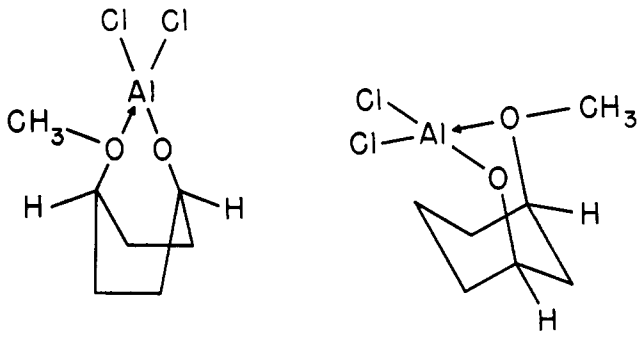

Figure 1

they might be formed from *both* isomers of 2-methoxycyclohexanol. Analysis of the chelates proved difficult (and is responsible for the delay in the publication of these results), for once formed the solids (which are quite hygroscopic) cannot be redissolved without decomposition. However, material was eventually obtained which was free of lithium (flame test) and which gave satisfactory analyses for C, H, and Al in the case of the 3-isomer and for Al and Cl in the case of the 4-isomer.[9]

Isolation of the species shown in Fig. 1 supports the hypothesis[3] that the active reagent formed from lithium aluminum hydride (1 mole) and aluminum chloride (>3 moles) is, in fact, $AlHCl_2$ and that the complexes formed from this reagent and substituted cyclohexanols which are subject to equilibration by ketones[6] are, in fact, of the composition $ROAlCl_2$.

The method here described probably lends itself to the separation of other epimeric pairs of alkoxycycloalkanols.

Experimental

4-Methoxycyclohexanol.—*cis*-Rich material was obtained by hydrogenating 124 g. (1.0 mole) of *p*-methoxyphenol in 300 ml. 95% ethanol at 130° and 2000 p.s.i. in the presence of 10 g. of Raney nickel. The theoretical amount of hydrogen was absorbed in 12 hr. The solution was filtered, concentrated, and partitioned between ether and water. The ether layer was washed, with 10% sodium hydroxide, followed by saturated aqueous sodium chloride, dried over magnesium sulfate, concentrated, and the residue distilled at 108–113° (24 mm.) to give 100.1 g. (77%) 4-methoxycyclohexanol. Gas chromatographic analysis on Tide (180°, He flow 24 ml./min.) indicated 61.6% *cis* isomer (retention time 13.7 min.) and 38.4% *trans* isomer (retention time 17.2 min.).

Chelate.—The mixed hydride reagent was prepared from 13.35 g. (0.10 mole) of aluminum chloride in 75 ml. of anhydrous ether and 0.025 mole of ethereal lithium aluminum hydride (*ca.* 1 *M*). To this solution was added with stirring 13.0 g. (0.10 mole) of the previous mixture of 4-methoxycyclohexanols in 50 ml. of anhydrous ether. The solution was stirred for 15 min., filtered in a dry atmosphere, and the precipitate was washed with four portions of anhydrous ether. It was dried in a desiccator at room temperature overnight for analysis.

Anal. Calcd. for $C_7H_{13}AlCl_2O_2$: Cl, 31.23; Al, 11.88. Found: Cl, 31.12; Al, 11.91.

In another run, the solid was stirred with ether and 10% aqueous sulfuric acid until two clear layers resulted. The ether layer was separated, washed successively with water, saturated sodium carbonate, and brine, dried over magnesium sulfate, and concentrated to give 4.09 g. (31.5% over-all or 51.1% of total *cis* isomer) of *cis*-4-methoxycyclohexanol of over 95% purity. The *p*-toluenesulfonate, formed in 75% yield, melted at 88–89.5° (lit.[7] m.p. 87.8–88.2°). Infrared spectrum of the alcohol was identical with one of pure *cis*-4-methoxycyclohexanol kindly provided by D. S. Noyce.

The ethereal filtrate by similar treatment yielded 3.90 g. (30% overall, or 78% of total *trans* isomer) of *trans*-4-methoxycyclohexanol of 87% purity, characterized by conversion to the hydrogen phthalate, m.p. 151–152° (lit.[7] m.p. 148.6–149.0) in 66% yield.

