TABLE III

DERIVATIVES OF 7-(DIALKYLAMINOALKYL)-BENZO[c]PHENOTHIAZINES

7-(Dialkylamino-alkyl group	—R in structure VIII— R_1	R_2	R_3	R_4	Derivative	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_2N(CH_3)_2$	H	H	H	H	Methiodide[b]	231–233	$C_{21}H_{23}IN_2S$	54.54	54.50	5.01	4.84	6.06	5.95
									54.49		5.23		5.70
$-(CH_2)_2N(CH_3)_2$	H	H	H	H	Picrate[c]	222–224	$C_{26}H_{23}N_5O_7S$					12.74	12.60
													12.95
$-(CH_2)_2N(C_2H_5)_2$	H	H	H	H	Picrate[c]	152.5–153.5	$C_{28}H_{27}N_5O_7S$					12.13	12.05
													12.20
$-(CH_2)_3N(CH_3)_2$	H	H	H	H	Methiodide[b]	238.5–240	$C_{22}H_{25}IN_2S$	55.46	55.31	5.29	5.66	5.88	5.61
$-(CH_2)_3N(CH_3)_2$	H	H	H	H	Picrate[c]	177–178	$C_{27}H_{25}N_5O_7S$					12.43	12.35
													12.60
$-(CH_2)_3N(CH_3)_2$	H	H	CH_3	H	Methiodide[b]	243–244	$C_{23}H_{27}IN_2S$	56.32	56.24	5.55	5.26	5.71	5.50
									56.21		5.56		5.60
$-(CH_2)_3N(CH_2)_2$	H	Cl	H	H	Methiodide[b]	217–218.5	$C_{22}H_{24}ClIN_2S$	51.72	51.87	4.74	4.81	5.48	5.46
									51.58		4.61		5.54
$-(CH_2)_3N(CH_3)_2$	CH_3	H	H	CH_3	Methiodide[a]	237–238.5	$C_{24}H_{29}IN_2S$	57.14	56.88	5.79	5.61	5.55	5.44
									57.03		5.65		5.72

[a] This compound when simply washed with ether gave the above m.p. and analysis. When recrystallized twice from 95% ethanol–ether the methiodide melted at 251–252.5° and gave the analysis: Calcd. for $C_{24}H_{29}IN_2S$: C, 57.14; H, 5.79; N, 5.55. Found: C, 57.78; H, 5.95; N, 5.19. [b] Recrystallization was from 95% ethanol–ether mixture. [c] Recrystallization was from 95% ethanol.

toluene in the presence of freshly-prepared sodamide gave the desired 7-(dialkylaminoalkyl)-benzo[c]phenothiazines (VIII) in yields of 40–63% (Table II). The N-alkylated benzophenothiazines are highly viscous yellow or yellow-orange oils with a green fluorescence. Picrate derivatives or quaternary salts with methyl iodide were prepared for further characterization and are listed in Table III.

The compounds prepared in this investigation are currently being tested by the Eli Lilly Co. of Indianapolis, Ind., for central nervous system effects and by the National Cancer Institute for anticancer activity. Significant results of these tests will be reported elsewhere.

Experimental

All melting and boiling point temperatures are uncorrected. Elemental microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England.

Preparation of N-Phenyl-β-naphthylamines (VI).—The secondary amines used as intermediates in this investigation were prepared using conventional condensation methods[9] with minor modifications. In general, a mixture of 1 mole of β-naphthol, 1.3 moles of the appropriately substituted aniline, and a catalytic amount of iodine was heated under reflux for 15–40 hours. The dark reaction mixture obtained was then fractionated *in vacuo* and the product recrystallized from an appropriate solvent.

Preparation of 7H-Benzo[c]phenothiazines (VII).—A mixture of the appropriate secondary amine (0.5 mole), sulfur (1.0 g. atom) and a small amount of iodine was heated at approximately 180° until the evolution of H_2S ceased (8 to 20 minutes). The dark sticky mass was recrystallized several times from benzene. In some instances chromatography of the dark reaction mixture in benzene solution on a 2 × 50 cm. column of Florisil adsorbent followed by elution with benzene aided in the purification. The 7H-benzo[c]-phenothiazines prepared in this manner are listed in Table I.

