**Table I.** Conversion of Olefins into Substituted Aldehydes by the Reaction of the Corresponding Organoboranes with 2-Substituted Acroleins

| Olefin | Product | Bp, °C (mm) | Yield, % Glpc | Yield, % Pmr | Yield, % isolated | Derivative,[c] mp, bp °C (mm) |
|---|---|---|---|---|---|---|
| 1-Butene[a] | 2-Bromoheptanal | 90 (16) | | 100 | 85 | DEA,[d] 74 (0.6) |
| 2-Butene[a] | 2-Bromo-4-methylhexanal | 60 (4.8) | | 90 | 81 | DEA,[d] 66 (0.8) |
| Isobutylene[a] | 2-Bromo-5-methylhexanal | 56 (4.0) | | 100 | 80 | DEA,[d] 64 (0.5) |
| Cyclohexene[a] | 2-Bromo-3-cyclohexylpropanal | 69 (0.8) | | 90 | 65 | DEA,[d] 98 (0.8) |
| 2-Butene[b] | 2,4-Dimethylhexanal | 84 (25) | 100 | | 95 | DNP,[e] 96.5–97.0 |
| Isobutylene[b] | 2,5-Dimethylhexanal | 66 (16) | 100 | 100 | 95 | DNP,[e] 101.5–102 |
| Cyclohexene[b] | 2-Methyl-3-cyclohexylpropanal | 99 (17) | 100 | | 92 | DNP,[e] 144–145 |
| Norbornene[b] | 2-Methyl-3-norbornylpropanal | 110 (17) | 100 | | 97 | DNP,[e] 144.5–145 |

[a] Reaction of $R_3B$ with 2-bromoacrolein. [b] Reaction of $R_3B$ with 2-methylacrolein. [c] Satisfactory analyses for all derivatives. [d] DEA = diethyl acetal. [e] DNP = 2,4-dinitrophenylhydrazone.

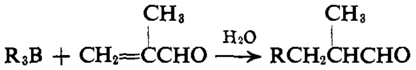
in the literature,[3] it proved to be impossible to prepare the 2,4-dinitrophenylhydrazones by the usual procedures. However, conversion to the corresponding diethyl acetals was convenient, and the products could be readily analyzed and stored as such.

In representative experiments involving the reaction of organoboranes with 2-bromoacrolein, analysis of the reaction mixture by pmr, before the addition of water, revealed the complete absence of either bromoacrolein or α-bromo aldehyde. However, immediately following the addition of water, the pmr spectrum revealed an essentially quantitative yield of α-bromo aldehyde. This confirms the earlier conclusion that the reaction must involve a 1,4 addition of the organoborane to the conjugated system to produce an enol borinate which is hydrolyzed by the water to the free aldehyde.[4,5]

The following procedure is representative for the synthesis of α-bromo aldehydes. A 100-ml flask fitted with an inlet carrying a rubber septum cap, a magnetic stirring bar, and a condenser was flushed with nitrogen. In the flask was placed 50 mmol of borane in 25 ml of tetrahydrofuran solution at room temperature. Then 150 mmol of cyclohexene in 20 ml of tetrahydrofuran was added, and the mixture was stirred at 50° for 3 hr to complete formation of the tricyclohexylborane.[6] Then 4.1 ml (50 mmol) of 2-bromoacrolein[7] was added. The reaction was exothermic and the temperature rose spontaneously to 40°. After cooling to room temperature, 0.95 ml (50 mmol) of water was added and stirred for 15 min. Benzene was added as an internal standard. Pmr examination indicated a yield of 90%. Distillation gave 7.2 g (65%) of 2-bromo-3-cyclohexylpropanal, bp 68–69° (0.8 mm). The product, 5.5 g (25 mmol), was dissolved in 25 ml of tetrahydrofuran, 4.6 ml (30 mmol) of triethyl orthoformate was added, followed by one drop of methanesulfonic acid.[8] The solution was refluxed for 0.5 hr. Distillation yielded 6.0 g (85%) of the diethyl acetal of 2-bromo-3-cyclohexylpropanal, bp 98° (0.8 mm).[9]

The results are summarized in Table I.

