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DIPTYCH-BOROXAZINES AND A NEW METHOD OF SEPARATING SOME DIASTEREOISOMERS

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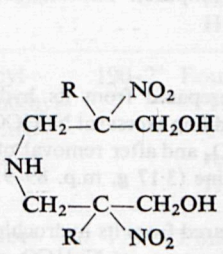
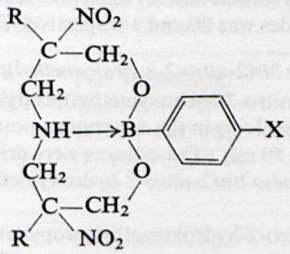
Abstract—Bis(3-propanol)amines can form diptychs containing 2-bora-1,3-oxazine rings. Those with two asymmetric centers can readily be separated into two diastereo isomers (*cis* and *trans*) owing to their different solubility. After isolation of pure isomers they can be hydrolysed to yield pure diastereoisomers of bis(3-propanol)amine.

Bis(3-propanol)amines of general formula bis(2-nitro-2-hydroxymethyl-alkyl amines) (I)[1a] should exist as two diastereoisomers, *meso*- and DL-, owing to the presence of two asymmetric centers in the molecule. The separation of the isomers proved a difficult task as after meticulous fractional crystallization one of the diastereoisomers was still very impure. It was finally concluded that a more efficient method would probably be to form complex compounds from I, and after separation to hydrolyse the complexes to yield pure isomers of I.

Thus by reacting I with phenylboronic acid and its derivatives substituted in the aromatic ring we obtained diptychs of a general formula II.



I



II

It is known that bis(ethanol)amines form diptychs with aryl boronic acid.[2] They are characterized by the presence of two five-member 2-bora-1,3-oxazol rings with a co-ordination N→B bond. When using compounds I to react with phenylboronic acid or its *para* substituted derivatives two six-member rings of 2-bora-1,3-oxazine

[1a] E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochynski, A. T. Thomas and T. Urbanski, *J. Chem. Soc.* 924 (1947); [b] T. Urbanski and E. Lipska, *Rocz. Chem.* **26**, 182 (1952).
[2] H. Weidmann and H. K. Zimmerman Jr., *Libigs. Ann.* **619**, 28 (1958); **620**, 4 (1948).

were formed. They readily hydrolyse to yield again I. In the present paper we describe results with a simple representative of I derived from nitroethane, i.e. when R = Me.

Bis(2-nitro-2-hydroxymethylpropyl)amine (I, R = Me) was prepared[1b] and isolated as a mixture of diastereo-isomeric hydrochlorides. The mixture was subjected to fractional crystallization from alcohol and after long and tedious work two kinds of crystals were separated: (1) long needles m.p. 188° and (2) sugar-like crystals m.p. 181–183° in the ratio 20:1.

The free bases obtained from each of the compounds gave (1) a compound, m.p. 89–91° and (2) a liquid, which indicated that at least compound (2) was of low purity. However, when a mixture of diastereoisomers (1) and (2) was subjected to the reaction with *p*-chlorophenylboronic acid, a mixture of boroxazine-diptychs resulted. It was found that two isomeric diptychs can readily be separated by fractional crystallization from benzene. One of the derivatives (1) m.p. 217–219° was practically insoluble in benzene, whereas the other one (2) m.p. 178° was significantly soluble.

The IR spectra have shown that NO_2 asymmetric stretching vibrations are split into two bands in the diptych formed from compound (1) and shows only a shoulder in the diptych from compound (2). This can be explained by admitting that diptych from compound (1) has a less symmetrical *cis* structure, whereas compound (2) is of a more symmetrical *trans* structure.

When reacting a pure base (1) of m.p. 89–91°, with *p*-chlorophenylboronic acid a diptych of m.p. 217–219° was obtained, identical with that previously described.

Hydrolysis of diptychs by alcoholic hydrochloric acid gave pure hydrochlorides which in turn furnished bases: (1) m.p. 92° and (2) m.p. 89°. We also prepared diptychs from I (R = Me) and phenylboronic acid.

EXPERIMENTAL

Preparation of bis(2-nitro-2-hydroxymethyl)propylamine hydrochlorides

Bis(2-nitro-2-hydroxymethyl)propylamine hydrochloride (a mixture of two diastereoisomers, probably DL and *meso*) was prepared and the mixture subjected to fractional crystallization from alcohol. After several crystallizations, two isomeric hydrochlorides were separated: (1) long needles m.p. 181–182°, less soluble and (2) sugar-like crystal m.p. 179° (impure). The ratio of two diastereoisomeric hydrochlorides was 20 and 1 respectively.

Preparation of free bis(2-nitro-2-hydroxymethyl)propylamines

1. *meso*-Bis(2-nitro-2-hydroxymethyl)propylamine was prepared from its hydrochloride (5 g, 0·0174 mole) by dissolving in the minimum amount of water, adding excess sat $NaHCO_3$ aq and extracting with ether (4 × 50 ml). The extracts were dried over $MgSO_4$ and after removal of the solvent and recrystallization *meso*-bis(2-nitro-2-hydroxymethyl)propylamine (3·17 g, m.p. 89–91°) was obtained with 72·5% yield.

