Synthesis of Boron-Substituted Pyrimidines and Borazaroquinazolines[1]

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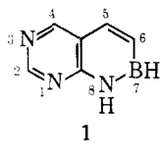
Received July 18, 1977

Two approaches to the synthesis of boron-substituted pyrimidines and borazaroquinazolines (1) have been explored First, (dibutoxyboryl)ethene and bromomalononitrile were converted to 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (**2**), which was reduced with triphenyltin hydride to 1,1-dicyano-3-(dibutoxyboryl)propane (**3**), which condensed with thiourea to yield 2-mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (**4a**). However, conversion of **4a** to a borazaroquinazoline was not attempted because the development of boron-substituted carbanion chemistry promised a more direct and efficient approach. This second method involved condensation of 4,6-dichloro-5-formylpyrimidine (**5**) with the carbanion from tetrakis(trimethylenedioxyboryl)methane to form 4,6-dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**), which on treatment with ammonia at 25 °C yielded 4-chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (**7a**), which reacted with ammonia at 75 °C to form the 4-amino derivative **8**. Improved yields were obtained in a similar sequence starting from tetrakis(ethylenedioxyboryl)methane. Characterization of the amino-substituted borazaroquinazolines was aided by ^{13}C NMR correlations.

Substitution of a boron atom for a carbon in a biochemically significant molecule might lead to antimetabolite activity. This hypothesis is reinforced by recent findings that phenylethaneboronic acid is a chymotrypsin inhibitor[2] and that a boron analogue of betaine shows some anticancer activity.[3] However, there are significant restrictions on the types of boron compounds that can be synthesized for such purposes. Instability toward hydrolysis is a problem with boron–nitrogen or boron–oxygen bonds, as well as with boron–carbon bonds activated by various neighboring functional groups. For example, purine analogues having boron in positions 2 or 8 (between nitrogen atoms) have been found to be unstable in hydroxylic media.[4,5] Boron-substituted pyrimidines made previously in this laboratory either deboronated easily or had the boron substituent in a position likely to interfere with rather than enhance any possible antimetabolite activity.[6] Butler and Soloway synthesized a boron analogue of dihydrouracil,[7] but they were unable to dehydrogenate it. Liao, Podrebarac, and Cheng made 5-dihydroxyboryluracil by a straightforward modernization of the classical boronic acid synthesis,[8] but this approach is not generally applicable to highly functionalized organoboron compounds.

7,8-Borazaroquinazoline (**1**) was chosen as the target ring system for synthesis for several reasons. Borazaro compounds



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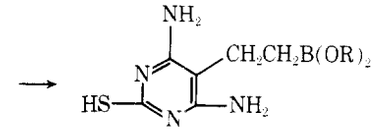
are generally stable, especially those having fused six-membered rings.[9] It appeared that there would be feasible synthetic routes to derivatives of **1**. For analogy to the purines, it would be better to have a five-membered ring rather than the six-membered borazaro ring of **1**, but it was hoped that biological activity might be found in spite of this weakness in design, and it was also hoped that knowledge of synthetic techniques and chemical properties gained in the synthesis of derivatives of **1** might eventually aid the synthesis of closer analogues to the purines.

Results and Discussion

The Bromomalononitrile–(Dibutoxyboryl)ethene Adduct. The first route attempted, with partial success, was based on the radical initiated addition of bromomalononitrile to (dibutoxyboryl)ethene (dibutyl vinylboronate), which

$$(NC)_2CHCH_2CHBrB(OC_4H_9)_2 \longrightarrow (NC)_2CHCH_2CH_2B(OC_4H_9)_2$$

2 **3**



4a, R = H
b, R = CH_3

yielded 85% of 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (**2**).[10] Conversion of the malononitrile group of **2** to a pyrimidine required prior replacement of the reactive bromo function since under basic conditions **2** undergoes rapid ring closure to 1,1-dicyano-2-(dibutoxyboryl)cyclopropane.[10] Attempts to replace the bromide by solvolysis in neutral or acidic aqueous ethanol also yielded only the cyclopropane derivative.

Reduction of **2** with triphenyltin hydride, which proceeds under free-radical conditions,[11] gave fair yields of the desired product, 1,1-dicyano-3-(dibutoxyboryl)propane (**3**). There was a substantial amount of higher boiling byproduct, which had an elemental composition corresponding to the 1:2 telomer of malononitrile with (dibutoxyboryl)ethane, perhaps formed via radical carbon–carbon bond cleavage and addition reactions.

The reaction of **3** with thiourea in the presence of potassium *tert*-butoxide followed by hydrolysis readily yielded 2-mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (**4a**), which on crystallization from methanol was converted to the dimethoxyboryl derivative **4b**.

Although cyclization and dehydrogenation of **4** should yield a derivative of **1**, unsolved problems remain. The sulfhydryl group precludes catalytic dehydrogenation, and oxidative methods may cleave the carbon–boron bond. Attempted dehydrogenation of a dihydroborauracil derivative has failed.[7] Therefore, this route was abandoned when a more attractive alternative became apparent.

