Hydrolysis of N^{α}-Carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine Methyl Ester.—A solution of 500 mg. of N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine methyl ester[3] in 5 ml. of dimethylformamide was added dropwise to a solution of 50 mg. of α-chymotrypsin in 40 ml. of 0.5 M ammonium acetate to which ammonium hydroxide had been added to adjust the solution to *p*H 7.5. The reaction mixture was stirred at 22° for 15 min. during which time a precipitate formed and redissolved. Acidification of the solution to *p*H 2 with hydrochloric acid gave 480 mg. of N^{α}-carbobenzyloxy-N^{g}-nitro-L-arginyl-L-valyl-L-tyrosine,[10] R_f^{BAm} 0.55 (N), $[\alpha]^{22}\text{D}$ $-13.4°$ (c 0.82, methanol). A sample recrystallized from ethanol melted at 178–182°.

Isoleucine-5 Angiotensin Methyl Ester.—Isoleucine-5 angiotensin has been synthesized[3] by (a) condensation of carbobenzyloxy-β-methyl ester-L-aspartyl-N^{g}-nitro-L-arginine with L-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine methyl ester, (b) alkaline hydrolysis of the condensation product, and (c) removal of the carbobenzyloxy and nitro groups by catalytic hydrogenation. Similarly, we condensed carbonbenzyloxy-β-benzyl ester-L-aspartyl-N^{g}-nitro-L-arginine[12] with the hexapeptide ester using dicyclohexyl-carbodiimide[13] as the condensing agent: hydrogenation of the product over a palladium catalyst yielded a mixture containing isoleucine-5 angiotensin methyl ester. This ester was carried through a 96-plate countercurrent distribution in the system butanol–propanol–acetic acid–water (30:15:5:50) followed by a 196-plate distribution of the peak fractions in butanol–acetic acid–water (4:1:5). The product from the major peak showed only one component, R^{BAW_7} 0.61 (N); $R_f^{\text{MPW}_7}$ 0.69 (N); $R_f^{\text{BAm}_7}$ 0.40 (N).

Chymotrypsin Hydrolysis of Isoleucine-5 Angiotensin Methyl Ester. Method A. (1–1000).—A 5.3-mg. sample of isoleucine-5 angiotensin methyl ester was added to 0.8 ml. of 0.5 M ammonium acetate containing 5.3 γ of chymotrypsin. Samples were examined periodically by radial paper chromatography in MPW; ninhydrin was used to locate the spots. In 2 min. considerable hydrolysis had occurred and chromatography showed that the free octapeptide, $R_f^{\text{MPW}_7}$ 0.48 (N,P,S), was being produced. In 40 min., however, cleavage of the peptide chain to give the tetrapeptides α-L-aspartyl-L-arginyl-L-valyl-L-tyrosine, $R_f^{\text{MPW}_7}$ 0.39 (N,P,S) and L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine, $R_f^{\text{MPW}_7}$ 0.62 (N, P), had occurred, while an observable amount of octapeptide ester $R_f^{\text{MPW}_7}$ 0.69 (N,P,S) remained unhydrolyzed.

Method B. (1–100,000)—A sample was treated as described in A above, except that 0.053 γ of chymotryspin was used. Under these conditions both ester and amide hydrolyses were slow—after 2 hr. only a small amount of ester hydrolysis and no amide hydrolysis was observed.

Method C. (1–10,000).—A 10.2-mg. sample of isoleucine-5 angiotensin methyl ester in 0.8 ml. of 0.05 M ammonium acetate was added to 0.28 ml. of water containing 1.0 γ of chymotrypsin. The solution was *p*H 6. In 2 hr. the ester was completely hydrolyzed as indicated by a single spot at R_f^{MPW} 0.48 (N,P,S). No cleavage of the peptide chain was observed. Only after 22 hr. was formation of a small amount of the tetrapeptides, R_f^{MPW} 0.39 (N,P,S) and R_f^{MPW} 0.62 (N,P), detected. The product isolated by lyophilization after 2 hr. of hydrolysis under the above conditions had a high order of biological activity. In normal anesthetized dogs, a dose of 1 γ/kg. produced a 60-mm. mean arterial pressure rise, while the starting octapeptide ester was essentially inactive at dosages up to 100 γ/kg.