Preparation of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines (VIII).—A general procedure employed in preparation of these compounds will be described. Sodamide (0.55 mole) (freshly prepared from sodium and liquid ammonia using a trace of ferric nitrate as catalyst) was covered with about 50 ml. of dry xylene or toluene. To this solution was added the appropriate benzo[c]phenothiazine (0.5 mole) and the resulting wine or red-colored solution was refluxed for one hour. To this refluxing solution was added the dialkylaminoalkyl chloride (0.7 mole) in 25 ml. of xylene or toluene over a period of 45 minutes. After complete addition of the chloride, the mixture was refluxed for a further period of 1–4 hours, the reaction mixture cooled, the product extracted with 4% HCl or 10% HOAc, the acid extracts combined, basified with NaOH pellets, and the dark oil which separated was extracted several times with ether. The combined ethereal extracts were dried over anhydrous Na_2SO_4, the ether removed, and the product vacuum distilled using a short Vigreux column. The 7-(dialkylaminoalkyl)-benzo[c]phenothiazines prepared in this manner are listed in Table II.

Acknowledgment.—The financial assistance of the National Institute of Mental Health (Grant M-1239) is gratefully acknowledged. The authors also wish to thank the Eli Lilly Co. for pharmacological evaluation of the compounds prepared in this investigation.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Organoboron Compounds. IX. 8-Quinolineboronic Acid, its Preparation and Influence on Reactions of Chlorohydrins[1]

BY ROBERT L. LETSINGER AND S. H. DANDEGAONKER

RECEIVED JULY 9, 1958

8-Quinolineboronic acid and several of its derivatives are described An unusual effect of 8-quinolineboronic on the rate of liberation of chloride ion from chlorohydrins is reported.

Organoboronic acids with basic functional groups located in the vicinity of the boron atom would be of particular interest since they might serve as selective catalysts for certain base-catalyzed reactions. As part of a general program concerned with catalytic properties of organoboron compounds we have therefore undertaken a study of hetero-

(1) This work was supported by the National Science Foundation. For the previous paper in this series see R. L. Letsinger and S. B. Hamilton, THIS JOURNAL, **80**, 5411 (1958).

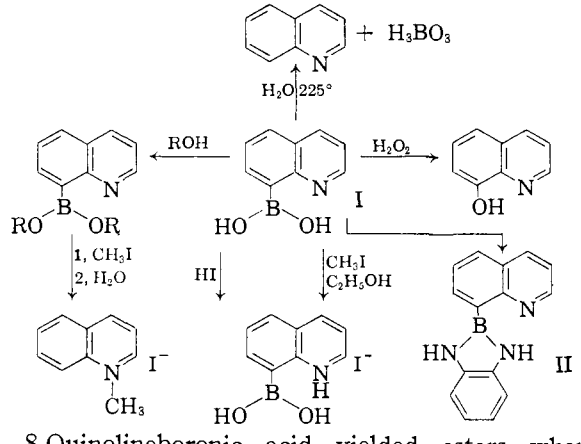
cyclic nitrogen bases which possess boronic acid groups. The preparation and some reactions of 8-quinolineboronic acid are described in this paper.

Very little information on boronic acid derivatives of nitrogen heterocyclic compounds has previously been available. Soddy attempted to prepare boronic acids by the reaction of butyl borate with 2-lithioquinoline, 3-lithioquinoline, 2-*p*-lithiophenylquinoline and 2-*m*-lithiophenylquinoline.[2] Only in the last case did he succeed in isolating a boronic acid.

8-Lithioquinoline was formed by a metal–halogen interchange between 8-bromoquinoline and butyllithium. The temperature was kept low (−78°) in order to minimize interaction of the organometallic compounds with the ammonoaldehyde system of quinoline. Reaction with butylborate, followed by hydrolysis, afforded a good yield of the desired 8-quinolineboronic acid (I). As expected for the functional groups present, compound I dissolved readily in dilute hydrochloric acid and in dilute sodium hydroxide solution, although it was only slightly soluble in water.

An attempt to prepare 6-quinolineboronic acid from 6-bromoquinoline by the same procedure was unsuccessful. No boronic acid was obtained and 82% of the initial 6-bromoquinoline was recovered. This result was not surprising since butyllithium–aryl bromide interchange reactions do not generally take place satisfactorily at −78°. It is likely that interchange is facilitated in the case of 8-bromoquinoline by coördination of butyllithium with nitrogen, which in 8-bromoquinoline is located near the bromine atom.