We also examined the feasibility of utilizing 2-methylacrolein (**2**). Again the reaction proceeded smoothly,



$$R_3B + CH_2{=}\overset{CH_3}{\overset{|}{C}}CHO \xrightarrow{H_2O} RCH_2\overset{CH_3}{\overset{|}{C}}HCHO \tag{2}$$

in excellent yield (Table I). The observation that both an electron-withdrawing group, such as bromine, and an electron-supplying group, such as methyl, can be accommodated in the 2 position of acrolein suggests that this synthetic route is a promising one of considerable generality.[10] It suffers from the disadvantage that only one of three alkyl groups on boron is utilized. However, we are achieving considerable success in overcoming this deficiency in the one-carbon homologation reaction[11] and in the two-carbon homologation reaction,[12] and we hope to find a solution to this problem for the present three-carbon homologation (propanalation) reaction.

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(3) For example, Bedoukian[1] reported that the 2,4-dinitrophenylhydrazone of 2-bromoheptanal had mp 106° and that the analysis for nitrogen was in agreement with the proposed formula. (No analyses for other elements were reported.) We also obtained a material with mp 105.5–106°. However, the analysis revealed the absence of bromine. Compare C. Stevens and B. Gillis, *J. Am. Chem. Soc.*, **79**, 3448 (1957).

(4) A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić, and M. W. Rathke, *ibid.*, **89**, 5708 (1967).

(5) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **89**, 5709 (1967).

(6) It should be pointed out that most other hydroborations go readily to completion at 25°, or even 0°.

(7) A. Berlande, *Bull. Soc. Chim. France*, **37** [4], 1385 (1925).

(8) In an alternative procedure, the triethyl orthoformate was added directly to the reaction mixture and the acetal was formed *in situ*. The residual organoboranes were then oxidized by hydrogen peroxide in the presence of excess sodium acetate and the product was distilled. This procedure results in somewhat higher recovery of the α-bromo diethyl acetal.

(9) For the α-methyl aldehydes, the procedure previously described[5] was followed except that the excess of 2-methylacrolein was reduced to 50%. Actually, the need for an excess has not yet been established. In the reactions involving 2-bromoacrolein, the theoretical quantity proved adequate to achieve nearly quantitative yields.

(10) However, crotonaldehyde and cinnamaldehyde failed to react with tri-*n*-butylborane under these conditions.

(11) H. C. Brown, R. A. Coleman, and M. W. Rathke, *J. Am. Chem. Soc.*, **90**, 499 (1968).

(12) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **90**, 818 (1968).

(13) Graduate research assistant on Grant GM 10937 from the National Institutes of Health.

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## Reaction of Organoboranes with Mannich Bases. A Convenient Procedure for the Alkylation of Cyclic and Bicyclic Ketones *via* Hydroboration

*Sir:*

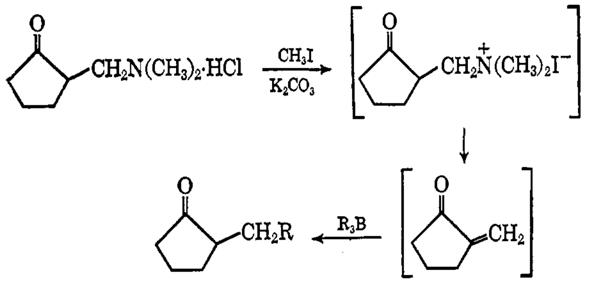
Mannich bases derived from cyclopentanone, cyclohexanone, and norbornanone, quaternized *in situ*, react smoothly in alkaline solution with organoboranes