3-Methoxycyclohexanol.—Catalytic hydrogenation of 50.0 g. (0.40 mole) of *m*-methoxyphenol in 125 ml. 95% ethanol in the presence of 10 g. of 5% rhodium on alumina at 52 p.s.i. and room temperature was complete in 2.5 hr. The material was worked up as described for the 4-isomer to give 47.9 g. (92%) of 3-methoxycyclohexanol, b.p. 112–116° (28 mm.). Gas chromatographic analysis on a 5-ft. silicone QF-1 column at 155° and 40 ml./min. of helium indicated the product to contain 45.5% *trans* isomer (retention time 8.3 min.) and 54.5% *cis* isomer (retention time 11.0 min.). In a second hydrogenation, the product was 60% *trans* isomer.

Chelate.—To the mixed hydride solution prepared from 20.0 g. (0.15 mole) of aluminum chloride in 100 ml. of anhydrous ether and 0.0375 mole of ethereal lithium aluminum hydride was added 15.6 g. (0.12 mole) of 3-methoxycyclohexanol (60% *trans*) in 75 ml. of ether. The complex was collected after 30 hr. and weighed 10.3 g.; it was dried *in vacuo* at 56° for 16 hr.

Anal. Calcd. for $C_7H_{13}AlCl_2O_2$: C, 37.02; H, 5.77; Al, 11.88. Found: C, 36.76; H, 6.08; Al, 11.90.

In another run, starting with 28.6 g. (0.22 mole) of material containing 45.5% *trans* isomer, 0.20 mole of aluminum chloride in 100 ml. of ether and 0.05 mole of ethereal lithium aluminum hydride there was obtained 26.8 g. of solid complex which was decomposed as described for the 4-isomer and yielded 11.4 g. (39.5% over-all or 72.5% of total *cis* isomer) of *cis*-3-methoxycyclohexanol of 90% purity. This was characterized as the hydrogen phthalate, m.p. 103–104° (lit.[8] m.p. 104–105°), obtained in 51% yield.

Decomposition of the filtrate as described for the 4-isomer gave 9.85 g. (34.5% over-all or 76% of total *trans* isomer) of *trans*-3-methoxycyclohexanol of over 99% purity (gas chromatography), b.p. 105–106° (24 mm.), $n^{20}D$ 1.4670. It was characterized as the 3,5-dinitrobenzoate, m.p. 104–105°.

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97. Found: C, 52.16; H, 5.28.

2-Methoxycyclohexanol.—Catalytic hydrogenation of guaiacol over rhodium on alumina (as described for 3-methoxycyclohexanol) yielded 2-methoxycyclohexanol, b.p. 66–67° (16 mm.), which was quite impure and required purification by preparative gas chromatography. The material collected was 90.3% *cis* and 9.7% *trans*. The pure *trans* isomer, b.p. 91.5–93.0° (24 mm.), $n^{20}D$ 1.4595 (lit.[10] b.p. 72.5–73.2° (10 mm.), $n^{25}D$ 1.4586), was obtained from cyclohexene oxide and methanol as previously described.[10] A mixture of the two preparations (5.20 g.) containing 52.3% *trans* alcohol was converted to the solid chelate in the manner described earlier. The alcohol recovered from the chelate (4.15 g.) contained 53.1% *trans* isomer whereas that recovered from the filtrate (0.58 g.) contained 73.1% *trans* isomer.

(9) Inner complexes of aluminum similar to those shown in Fig. 1 have been described previously by G. Bähr and G. E. Müller, *Chem. Ber.*, **88**, 251 (1955).

(10) S. Winstein and R. B. Henderson, *J. Am. Chem. Soc.*, **65**, 2196 (1943).

Dibutyl 2-Bromoethaneboronate[1]

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Received January 22, 1963

Radical-catalyzed additions to dibutyl ethyleneboronate have made a variety of new types of carbon-functional organoboron compounds available.[2] Extension

(1) Supported by PHS research grant CY-5513 from the National Institutes of Health, Public Health Service.

(2) D. S. Matteson, *J. Am. Chem. Soc.*, **82**, 4228 (1960).

$$CH_2{=}CHB(OC_4H_9)_2 + HBr \xrightarrow{\text{ultraviolet}} BrCH_2CH_2B(OC_4H_9)_2$$

to hydrogen bromide has resulted in the efficient preparation of dibutyl 2-bromoethaneboronate.