The structure of I was confirmed by conversion to 8-hydroxyquinoline with hydrogen peroxide, by the preparation of a dihydrobenzoboradiazole derivative (II)[1] by reaction with phenylenediamine, and by the isolation of a hydriodide. Water at 225° cleaved the carbon–boron bond to give quinoline and boric acid. At lower temperatures this bond was much more stable toward hydrolysis. Thus, the recoveries of samples of I which had been heated for 25 hours is aqueous 60% ethanol and aqueous 50% acetic acid amounted to 95 and 70% respectively.



8-Quinolineboronic acid yielded esters when heated with butanol and 2-chloroethanol in toluene; however, chloroethanol ionized in the presence of quinolineboronic acid in hot dimethylformamide solution, losing hydrogen chloride in the process. With refluxing methyl iodide the liquid butyl ester formed a solid, probably the methiodide. When subjected to the action of boiling water, this substance produced methylquinolinium iodide. Evidently the carbon–boron bond in the quaternary salt is more susceptible to hydrolytic cleavage than the carbon–boron bond in the free base. 8-Quinolineboronic acid was converted in high yield to the hydriodide when it was heated with methyl iodide in ethanol solvent. Under similar conditions quinoline gave methylquinolinium iodide.

The infrared spectra of 8-quinolineboronic acid and its derivatives were particularly interesting in the 7–8 μ region. Generally boronic acids and alkyl esters exhibit a very strong band at about 7.4–7.5 μ,[3] independently of whether the sample is dispersed in a potassium bromide plate or dissolved in chloroform. Absorption in this region is much weaker for amino derivatives, such as the diethanolamine esters of the boronic acids and the ethanolamine esters of the borinic acids. It has been suggested that this decreased absorption is a consequence of complexation involving nitrogen and boron.[1] The spectra of 8-quinolineboronic acid and its chloroethyl ester which were taken in potassium bromide resembled the spectra of the aminoalkyl esters in that only a weak band at 7.6 μ was evident. In chloroform solution, however, both compounds showed a dominant band at 7.45 μ. As a tentative explanation we suggest that intermolecular boron–nitrogen association is important in 8-quinolineboronic acid and its ester in the solid state, but that it is not important when these substances are dissolved in chloroform. In agreement with this idea, the liquid dibutyl ester IIIa absorbed in chloroform very strongly at 7.45 μ, and the hydriodide of 8-quinolineboronic acid, for which boron–nitrogen association is not possible, in potassium bromide showed a strong band at 7.5 μ.

Effect of I on Reactions of Chlorohydrins.—In connection with possible catalytic applications, it was desirable to determine whether the boronic acid group in a substance such as 8-quinolineboronic acid would facilitate a reaction involving the nearby nitrogen atom and a functional group of a substrate. Suitable substrates for such substances would include substituted alcohols, which could be reversibly bound to boron by esterification or complexation.

As a test of this point a comparison was made of the reactivity of three chlorohydrins, 2-chloroethanol, 3-chloro-1-propanol and 4-chloro-1-butanol, in dimethylformamide solution in the presence of 8-quinolineboronic acid and quinoline. The quantity of each of the chlorohydrins and added components was 8.00 mmoles. Dimethylformamide was added to make the total volume of each solution 50.0 cc. and the temperature was maintained at 90.0 or 89.3°. At intervals 5.00 cc. aliquots were removed, added to dilute nitric acid, and titrated by the Volhard procedure.

(2) T. S. Soddy, *Diss. Abstr.*, **17**, 2826 (1957).

(3) R. L. Werner and K. G. O'Brian, *Aust. J. Chem.*, **8**, 355 (1955); S. H. Dandegaonker, W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 2872 (1957).

As shown in Table I, the rate of liberation of chloride ion was very slow for 2-chloroethanol (experiments 1,2), 3-chloro-1-propanol (5,6) and 1-chloropentane (8,9) in dimethylformamide in the presence or absence of quinoline. It was also slow for 2-chloroethanol with an equimolar mixture of quinoline and benzeneboronic acid (3) and for a solution containing 1-chloropentane, 1-butanol and 8-quinolineboronic acid (10). On the other hand, the reactions of 2-chloroethanol (4) and 3-chloropropanol (7) in the presence of 8-quinolineboronic acid were, relative to the former reactions, fast ones (see Fig. 1 for further details). 8-Quinolineboronic acid increased the initial rate of formation of chloride ion from chloroethanol by a factor of about 60.

