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THE STRUCTURE OF BOROXAZOLIDINES RELATED TO THREO-1-PHENYL-2-AMINOPROPANE-1,3-DIOL

G. FODOR, O. FUCHS and A. R. KATRITZKY
The Sterochemical Laboratory
The Hungarian Academy of Sciences, Budapest;
The Research Institute for Pharmaceutical Industry, Budapest;
University Chemical Laboratory, Cambridge, England

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Abstract—*p*-Nitrophenylserine butyl ester when reduced with calcium borohydride, gave a compound which could have had structure A, B, or C. Spectropolarimetric, IR, and NMR evidence indicated structure IV, a calcium boroxazolidine related to A. A zwitterionic boroxazolidine II was synthesized from threo-1-*p*-nitrophenyl-2-aminopropane-1,3-diol and ethyl borate.

IT HAS long been known[1] that boric acid and vicinal diols with *cis*-vicinal hydroxyl groups (e.g. sugars) form cyclic esters of spirane structure with a negative charge on the central boron atom. The nucleophilicity and also the co-ordination tendency of nitrogen towards many elements is higher than that of oxygen. The failure of amino sugars[2] to enhance the conductivity of boric acid misled Boeseken and it was not till 1958 that Weidmann and Zimmerman[3] prepared very stable cyclic derivatives from B-substituted boric acids with amino alcohols such as 1-aminopropane-2-ol, diethanolamine, triethanolamine, 3-aminopropane-1-ol. Potentiometric titration[3] and IR spectra[4] showed the presence of a semipolar N–B bond. Hence the boroxazolidine 5-membered ring structure was assumed for these compounds and the boroxazine 6-membered ring structure for those derived from 3-amino alcohols. Direct evidence for the five-membered ring was not previously available.

Some years ago, one of us (O. F.) with Hajós[5] reduced *p*-nitrophenylserine butyl ester with calcium borohydride and proposed two structures for the product. One contains a ring-system with two oxygen atoms linked to boron, while the alternative formulae had the boron bound to nitrogen. In view of the above work[3] we investigated the constitution and configuration of that compound. We have also studied the the condensation products of 1-phenyl-2-aminopropane-1,3-diol and its 4-nitro derivative with ethyl borate.

An important difference between the boroxazolidines previously studied[3] and those of the present investigation is the presence in the latter of an additional hydroxyl group. Either the primary or the secondary hydroxyl could be involved in cyclization with the boron atom. The boroxazolidines from simple amino alcohols and those

[1] P. W. Kent and M. W. Whitehouse, *Biochemistry of the Amino Sugars* pp. 166, 246. Academic Press, N.Y. (1955).
[2] J. Boeseken, *Advances in Carbohydrate Chemistry* **4**, 189, Academic Press, N.Y. (1949).
[3] H. Weidmann and H. Zimmerman jr., *Liebigs Ann.* **619**, 28 (1958).
[4] H. Weidmann and H. Zimmerman jr., *Liebigs Ann.* **620**, 4 (1959).
[5] O. Fuchs and A. Hajós, *Acta Chim. Acad. Sci. Hungar.* **24**, 411 (1960).