The Triborylmethide–Aldehyde Route. Tetrakis(organyldioxyboryl)methanes are easily converted to tris(organyldioxyboryl)methide ions, which condense efficiently with aldehydes.[12] This reaction is the basis for the successful route to a derivative of borazaroquinazoline (**1**). Lithium tris(trimethylenedioxyboryl)methide[13,14] and 4,6-dichloro-5-formylpyrimidine[15] gave mediocre yields of the expected product 4,6-dichloro-5-[2,2-bis(trimethylenedioxyboryl)-

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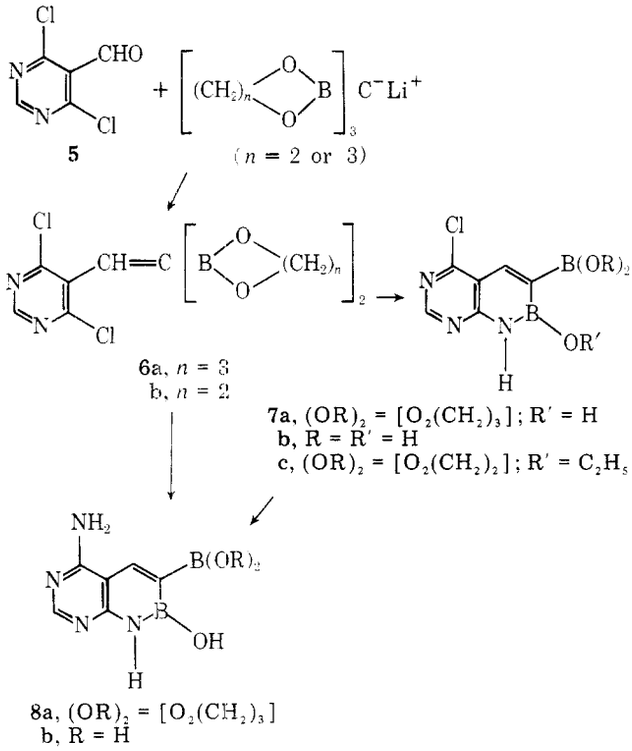
vinyl]pyrimidine (**6a**).

$$[(RO)_2B]_4C \xrightarrow{BuLi} [(RO)_2B]_3C^- \xrightarrow{R'CHO} R'CH{=}C[B(OR)_2]_2$$

The geminal boron functions in **6a** constitute an essential part of the synthetic strategy since subsequent ring closure requires the presence of a cis boron on the vinylic substituent and stereoselective synthesis of the cis isomer would be difficult.

Reaction of **6a** with liquid ammonia at 25 °C in a pressure vessel yielded 4-chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (**7a**). The acquisition of the 7-hydroxyl group requires hydrolysis and implies that moisture was not fully excluded. Treatment of either **6a** or **7a** with liquid ammonia under autogenous pressure at 75 °C resulted in replacement of the second chlorine atom and formation of 4-amino-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (**8a**), which hydrolyzed to the 6-dihydroxyboryl derivative **8b** on aqueous workup. However, both **8a** and **8b** proved uncommonly difficult to purify and characterize, presumably because of interactions between the boron and amino functions, and the remainder of this work was devoted to proving these structures. Considerable improvement in the details of the synthesis resulted as a byproduct of this effort.



A significant improvement in yields resulted from the use of lithium tris(ethylenedioxyboryl)methide, $[(CH_2)_2O_2B]_3C^-Li^+$, in place of the trimethylene homologue, $[(CH_2)_3O_2B]_3C^-Li^+$, which had been used in previous work.[14] The insolubility of tetrakis(ethylenedioxyboryl)methane, $[(CH_2)_2O_2B]_4C$, in tetrahydrofuran (THF) had led to the belief that this compound could not be used for carbanion generation.[16] However, on reinvestigation the use of the ethylenedioxyboryl ester resulted in about the same yields of **6b** as had been obtained previously in the preparation of **6a**. Yields were significantly improved when special care was taken to ensure the purity of the tetrakis(ethylenedioxyboryl)methane and when dichloromethane was incorporated into the solvent mixture to increase the solubility, with about a 3:1 mixture of THF/dichloromethane providing excellent results. Preparations of **6a** had consistently given 30–35% yields, but the improved preparation of **6b** gave 77%, with much less formation of tarry byproducts.

Since previous work with lithium tris(trimethylenedioxyboryl)methide had generally given high yields of aldehyde condensation products,[14] the inefficient reaction of 4,6-dichloro-5-formylpyrimidine (**5**) may result from steric hindrance to attack at the aldehyde group, coupled with the availability of alternative reactive sites at the 4 and 6 positions of the pyrimidine. The ethylenedioxyboryl analogue should be less hindered at the carbanionic site.

The conversion of **6b** to **8b** in one step proceeded in about the same yield (80%) as conversion of **6a**. Conversion of **6a** to **7a** was only about 30%, but this is apparently an isolation problem dependent on the presence of sufficient fortuitous moisture to hydrolyze the BOR′ group but not the $B(OR)_2$ to provide the particular species which happens to crystallize readily. From **6b**, two products, **7b** and **7c**, were isolated, one having exclusively hydroxy ligands on boron and the other having one ethylene glycol and one ethanol (recrystallization solvent) ligand, each in about 30% yield. However, since **7a** had already been fully characterized and **7** was not the major objective, no further attempts were made to simplify and improve this synthesis.