TABLE I

CHLORIDE ION FORMATION AT 90.0° IN DIMETHYLFORMAMIDE[a]

Expt.	Halide (8.00 mmoles)	Added component (8.00 mmoles each)	Reaction after 24 hr., %
1	2-Chloroethanol	....	4.0
2	2-Chloroethanol	Quinoline	4.3
3	2-Chloroethanol	Quinoline + Benzeneboronic acid	3.4
4	2-Chloroethanol	8-Quinolineboronic acid	44.3
5	3-Chloro-1-propanol	....	2.9
6	3-Chloro-1-propanol	Quinoline	3.6
7	3-Chloro-1-propanol	8-Quinolineboronic acid	44.5
8	1-Chloropentane	....	3.6
9	1-Chloropentane	Quinoline	2.2
10	1-Chloropentane	8-Quinolineboronic acid + 1-Butanol	3.5

[a] Volume of solution, 50.0 cc.

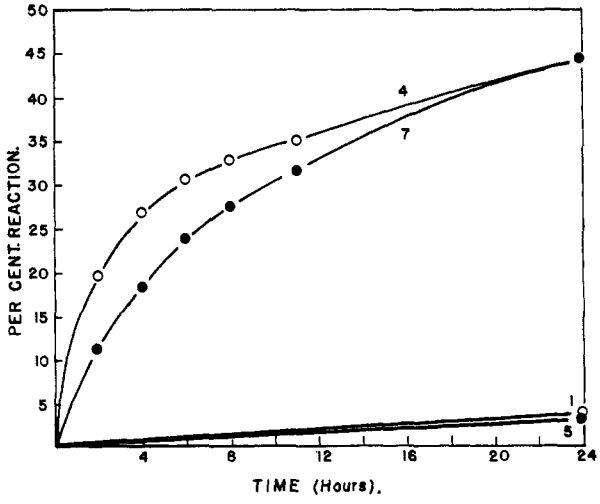


Fig. 1.—Chloride ion formation from 2-chloroethanol, O, and 3-chloro-1-propanol, ●, in dimethylformamide. Reactions 4 and 7 had 8-quinolineboronic acid added.

The essential structural features for an accelerated reaction therefore appear to be: (1) a basic functional group (heterocyclic nitrogen in this case), (2) a boronic acid group situated near the basic group and (3) an hydroxyl group in the halide molecule. These features are consistent with the concept that the chlorohydrin is initially bound to boron by esterification or complexation, and that within this intermediate the basic nitrogen assists in the reaction leading to formation of chloride ion.

Information relative to 4-chlorobutanol is summarized in Fig. 2. The first-order rate constant for 4-chlorobutanol in dimethylformamide, k = 0.09 hr.$^{-1}$, is of the order of 60–80 times greater than the rate constants for chloroethanol and chloropropanol. An enhanced rate was to be expected because chlorobutanol is known to hydrolyze 220 times as fast as 3-chloro-1-propanol in aqueous solution,[4] a result explained on the assumption that the chlorobutanol reaction proceeds *via* a five-membered cyclic transition state with intramolecular displacement of chloride by the hydroxyl group.[4] Quinoline had very little effect on the reaction of 4-chlorobutanol in dimethylformamide (Fig. 2), however benzeneboronic acid reduced the rate by a factor of two, as might be expected since the boronic acid should tie up the alcohol groups by esterification and thereby interfere with the intramolecular displacement. In contrast, 8-quinolineboronic acid doubled the rate of the chlorobutanol reaction[5] even though an equimolar mixture of quinoline and benzeneboronic acid behaved like benzeneboronic acid alone. 8-Quinolineboronic acid, therefore, accelerates the reaction of chlorobutanol as well as that of chloroethanol and chloropropanol.

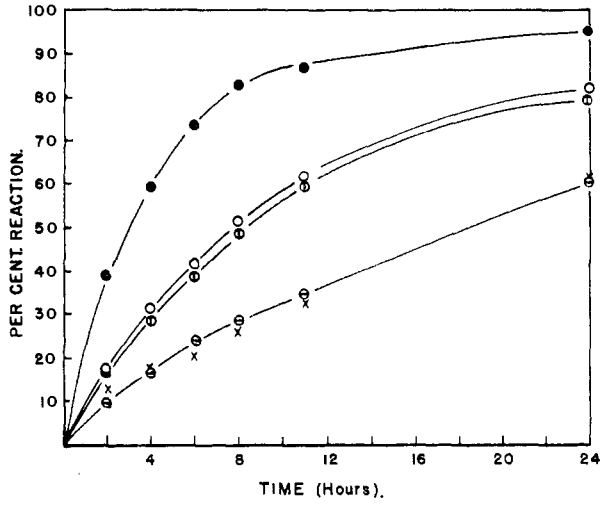


Fig. 2.—Rate of chloride ion formation from 4-chlorobutanol (8.00 mmoles) in dimethylformamide solution (50 cc.) at 89.3°. The points correspond to reactions with the following added components: O, none; ⊙, quinoline; ⊖, quinoline + benzeneboronic acid; ×, benzeneboronic acid; ●, 8-quinolineboronic acid.