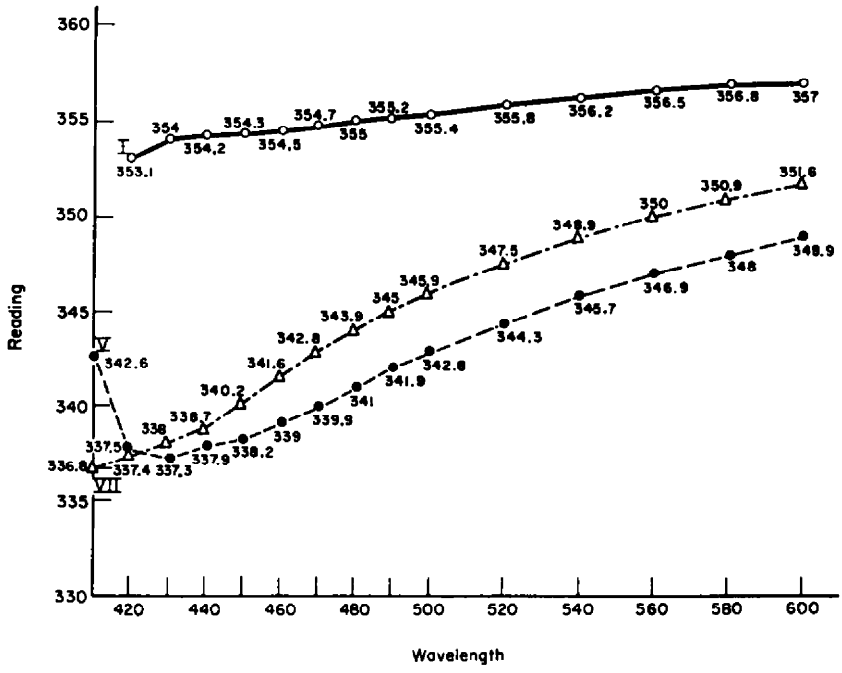


FIG. 1. Rotary dispersion curves of I, V, VII

prepared from amino-diols are of zwitterionic structure in contrast to the reduction product mentioned above[5] which is a salt (one equivalent of calcium to each boron atom).

EXPERIMENTAL

The salt character of the reduction product from *p*-nitrophenylserine follows from its equivalent conductivity: 147·7 $\lambda/cm^2 . ohm^{-1} . -eq^{-1}$. The equivalent conductivity of threo-1-*p*-nitrophenyl-2-aminopropane-1,3-diol at 24·95° and M/100 solution is only 8·64 $\lambda cm^2 . ohm^{-1} . -eq^{-1}$. The boroxazolidines prepared from boric acid and amino alcohols and those from amino-diol II do not have appreciable conductivity because of their zwitterionic character.[4]

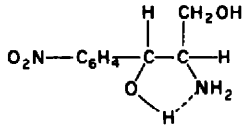
Polarimetric measurements

Dimethyl formamide is the only good common solvent for all the compounds studied. There is a large difference between the $[\alpha]_D$ values of the open chain amino-diol (or its N-acyl derivatives) and the boroxazolidine, particularly in the visible region. The amino-diol shows an $[\alpha]_D$ value of −38°, its N-dichloroacetyl derivative −28°, while the boroxazolidine (II) shows $[\alpha]_D = -127°$ and the calcium boroxazolidine (IV) $[\alpha]_D = -107°$. *Trans*-2-phenyl-4-hydroxymethyl-5-*p*-nitrophenyloxazolidine (presumably one of the C_2-epimers) has the $[\alpha]_D$ value −109°. When these measurements were extended to a wider UV region, interesting spectropolarimetric data were obtained. The rotatory dispersion curves of the amino-diol and its N-acetylated derivative are nearly linear (Fig. 1) while the corresponding boroxazolidines show steep curvature towards longer wave lengths (Fig. 2).*

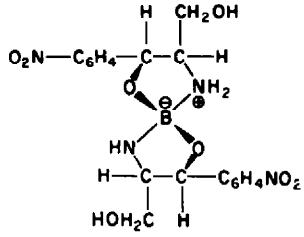
Infra-red spectra

The following compounds were examined by IR spectroscopy: (−)threo-1-*p*-nitrophenyl-2-aminopropane-1,3 diol (I), threo-4-hydroxymethyl-5-*p*-nitrophenylboroxazolidine (II), the calcium boroxazolidine (III) obtained from phenylserine ester by reduction, product (IV) from *p*-nitrophenyl

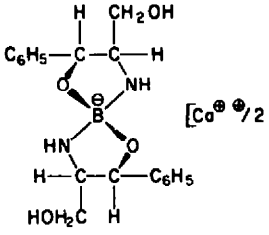
* All these measurements were taken in 10% solution, except with VII where 2% was the highest we could attain.