Characterization of 8. Although all of the precursors **6** and **7** readily gave good elemental analyses and had ^1H NMR spectra consistent with their assigned structures, neither **8a** nor **8b** yielded satisfactory analytical results at first, and the ^1H NMR spectra of these compounds, which have only two carbon-bound and therefore nonexchangeable protons on the borazaroquinazoline ring system, were not very informative even though the results were consistent with the assigned structures.

The problem with characterization of **8a** appeared to be an unusually tenacious retention of chloroform, the solvent which was used to crystallize this particular species. After normal drying procedures, samples of **8a** showed an extra ^1H NMR peak at δ 8.35 in perdeuteriodimethyl sulfoxide (Me_2SO-d_6), which was shown to correspond to chloroform in Me_2SO-d_6 by comparison with an authentic sample. Even after prolonged drying, the elemental analysis corresponded to retention of a small amount (~7 mol %) of chloroform even though it was not quite enough to detect using NMR.

The problems with the fully hydroxylated compound **8b** were more complicated. Recrystallized (microcrystalline) samples gave variable analytical results, generally low in nitrogen and high in boron. Two analytically pure samples were finally obtained after chromatography on cellulose with methanol/water as the eluting solvent. However, further structural confirmation was sought.

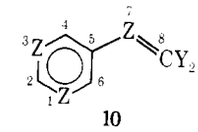
The ^1H NMR spectrum of **8b** showed the expected two singlets in the aromatic region. The low solubility of **8b** even in dimethyl sulfoxide made it difficult to get adequate NMR data, but in Me_2SO-d_6 it was possible to detect two broadened peaks attributed to NH in addition to the residual H_2O peak, which evidently included the B–OH and perhaps one NH absorption due to rapid exchange between these groups and water, or possibly due to water eliminated by condensation of B–OH to B–O–B or B–N linkages. The separate NH peaks were shown to undergo exchange broadening and shifting on addition of methanol.

The ^{11}B NMR spectrum of **8b** consisted of an exceedingly broad, ill-defined absorption and was of no use in characterization.

Ultraviolet spectra of **7b** and **8b** were consistent with the assigned structures.

Finally, in the hope of obtaining some additional data re-

Table I. 22.63-MHz ^{13}C NMR Spectra of Borylvinylpyrimidines and Related Compounds with Carbon Atoms Numbered as in Structure 10



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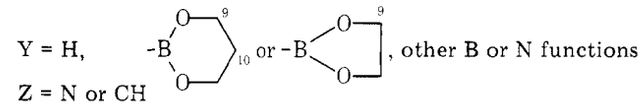
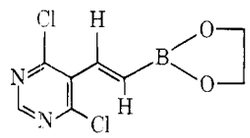


Compound	Registry no.	Solvent	δ (relative to Me_4Si) C_2	C_7	$C_{4,6}$, C_5	Other
9	64705-49-3	Me_2SO-d_6	156.6	139.4	159.5[a]	C_9, 65.7
6a	64705-50-6	Me_2SO-d_6	156.2[b]	142.6[c]	158.9[a]	C_9, 61.4, 61.6;[d] C_{10}, 26.5, 26.8[e]
		$CDCl_3$	154.3	142.6	158.5[a]	C_9, 60.8, 61.0; C_{10}, 25.8, 26.1
8a	64705-51-7	Me_2SO-d_6	157.4[f]	148.4	161.4	C_9, 61.4; C_{10}, 27.0
8b	64705-52-8	CD_3OD	158.3	148.0[g]	159.1[a]	
		Me_2SO-d_6	156.7[h]	148.2[g]	161.0[a,h]	Impurities, 98.5, 57.5[h]
Adenosine[i]		Me_2SO-d_6	152.7		C_4, 156.3; C_6, 149.2; C_5, 119.6; C_8, 140.5	
$C_6H_5CH{=}C[BO_2(CH_2)_3]_2$[j]		Me_2SO-d_6	128.0	149.1	$C_{1,3}$, $C_{4,6}$ 127.7, 128.5; C_5, 140.2;[a] C_9, 61.5; C_{10}, 26.8, 27.0	

[a] Weak. [b] From undecoupled spectrum, J_{CH} = 217 Hz. [c] J_{CH} = 168 Hz. [d] J_{CH} = 146 Hz; two peaks because of nonequivalent $BO_2(CH_2)_3$ groups. [e] J_{CH} = 141 Hz. [f] Paired with peak at δ 157.1. [g] 25–30 Hz wide at half height. [h] Spectrum very weak; additional peaks at δ 155.9, 160.5, 162.0, and in between, as if several related compounds are present. [i] Assigned in accord with ref 18 and 19. [j] For synthesis, see ref 14.

garding the more inaccessible parts of the structure of **8**, a series of ^{13}C NMR spectra were run on **6a**, **8a**, **8b**, and some related compounds. Fortunately, the ^{13}C NMR data proved consistent with the assigned structures (**8**), but unfortunately, only the two H-substituted carbons of the borazaroquinazoline ring could be detected unequivocally, with one additional ring carbon appearing as a weaker peak. The carbon bonded to two boron atoms was not detectable either in **8** or in model compounds. In an effort to obtain some clue as to where to look for



9

this elusive carbon absorption, 4,6-dichloro-5-[*trans*-2-(ethylenedioxyboryl)vinyl]pyrimidine (**9**) was synthesized from tris(ethylenedioxyboryl)methane[17] and 4,6-dichloro-5-formylpyrimidine (**5**), but in spite of the presence of the proton, the boron-bound carbon was not found. The ^{13}C NMR spectra are summarized in Table I.