It is the purpose of this paper to demonstrate that 8-quinolineboronic acid has an unusual influence on the reactions of chloroalcohols. The mechanisms of these reactions will be the subject of later studies. At this time, however, it may be noted that hydrogen chloride is liberated in the reactions involving 8-quinolineboronic acid. For example, titration of an aliquot taken from reaction 4 (8-quinolineboronic acid and chloroethanol)

(4) H. W. Heine, A. D. Miller, W. H. Barton and R. W. Graine, THIS JOURNAL, **75**, 4778 (1953).

(5) The reaction of chlorobutanol in the presence of quinolineboronic acid was continued to a time of 100 hours in order to get a value for an effective "infinite" time. The per cent. reaction corresponding to this time, as determined by titration of chloride ion, was 97.2%.

at the end of 24 hours consumed sodium hydroxide equivalent in moles to 80% of the liberated chloride ion. Furthermore, 80% of the original 8-quinolineboronic acid was recovered from the neutralized solution. A mechanism involving esterification of the alcohol followed by intramolecular displacement of chloride by nitrogen therefore seems unlikely, at least insofar as the major reaction is concerned.

Experimental Part[6]

8-Quinolineboronic Acid.—A solution of 8-bromoquinoline (18 g., 0.087 mole) in 60 cc. of ether was cooled to −39° and added over a period of 20 minutes to an ether solution of butyllithium (0.216 mole) which had been cooled to −78° After a subsequent 30-minute period of stirring at this temperature, tributyl borate (76 g., 0.33 mole) in 100 cc. of ether at −39° was dropped in (20-minute period). The reaction mixture was stirred for another two hours, then allowed to warm to room temperature overnight. Cold, dilute hydrochloric acid was then added, the ether layer separated, and the aqueous layer neutralized with sodium bicarbonate. 8-Quinolineboronic acid precipitated. It was filtered off, washed, dried, and recrystallized from alcohol; m.p. higher than 300°, yield 11.85 g. (79%). The principal bands in the infrared spectrum occurred at 3.0, 6.3, 6.7, 7.3, 8.0, 8.6, 8.9, 10.5, 11.9 and 12.7 μ.

Oxidation of I.—8-Quinolineboronic acid (0.65 g.) was dissolved in 15 cc. of acetic acid and 7 cc. of water and treated with 15 cc. of 30% hydrogen peroxide at room temperature. On dilution with water and neutralization with sodium bicarbonate, 8-hydroxyquinoline (0.415 g., 76%, m.p. 69–70°) separated out as needles.

Hydrolysis of I.[7]—The boronic acid (0.630 g.) was heated with 0.5 g. of water for 36 hours at 225° in a sealed tube. Extraction of the products with ether yielded quinoline, identified as its methiodide (97% yield based on I, characterized by infrared spectrum and melting point; m.p. and mixed melting point with an authentic sample, 133–134°).

The aqueous filtrate on evaporation to dryness afforded boric acid (0.164 g., 73%).

Phenylenediamine Derivative of I.—The boronic acid (0.358 g.) and an equimolar amount of *o*-phenylenediamine (0.23 g.) were heated in refluxing benzene (50 cc.). The benzene was then removed by distillation and the residual solid recrystallized from carbon tetrachloride to give 0.50 g. (96%) of II, m.p. 188–189°. The infrared spectrum had peaks at 2.85 and 6.95 μ characteristic of the dihydrobenzoboradiazole system.[1]

Anal. Calcd. for $C_{15}H_{12}BN_3$: N, 17.15. Found: N, 17.08.

(6) All nitrogen analyses by Miss H. Beck.

(7) Method of E. W. Abel, W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 1451 (1958).

8-Quinolineboronic Acid Hydriodide.—The hydroiodide, prepared from the boronic acid and hydriodic acid in 92% yield, melted at 166–168° and titrated as a dibasic acid. (The amine salt was titrated with sodium hydroxide; subsequently mannitol was added and the addition of sodium hydroxide continued in order to titrate the boronic acids.)

