Tetrahedron, 1963, Vol. 19, pp. 821 to 826. Pergamon Press Ltd. Printed in Northern Ireland

ARYLBORONIC COMPOUNDS—VIII

SOME REACTIONS OF HYDROXY AND CARBOXYPHENYLBORONIC ACIDS

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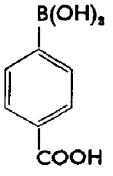
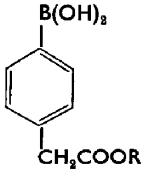
(*Received* 2 *December* 1962)

Abstract—Some new derivatives of carboxy and hydroxyphenylboronic acid (I–VI) have been prepared and the direct halogenation of *ortho* and *para* hydroxy and methoxyphenylboronic acids has been investigated.

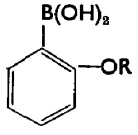
CONTINUING our investigation on the biological active derivatives of phenylboronic acid, some new derivatives of *p*-carboxyphenylboronic acid (I), *p*-boronophenylacetic acid (II), *o*-hydroxyphenylboronic acid (III) and its *p*-isomer (V) have been prepared.



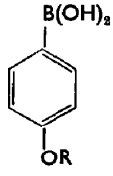
I



II R = H



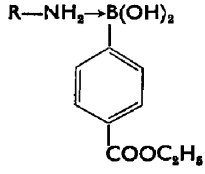
III R = H
IV R = CH_3



V R = H
VI R = CH_3

Esterification of *p*-carboxyphenylboronic acid with aliphatic alcohols in the presence of hydrogen chloride,[1,2] yields crystalline esters (Ia–d) in 60–79% yields. Esterification of I with 2-amino-, 2-diethylamino- and 2-piperidinoethanols respectively, was unsuccessful; similary, *trans*estrification of the methyl ester of I with aminoalcohols in the presence of sodium and the reaction of the corresponding acid chloride with aminoalcohols failed; nor do the β-chloro- and β-bromoethylesters (Ie and If) react with excess diethylamine or piperidine to yield aminoesters of I.

The action of ammonia, hydrazine and hydroxylamine on the ethyl ester of I produces crystalline complexes Ig, Ih and Ii respectively, no esterification of the carbethoxy group taking place.[3]



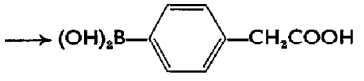
Ig R = H
Ih R = NH_2
Ii R = OH.

Complexes Ig, Ih and Ii are crystalline products stable to recrystallization from

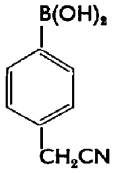
[1] K. Torsell, *Arkiv Kemi*, **10**, 473 (1957).
[2] B. Serafinowa, M. Makosza and A. Jośkiewicz, *Roczniki Chem.* **36**, 531 (1962).
[3] B. Serafinowa, M. Szreter and M. Makosza, *Roczniki Chem.* **35**, 489 (1961).

dilute ethanol but they decompose in aqueous solutions on heating, yielding the ethyl ester of I and the starting amines.[3]

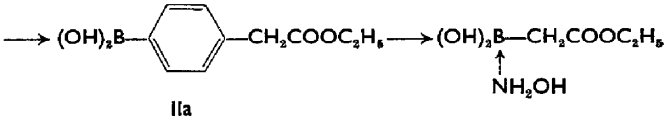
It has been shown, that the ethyl ester of *p*-(carboxymethyl)-phenylboronic acid (IIa; R = C_2H_5) does not react with ammonia or hydrazine but with hydroxylamine a complex (IIb), was isolated. It is less stable than its analogue (Ii) and decomposes in aqueous media into the ester (IIa) and hydroxylamine.[6] The acid (II), obtained by hydrolysis of *p*-cyanomethylphenylboronic acid (IIc) may be esterified to IIa or the latter may be produced in good yield by alcoholysis of *p*-cyanomethylphenylboronic acid. Partial acid hydrolysis of IIc to yield the amide IId failed, unchanged IIc or acid II being isolated.[6]



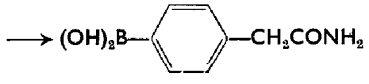
II



IIc

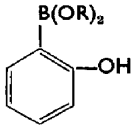


IIa IIb



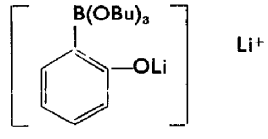
IId

Further, acetylation of the hydroxyl group in either *o*- and *p*-hydroxyphenylboronic acid (III and V) with acetic anhydride, acetyl chloride, ketene or acetic anhydride–sodium acetate mixture failed to give positive results, the starting acids being either recovered or decomposed to phenol. Similarly, benzoylation of *o*-hydroxyphenyl-boronic acid and acetylation of the ethyl ester (IIIa) or of the lithium complex was unsuccessful.