We expected that the 2-bromoethaneboronate would be deborobrominated in the presence of bases.[3] The general reaction with a base, Z^-, presumably proceeds *via* addition of the base to the boron atom.[2]

$$BrCH_2CH_2B(OC_4H_9)_2 + Z^- \longrightarrow BrCH_2CH_2B(OC_4H_9)_2^- \longrightarrow$$
$$\begin{array}{c} | \\ Z \end{array}$$
$$Br^- + C_2H_4 + ZB(OC_4H_9)_2 \longrightarrow$$
$$BZ_3 + B(OC_4H_9)_3 \text{ (or solvolysis products)}$$

Accomplishment of this elimination under mild conditions would, in addition to the method of synthesis, serve as a structure proof.[2] Treatment with water at 25° has turned out to be sufficient.

$$BrCH_2CH_2B(OC_4H_9)_2 + 3H_2O \longrightarrow$$
$$C_2H_4 + B(OH)_3 + HBr + 2C_4H_9OH$$

The hope that weakly basic but highly nucleophilic reagents might displace bromide ion from dibutyl 2-bromoethaneboronate was realized only with iodide ion, which yielded the iodo compound, $ICH_2CH_2B(OC_4H_9)_2$. Competition experiments indicated that allyl bromide reacts 4 to 5 times as fast as dibutyl 2-bromoethaneboronate with sodium iodide in acetone. Since allyl bromide reacts 65–70 times as fast as butyl bromide,[4] the bromoethaneboronic ester must react a number of times as fast as ordinary alkyl bromides. A competition experiment with ethyl bromide confirmed this order of reactivity, although the onset of side reactions after a time made it impossible to run the reaction long enough to get accurate data. This activating effect of the dibutoxyboryl group is consistent with the expectation that the boron atom should be electron-donating toward carbon in the absence of π-bonding[2] and contrasts with the very slight deactivating effect (relative to hydrogen) of a carbethoxy group at the same position. However, there is some uncertainty in this interpretation because of some anomalously high reactivities in the carbonyl series.[5]

With reagents more basic than iodide ion, dibutyl 2-bromoethaneboronate yielded only ethylene, bromide ion, and boric acid derivatives. The most carefully studied reaction was that with sodium thiocyanate in acetone. Sodium bromide crystallized from the reaction mixture, ethylene was evolved in 90% yield, and the remaining solution contained tributyl borate and an unstable oily liquid partially immiscible with tributyl borate, presumably tri(iso)thiocyanoboron. Similar gas evolution and butyl borate formation occurred with potassium cyanate in acetone, aniline in tetrahydrofuran, pyridine, sodium nitrite in dimethylformamide, and others. Even lithium bromide in acetone catalyzes the elimination after an induction period of a few minutes, and decomposition sets in within a few hours in the reaction mixtures with sodium iodide. Boron bromide (or iodide), a product which would result from the elimination reaction in a nonbasic medium, is presumably the active catalyst in these autocatalytic decompositions; boron trifluoride etherate catalyzes similar decomposition.

In the hope that steric hindrance about the boron atom might retard elimination enough to permit displacements of bromide, the butyl ester was transesterified with diisobutylcarbinol, chosen because tris(diisobutylcarbinyl) borate hydrolyzes far more slowly than most borate esters.[6] Somewhat surprisingly, the transesterification proceeded without difficulty, suggesting that anions of the type $BrCH_2CH_2B(OR)_3^-$ are not intermediates; the necessary proton shifts could be concerted or acid catalyzed. Treatment of bis(diisobutylcarbinyl) bromoethaneboronate with sodium thiocyanate resulted in the usual elimination.

Experimental[7]

Dibutyl 2-Bromoethaneboronate.—Dibutyl ethyleneboronate (16.7 g.) in a Pyrex flask was kept at approximately 70°, stirred, and irradiated with a Hanovia 500-watt mercury vapor ultraviolet lamp for 4 hr. while hydrogen bromide was bubbled through the liquid. Distillation through a short column packed with Podbielniak nichrome helices yielded 18.2 g. (76%) of dibutyl 2-bromoethaneboronate, b.p. 48–50° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{22}BO_2Br$: C, 45.32; H, 8.37; B, 4.08; Br, 30.16. Found: C, 45.54; H, 8.60; B, 4.34; Br, 29.94.

Dibutyl 2-Iodoethaneboronate.—A solution of 5.0 g. of sodium iodide and 6.21 g. of dibutyl 2-bromoethaneboronate in 30 ml. of acetone was allowed to stand under nitrogen in the dark 30 min. After filtration of the sodium bromide the solution was distilled through a spinning band column to yield 1.5 g. (20%) of dibutyl 2-iodoethaneboronate, b.p. 66° (0.2 mm.), with up to 1 g. loss in the forerun. The following infrared bands are useful for distinguishing the iodo from the bromo compound: 3.23 (m), 8.67 (m), 9.15 (w), 11.46 (w), 12.25 (w), 13.78 (w) microns for the iodo compound; 8.51 (m), 8.67 (w), 9.03 (w), 12.03 (w), 13.46 (w) for the bromo; the other bands differ only slightly.