It is apparent from Table I that the ^{13}C chemical shift pattern characteristic of the vinylpyrimidine group appears consistently throughout the series **6a**, **8a**, **8b**, and **9**, that the pyrimidine C_2 is not far from that in adenosine, and that the vinylic carbon β to boron (C_7 in **10**) has a similar chemical shift in both the pyrimidine series and in $C_6H_5CH{=}CH$-$[BO_2(CH_2)_3]_2$. The assignments are further confirmed by the CH coupling constants observed in an undecoupled spectrum of **6a**. The spectrum of **8b** in CD_3OD is consistent with the rest of the series, but the saturated solution was dilute and the spectrum was weak. Therefore, Me_2SO-d_6 was tried as solvent, but the spectrum was anomalously very weak and consisted of clusters of closely spaced peaks only partially distinguishable from background noise even with 56 000 scans. Evidently **8b** undergoes a variety of condensation reactions involving the NH and BOH groups in Me_2SO, resulting in the formation of a multiplicity of related species, probably oligomers. The molecular weight measured osmometrically in dimethylformamide was 220 (theory, 206), though this is not necessarily inconsistent with condensations which liberate water. The spectrum of **8a** showed a stronger than normal peak for C_4 (or C_5 or C_6) of structure **10**, as well as an anomalous double peak at δ 157.1–157.4 in the C_2 region, which might arise from the presence of two closely related species (e.g., BOH vs. BOB linkages) or detection of one of the normally missing carbon absorptions of the ring.

The failure to detect three out of four of the quaternary carbons in **6a**, **8a**, and **8b**, though frustrating for purposes of proof of structure, is not unprecedented.[20] If the relaxation time is longer than the pulse interval, the signal becomes saturated. With the very dilute solutions available for the compounds of primary interest, unduly long scan times would be required, and further attempts to detect the missing quaternary carbon signals were not undertaken.

It may be noted incidentally that the geometry of the borylvinyl group in **9** is trans, as shown by the ^1H NMR spectrum (J_{H-H} = 20 Hz) and expected on the basis of previous results.[14] Thus, **9** is not a suitable candidate for ring closure to borazaro compounds.

Compound **8b** was inactive in the standard P388 leukemia screen (Drug Development Branch, National Cancer Institute).

Experimental Section

Reactions were run under nitrogen or argon. Tetrahydrofuran (THF) and dichloromethane were dried over calcium hydride and distilled. Other reagent grade chemicals were used as supplied. The ^1H NMR spectra were obtained at 100 MHz with a JEOL JNM-MH-100 instrument or at 60 MHz with a Varian A-60 and are referred to internal tetramethylsilane (Me_4Si). ^{11}B NMR spectra were obtained at 32.1 MHz with the Varian HA-100 at the University of Idaho. ^{13}C NMR were obtained at 22.63 MHz with a Bruker WH-90 Fourier transform instrument and are referred to external Me_4Si. A Cary Model 15 ultraviolet spectrometer, a Beckman IR-5A infrared spectrometer, and a Varian M-66 mass spectrometer were used. Microanalyses were performed by Spang, Schwarzkopf, and Galbraith Laboratories. Melting points are uncorrected.

1,1-Dicyano-3-(dibutoxyboryl)propane (3). A mixture of 12.1 g of 1,1-dicyano-3-bromo-3-(dibutoxyboryl)propane (**2**),[10] 13.5 g of triphenyltin hydride,[11] and 0.1 g of azobis(isobutyronitrile) was heated at 70–80 °C for 2 h, and an additional 0.07 g of azobis(isobutyronitrile) was added, which led to the formation of a precipitate of triphenyltin bromide within a few seconds. The mixture was treated with 20 mL of water and filtered to remove the triphenyltin bromide (16 g, 97%).

The filtrate was extracted with ether, 20 mL of butanol was added, and the product was distilled, yield 3.14 g (34%), bp 94–103 °C (0.04 Torr). Anal. Calcd for $C_{13}H_{23}BN_2O_2$: C, 62.42; H, 9.27; B, 4.32; N, 11.20. Found: C, 62.24; H, 9.42; B, 4.10; N, 10.92.

A higher boiling byproduct, bp 110–160 °C (0.04 Torr), yield 3.0 g, was also obtained. This was redistilled, major portion bp 155–175 °C (0.04 Torr), and yielded an analysis not quite satisfactory for an adduct of 1 mol of malononitrile with 2 mol of dibutyl vinylborate. Anal. Calcd for $C_{23}H_{44}B_2N_2O_4$: C, 63.62; H, 10.21; B, 4.98; N, 6.45. Found: C, 62.73; H, 10.06; B, 5.51; N, 6.70.