III R = H

IIIa R = C_2H_5



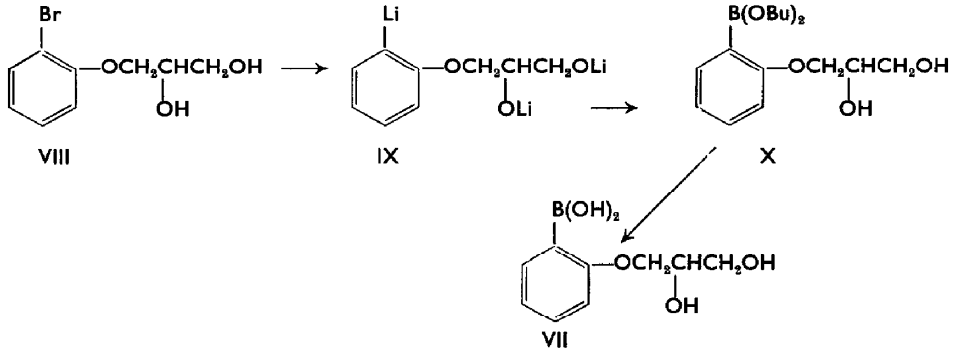
IIIb

Methylation of III with dimethyl sulphate yielded *o*-anisylboronic acid IV, prepared earlier .[7]

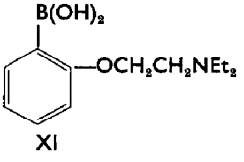
Although both the acid III and the lithium complex IIIb failed to react with glycerol α-chlorohydrin to give 2-(β,γ-dihydroxypropoxy) phenylboronic acid (VII); the latter

[4] H. Gilman, D. R. Swayampati and R. O. Rauck, *J. Amer. Chem. Soc.* **80,** 1357 (1958).
[5] B. Serafinowa, M. Makosza and I. Szczerek, *Roczniki Chem.* **36,** 889 (1962).
[6] B. Serafinowa, M. Makosza and J. Wòjcicka, *Roczniki Chem.* In press.
[7] W. König and W. Scharrnbeck, *J. prakt. Chem.* **128,** 153 (1930).

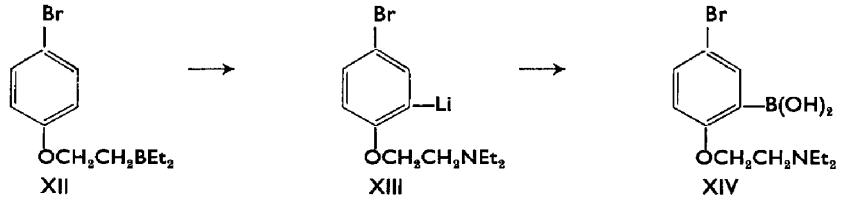
was obtained from *o*-(β,γ-dihydroxypropoxy)-bromobenzene (VIII) according to the following reactions:



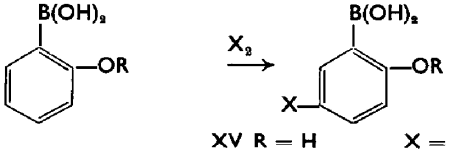
Similarly, 2-(β-diethylaminoethoxy)-phenylboronic acid (XI) was prepared from *o*-(β-diethylaminoethoxy)-bromobenezene.