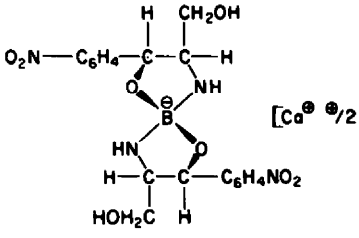
I $[\alpha]_D = -38°$



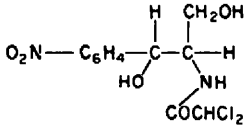
II $[\alpha]_D = -127°$



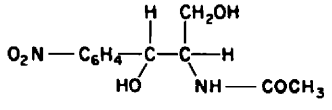
III



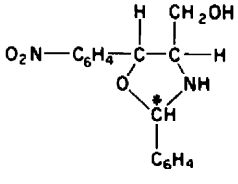
IV $[\alpha]_D = -107°$



V $[\alpha]_D = -26°$



VI



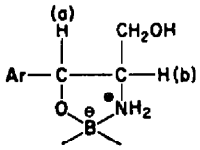
VII $[\alpha]_D = -109°$

serine ester, chloramphenicol [D(−)-threo-1-*p*-nitrophenyl-2-dichloracetylaminopropane-1,3-diol] (V), threo-1-*p*-nitrophenyl-2-acetamidopropane-1,3-diol (VI) and the benzal derivative of 1-*p*-nitrophenyl-2-aminopropane-1,3-diol i.e. *trans*-2-phenyl-4-hydroxymethyl-5-*p*-nitrophenyloxazolidine (VII).

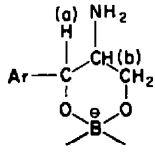
The amino-diol (I) possesses a characteristic broad band at 3391 cm^{-1} and another at 2600 cm^{-1}, both due to a very strong hydrogen bridge. Both bands disappear when the nitrogen becomes acetylated or dichloroacetylated (VI or V); these bands are also absent in the boroxazolidines (II, III and IV), i.e. in all the boron containing derivatives of the amino-diol. Obviously, the acetyl groups or the boron atom modify the hydrogen bridge.

Further characteristic difference between the spectra of the aminodiol (I) and of the boron containing derivatives (II, III and IV) are found in the regions near 1610 cm^{-1} and 800–900 cm^{-1}. Near 1100 cm^{-1}, a characteristic band appears in the spectrum of the boroxazolidine which may

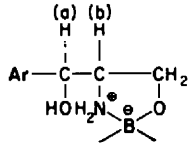
be the B–N-linkage. The spectrum of the boroxazolidine (II) is very similar to that of the calcium boroxazolidine (IV).



(A)



(B)



(C)

Nuclear magnetic resonance

Direct evidence for the five-membered ring structure of the compound (II) from the aminodiol and ethyl borate was obtained using NMR spectrography. In principle, there are three alternatives for the structure of that compound:

(A) in which the secondary hydroxyl and the amino group are involved in heterocyclic ring formation.

(B) boric acid ester formation with both the primary and the secondary hydroxyl group.

(C) a spirane structure involving the amino nitrogen and the primary hydroxyl group.

To simplify the spectrum all active hydrogen atoms were replaced by deuterium by repeated treatment with deuterium oxide and evaporating. The measurements were carried out in perdeuteromethanol.

BOROXAZOLIDINE (II) OBSERVED SPECTRUM

Chemical shift	Multiplicity	J(c/s)	Assignment
1·79	2	9	aromatic ring
2·33	2	9	
4·95	2	4	Ar—CH—O (a)
6·20	1 (broad)	–	—CH_2O (c)
6·87	3	4	CH—N (b)

The chemical shifts were assigned by comparison with literature values[6] and coupling constants were calculated for the three alternative structures.[7] The main factor influencing the coupling constants is the dihedral angle betweed the (secondary) hydrogen atoms 'a' and 'b', which varies as follows:

Structure	Dihedral angle a/b	Predicted coupling constant
A	−120°	4·5 c/s
B	−60°	1·5 c/s
C	−ca. 180°	ca. 11 c/s

The J value found for the compound is thus in excellent agreement with that calculated for A and eliminates structures B and C.

The experimental data for hydrogen 'b' probably indicates that it is coupled to one of the 'c' hydrogens (which are not equivalent) by approximately the same amount. The 'c' hydrogen peak would thus be due to the superposition of the two (non equivalent) protons and its broad nature reflects its complex structure. The chemical shifts are only slightly displaced from those of the aminodiol, the boron atom would not be expected to influence these largely.

[6] L. H. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy* p. 59. Pergamon, London (1952).

[7] H. Conroy, *Nuclear Magnetic Resonance in Organic Structural Elucidation*, in *Advances in Organic Chemistry* Vol. II, R. A. Raphael, E. C. Taylor, H. Wynberg, Interscience, N.Y. (1960).