2-Mercapto-4,6-diamino-5-(2-dihydroxyborylethyl)pyrimidine (4a). A solution of potassium *tert*-butoxide was prepared from 0.4 g of potassium metal and 30 mL of *tert*-butyl alcohol. A 0.53-g amount of thiourea and 1.5 g of 1,1-dicyano-3-(dibutoxyboryl)propane (**3**) were added, and the mixture was refluxed 17 h. The mixture was cooled, neutralized with acetic acid to pH 5, treated with 40 mL of water, and extracted with three 50-mL portions of ether. On standing 2 days at 5 °C, 0.52 g of product crystallized from the aqueous phase, and an additional 0.23 g was obtained by concentrating the mother liquor, total yield 60%; a sample did not melt but appeared to decompose at 270–325 °C. The analytical sample was recrystallized from water; IR (KBr) (Beckman IR 8) 3330 s, 3205 s, 2940 sh, 1620 s, 1550 s, 1515 s, 1475 m, 1408 m, 1380 s, 1357 sh, 1277 m, 1230 m, 1200 m, 1168 m, 1124 m, 1030 w, 968 w, 746 brd w cm^{-1}. Anal. Calcd for $C_6H_{11}BN_4O_2S + H_2O$: C, 31.05; H, 5.65; B, 4.66; N, 24.14; S, 13.82. Found: C, 31.32; H, 5.52; B, 4.52; N, 23.96; S, 14.09.

2-Mercapto-4,6-diamino-5-(2-dimethoxyborylethyl)pyrimidine (4b). When 200 mg of the dihydroxyboryl compound **4a** was dissolved in 1 mL of absolute methanol, the dimethoxy compound **4b** precipitated after a few seconds, yield 100–150 mg; 60-MHz ^1H NMR (Me_2SO-d_6) δ 3.17 (s, 6, OCH_3) and a series of broad, ill-defined peaks at δ 7.03 (s, 1, NH), 6.7 (s, 1 NH), 6.4 (s, 2, NH_2), 4.9 (~70 Hz wide, ~4, H_2O?), 2.3 (m?, 4?, CCH_2), 0.8 (~60 Hz wide, 4?, CH_2B). The integral values are probably grossly in error, and the spectrum is otherwise consistent with the assigned structure: IR (KBr) 3300 s, 3185 s, 2878 m, 1607 s, 1542 s, 1508 m, 1372 m, 1312 w, 1287 w, 1214 m, 1124 w, 1088 vw, 1047 w, 1002 w, 960 vw, 885 m, 850 vw, 797 w, 736 w, 697 vw, 671 vw cm^{-1}. Anal. Calcd for $C_8H_{15}BN_4O_2S$: C, 39.69; H, 6.25; B, 4.47; N, 23.14; S, 13.24. Found: C, 39.48; H, 6.49; B, 4.65; N, 22.98; S, 13.25.

4,6-Dichloro-5-formylpyrimidine (5) was prepared by the literature method[15] and later was purchased on special order from Aldrich. In order to obtain good yields (up to 55%), it appeared to be essential to extract the aldehyde product promptly with ether during hydrolysis of the crude reaction mixture with ice and water. The exothermic hydrolysis was controlled by the addition of ice.

4,6-Dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (6b). A slurry of 25.4 g (0.09 mol) of tetrakis(ethylenedioxyboryl)-methane[16] in 180 mL of dichloromethane and 600 mL of THF was cooled at −78 °C, and 36 mL of 2.4 M butyllithium in hexane was added dropwise with vigorous stirring for 30 min. The mixture was stirred for 2 h at −78 °C, and then a solution of 4,6-dichloro-5-formylpyrimidine (**5**) in 50 mL of THF was added. Stirring was continued while the mixture warmed to room temperature and the solids dissolved. After stirring overnight, the solution was concentrated and the residue was treated with a mixture of 250 mL of toluene and 250 mL of chloroform. The insoluble material was filtered and discarded, and the filtrate was concentrated under vacuum to crystallize the product, yield 21 g (77%), recrystallized from chloroform/toluene or chromatographed on cellulose with 1:1 chloroform/toluene as eluting solvent, mp 118–121 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.68 (s, 1, NCHN), 7.80 (brd s, 1, $CH{=}CB_2$), 4.40 (s, 4, OCH_2CH_2O), 4.16 (s, 4, OCH_2CH_2O); ^{11}B NMR ($CDCl_3$) broad peak (~600 Hz) 15.6 ppm downfield from $B(OCH_3)_3$; IR (KBr) 2976 m, 2907 m, 1592 s, 1534 m, 1504 s, 1481 s, 1404 s, 1355 s, 1307 s, 1264 s, 1245 s, 1227 s, 1209 s, 1159 m, 1126 m, 1041 s, 1004 s, 985 m, 954 m, 941 m, 909 s, 840 s, 808 s, 792 s, 776 s, 740 s, 703 m, 692 s, 668 m, 649 m cm^{-1}. Anal. Calcd for $C_{10}H_{10}B_2Cl_2N_2O_4$: C, 38.16; H, 3.20; B, 6.87; Cl, 22.53; N, 8.90. Found: C, 38.00; H, 3.14; B, 6.82; Cl, 22.65; N, 8.86.