Anal. Calcd. for $C_{10}H_{22}BO_2I$: C, 38.49; H, 7.11; B, 3.47; I, 40.67. Found: C, 38.73; H, 7.18; B, 3.68; I, 40.50.

Relative Rates.—A solution 0.5 *M* each in allyl bromide, dibutyl 2-bromoethaneboronate, and sodium iodide in acetone was allowed to stand 45 min. at 23–25°. The yield of precipitated sodium bromide was 94%. Vacuum distillation yielded a mixture of the 2-haloethaneboronic esters shown by infrared comparison with authentic mixtures to contain 26 (±3) mole per cent dibutyl 2-iodoethaneboronate. Assuming 100% completion of the reaction, the rate constant for allyl bromide is 4.5 times that for dibutyl 2-bromoethaneboronate. The uncertainties in the ratio of products and extent completion of the reaction lead to an uncertainty in the ratio of rate constants which we judge to be about ±25%. In a similar competition with ethyl bromide run 90 min. the resulting mole ratio of dibutyl 2-bromo- to 2-iodoethaneboronate was 47:53 (±5%), but the reaction was estimated to be only 80–90% complete under these conditions and some tributyl borate formed as a by-product. Further confirmation of the order of rate constants, allyl > dibutoxyboronoethyl > ethyl bromide, was obtained by examining the order of appearance of sodium bromide precipitates in a set of reaction mixtures at the same molar concentrations. The gradual appearance of the precipitates seemed to indicate that supersaturation sufficient to reverse any apparent order of reactivities was not occurring. These qualitative tests support the assumption that the competition experiments measure rate constants, not equilibrium constants.

Bis(diisobutylcarbinyl) 2-Bromoethaneboronate.—Simple distillation of butanol at 20 mm. from a mixture of 23.9 g. of dibutyl 2-bromoethaneboronate and 50 ml. of diisobutylcarbinol (redistilled) in a bath at 65° 2.5 hr., then up to 90°, then distillation of diisobutylcarbinol at 0.2 mm. followed by fractionation of the residue yielded 33.4 g. (91%) of the diisobutylcarbinyl ester, b.p. 92–93° (0.1 mm.).

(3) B. M. Mikhailov and P. M. Aronovich, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 927 (1961); *Chem. Abstr.*, **55**, 24541*d* (1961).

(4) P. D. Bartlett and L. J. Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942).

(5) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co. Inc., New York, N. Y., 1962, pp. 176–178.

(6) H. Steinberg and D. L. Hunter, *Ind. Eng. Chem.*, **49**, 174 (1954).

(7) Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_{20}H_{42}BO_2Br$: C, 59.31; H, 10.38; B, 2.67; Br, 19.73. Found: C, 59.64; H, 10.43; B, 2.95; Br, 19.47.

Eliminations.—Treatment of 0.28 g. of dibutyl-2-bromoethaneboronate with 10 ml. of water yielded 96% of ethylene, confirmed by infrared comparison with an authentic sample. Treatment of 0.5 g. of dibutyl 2-bromoethaneboronate with 0.6 g. of sodium thiocyanate in 3 ml. of acetone yielded 90% of ethylene in 2 hr. Tributyl borate (identified by infrared) and an unstable oil were isolated from the solution. The oil was only slightly soluble in butyl borate, but appeared to separate slowly over a period of several days. The infrared spectrum was consistent with the presence of thiocyano or isothiocyano groups. Extensive decomposition occurred on attempted distillation. Bis(diisobutylcarbinyl) 2-bromoethaneboronate underwent similar elimination in the presence of sodium thiocyanate to yield tris(diisobutylcarbinyl) borate,[6] m.p. 102°, further confirmed by microanalysis. In the other eliminations mentioned in the discussion section, evolution of gas on mixing and isolation of butyl borate from the reaction mixture were considered sufficient evidence that elimination was occurring.

Acetylation of Serine during Bradykinin Synthesis

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Received March 4, 1963

In a previous report[1], we described two carbobenzoxypentapeptide intermediates obtained during the synthesis of bradykinin which did not appear to be identical, but which gave the same carbobenzoxyhexapeptide on further reaction. The pentapeptides were obtained by different procedures. In the first case carbobenzoxy-L-phenylalanine *p*-nitrophenyl ester reacted with L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine methyl ester and secondly, carbobenzoxy-L-phenylalanyl-L-seryl azide reacted with L-prolyl-L-phenylalanylnitro-L-arginine methyl ester. Both of the pentapeptides were crystalline but differed in melting point by 65° and in rotation by 15°. The infrared curves of the two compounds were not significantly different enough to confirm any structural anomalies. X-Ray diffraction patterns of the two peptides revealed dissimilarities which could possibly be due to different crystalline forms, but seeding a solution of one of the pentapeptides with the other failed to induce crystallization.

