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A novel synthetic method for quinazoline and 4*H*-3,1-benzoxazine derivatives is described. Reaction of 4-chloro-2*H*-1,3-benzoxazine (**1**) with 2-aminoacetophenone (**2a**) gave rise to the quinazoline derivative (**4a**) in good yield, while treatment of aminobenzophenones (**2b**—**e**) with **1** afforded only substituted compounds (**3b**—**e**), which could be converted into quinazoline derivatives (**4b**—**e**) on heating in the presence of *p*-toluenesulfonic acid in toluene. Derivatives of 4*H*-3,1-benzoxazines (**10a**—**e**) were prepared by the reaction of the aminobenzyl alcohols (**7a**—**e**) with **1**.

A possible mechanism for the formation of these reaction products is discussed.

Keywords——1,3-benzoxazine; imidoyl chloride; aminoacetophenone; aminobenzophenone; quinazoline; 4*H*-3,1-benzoxazine; reaction mechanism

In a preceding paper of this series, we reported a new synthetic route for benzoxazole, benzimidazole and benzothiazole derivatives[1] possessing a 2-hydroxyphenyl substituent at the 2-position by the reaction of 4-chloro-2*H*-1,3-benzoxazine with aminophenols, phenylenediamines and aminothiophenols as outlined in Chart 1.

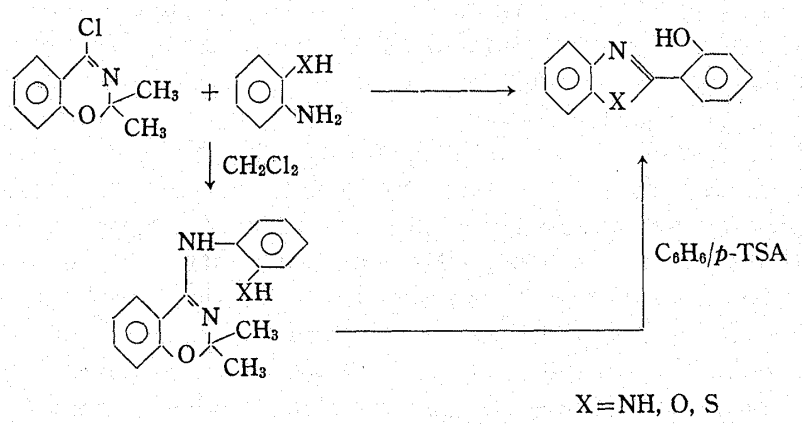


Chart 1

Many reports concerning synthetic methods for quinazoline derivatives have accumulated.[2]

This paper describes the formation of quinazolines and 4*H*-3,1-benzoxazines having a 2-hydroxyphenyl substituent by the reaction of 4-chloro-2*H*-1,3-benzoxazines with aminoacetophenone, aminobenzophenones and aminobenzyl alcohols under mild conditions.

Treatment of 4-chloro-2,2-dimethyl-2*H*-1,3-benzoxazine (**1**)[3] with 2-aminoacetophenone (**2a**, R_1=CH_3, R_2=H) in chloroform under reflux for 3 h afforded 2-(2-hydroxyphenyl)-4-methylquinazoline (**4a**) in 92% yield. The structure of **4a** was assigned on the basis of elemental analysis and spectroscopic data. The molecular formula was confirmed to be $C_{15}H_{12}N_2O$ by elemental analysis and mass spectroscopy (M^+: *m/e* 236). The nuclear magnetic resonance (NMR) spectrum revealed a singlet at 3.03 ppm (3H) due to the methyl group on