In the case of the *p*-isomer (XII) reaction with *n*-butyllithium resulted in (XIII) and hence the final product was 2-(β-diethylaminoethoxy)-5-bromophenylboronic acid (XIV):[5]



Bromination of *o*-hydroxy and *o*-methoxyphenylboronic acid (III and IV) using equimolar amount of bromine in acetic acid, water, dioxane and carbon tetrachloride or dioxane dibromide in ethyl ether resulted in all cases, except bromination of acid III in water* in the 5-bromo substituted derivatives (XV and XVI) in 53–80%. Similarly, chlorination yielded the 5-chloro-derivatives XVII and XVIII:



XV R = H X = Br
XVI R = CH_3 X = Br
XVII R = H X = Cl
XVIII R = CH_3 X = Cl

The action of bromine on *o*-hydroxyphenylboronic acid (III) in pyrydine yielded the 5-bromo-2-hydroxyphenylboronic acid pyridine complex (XIX), identical with

* In this reaction deboronization occurred and 2-bromophenol was formed.

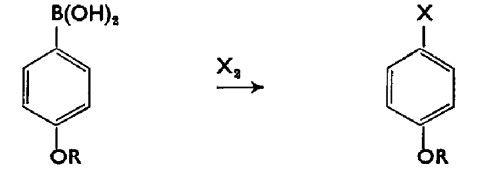
the compound obtained from XV and pyridine.[8] Hydrolysis of XIX failed; it is stable in dilute acids and alkalis at room temperature and decomposes on heating in these media to *p*-bromophenol.[8]

5-Bromo- and 5-chloro-2-hydroxyphenylboronic acids (XV and XVII) were characterized by removal of boronic acid group and condensation of the resulting chloro and bromophenols with chloroacetic acid to the *p*-bromo- and *p*-chlorophenoxyacetic acids, identical with authentic samples.

The cleavage of ring-boron bond in 5-bromo- and 5-chloro-2-methoxyphenylboronic acids (XVI and XVIII) was carried out in silver nitrate ammonia solution yielding 5-bromo- and 5-chloroanisol respectively.

Treatment of the acids III and IV with iodine chloride in various solvents yields, *o*-iodophenol or *o*-iodoanisol respectively, the boronic acid group being replaced.

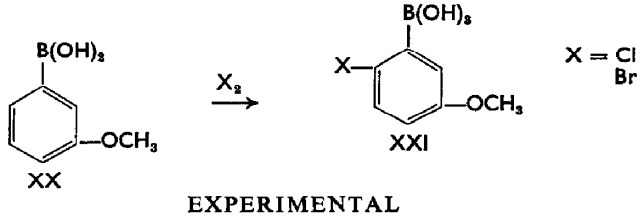
Similarly, halogenation with chlorine, bromine or iodine chloride of *p*-hydroxy and *p*-methoxyphenylboronic acids V and VI resulted in replacement of the boronic acid group and formation of *p*-halogenophenols or -anisols.



III R = H
IV R = CH_3

R = H, CH_3
X = Cl, Br, J.

Kuivilla *et al.*[9] recently published the halogenation of *m*-methoxyphenylboronic acid (XX) and formation of 2-halogen-5-methoxyphenylboronic acids (XXI).

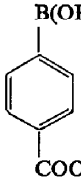


XX XXI

EXPERIMENTAL

Esters of *p*-carboxyphenylboronic acid (I)[2] were obtained by heating for 1 hr 0·9 g *p*-carboxyphenylboronic acid in 8 ml alcohol containing 10% hydrogen chloride. Compounds, m.p.s, analyses and yields are given in Table 1.

TABLE 1



I

No	R	m.p.	Yield %	Mol. wt. Calc.	Mol. wt. Found
Ia	n-C_3H_7	162–164°	64	208	209
Ib	n-C_4H_9	178–181°	60	222	221
Ic	i-C_4H_9	170–172°	60	222	220
Id	C_6H_{11}	172–176°	46	256	249
Ie	CH_2CH_2Cl	188–193°	56	228	227
If	CH_2CH_2Br	172–176°	90	273	269

[8] B. Serafinowa, M. Makosza and H. Duda, *Roczniki Chem.* In press.

[9] H. G. Kuivilla, L. E. Benjamin, J. J. Murphy, A. D. Price and J. H. Polevy, *J. Org. Chem.* **27**, 825 (1962).

p-*Carbethoxyphenylboronic acid complexes* (Ig, Ih *and* Ii)[9] were prepared by heating *p*-carbethoxyphenylboronic acid and amine in alcohol for 1 hr (except Ii which is formed at room temp). The products were recrystallized from 30% ethanol.