The solution to the problem of the two pentapeptides came with the attempted preparation of the O-acetyl analog of bradykinin. The intermediate carbobenzoxy 6-O-acetylserine pentapeptide was found to possess the physical properties of the pentapeptide obtained by the one plus four coupling. O-Acetyl analysis confirmed the presence of this functional group in both compounds while the pentapeptide prepared by the two plus three reaction did not contain an O-acetyl. Reexamination of the other bradykinin intermediates from the hexapeptide to the tricarbobenzoxynonapeptide also revealed the presence of O-acetyl groups. The results are given in Table I. The acetate group is undoubtedly lost during hydrolysis of the protecting methyl ester since it does not appear in any of the products after this step.

The O-acetyl group on serine probably is introduced during the hydrobromine acid–acetic acid cleavage of the carbobenzoxy group since this side reaction has been reported previously.[2] The consequences of this reaction are usually not troublesome and in practice we have found that the products containing this group are higher melting and more easily crystallized than peptides without it. Care should be exercised, however, in preparing peptides containing serine in which a step involving hydrolysis with alkali is not involved.

Experimental[3]

Carbobenzoxy-O-acetyl-L-seryl-L-propyl-L-phenylalanylnitro-L-arginine Methyl Ester.—To a cold (5°) solution of 4.3 g. (0.0078 mole) of L-propyl-L-phenylalanylnitro-L-arginine methyl ester hydrobromide[1] in 50 ml. of dimethylformamide was added 1.5 g. of triethylamine. After 5 min., the precipitate was removed by filtration; to the filtrate was added 3.2 g. (0.078 mole) of N-carbobenzoxy-O-acetyl-L-serine *p*-nitrophenyl ester.[4,5] The yellow solution was kept 18 hr. at 25°, diluted with 250 ml. of ethyl acetate, and washed with water, aqueous 5% sodium carbonate, water, dilute hydrochloric acid, dried, and evaporated. Ether was added giving a white solid which was recrystallized from methanol–ether, 4 g. (70%), m.p. 166–168°, $[\alpha]^{23}D$ −55.7° (*c* 1.06, dimethylformamide); reported[5] m.p. 170–172°, $[\alpha]^{20}D$ −56.6° (*c* 1.06, dimethylformamide).

Anal. Calcd. for $C_{34}H_{44}N_8O_{11}$: C, 55.12; H, 5.98; N, 15.12. Found: C, 54.96; H, 6.17; N, 15.12.

Carbobenzoxy-L-phenylalanyl-O-acetyl-L-seryl-L-prolyl-L-phenylalanylnitro-L-arginine Methyl Ester.—To a cold (10°) solution of the carbobenzoxytetrapeptide, 7 g. (0.0095 mole), in 100 ml. of glacial acetic acid was added 6 g. of anhydrous hydro-

TABLE I

BRADYKININ INTERMEDIATES

		Formula	Calcd. % C	H	N	O-Ac	Found, % C	H	N	O-Ac
1.	CBZ-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{43}H_{53}N_9O_{12}$	58.17	6.02	14.20	4.85	58.05	6.06	14.83	5.9
2.	CBZ-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{45}H_{56}N_{10}O_{13}$	57.20	5.97	14.83	4.56	57.43	6.11	15.00	4.15
3.	CBZ-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Phe-NO_2-L-Arg-OCH_3	$C_{50}H_{63}N_{11}O_{14}$	57.62	6.09	14.78	4.12	57.34	6.10	15.24	3.50
4.	CBZ-L-Pro-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{55}H_{70}N_{12}O_{15}$	57.99	6.19	14.76	3.92	57.66	6.13	14.98	4.23
5.	TRICBZ-L-Arg-L-Pro-L-Pro-Gly-L-Phe-O-Ac-L-Ser-L-Pro-L-Phe-NO_2-L-Arg-OCH_3	$C_{77}H_{94}N_{16}O_{20}$	59.14	6.06	14.34	2.75	58.92	6.14	14.66	3.24

(1) E. D. Nicolaides and H. A. DeWald, *J. Org. Chem.*, **26**, 3872 (1961).

(2) St. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).

(3) Melting points were taken using a Thomas–Hoover capillary melting point apparatus and are corrected.

(4) H. A. DeWald and E. D. Nicolaides, to be published.

(5) M. A. Ondetti, *J. Med. Chem.*, **6**, 10 (1963).