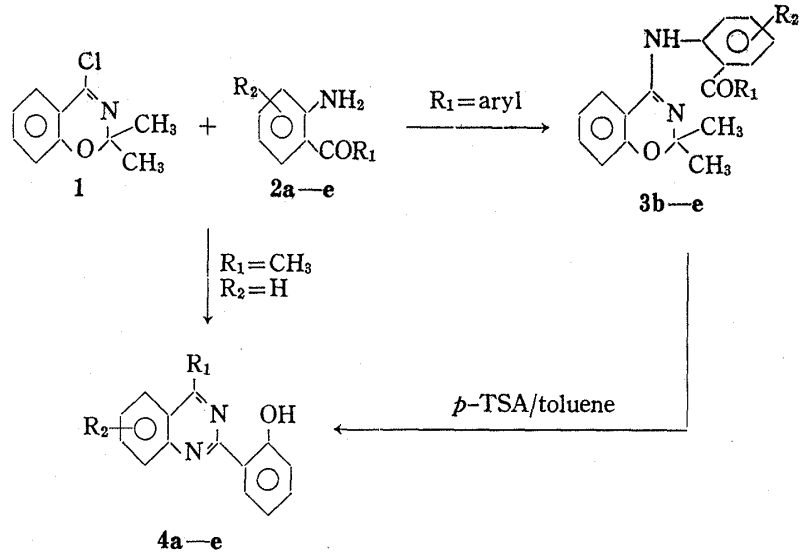


Chart 2

the quinazoline ring, a broad singlet at 13.83 ppm (1H) assigned to the hydroxyl group on the benzene ring and an aromatic multiplet at 6.80—8.80 ppm (8H). The signals corresponding to the dimethyl ketal groups of the benzoxazine ring had disappeared. The infrared (IR) spectrum showed no carbonyl absorption band at 1650 cm^{-1} region. The structure of **4a** was further confirmed by comparison of the IR and NMR spectra with those of an authentic sample prepared independently by the reaction of *O*-acetylsalicyl chloride with **2a** followed by cyclization according to the literature method.[4] On the other hand, the reaction of **1** with aminobenzophenone derivatives (**2b—e**) gave only substituted compounds (**3b—e**). When 2-aminobenzophenone (**2b**, R_1=Ph, R_2=H) was treated with **1** under similar reaction conditions, 2,2-dimethyl-4-(2-benzoylphenyl)amino-2*H*-1,3-benzoxazine (**3b**) was obtained in 79% yield. The analytical values and mass spectrum (M^+: *m/e* 356) were consistent with the empirical formula $C_{23}H_{20}N_2O_2$, which suggested the formation of a substituted compound with loss of hydrogen chloride from the adduct of **1** and **2b**. The NMR spectrum of **3b** exhibited a singlet at 1.67 ppm (6H) due to the dimethyl ketal groups, another singlet at 11.27 ppm (1H) due to the NH group and an aromatic multiplet at 6.80—9.20 ppm (13H). The IR spectrum showed a carbonyl absorption band at 1630 cm^{-1} and a band due to the secondary amine at 3250 cm^{-1}. In the case of the reaction of **2a** with **1**, **3a**, which might be an intermediate of **4a**, could not obtained. The differences in the formation reactions of **4a** and **3b—e** may be due to the electronic effect on the carbonyl group and the steric effects of the methyl and the aryl groups. Compound **3b**, however, was converted into the quinazoline derivative (**4b**)[4] in 93% yield by refluxing in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in toluene. The hydrochloride of **3b** was also readily transformed into **4b** in 89% yield on heating to its melting point. However, **4b** could not be obtained even when the reaction temperature of **3b** was raised to 140°C (reflux in xylene) in the absence of acid. These results suggested that the transformation of **3** into **4** proceeds in an acidic medium. A plausible mechanism for the formation of **4** is illustrated in Chart 3. As depicted in **5**, protonation occurs at the carbonyl group first, then a lone pair of nitrogen in the benzoxazine ring attacks the carbonyl carbon to afford the cyclic intermediate (**6**), followed by elimination of acetone to give the product (**4**).

Similar reactions were attempted with some derivatives of **2**, and the results are summarized in Tables I and II.

Next we investigated the reaction of aminobenzyl alcohols (**7a—e**) with **1** under similar reaction conditions.