Complex	Ig	X—NH_2		m.p.	Yield		Formula	Analysis N%	
		X	Amount		g	%		Calc.	Found
Ig	1·5	H	5 ml conc.	195–198°	1·0	70	$C_9H_{14}O_4NB$	6·66	6·90
Ih	1·5	NH_2	0·9 g 40%	179–181°	1·44	82	$C_9H_{15}O_4N_2B$	12·44	12·73
Ii	1·5	OH	0·33 g	199–201°	1·35	80	$C_9H_{14}O_5NB$	6·19	5·98

p-*Cyanomethyl-phenylboronic acid* (IIc). To 3 g potassium cyanide in 10 ml 50% acetone 4·2 g *p*-bromomethyl-phenylboronic acid in 10 ml ethanol was added at 60° and the mixture refluxed for 1 hr. After cooling and acidification with 50% sulphuric acid the resulting solid was filtered off, the filtrate evaporated until crystallization occurred and the crude product recrystallized twice from water using charcoal; 1·6 g (47%) *p*-cyanomethyl-phenylboronic acid[11] (IIc) m.p. 214–215° was obtained.

p-*Carboxymethyl-phenylboronic acid* (II). *p*-Cyanomethylphenylboronic acid (IIc; 2 g) in 40 ml 20% sodium hydroxyde was refluxed for 1 hr, the solution acidified with hydrochloric acid and the resulting solid recrystallized from water yielding 1·6 g (73%) m.p. 165–166°. (Found: C, 53·0; H, 5·1. $C_9H_9O_4B$ requires: C, 53·3; H, 5·0%).

p-*Carbethoxymethyl-phenylboronic acid* (IIa). *p*-Cyanomethyl-phenylboronic acid (IIc; 1 g) in 10 ml ethanol saturated with hydrogen chloride was refluxed for 1 hr, poured on ice and the precipitate recrystallized twice from water yielding colourless needles (Ia; 0·54 g; 24%), m.p. 145–146°. (Found: C, 58·1; H, 6·0. $C_{10}H_{13}O_4B$ requires: C, 57·7; H, 6·2%).

2-*β*, *γ*-*Dihydroxypropoxy-phenylboronic acid* (VII)[5] was obtained by reacting 20·9 g 2-*β*, *γ*-dihydroxypropoxy-bromobenzene in 250 ml ether with 1·94 mole n-butyllithium in 130 ml ether under nitrogen and subsequent reaction with 23·0 g n-butylborate in 80 ml ether at 70° followed by hydrolysis of the reaction mixture with 100 ml of 12% HCl. The colourless oil, b.p. 177–180°/10 mm was redistilled at 133–135°/2 mm yielding 2·9 g. (Found: mol. wt. 203; $C_9H_{13}O_5B$ (acid) requires mol. wt. 212; $C_9H_{11}O_4B$ (anhydride) requires mol. wt. 194.)*

2-(*β*-*Diethylaminoethoxy*)-*phenylboronic acid* (XI)[5] was obtained from 10 g 2-(*β*-diethylaminoethoxy)-bromobenzene in 50 ml ether and 1·2 g lithium in 100 ml ether, followed by addition of 9·2 g n-butyl borate in 100 ml ether at 70°, hydrolysis with dil. HCl at 0° and precipitation of the product at pH 10. After recrystallization from ethanol m.p. 116–118[8] (XI) the product was dried over P_2O_5 yielding the anhydride, m.p. 102–110°. (Found: N, 6·40; $C_{12}H_{18}O_2NB$ requires: N, 6·77%).

Bromination of 2-*hydroxyphenylboronic acid* (III)

(a) *With bromine.* To 0·6 g 2-hydroxyphenylboronic acid (III) in 50 ml acetic acid† 0·8 g bromine in 20 ml acetic acid was added at 20–30°, the mixture heated to 50°, cooled and the solvent distilled off under red. press. The crude 5-bromo-2-hydroxyphenylboronic acid (XV; 0·7 g; 65%) m.p. 150–155°, was recrystallized from 20% acetone and the m.p. raised to 191–192°.

(b) *With dioxane dibromide.* Dioxane dibromide (1 g) in 10 ml ethyl ether was added to 0·6 g *o*-hydroxyphenylboronic acid (III) in 30 ml ethyl ether, the mixture refluxed for 15 min and worked up as described under (a), yield 0·8 g (XV), m.p. 150–155° (crude). (Found: mol. wt. 216; $C_6H_6O_2BBr$ requires: mol. wt. 215).