The biological assays were carried out by Dr. L. S. Watson in these laboratories.

---

(12) L. T. Skeggs, Jr., K. E. Lentz, J. R. Kahn, and N. P. Shumway, *J. Exp. Med.*, **108**, 283 (1958).

(13) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

---

o-Trifluoromethyl- and Some *ortho, meta*-Disubstituted Benzeneboronic Acids and Anhydrides

L. SANTUCCI, L. TAVOLETTI, AND D. MONTALBANO

Department of General Chemistry, University of Rome and Chemical Laboratory, Istituto di Patologia del Libro, Rome, Italy

Received December 18, 1961

In connection with a reaction mechanism study, the organolithium procedure followed by boronation with tri-*n*-butyl borate was satisfactorily employed to prepare a series of known boronic acids and anhydrides[1] and the new ones reported herein.

Except for *o*-trifluoromethylbenzeneboronic acid and its anhydride, these compounds are analogs or isomers of others described in another work,[2] reference to which should be made for general remarks on difficulties of purification and characterization. Unfortunately, no infrared spectral analysis was available to us: we regret the lack of such a facility for improving characterization of our compounds, and because of some discussion[3] on previous observations of one of us.[2]

Dehydration of acids to anhydrides, as it was pointed out,[2,3] in some cases is accomplished simply by moderate heating in anhydrous solvents, but sometimes does require temperatures over 100°.[4] The application of vacuum, even in the presence of dehydrating agents, in our experience was seldom effective.

Another striking example of the influence of substituents on ease of dehydration is offered by the comparison of the two isomeric hydroxybromobenzeneboronic anhydrides reported herein: they both have a bromine atom in the *meta* position with respect to the borono group, but whereas the one brominated *para* to the hydroxyl required a long time of heating above 100° to be obtained from the acid, the other one with bromine *ortho* to hydroxyl is so much more stable that the acid could not even be detected in the product crystallized from water. A hydroxyl *ortho* to the borono group is known to favor stabilization of the anhydride, as compared with the unsubstituted benzeneboronic compound[5]: apparently, the disturbing action of bromine is neutralized when this substituent is *ortho* to the hydroxy group, possibly by hydrogen-bonding.

The only other trifluoromethyl derivative of a boronic acid hitherto reported appears to be the *m*-

---

(1) L. Santucci, *Boll. Ist. patol. libro*, **20**, 123 (1961).

(2) L. Santucci and H. Gilman, *J. Am. Chem. Soc.*, **80**, 193 (1958).

(3) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 3611 (1958).

(4) See also H. G. Kuivila and A. R. Hendrickson, *J. Am. Chem. Soc.*, **74**, 5068 (1952).

(5) H. Gilman, L. Santucci, D. R. Swayampati, and R. O. Ranck, *J. Am. Chem. Soc.*, **79**, 3077 (1957).

trifluoromethylbenzeneboronic anhydride.[6] The *ortho* isomer we obtained was probably contaminated by the former when crude, according to the literature description[7] of the isolation of carboxylic analogs obtained by metalation and carbonation of the same starting compound, but we made no attempt to isolate it. One noteworthy property of our compound is its remarkable water solubility.

The proof of structure depended on characterization of the corresponding aryllithium compounds, obtained by carbonation of the metalation mixtures.

Experimental

Melting points are uncorrected, and were usually obtained with a bath pre-heated to within 5–15° of the melting temperature, applying heat very slowly: in the case of *o*-trifluoromethylbenzeneboronic acid, however, it was necessary to introduce the capillary tube no more than 1° below melting. All reactions were carried out under a dry, oxygen-free nitrogen atmosphere, and employed ether dried over sodium. The *n*-butyllithium reagent was always prepared according to literature procedures.[8] For the neutralization equivalents, the samples were dissolved in 50% ethanol (except for *o*-trifluoromethylbenzeneboronic acid and anhydride, which could be easily dissolved in water) containing twenty times the sample weight of D-mannitol, and the titration was carried out with standard sodium hydroxide using phenolphthalein to detect the end point.