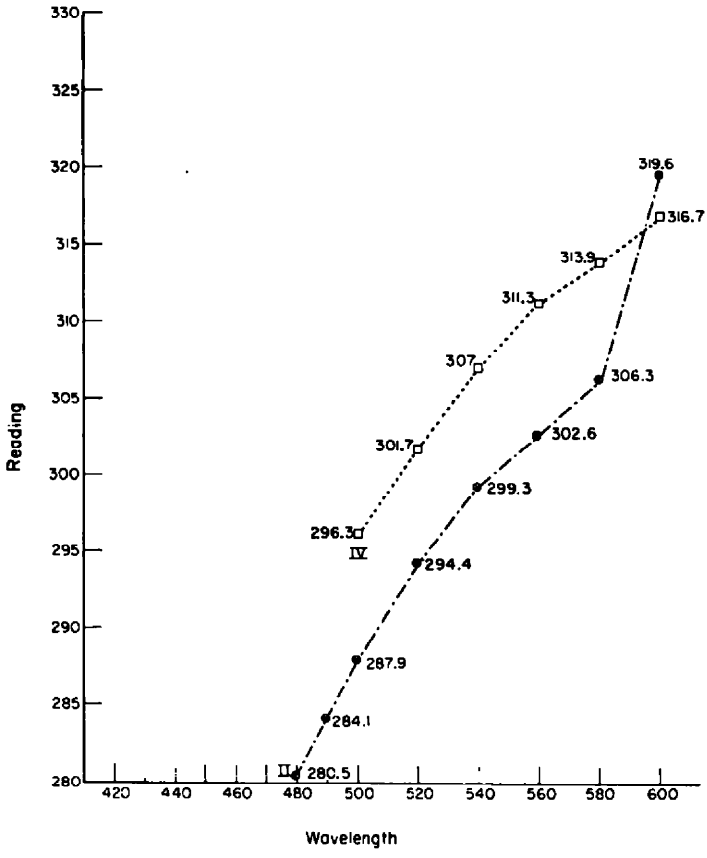


FIG. 2. Rotary dispersion curves of II, IV

Hence, the compound (II) prepared from the aminodiol is unequivocally a boroxazolidine derivative with ring formation involving the secondary hydroxyl and the amino nitrogen. X-ray diffraction of bromomycetine obtained by Dunitz[8] showed, in agreement with chemical evidence[9] that the secondary hydroxyl was closely adjacent to the substituted nitrogen while the primary hydroxyl is remote. Accordingly, it is not surprising that the neighbouring secondary hydroxyl and nitrogen react with boric acid.

The measurements taken with the reduction product (IV) from *p*-nitrophenylserine using the same NMR technique as with the boroxazolidine (II) gave figures closely related to the aforementioned compound.

Chemical shift	Multiplicity	J(c/s)	Assignment
1·75	2	9	aromatic ring
2·35	2	9	
4·95	2	3	Ar—CH—O (a)
6·0–6·5 broad peak with much structure			CH_3—O and contaminant CH_3
6·98	3	4	CH—N (b)

The coupling constant is again 3–4 c/s as expected for the dihedral angle between protons *a* and *b* in structure IV.

[8] J. P. Dunitz, *J. Amer. Chem. Soc.* **74**, 995 (1952).
[9] G. Fodor, J. Kiss and I. Sallay, *J. Chem. Soc.* 1858 (1951).

DISCUSSION

More stable bonding of boron between the amino nitrogen and the secondary hydroxyl group in IV is evident although this may be surprising in view of the initial attack of borohydride ion upon the original ester grouping.

Accordingly the compound previously referred to as "Borkomplexverbindung" and depicted tentatively as a cyclic boric acid ester of the amino-diol is actually a boroxazolidine (IV) involving the secondary hydroxyl group and the amino nitrogen atom. Possibly the boroxazolidine ring primarily formed form serine ester and borohydride ion rearranges prior to isolation because of steric factors. In any case the compound Fuchs and Hajós[5] isolated is a boroxazolidine; the alternative cyclic boric ester formula, B, is also unlikely in view of the relative nucleophilicity of nitrogen and oxygen.

The boroxazolidines as zwitterionic compounds show a marked resistance toward acylating agents. However, when the calcium boroxazolidine (IV) was treated in dimethyl formamide with methyl dichloroacetate, an acyl derivative $[\alpha]_D = -81°$ was isolated; no fundamental change in the basic skeleton of the ring-system occurred. This discrepancy in behaviour may be explained by the fact that the nitrogen in the calcium boroxazolidine is not positively charged since the positive charge which compensates the formal negative charge on boron is carried by the outer calcium cation. Hence, the calcium boroxazolidine can be converted into the N-acyl derivative without destruction of the heterocyclic ring.