4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (6a). The method was essentially the same as that used for the preparation of **6b**. The carbanion was prepared from 9.5 g (0.03 mol) of tetrakis(trimethylenedioxyboryl)methane in 150 mL of THF with 0.03 mol of butyllithium at −78 °C,[14] warmed to 0 °C, and cooled again to −78 °C before adding the 4,6-dichloro-5 formylpyrimidine (**5**). The yield was 3.1 g (33%), mp 156–157 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.64 (s, 1, NCHN), 7.39 (brd s, 1, $CH{=}CB_2$), 4.10 (t, 4, OCH_2CH_2), 3.85 (t, 4, OCH_2CH_2), 1.93 (m, 4, $CH_2CH_2CH_2$); IR (KBr) 2967 m, 2899 m, 1600 s, 1531 m, 1508 s, 1481 s, 1418 s, 1376 s, 1339 s, 1311 s, 1274 s, 1250 s, 1212 s, 1140 m, 1111 s, 1004 m, 925 m, 904 m, 889 m, 856 m, 850 sh, 791 s, 769 m, 732 m, 714 s, 684 m, 669 s cm^{-1}. Anal. Calcd for $C_{12}H_{14}B_2Cl_2N_2O_4$: C, 42.05; H, 4.12; B, 6.31; N, 8.17. Found: C, 42.28; H, 4.05; B, 6.17; N, 7.90.

4,6-Dichloro-5-[2-(ethylenedioxyboryl)vinyl]pyrimidine (9). The procedure was essentially the same as that used for the preparation of **6a**. The carbanion was generated from 4.53 g (0.02 mol) of tris(ethylenedioxyboryl)methane[17] in 140 mL of THF at −78 °C. The yield was 0.85 g (17%), mp 81–88 °C: 100-MHz ^1H NMR ($CDCl_3$) δ 8.68 (s, 1, NCHN), 7.36 (d, J = 20 Hz, 1, $CH{=}CHB$), 6.46 (d, J = 20 Hz, 1, $CH{=}CHB$), 4.36 (s, 4, OCH_2CH_2O); IR (KBr) 3067 w, 2994 m, 2915 m, 1938 w, 1610 s, 1504 s, 1389 s, 1350 brd, 1311 s, 1236 s, 1221 s, 1175 s, 1122 m, 1019 s, 999 s, 985 sh, 949 s, 863 s, 847 m, 836 sh, 788 s, 706 w, 675 w, 651 w, 631 s cm^{-1}. Anal. Calcd for $C_8H_7BCl_2N_2O_2$: C, 39.24; H, 2.88; B, 4.41; Cl, 28.96; N, 11.44. Found: C, 39.31; H, 3.00; B, 4.24; Cl, 29.04; N, 11.38.

4-Chloro-6-dihydroxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (7b) and 4-Chloro-6-ethylenedioxyboryl-7-ethoxy-7,8-dihydro-7,8-borazaroquinazoline (7c). Liquid ammonia (22 mL) was distilled from sodium into a chilled (−78 °C) stainless steel bomb containing 4.3 g of 4,6-dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (**6b**) and a magnetic stirrer. The vessel was sealed (with care taken to prevent the entry of moisture), and the contents were stirred for 24 h at 20–25 °C (10 atm). The ammonia was vented, and the residue was treated with 100 mL of chloroform. The insoluble material, which was the hydroxy compound **7b**, was filtered, dissolved in 160 mL of 95% ethanol, and concentrated to crystallize the product, yield 1.0 g (33%). The analytical sample was recrystallized from 95% ethanol and finally from aqueous 33% ethanol in order to obtain material free from ethoxy groups (by NMR analysis), mp 217 °C dec; 100-MHz ^1H NMR (Me_2SO-d_6) δ 9.57 (brd s, 1, NH), 8.56 (s, 1, CH), 8.25 (brd s, 2, $B(OH)_2$), 7.79 (brd s, 1, BOH); UV (0.1 N HCl) 217 nm (ϵ 3.45 × 10^4), 302 (1.41 × 10^4); UV (H_2O) 216 nm (ϵ 3.31 × 10^4), 302 (1.205 × 10^4); UV (0.1 N NaOH) 3.17 nm (ϵ 1.60 × 10^4); IR (KBr) 3356 sh, 3175 s, 1592 s, 1563 s, 1471 m, 1377 s, 1337 s, 1297 m, 1261 s, 1149 m, 1130 sh, 1085 sh, 961 w, 925 w, 842 m, 795 m, 718 s cm^{-1}. Anal. Calcd for $C_6H_6B_2ClN_3O_3$: C, 32.00; H, 2.69; B, 9.60; Cl, 15.74; N, 18.66. Found: C, 31.88; H, 2.82; B, 9.59; Cl, 15.60; N, 18.48.