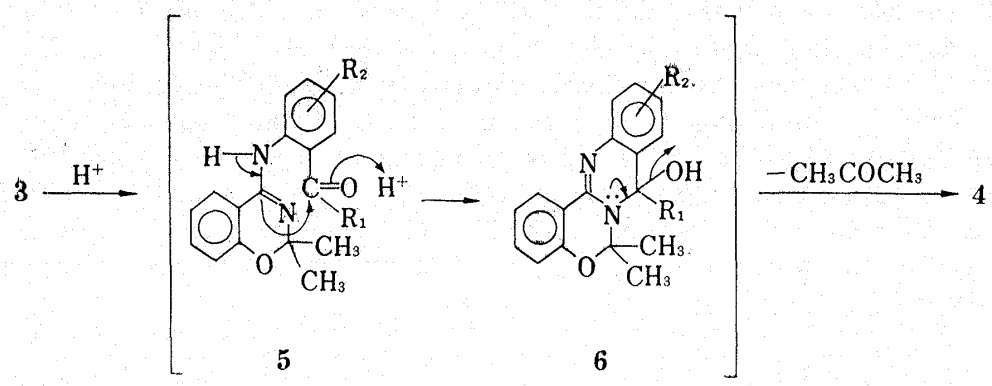
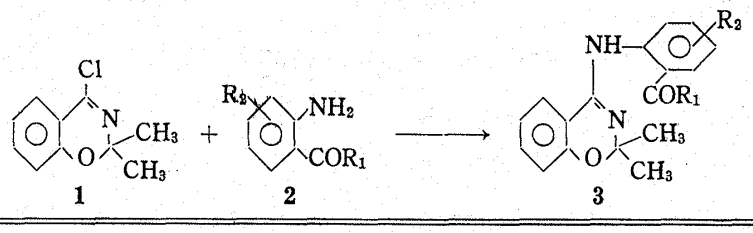


Chart 3

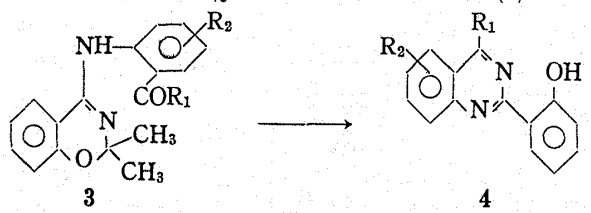
TABLE I. Reaction of 4-Chloro-2*H*-1,3-benzoxazine (**1**) with Aminobenzophenones (**2**)



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	CH_3	H	—	—[a]				
3b	Ph	H	115—116	79	$C_{23}H_{20}N_2O_2$	77.50 (77.62	5.66 5.64	7.86 8.01)
3c	Ph	4-Cl	134—135	89	$C_{23}H_{19}ClN_2O_2$	70.67 (70.96	4.89 4.89	7.16 7.11)
3d	Ph-CH_3 (*p*)	H	137—139	85	$C_{24}H_{22}N_2O_2$	77.81 (77.65	5.99 5.88	7.56 7.49)
3e	2-Pyridyl	4-Br	160—162	70	$C_{22}H_{18}BrN_3O_2$	60.56 (60.59	4.15 4.17	9.63 9.45)

a) **3a** was isolated as the corresponding quinazoline.

TABLE II. Quinazoline Derivatives (**5**)



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	CH_3	H	118—120	92	$C_{15}H_{12}N_2O$	76.25 (76.20	5.12 4.97	11.96 11.85)
4b	Ph	H	169—171	93	$C_{20}H_{14}N_2O$	80.51 (80.41	4.73 4.66	9.39 9.54)
4c	Ph	6-Cl	215—216	86	$C_{20}H_{13}ClN_2O$	72.18 (72.23	3.93 3.76	8.41 8.36)
4d	Ph-CH_3 (*p*)	H	171—173	83	$C_{21}H_{16}N_2O$	80.75 (80.70	5.16 5.07	8.97 8.85)
4e	2-Pyridyl	6-Br	210—212	88	$C_{19}H_{12}BrN_3O$	60.33 (60.42	3.19 3.17	11.10 11.16)

Treatment of 2-aminobenzyl alcohol (**7a**, R_1, R_2=H) with **1** in acetonitrile under reflux for 3 h afforded 2-(2-hydroxyphenyl)-4*H*-3,1-benzoxazine (**10a**) in 68% yield. The structural assignment of **10a** was based on the elemental analysis ($C_{14}H_{11}NO_2$) and mass spectrum (M^+: *m/e* 225). The NMR spectrum of **10a** showed no dimethyl ketal groups but showed a singlet at 5.42 ppm (2H) due to the methylene group, another singlet at 13.67 ppm (1H) assignable to the hydroxyl group and an aromatic multiplet at 6.70—8.00 ppm (8H). The downfield shift of the signal due to the hydroxyl proton indicated the formation of hydrogen bonding with nitrogen of the benzoxazine ring. The IR spectrum showed the –C=N– absorption band at 1620 cm^{-1}.