2. DL-Bis(2-nitro-2-hydroxymethyl)propylamine was prepared from its hydrochloride (4 g, 0·0015 mole), by dissolving in the minimum amount of water, adding excess sat $NaHCO_3$ aq and extracting with ether (5 × 50 ml). After drying and removal of the solvent the remaining amino-dinitro-diol (2·70 g, 77%) failed to crystallize and therefore was purified further by reaction with an equimolar amount of *p*-chlorophenylboronic acid to produce the diptychboroxazines:

(a) Insoluble *cis*-diptych-B-*p*-chlorophenyl-4,8-dimethyl-4,8-dinitro-2-bora-1,3-oxazine (m.p. 217–219°) was filtered off,

(b) Soluble *trans*-diptych-B-*p*-chlorophenyl-4,8-dimethyl-4,8-dinitro (m.p. 178°) was isolated by removal of the solvent (benzene) and recrystallization from a small amount of benzene. Yields varied: usually the amino-dinitro-diol (liquid) contained about 80% of the DL-isomer and 10% of the *meso*, the rest being impurities. The resulting *trans*-diptych-B-*p*-chlorophenyl-4-8-dimethyl-4,8-dinitro-2-bora-1,3-oxazine (2·0 g, 0·005 mole) was hydrolysed by boiling it in 20% alcoholic HCl to give pure

DL-bis(2-nitro-2-hydroxymethyl)propylamine hydrochloride which was washed with a small amount of alcohol and dried (1·43 g, 90% yield, m.p. 181°). The resulting pure hydrochloride (1·55 g; 0·004 mole) was transferred into free DL-bis(2-nitro-2-hydroxymethyl)propylamine (0·74 g, 0·003 mole, 73·5% yield, m.p. 92°), by the method described.

*Preparations of diptych-*B*-aryl-*4,8*-dimethyl-*4,8*-dinitro-*2*-bora-*1,3*-oxazines*

All the compounds were prepared as follows: the soln of the base (200 mg, 0·008 mole) in anhydrous benzene (50 ml) was mixed with a benzene (100 ml) soln of the corresponding boronic acid (0·008 mole). The mixture was placed in a distillation apparatus and the benzene slowly distilled off. Water was azeotropically removed and the diptych-boroxazines pptd. In the case of the *p*-chlorophenyl derivative, almost all the benzene had to be removed (2 ml remained). The yields of the reaction were almost 100%. The products obtained were filtered on a sintered glass funnel and dried at 60°. IR spectra were examined on a Hilger H 800 double beam spectrophotometer. The properties and analyses of all compounds are presented in the Table. The conformation of the diptychs was tentatively estimated by means of Dreiding Models.

TABLE

Compound	M.p.	Analyses	IR bands	Properties
DL-Bis(-2-nitro-2-(hydroxymethyl) propylamine	89°	Found: C, 38·6; H, 6·9; N, 16·5 $C_8H_{17}O_6N_3$ requires; C, 38·3; H, 6·8; N, 16·7%		Soluble in alcohol and benzene
meso-Bis(2-nitro-2-hydroxymethyl) propylamine	92°	Found: C, 38·6; H, 6·9; N, 16·5 $C_8H_{17}O_6N_3$ requires: C, 38·6; H, 6·8; N, 16·7%		Soluble in alcohol and benzene
Diptych-B-phenyl-4a, 8e-dimethyl-4e, 8a-dinitro-2-bor-1-3-oxazine (*trans*)	186–7°	Found: C, 50·2; H, 6·0; N, 12·3 $C_{14}H_{20}O_6B\,N_3$ requires: C, 49·9; H, 5·9; N, 12·4%	NH stretching 3271 cm^{-1} *vs* NO_2 asym. str. (1) 1550 cm^{-1} *vs* (2) 1548 cm^{-1} *vs*	Slightly soluble in benzene and chf
Diptych-B-phenyl-$4a_{(e)}$ $8a_{(e)}$-dimethyl-$4e_{(a)}$ $8e_{(a)}$-dinitro-2-bor-1,3 oxazine (*cis*)	190–2°	Found: C, 50·1; H, 5·9; N, 12·2 $C_{14}H_{20}O_6B\,N_3$ requires: C, 49·9; H, 5·9%	NH stretching 3230 cm^{-1} *vs* NO_2 asym. str. (1) 1548 cm^{-1} *vs*	Insoluble in: benzene, chf and CCl_4 Slightly soluble in acetone
Diptych-B-p-chlor-phenyl-4a,8e-dimethyl-4e,8a-dinitro-2-bor-1,3-oxazine (*trans*)	178°	Found: C, 45·0; H, 5·2; N, 11·1 $C_{14}H_{19}O_6B\,ClN_3$ requires: C, 45·2; H, 5·1; N, 11·3%	NH stretching 3224 cm^{-1} *vs* NO_2 asym. str. (1) 1547 cm^{-1} *vs* (2) 1545 cm^{-1} *vs*	Soluble in benzene, chf and acetone
Diptych-B-p-chlor-phenyl-$4a_{(e)}8a_{(e)}$-dimethyl-$4e_{(a)}8e_{(a)}$-dinitro-2-bor-1,3-oxazine (*cis*)	217–9°	Found: C, 45·0; H, 5·2; N, 11·1 $C_{14}H_{19}O_6B\,ClN_3$ requires: C, 45·2; H, 5·1; N, 11·3%	NH stretching 3224 cm^{-1} *vs* NO_2 asym. str. (1) 1550 cm^{-1} *vs*	Insoluble in benzene and chf Slightly soluble in acetone

Hydrolysis of diptychs. Diptych (0·003 mole) was suspended in alcoholic HCl (20 ml) and heated under reflux for 3 hr. The reaction mixture was evaporated to half of its volume and upon slow cooling long needles of the aminodiol hydrochloride pptd. They were washed with small amount of cold alcohol, yield 90–5%.

Phenylboronic acid or its derivatives remained in solns as their diethyl esters.