2-Phenoxy-5-bromobenzeneboronic Acid.—A mixture of 0.026 mole of *n*-butyllithium and 13.0 g. (0.052 mole) of *p*-bromodiphenyl ether in 25 ml. of ether was stirred for 16 hr. at room temperature,[9] and then added very slowly to a stirred solution of 12.0 g. (0.052 mole) of tri-*n*-butyl borate in 15 ml. of ether, previously cooled to −70° by means of a Dry Ice–acetone bath. After 2 hr. at the low temperature, the mixture was allowed to warm to 0° and hydrolyzed with 10% hydrochloric acid. The aqueous layer was separated from the ether and washed four times with fresh ether. The combined ether layers were extracted with 8% sodium hydroxide, but no precipitation occurred upon acidification of the alkaline extracts. The ether solution was then dried and evaporated, thus obtaining 2.5 g. of a residue that was dissolved in water and precipitated by acidification. This yielded 1.03 g. of a boron- and bromine-containing material, which melted at 106–113°, corresponding to a 13% yield based on *n*-butyllithium. Recrystallization from petroleum ether (b.p. 60–80°) gave 0.78 g. of product, m.p. 108–113°. After two additional recrystallizations from 4:1 water–acetone mixture the melting point was 108–110°.

Anal. Calcd. for $C_{12}H_{10}BBrO_3$: C, 49.21; H, 3.44; neut. equiv., 292.83. Found: C, 48.77; H, 3.53; neut. equiv., 296.3.

2-Methoxy-5-bromobenzeneboronic Anhydride.—This anhydride of a previously reported acid[2] was obtained by heating the latter less than 2 hr. at 115–120°, and had a melting point of 176–179°. It should be noted that this compound, presumably owing to volatilization, did not attain constant weight even within 15 hr. of heating, although melting point and neutralization equivalent remained unchanged throughout. Heating at lower temperatures under water vacuum and in the presence of phosphorus pentoxide did not prove to be an equally efficient procedure.

Anal. Calcd. for $C_7H_6BBrO_2$: neut. equiv., 212.87. Found: neut. equiv., 209.4.

2-Hydroxy-5-bromobenzeneboronic Anhydride.—Dehydration of the previously reported acid[2] was accomplished after 34 hr. of heating at 95–110° or 15 hr. at 115–120°: different combinations of lower temperatures, vacuum, and dehydrants were all ineffective. The anhydride melted at 323–325°.

Anal. Calcd. for $C_6H_4BBrO_2$: neut. equiv., 198.86. Found: neut. equiv., 195.0, 200.1.

2-Hydroxy-5-chlorobenzeneboronic Acid.—To a stirred solution of 14.5 g. (0.068 mole) of 2-(*p*-chlorophenoxy)tetrahydropyran[9] in 60 ml. of ether, 0.10 mole of *n*-butyllithium in 70 ml. of ether was added at room temperature over 25 min. The mixture was stirred for another 30 min., then added slowly to a solution of 31.6 g. (0.137 mole) of tri-*n*-butyl borate in 40 ml. of ether while cooling at −70°. After stirring for 3 hr., the reaction mixture was permitted to warm to 0° and hydrolyzed with 10% hydrochloric acid. The ether layer was separated from the aqueous layer, the latter being washed twice with 50-ml. portions of fresh ether which were combined with the main portion, and extracted with 8% sodium hydroxide. Some water had to be added to the alkaline extracts in order to dissolve a solid which had precipitated, then the solution was acidified with 10% hydrochloric acid and the material obtained recrystallized from a 3:1 water–acetone mixture: there was obtained 5.8 g. (63.4%) of a crude material melting over the range 143–180°. Three additional recrystallizations from ethylene chloride gave a final 2.29 g. of white crystals melting at 185–188°. This represents a 36% yield of pure 2-hydroxy-5-chlorobenzeneboronic acid.

Anal. Calcd. for $C_6H_6BClO_3$: neut. equiv., 172.38. Found: neut. equiv., 173.1, 172.6.

2-Hydroxy-5-chlorobenzeneboronic Anhydride.—The anhydride was obtained by heating the acid in an oven at 115–120° to constant weight, which was attained in about 5 hr. The loss in weight corresponded to that expected for the transition of acid to anhydride, and the melting point was raised to 333–337°. No loss in weight was observed after keeping the sample under water vacuum and in the presence of phosphorus pentoxide for periods up to 60 hr. at room temperature.