The chloroform solution from the foregoing preparation contained the ethylenedioxyboryl compound **7c**. After concentration under vacuum, the residue was dissolved in absolute ethanol and concentrated to crystallize the product, 1.2 g (35%); 100-MHz ^1H NMR ($CDCl_3$) δ 8.86 (s, 1, NCHN), 8.67 (s, 1, CH=C), 7.85 (brd s, 1, NH), 4.41 (s, impurity), 4.33 (s, 4, OCH_2CH_2O), 4.07 (q, <2, OCH_2CH_3), 3.73 (q?, impurity), 1.31 (t, ~3, CH_2CH_3); IR (KBr) 3378 s, 3195 s, 3115 sh, 2967 s, 1597 s, 1565 s, 1471 s, 1368 s, 1340 s, 1287 s, 1261 s, 1185 w, 1157 w, 1104 w, 1046 s, 990 m, 912 m, 862 m, 836 m, 795 m, 717 s, 706 s, 668 m, 640 s cm^{-1}. Anal. Calcd for $C_{10}H_{12}B_2ClN_3O_3$: C, 43.16; H, 3.98; B, 7.77; Cl, 12.74; N, 15.10. Found: C, 42.30; H, 4.08; B, 8.14; Cl, 13.07; N, 15.37.

4-Chloro-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (7a). 4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**) was used in place of the ethylenedioxyboryl analogue **6b** in the procedure described for the preparation of **7b** and **7c**. In this case, the chloroform-insoluble material was not examined, but the filtrate was concentrated and the residue recrystallized from absolute ethanol, yielding 36% of **7a**; 100-MHz ^1H NMR ($CDCl_3$) δ 8.60 (s, 2, NCHN and $CH{=}CB_2$), 7.60 (brd s, 1, NH), 6.36 (s, 1, BOH), 4.18 (t, 4, OCH_2CH_2), 2.10 (m, 2, $CH_2CH_2CH_2$); ^1H NMR (Me_2SO-d_6) δ 9.80 (brd s, 1, NH), 8.64 (s, 1, NCHN), 8.40 (s, 1, $CH{=}CB_2$), 7.06 (s, 1, BOH). 4.15 (t, 4, OCH_2CH_2), 2.00 (m, 2, $CH_2CH_2CH_2$); IR (KBr) 3521 s, 3185 s, 3115 s, 2976 s, 2890 s, 1597 s, 1567 sh, 1548 sh, 1479 s, 1447 m, 1420 m, 1368 s, 1330 s, 1289 s, 1261 s, 1135 m, 1104 s, 1066 s, 1046 s, 997 w, 958 w, 892 m, 847 s, 822 m, 796 m, 727 s, 714 s, 682 w, 663 m, 643 s cm^{-1}; mass spectrum, m/e 267 (29), 266 (38), 265 (59, P), 264 (21), 211 (21), 210 (21), 209 (21), 208 (25), 196 (21), 195 (38), 183 (17), 182 (29), 181 (29), 167 (17), 166 (25), 153 (22), 128 (21), 127 (48), 126 (25), 103 (15), 120 (38), 101 (100). Anal. Calcd for $C_9H_{10}B_2ClN_3O_3$: C, 40.75; H, 3.80; B, 8.15; Cl, 13.36; N, 15.84. Found: C, 40.95; H, 3.85; B, 8.45; Cl, 13.18; N, 15.60.

4-Amino-6-dihydroxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (8b). Anhydrous ammonia (22 mL) was distilled from sodium into a chilled (−78 °C) stainless steel bomb containing 4.0 g of 4,6-dichloro-5-[2,2-bis(ethylenedioxyboryl)vinyl]pyrimidine (**6b**) and a magnetic stirrer. The lower half of the vessel was heated in an oil bath at 75 °C and stirred for 2 days (~30 atm). The vessel was cooled to 25 °C and vented. The residue was dissolved in 600 mL of methanol and filtered, and the filtrate was treated with 20 mL of water and concentrated under vacuum to precipitate the microcrystalline product, yield 2.1 g (80%). This material was chromatographed on cellulose with 4:1 methanol/water and then found to give only one spot

with TLC on silica gel with dimethylformamide (R_f 0.9) or aqueous 80% methanol (R_f 0.8). Attempted recrystallization usually resulted in partial decomposition, as shown by TLC. The analytical sample was dried for 9 h at 0.1 Torr at 100 °C. The compound darkened above 240 °C but did not melt up to 400 °C; 100-MHz ^{1}H NMR (Me_2SO-d_6) δ 8.55 (s, 1, NCHN), 8.10 (s, 1, CH=CB_2), 7.64 (broadened s, 1, NH), 7.18 (broadened s, 1, NH), 3.42 (s, ~10, NH, BOH, and H_2O from solvent); on addition of methanol dropwise, the δ 7.64 peak broadened, shifted downfield, and disappeared, and the δ 7.18 peak broadened somewhat without shifting; ^{1}H NMR (CD_3OD) δ 8.31 (brd s, CH=CB_2), 8.20 (s, NCHN); IR (KBr) 3205 brd s, 1656 sh, 1587 s, 1477 s, 1456 s, 1395 sh, 1339 s, 1270 brd s, tapering off with some irregularities to 950, 909 m, 803 m, 722 s, 691 m cm^{-1}; UV (H_2O) 203 nm (ϵ 19 550), 233 (16 870), 284 (8850), 302 (10 700); UV (0.1 N HCl) 225 nm (ϵ 17 150), 283 (12 650), 300 (10 460); UV (0.1 N NaOH) 228 nm (ϵ 19 400), 288 (10 610). Anal. Calcd for $C_6H_8B_2N_4O_3$: C, 35.03; H, 3.92; B, 10.51; N, 27.22; mol wt 206. Found: C, 35.24, 35.08; H, 3.74, 3.92; B, 10.44; N, 27.15. 27.08; mol wt (dimethylformamide) 220, (methanol) 235.