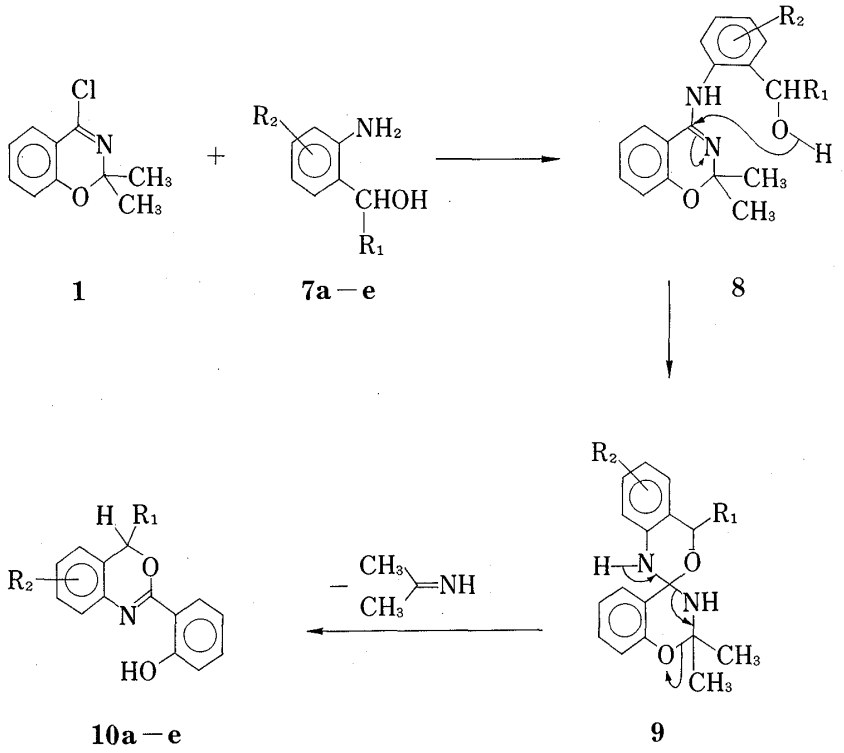
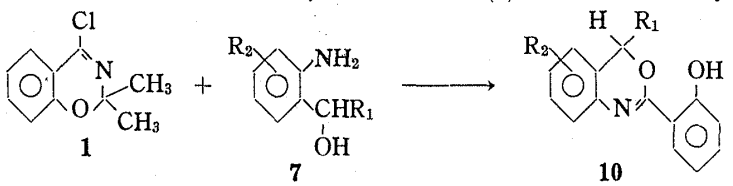


Chart 4

TABLE III. Reaction of 4-Chloro-2*H*-1,3-benzoxazine (**1**) with Aminobenzyl Alcohols (**6**)



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (in $CDCl_3$) ppm[a] C-4 (H)	–OH
10a	H	H	93—95	68	$C_{14}H_{11}NO_2$	74.65 (74.46	4.92 4.82	6.22 6.26)	5.42 (2H, s)	13.63 (br s)
10b	CH_3	H	55—57	74	$C_{15}H_{13}NO_2$	75.30 (75.18	5.48 5.40	5.85 5.87)	5.57 (1H, q)	13.70 (br s)
10c	Ph	H	117—119	63	$C_{20}H_{15}NO_2$	79.71 (79.51	5.02 4.94	4.65 4.51)	6.40 (1H, s)	13.60 (br s)
10d	Ph	6-Cl	127—128	84	$C_{20}H_{14}ClNO_2$	71.53 (71.79	4.20 4.19	4.17 4.11)	6.40 (1H, s)	13.37 (br s)
10e	2-Pyridyl	6-Br	153—155	79	$C_{19}H_{13}BrN_2O_2$	59.86 (60.12	3.43 3.23	7.34 7.11)	6.55 (1H, s)	13.30 (br s)

a) s: singlet, q: quartet, br s: broad singlet.