Anal. Calcd. for $C_6H_4BClO_2$: C, 46.68; H, 2.61; neut. equiv., 154.37. Found: C, 47.91; H, 2.42; neut. equiv., 152.2, 153.6, 153.4.

2-Hydroxy-3-bromobenzeneboronic Anhydride.—A 0.02-mole sample of *n*-butyllithium in 15 ml. of ether were added as fast as possible to a stirred solution of 2.52 g. (0.01 mole) of 2,6-dibromophenol in 40 ml. of ether kept at −18° by means of a salt–ice bath,[9] then the reaction mixture was immediately chilled with a Dry Ice–acetone bath and siphoned over 30 min. into a stirred solution of 6.80 g. (0.03 mole) of tri-*n*-butyl borate in 10 ml. of ether maintained at −70°. After standing overnight at this temperature, the mixture was warmed to 0° and hydrolyzed with 8% hydrochloric acid. The strongly acidic aqueous layer was separated from the ether and washed with fresh ether, which was combined with the main portion. The whole was extracted with 70 ml. of 15% sodium carbonate in nine portions, then the alkaline extract was made strongly acidic with 8% hydrochloric acid and extracted with fresh ether. Upon evaporation of the ether, 0.68 g. (31%) of material melting over the range 150–170° was obtained. This was recrystallized from ethylene chloride, yielding 0.29 g. (9.3%) of crystals melting at 187.5–191°. Another two recrystallizations from the same solvent raised the melting point to 213–214°.

The original ether layer was also extracted with 8% sodium hydroxide, and subsequently evaporated. These two operations yielded an over-all amount of 0.46 g. of oily material, from which no crystalline product could be obtained. In another experiment using the same amounts, the carbonate extract was acidified without extracting with ether, and

---

[6] K. V. Nahabedian and H. G. Kuivila, *J. Am. Chem. Soc.*, **83**, 2167 (1961).

[7] J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946).

[8] R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951). H. H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 258 (1954).

[9] L. Santucci, L. Tavoletti, and D. Montalbano, *Ricerca Sci.*, in press.

0.62 g. of precipitate was obtained, with a melting range of 135–180°. One recrystallization from ethylene chloride yielded 9% of product melting at 205–208°.

The product recrystallized three times from ethylene chloride was used as an analytical sample and dried for 1.5 hr. at 108°, which did not affect the weight or the melting point. Neutralization equivalent and elementary contents suggested formulation as an anhydride. An attempt was made to obtain the acid by recrystallization from acetone and water, in the ratio of 1 ml. of acetone and 3.5 ml. of water per 0.1 g. of product, followed by drying at room temperature in the open for 3 hr.: however, although the melting point decreased to 194–195°, the neutralization equivalent remained unchanged.

Anal. Calcd. for $C_6H_4BBrO_2$: C, 36.23; H, 2.03; Br, 40.19; neut. equiv., 198.86. Found: C, 36.02; H, 2.26; Br, 40.34; neut. equiv., 199.0; 195.8, 196.2.

***o*-Trifluoromethylbenzeneboronic Acid.**—To a stirred solution of 23.0 g. (0.10 mole) of tri-*n*-butyl borate in 20 ml. of ether 0.05 mole of *o*-trifluoromethylphenyllithium, prepared by refluxing equimolar amounts of α,α,α-trifluorotoluene and *n*-butyllithium for 6 hr.,[7] was added slowly while cooling at −70°. The mixture was left overnight at this temperature, then hydrolyzed with 30 ml. of 8% hydrochloric acid, and the ether layer extracted with 50 ml. of 15% sodium carbonate and 60 ml. of 8% sodium hydroxide in five portions. Upon acidification to pH 3 and subsequent extraction with ether, the carbonate extracts did not yield any significant amount of product, whereas 4.60 g. (48.5%) of a crystalline material, melting range 50–85°, was obtained from the sodium hydroxide solution. It is worth noting that the etheral extraction of the carefully acidified solution was particularly necessary in this case, since the precipitate was small and appeared to be soluble in excess acid. The crude material was recrystallized from petroleum ether (b.p. 60–80°), to yield 1.80 g. (19%) of crystals melting at 86–94°. Another recrystallization from the same solvent and then from ethylene chloride raised the melting point to 106–107°.