4-Amino-6-trimethylenedioxyboryl-7-hydroxy-7,8-dihydro-7,8-borazaroquinazoline (8a). 4,6-Dichloro-5-[2,2-bis(trimethylenedioxyboryl)vinyl]pyrimidine (**6a**) was used in place of the ethylenedioxyboryl analogue **6b** in the procedure described for the preparation of **8b** Instead of methanol, the product was dissolved in 500 mL of chloroform, concentrated under vacuum to crystallize it, yield 70%, and recrystallized from chloroform and finally from toluene/absolute ethanol. The compound tenaciously retained 1 mol of chloroform, as shown by the persistent ^{1}H NMR peak at δ 8.35. After prolonged drying (56 °C, 30 h, 0.1 Torr) the NMR evidence of chloroform disappeared, but the analysis suggested the persistence of 7 mol % $CHCl_3$. The product did not melt at up to 300 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.92 (brd s, 1, NH), 8.44 (s, 1, NCHN), 8.05 (s, 1, CH=CB_2), 7.21 (brd s, 2, NH_2), 6.41 (s, 1, BOH), 4.07 (t, 4, OCH_2CH_2), 1.97 (m, 2, $CH_2CH_2CH_2$); IR (KBr) 3497 s, 3279 s, 3096 s, 2959 s, 1587 s, 1475 s, 1464 s, 1441 s, 1323 s, 1285 s, 1152 s, 1099 s, 1066 s, 961 m, 903 s, 838 m, 803 m, 745 s, 719 s, 692 s, 657 sh, 638 s cm^{-1}. Anal. Calcd for $C_9H_{12}B_2N_4O_3$ + 0.07 $CHCl_3$: C, 42.82; H, 4.78; B, 8.50; Cl, 3.02; N, 22.02 (calcd for $C_9H_{12}B_2N_4O_3$: C, 43.97; H, 4.92; B, 8.80; N, 22.79). Found: C, 42.44; H, 4.82; B, 8.47; Cl, 3.02; N, 21.91.

Acknowledgment. We thank Dr. James A. Magnuson for helpful discussions regarding the ^{13}C NMR spectra.

Registry No.—**2,** 5271-82-9; **3,** 64728-21-8; **4a,** 64705-53-9; **4b,** 64728-22-9; **5,** 5305-40-8; **6b,** 64705-54-0; **7a,** 64705-55-1; **7b,** 64705-56-2; **7c,** 64705-57-3; thiourea, 62-56-6; tetrakis(ethylenedioxyboryl)methane, 50485-33-1; tetrakis(trimethylenedioxyboryl)methane, 42495-90-9; tris(ethylenedioxyboryl)methane, 59278-44-3.

References and Notes

(1) Supported by Public Health Service Grant No. CA-05513 from the National Cancer Institute. Funds for the purchase of the Bruker WH-90 NMR spectrometer were provided in part by National Science Foundation Grant No. MPS75-06301.
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Reaction of Tertiary Glycidamides with Boron Trifluoride Etherate. Evaluation of the Potential for Rearrangement with Amide Group Migration[1]

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Received August 8, 1977

The reaction of a series of tertiary glycidamides with boron trifluoride etherate in benzene, methylene chloride, or chloroform was studied. The major process observed with (*E*)- and (*Z*)-*N,N*-diphenyl-3-phenylglycidamides (**1a,b**) as well as (*E*)- and (*Z*)-*N,N*-diphenyl-3-methyl-3-phenylglycidamides (**1c,d**) was stereospecific intramolecular Friedel–Crafts cyclization to give the corresponding 1,4-diphenyl-3-hydroxy-2(1*H*)-quinolinones (**2**). A similar reaction was observed in the rearrangement of (*E*)-*N*-phenyl-*N*-methyl-2-methyl-3-phenylglycidamide (**1g**), although condensation with benzene solvent was also found in this case. The reaction of *N,N*-dialkyl-3-methyl-3-phenylglycidamides (**1e,f**) with boron trifluoride etherate led to formation of the corresponding *N,N*-dialkyl-2-hydroxy-3-phenyl-3-butenamides (**5d,f**). Finally (*E*)- and (*Z*)-*N,N*-dimethyl-2-methyl-3-phenylglycidamides (**1h,i**) gave fluorohydrin (**7a**) along with its BF_2 derivative (**7b**). Under more severe conditions **1i** was converted to *N,N*-dimethyl-2-phenylacetoacetamide (**9**), the product anticipated from amide group migration, along with *N,N*-dimethyl-3-phenyl-3-methylpyruvamide (**8**), formed by α-methyl migration.

Since House's[2] discovery of ketone migration in the boron trifluoride induced rearrangement of α,β-epoxy ketones, attention has been given to studies of rearrangement of various other α,β-epoxy carbonyl systems, including glycidic esters,[3] glycidic thiol esters,[4] and α,β-epoxy diazo ketones.[5] The reaction is of some mechanistic interest[2-4,6] in that it involves migration of an electron-deficient carbonyl carbon to a positive migration terminus. Recent work suggests that the

0022-3263/78/1943-0954$01.00/0