Deboronization of (XV). Compound (XV) (2 g) in 50 ml zinc chloride solution was boiled for 2 hr, acidified with hydrochloric acid and extracted with benzene. The organic layer was washed with saturated sodium bicarbonate solution, dried with magnesium sulphate and the solvent removed under red. press., yielding *p*-bromophenol, m.p. 63° and converted into *p*-bromo-phenoxyacetic acid, m.p. 154–155°.

* All mol. wts were determined by titration of the sample with 0·1 N NaOH in the presence of sorbitol and phenolphtalein.

† Instead of acetic acid, dioxan or carbon tetrachloride may be used.

[10] H. N. Fales, *J. Amer. Chem. Soc.* **77**, 5118 (1955).

[11] B. Serafinowa and M. Makosza, *Roczniki Chem.* **35**, 359 (1961).

Bromination of 2-methoxyphenylboronic acid (IV)

(a) *With bromine in organic solvents.* To 1·5 g 2-methoxyphenylboronic acid (IV) in 30 ml acetic acid* 1·6 g bromine in the same solvent was added, the mixture kept at room temp. for 1 hr and then poured into cold water (250 ml). The precipitate of 5-bromo-2-methoxyphenylboronic acid (XVI) was crystallized from water, m.p. 131–132°; yield 1·6 g (68%).

(b) *With bromine in water.* Bromine (1·6 g) in 20% acetic acid was added to a suspension of 1·5 g 2-methoxyphenylboronic acid (IV) in water at 30°. The product (XVI) was washed with ice-water and dried; yielding 1·7 g (85%), m.p. 129–130° (crude).

(c) *With bromine in statu nascendi.* To 1·5 g of 2-methoxyphenylboronic acid (IV) in 15 ml acetic acid, 4·1 g 40% hydrobromic acid and the calculated amount of sodium chlorate solution was added at room temp and the mixture heated slowly to 50°. After cooling the mixture was poured into 200 ml water to precipitate XVI, m.p. 129–130° (crude), yield 1·5 g (65%).

(d) *With dioxane dibromide.* The reaction was carried out with 1·5 g 2-methoxyphenylboronic acid (IV) and 2·1 g dioxane dibromide in dry ethyl ether as described for (XV), m.p. 129–131° (crude), yield 1·15 g (50%). (Found: mol. wt. 231; $C_7H_8O_3BBr$ requires: mol. wt. 230·9).

Deboronization of (XVI). Compound XVI (2·3 g) was mixed with 30 ml 15% ammonia and 30 ml 5% silver nitrate solution and refluxed for 2 hr, the resulting *p*-bromoanisole was separated by steam distillation, extracted with ether and identified as anisaldehyde 2,4-dinitrophenylhydrazone,[10] m.p. 253–254°.

Chlorination of 2-hydroxyphenylboronic acid (III)

To 1·2 g *o*-hydroxyphenylboronic acid (III) in 50 ml acetic acid,† 0·7 g chlorine was bubbled in at 30°, the solvent removed under red. press. and the crude 5-chloro-2-hydroxyphenylboronic acid (XVII) washed with pet ether. Crystallization from benzene gave a colourless product, m.p. 241–242°, yield 1·3 g (75%). (Found: mol. wt. 171; Calc. for $C_6H_6O_3BCl$: mol. wt. 172).

Deboronization of (XVII) was carried out as described for XV. From XVII, *p*-chlorophenol, m.p. 43° and *p*-chlorophenoxyacetic acid, m.p. 157–158°, were obtained.

Chlorination of 2-methoxyphenylboronic acid (IV)

Similarly 1·5 g 2-methoxyphenylboronic acid (IV) and chlorine yielded 1·4 g (75%) crude 5-chloro-2-methoxyphenylboronic acid (XVIII), m.p. 138–140°, and after recrystallization from dilute acetone m.p. 141–142°. (Found: mol. wt. 183; Calc. for $C_7H_8O_3BCl$: mol. wt. 185).

Deboronization of (XVIII) with silver nitrate ammonia solution gives *p*-chloroanisole, identified as anisaldehyde 2,4-dinitro-phenylhydrazone,[10] m.p. 253–254°.

* Instead of acetic acid, dioxane or carbon tetrachloride may be used.

† Instead of acetic acid, ethyl ether, carbon tetrachloride or water may be used.