In another experiment, employing the same amounts, the reaction mixture was hydrolyzed with water and the ether layer evaporated to yield 4.54 g. of crude material. Another 0.20 g. was obtained by acidification and ether extraction of the aqueous layer. One recrystallization from petroleum ether yielded a 16% of product melting at 92–98.5°.

Anal. Calcd. for $C_7H_6BF_3O_2$: neut. equiv., 189.95. Found: neut. equiv., 187.2.

***o*-Trifluoromethylbenzeneboronic Anhydride.**—The anhydride was obtained by recrystallizing the acid twice from anhydrous ethylene chloride, and had a melting point of 136.5–141°. Heating at 108° for over 1 hr. failed to attain a constant weight, but the melting point and neutralization equivalent were practically unaffected.

Anal. Calcd. for $C_7H_4BF_3O$: C, 48.89; H, 2.35; F, 33.15; neut. equiv., 171.94. Found: C, 48.95; H, 2.66; F, 32.75; neut. equiv., 172.5.

Grignard Route to 4,4′-Dichlorobenzophenone

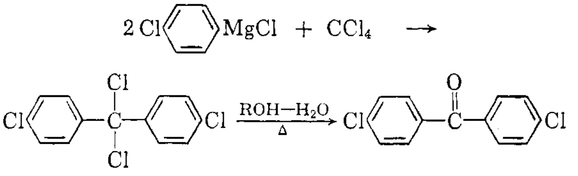
J. R. LEEBRICK AND H. E. RAMSDEN[1]

Research Laboratories, Metal & Thermit Corp., Rahway, N. J.

Received December 18, 1961

Literature references to the reaction of Grignard reagents with carbon tetrachloride are relatively few. Binaghi[2] isolated triphenylmethyl peroxide, hexaphenylethane, and triphenylcarbinol from the reaction of carbon tetrachloride with phenylmagnesium bromide. Kinney and Spliethoff[3] obtained 1,1,1-trichloropentane from the reaction of butylmagnesium chloride with carbon tetrachloride.

Satisfactory yields of 4,4′-dichlorobenzophenone were obtained in our laboratory by the following sequence of reactions:



The Grignard reagent[4] was added to solutions of carbon tetrachloride in tetrahydrofuran, benzene, pentane–benzene, and toluene over wide temperature ranges without gross differences in yield. Thickening was observed with hydrocarbon solvents. Extensions of the above reaction are under investigation.

Experimental

To a solution of 34 g. (0.222 mole) of carbon tetrachloride in 200 ml. of tetrahydrofuran was added 0.45 mole of *p*-chlorophenylmagnesium chloride[4] over a period of 30 min. with vigorous stirring. The temperature was maintained at 10° utilizing a Dry Ice–acetone bath. The reaction mixture was stirred for 30 min. and then hydrolyzed by the cautious addition of 150 ml. of 10% sulfuric acid at room temperature. The organic phase was separated and the aqueous phase was extracted twice with 100-ml. portions of diethyl ether. Solvents were distilled from the combined organic fractions under reduced pressure leaving a dark brown residue. Hydrolysis of the intermediate 4,4′-dichlorobenzophenone dichloride was effected by adding the residue to 300 ml. of 50% ethanol and refluxing the mixture for 90 min. with stirring. Following cooling to room temperature and decantation of the liquid portion, the tan product was slurried with 100 ml. of petroleum ether. The crude ketone was then filtered and washed with petroleum ether. A crude yield of 23.0g. (41%) melting at ca. 134° was obtained. Recrystallization from absolute ethanol gave white plates melting at 149–150°. Recrystallization from isomeric heptanes did not change the melting point. Admixture with authentic 4,4′-dichlorophenzophenone showed no depression. The 2,4-dinitrophenylhydrazone melted at 237.5–239.5° (lit.,[5] m.p. 238–240°).

---

[1] Present address: Esso Research & Engineering Co. Research Center, Linden, N. J.

(2) R. Binaghi, *Gazz. chim. ital.*, **53**, 879 (1923).

(3) C. R. Kinney and W. L. Spliethoff, *J. Am. Chem. Soc.*, **71**, 746 (1949).

(4) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

(5) H. L. Haller *et al.*, *J. Am. Chem. Soc.*, **67**, 1591 (1945).