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AMINE—BORANES

II*. A NOVEL SYNTHESIS OF THE 1,3,2-BENZOXAZABORINE RING SYSTEM

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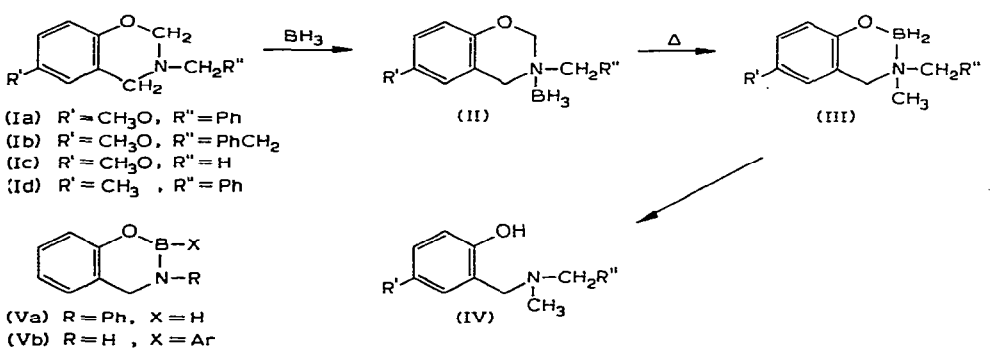
Summary

The amine—boranes of 3,4-dihydro-2*H*-1,3-benzoxazines were found to be unstable to heat forming [4*H*]-1-oxa-3-azonia-2-boratanaphthalenes. The spectra of these compounds showed them to exist in the cyclic form.

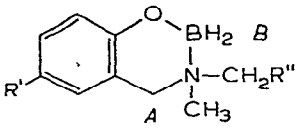
The borane Lewis salt of the basic nitrogen of 3-benzyl-6-methyl-3,4-dihydro-2*H*-1,3-benzoxazine (Ia) [2] was prepared in order to study the stereochemistry of the tetrahedral nitrogen of this cyclic amine—borane. However, on heating the amine—borane II, a new, isomeric compound III was formed. The NMR spectrum of III clearly indicated the presence of an *N*-methyl substituent which resulted from the reduction of the 2-methylene by the borane. This reduction was confirmed by hydrolysis of III to 2-(benzylaminomethyl)-4-methylphenol (IV). Such a reaction would be formally analogous to the reduction of the anil of salicylaldehyde by borane which has been reported to give 3-phenyl-3,4-dihydro-2*H*-1,3,2-benzoxazaborine (Va) [3,4].



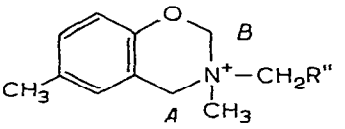
* For Part I see ref. 2.

TABLE 1

PROTON MAGNETIC RESONANCE SPECTRA OF [4*H*]-1-OXA-3-AZONIA-2-BORATANAPHTHALENES (II)



(III)



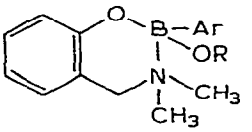
(Xa) R"=Ph

(Xb) R"=H

Compound	*A*				*B*			
	Multiplicity	δ (ppm)	*J* (Hz)	Δν (Hz)	Multiplicity	δ (ppm)	*J* (Hz)	Δν (Hz)
IIIa	AB	4.04	14	19.5	AB	3.84	14	15.6
IIIb	AB	3.98	14.5	8.9	M	3.08		
IIIc	S	3.96			S	2.68		
IIId	AB	4.04	13	17.7	AB	3.80	14.5	16.4
Xa	AB	4.84	15.5	31.4	S	3.82 [a]		
Xb	S	5.16			S	5.36		

[a] The ring methylene at position 2 gave a signal as an AB quartet at 5.40, *J* 8.5 Hz, Δν 11 Hz.

Cyclization to the 1,3,2-benzoxazaborine (V) apparently occured with elimination of hydrogen from the intermediate borane adduct to the anil bond forming a cyclic aminoborane (V). The intermediate prior to hydrogen elimination, was reported [3] to exist in an acyclic, polymeric form rather than in the cyclic, amine—borane structure (VI). Because the nitrogen in I was tertiary, such an elimination of hydrogen could not occur following the reduction. The NMR spectrum of III required that the reduction product be cyclic, however, for the resonance signal of the methylene protons of the phenolic benzyl group appeared as an AB quartet (Table 1). These hydrogens would be diastereotopic and appear as an AB quartet only if the compound was cyclic or if the nitrogen inversion was slow on the NMR time scale [5]. The former condition is a more reasonable explanation, for III gave no ferric chloride test for phenols nor did it show absorption in the infrared spectrum for OH stretching vibration. Thus the isomeric product of the amine—borane IIa was assigned the cyclic structure, 3-benzyl-3,6-dimethyl-[4*H*]-1-oxa-3-azonia-2-boratanaphthalene (IIIa)*.