A possible mechanism for the formations of **10a** is depicted in Chart 4. The initially formed substituted compound (**8**) undergoes intramolecular cyclization follwed by the elimination of isopropylideneimine to give **10**. Reaction products bearing some substituents on the benzoxazine ring were also prepared by this method, and the results are summarized in Table III.

In order to obtain a seven-membered ring compound, we attempted the reaction of 2,2-dimethyl-4-[2-(2-hydroxyethyl)phenyl]amino-2*H*-1,3-benzoxazine (**11**), which was prepared by the reaction of *o*-aminophenethyl alcohol with **1**, with base or acid, but the desired compounds was not obtained.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrophotometer. NMR spectra were determined on a Varian A-60 or HA-100 instrument using tetramethylsilane as an internal standard; couling constants are given in Hz. MS were taken on a JEOL JMS-01SG instrument.

Reaction of 4-Chloro-2,2-dimethyl-2*H*-1,3-benzoxazine (1) with 2-Aminoacetophenone (2a)——A solution of chlorobenzoxazine (**1**, 3.0 g) and **2a** (2.1 g) in chloroform (150 ml) was refluxed for 3 h with stirring. After cooling to room temperature, the solution was washed with 2.8% NH_4OH and the solvent was evaporated off. The residual solid was recrystallized from C_2H_5OH to give 2-(2-hydroxyphenyl)-4-methylquinazoline (**4a**) (3.3 g). Melting point and analytical data are recorded in Table II.

General Procedure for the Preparation of 2,2-Dimethyl-4-(Substituted phenylamino)-2*H*-1,3-benzoxazines (3b—e)——A solution of a 2-aminobenzophenone (0.012 mol) and **1** (0.01 mol) in chloroform (50—150 ml) was refluxed for 1—3 h with stirring. After cooling, the reaction mixture was washed with 2.8% NH_4OH and the solvent was evaporated off *in vacuo*. The resulting solid was recrystallized from ethyl acetatehexane to give **3**. Yields, melting points and analytical data of the products are listed in Table I.

General Procedure for the Preparation of 2,4-Disubstituted Quinazolines (4b—e)——A solution of **3b—e** (0.005 mol) and *p*-toluenesulfonic acid (0.2—0.5 g) in toluene (30—50 ml) was refluxed for 3—5 h with stirring The reaction mixture was poured into ether, then the organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent by evaporation, the residual solid was recrystallized from methylene chloride–hexane to give **4**. The results are summarized in Table II.

Conversion of the Hydrochloride of 3b to 4b——The hydrochloride of **3b** (1.5 g) was melted at 130—140°C under reduced pressure. The reaction mixture was dissolved in chloroform and the chloroform layer was washed with 2.8% NH_4OH, dried over Na_2SO_4 and concentrated. The resulting solid was recrystallized from chloroform–hexane to give **4b** (0.91 g). This compound was identical with the sample prepared by the reaction of **3b** with *p*-TSA.

General Procedure for the Preparation of 2-(2-Hydroxyphenyl)-4*H*-3,1-benzoxazines (10a—e)——A solution of a 2-aminobenzylalcohol (**7a—e**, 0.02 mol) and **1** (0.01imol) in acetonitrile (30—100 ml) was refluxed for 3—5 h with stirring. The reaction mixture was poured into water, and this solution was made basic with NH_4OH then extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel with benzene–ethyl acetate, to give **10**. The results are summarized in Table III.

2,2-Dimethyl-4-[2-(2-hydroxyethyl)phenyl]amino-2*H*-1,3-benzoxazine (11)——A solution of *o*-aminophenethyl alcohol (3.0 g) and **1** (4.0 g) in methylene chloride (30 ml) was refluxed for 11 h with stirring. After cooling, the solution was washed with 2.8% NH_4OH and the solvent was evaporated off. The residual solid was recrystallized from methylene chloride–hexane to give 5.8 g of **11**, mp 95—96°C. *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45, Found: C, 73.10; H, 6.80; N, 9.51.

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