Reaction of 8-Quinolineboronic Acid with Methyl Iodide.—A solution containing 13.0 g. of methyl iodide, 2.70 g. of 8-quinolineboronic acid and 200 cc. of absolute ethanol was refluxed for 15 hours. Concentration of the solution yielded 4.30 g. of a yellow solid product identical with the hydriodide prepared directly from hydrogen iodide; yield 92%, m.p. 166–168°. The analytical sample, prepared by recrystallization from ethanol, melted at 168–169°.

Anal. Calcd. for $C_9H_9O_2BNI$: B, 3.60; N, 4.66. Found: B, 3.64; N, 4.82.

By way of comparison, a solution containing 3.25 g. of quinoline, 14.85 g. of methyl iodide and 50 cc. of ethanol was refluxed for 18 hours. Removal of the solvent left 6.78 g. (99.6%) of crude product, which on recrystallization melted at 133° and had an infrared spectrum identical with that of methylquinolinium iodide.

Butyl 8-quinolineboronate was prepared by azeotropic distillation of a solution of 10 g. of *n*-butyl alcohol, 2.9 g. of 8-quinolineboronic acid and 60 cc. of benzene. Vacuum distillation of the residue yielded 2.8 g. (59%) of butyl 8-quinolineboronate, b.p. 180° (4 mm.), $n^{25}D$ 1.4840.

Anal. Calcd. for $C_{17}H_{24}O_2BN$: B, 3.79; N, 4.91. Found B, 3.6; N, 5.24.

Methiodide of Butyl 8-Quinolineboronate.—A solution of 5 g. of methyl iodide and 4.93 g. of butyl 8-quinolineboronate was warmed on a steam-bath for 12 hours; volatile material was then removed at reduced pressure, and the residue washed with ether and pentane. The hygroscopic solid which remained (7.10 g., 96%, m.p. 70–75°) titrated with alkali in the presence of mannitol as expected for butyl 8-quinoline-boronate methiodide; neut. equiv. found 420, calcd. 434. A sample of this product (2.21 g.) was subjected to steam distillation to remove butanol. Evaporation of the water left quinoline methiodide, 1.81 g. (91%), m.p. 135–136° (the melting point was not depressed when the sample was mixed with an authentic sample).

Chlorohydrins.—2-Chloroethanol (Eastman Organic Chemicals) and 3-chloro-1-propanol (Matheson) were distilled to give samples boiling at 127° ($n^{20}D$ 1.4415) and 62° (13 mm.) ($n^{20}D$ 1.4470), respectively. 4-Chloro-1-butanol, b.p. 85° (16 mm.), $n^{20}D$ 1.4520, was obtained by distillation of Eastman practical grade material.

Chloroethyl 8-Quinolineboronate.—A solution of 40 cc. of toluene, 5 g. of 2-chloroethanol and 0.82 g. of 8-quinolineboronic acid was partially distilled. On cooling, 1.31 g. (93%) of a solid ester separated, m.p. 193–194° after recrystallization from toluene.

Anal. Calcd. for $C_{13}H_{14}O_2NCl_2B$: B, 3.63; N, 4.70. Found: B, 3.69; N, 4.73.

EVANSTON, ILL.

COMMUNICATIONS TO THE EDITOR

PRESSURE-AREA ISOTHERM FOR STEARIC ACID SPREAD WITHOUT SOLVENT

Sir:

In film-balance studies of monolayers of fatty acids and related materials, volatile solvents generally are used to aid in the spreading process. Solvents also permit accurate measurement of small quantities of monolayer-forming substances. Possible influences of such solvents on monolayers, however, are still not clear.[1,2,3] To clarify this point, pressure–area isotherms have now been obtained for stearic acid spread without solvent.

(1) R. J. Archer and V. K. LaMer, *J. Phys. Chem.*, **59**, 200 (1955); H. S. Rosano and V. K. LaMer, *ibid.*, **60**, 348 (1956); V. K. LaMer and M. L. Robbins, *ibid.*, **62**, 1291 (1958).

(2) G. P. Semeluk, J. W. V. Hahn and J. L. Morrison, *Can. J. Chem.*, **34**, 609 (1956).

(3) H. D. Cook and H. E. Ries, Jr., *J. Phys. Chem.*, **60**, 1533 (1956).