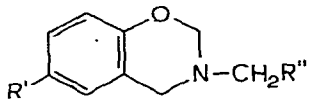


(VI)

Derivatives of the ring system III have been reported to be formed from the reaction of dihydroxyarylboranes and 2-dimethylaminomethylphenol and were

* The nomenclature of the ring system was suggested by Dr. Kurt Koening of the Chemical Abstract Service.

TABLE 2
PREPARATION OF 3,4-DIHYDRO-2*H*-1,3-BENZOXAZINES (I)



(I)

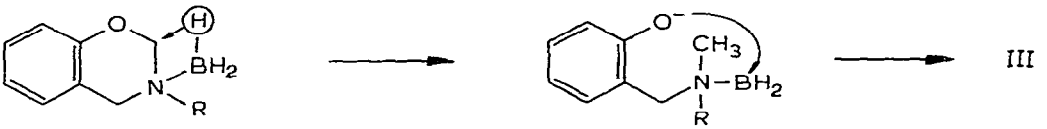
Compound	R'	R''	Yield (%)	m.p. (°C)	lit [2] m.p. (°C)
Ia	CH_3O	Ph	41	73 - 74	74 - 75
Ib	CH_3O	$PhCH_2$	63	72 - 74	73 - 74
Ic	CH_3O	H	44	41 - 43	*a*
Id	CH_3	Ph	54	70 - 71	71 - 72

[a] Anal. found: C, 67.19; H, 7.34; N, 8.02. $C_{10}H_{13}NO_2$ calcd.: C, 67.02; H, 7.31; N, 7.82%.

shown to exist in a cyclic form (VI) [6]. With a primary or secondary amine this reaction occurs with elimination to give derivatives of Vb [7].

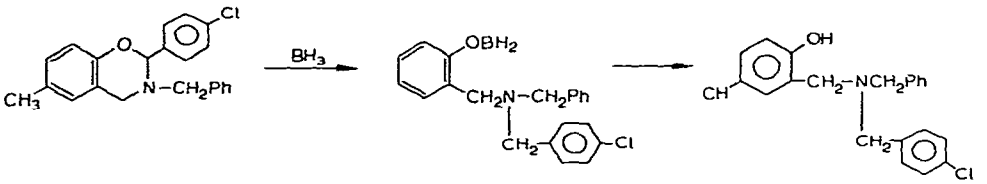
The ease of preparation of 3,4-dihydro-2*H*-1,3-benzoxazines (I) [2,8,9] from a phenol, formaldehyde, and an amine and the ease of conversion of these compounds to derivatives of [4*H*]-1-oxa-3-azonia-2-boratanaphthalene (III) led to an investigation of the scope of the reaction. The results are given in Table 2 and they indicate that the reaction sequence is applicable to the synthesis of a variety of derivatives of III. The rearrangement of the amine—borane (II) appeared to occur without dissociation, for there was no evidence of free borane during the reaction and excess borane does not cause the conversion.

The most probable mechanism for the rearrangement involves a nucleophilic displacement of the heterocyclic phenoxide by hydride. Cyclization by an acid—base reaction of the phenoxide ion with the boron gives the product III which is stable in the cyclic form because of the stability of the tetracovalent boron in III.



III

The reaction sequence was attempted with 2-*p*-chlorophenyl-3-benzyl-6-methyl-3,4-dihydro-2*H*-1,3-benzoxazine (VII) prepared from *p*-chlorobenzaldehyde and 2-benzylaminomethyl-4-methylphenol. The reaction of VII with borane gave a THF-insoluble solid. The properties are similar to those reported for the acyclic polymeric analogs of III, VIII [3]. The failure of VIII to cyclize probably results from the steric interferences provided by the additional large group on the nitrogen. Heating VIII gave loss of the boron, probably by hydrolysis, to yield benzyl, *p*-chlorobenzyl, 5-hydroxy-2-methylbenzylamine (IX).



(VII) (VIII) (IX)

Experimental

General preparation of substituted 3,4-dihydro-2H-1,3-benzoxazines (I). The reaction of 0.10 mol of the phenol with 6.6 g (0.066 mol) of formaldehyde and 0.10 mol of the primary amine gave the derivatives of I following the procedure of Burke [2]. Isolation of the products by the reported method gave the derivatives of I given in Table 1.

General procedure for the preparation of the derivatives of [4H]-1-oxa-3-azonia-2-boratanaphthalene (III). To an ice cold solution of 0.005 mol of the appropriate 3,4-dihydro-2*H*-1,3-benzoxazine (I) in 10 ml of tetrahydrofuran was added 6 ml of 1 *M* borane in tetrahydrofuran, and the solution was stirred at ice bath temperatures for 0.5 h. The solvent was then evaporated to yield a white solid. An NMR spectrum of this solid was recorded (Table 2). The solid was then heated neat under a nitrogen atmosphere at 200° for 20 min. On cooling, the melt crystallized and this solid was recrystallized from cyclohexane—benzene to yield the corresponding [4*H*]-1-oxa-3-azonia-2-boratanaphthalene (III). All analytical and spectral data were then obtained.

3-Benzyl-3-methyl-6-methoxy-[4H]-1-oxa-3-azonia-2-boratanaphthalene borane (IIIa). The above procedure gave 0.7 g (53%) of IIIa, m.p. 141 - 144° (dec.). IR: 2300, 2360, 2410 (BH). Anal. found: C, 71.00; H, 7.33; N, 5.34. $C_{16}H_{20}BNO_2$ calcd.: C, 71.40; H, 7.49; N, 5.21%.

3-Methyl-3-(β-phenethyl)-6-methoxy-[4H]-1-oxa-3-azonia-2-boratanaphthalene (IIIb). The above procedure gave 1.1 g (78%) of IIIb, m.p. 103 - 110° (dec.). IR: 2270, 2340, 2400 (BH). Anal. found: C, 71.70; H, 7.62; N, 5.22. $C_{17}H_{22}BNO_2$ calcd.: C, 72.10; H, 7.83; N, 4.95%.

3,3-Dimethyl-6-methoxy-[4H]-1-oxa-3-azonia-2-boratanaphthalene (IIIc). The above procedure gave 1.3 g (68%) of IIIc, m.p. 133 - 135° (dec.). IR: 2340, 2400 (BH). Anal. found: C, 62.46; H, 8.06; N, 7.13. $C_{10}H_{16}BNO_2$ calcd.: C, 62.21; H, 8.36; N, 7.26%.

3-Benzyl-3,6-dimethyl-[4H]-1-oxa-3-azonia-2-boratanaphthalene (IIId). The above procedure gave 0.7 g (54%) of IIId, m.p. 159 - 161° (dec.). IR: 2350, 2400, 2430 (BH). Anal. found: C, 75.95; H, 7.91; N, 5.53. $C_{16}H_{20}BNO$ calcd.: C, 75.91; H, 7.96; N, 5.53%.

Preparation of 2-(benzylaminomethyl)-4-methylphenol. A solution of 7.2g (0.03 mol) of 3-benzyl-6-methyl-3,4-dihydro-1,3-2*H*-benzoxazine (Id) in 50 ml of ethanol was treated with 15 ml of concentrated hydrochloric acid and the solution was allowed to stand at ambient temperature overnight. The solution was concentrated and the residue was partitioned between 100 ml of methylene chloride and 100 ml of saturated aqueous sodium bicarbonate. After separation, the organic layer was washed with water, dried over anhydrous potassium carbonate, and evaporated to yield an oil which crystallized on cooling. The white solid was recrystallized from pentane to yield 5.0 g (73%) of 2-(benzylaminomethyl)-4-methylphenol as white needles, m.p. 30 - 32°.

Preparation of p-chlorophenyl-3-benzyl-6-methyl-3,4-dihydro-2H,1,3-benzoxazine (VII). A solution of 2.3 g (0.01 mol) of 2-benzylaminomethyl-4-methylphenol and 1.4 g (0.01 mol) of *p*-chlorobenzaldehyde in 25 ml of benzene was heated under reflux for 24 h utilizing a Dean—Stark apparatus to remove water. The benzene solution was then concentrated and the residual brown oil crystal-

lized to a tan solid after cooling for three days. The solid was recrystallized from isopropanol to yield 2.3 g (66%) of Ie as a white solid, m.p. 76 - 78°. Anal. found: C, 75.61; H, 5.92; N, 4.24. $C_{22}H_{20}ClNO$ calcd.: C, 75.52; H, 5.76; N, 4.00%.

Reaction of 2-p-chlorophenyl-3-benzyl-6-methyl-3,4-dihydro-1,3,2H-benzoxazine (VII) with borane. To an ice cold solution of 1.2 g (0.005 mol) of 2-*p*-chlorophenyl-3-benzyl-6,3,4-dihydro-1,3,2*H*-benzoxazine (VII) in 10 ml of the tetrahydrofuran was added 6 ml of 1 *M* borane diethyl etherate in tetrahydrofuran, and the solution was stirred at ice bath temperatures for 1.0 h. A white solid (VIII), m.p. 196°, had precipitated from the solution during this time. The infrared spectrum of this compound (VIII) showed a B—H stretching absorption at 2400 cm^{-1}.

The white solid VIII was heated neat at 220° for 20 min under a nitrogen atmosphere. The resulting solid, IX, was not the expected product of rearrangement but was shown by its chemical, physical and spectral properties to be benzyl, *p*-chlorobenzyl, 3-hydroxy-2-methylbenzyl amine (IX), m.p. 56 - 58° (pentane). Anal. found: C, 75.31; H, 6.28; N, 4.12. $C_{22}H_{22}ClNO$ calcd.: C, 75.09; H, 6.30; N, 3.98%.

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