**Table I.** Alkylation of Cyclic Ketones by Reaction of Organoboranes with the Corresponding Mannich Bases Quaternized *in Situ*

| Mannich base from ketone | Organoborane from olefin | Reaction time, hr | Product[a] | Yield, % Glpc | Yield, % Isol. | Properties, °C Bp (mm) | Properties, °C Mp DNP |
|---|---|---|---|---|---|---|---|
| Cyclopentanone | Ethylene[b] | 24 | 2-Propylcyclopentanone | 90 | 72 | 66 (15) | 148–149 |
| Cyclohexanone | Ethylene[b] | 12 | 2-Propylcyclohexanone[c] | 85 | | | |
| | 2-Butene | 48 | 2-(2-Methylbutyl)-cyclohexanone | 61 | 54 | 118 (17) | 65–75[d] |
| | Cyclopentene | 24 | 2-(Cyclopentyl-methyl)cyclopentanone | 90 | 85 | 78 (0.5) | 120.5–121 |
| Norbornanone | Ethylene[b] | 48[e] | 3-Propyl-norbornanone[f] | 94 | 90 | 108 (17) | 113–115 |

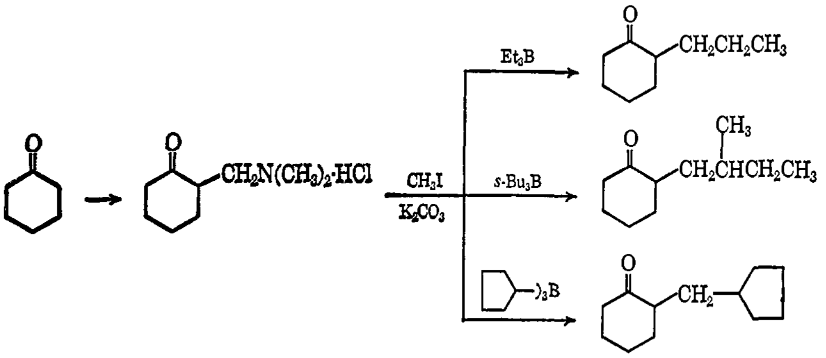
[a] All new products and their 2,4-dinitrophenylhydrazones gave satisfactory elemental analyses. [b] Commercial triethylborane was used. [c] Product compared directly with an authentic sample synthesized by established procedures. [d] Product is a mixture of diastereoisomers. [e] Reaction carried out in refluxing tetrahydrofuran. [f] Stereochemistry not established.

to produce the corresponding alkylated ketones. The reaction presumably proceeds through the 1,4 addition of the organoborane to the $\alpha,\beta$-unsaturated carbonyl compound[1-3] formed as a labile intermediate (eq 1).



(1)

A wide variety of cyclic ketones are readily converted to the corresponding Mannich bases *via* the Mannich reaction.[4] Consequently, this development offers a simple technique for the alkylation of such ketones without the necessity of preparing and isolating the highly reactive, unstable $\alpha$-methylene derivatives.



(2)

(3)

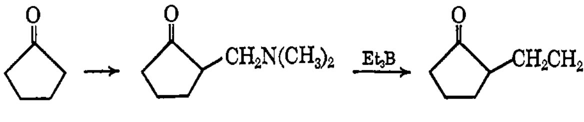
(4)

The facile reaction of organoboranes with $\alpha,\beta$-unsaturated carbonyl derivatives, such as methyl vinyl ketone,[1] acrolein,[2] $\alpha$-methylacrolein,[3] and $\alpha$-bromoacrolein,[3] offers a convenient synthesis of a wide variety of substituted aldehydes and ketones. These reagents are all readily available and easily handled. Unfortunately, many other such derivatives are exceedingly difficult to synthesize and difficult to isolate and utilize.

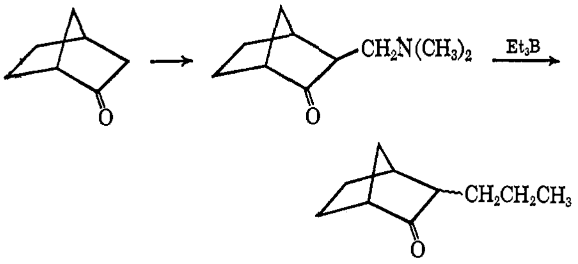
Robinson had previously overcome a similar difficulty in the Michael addition by the use of Mannich bases for the generation *in situ* of the reactive $\alpha,\beta$-unsaturated carbonyl compound.[5] Accordingly, we decided to test this possibility.

Cyclohexanone was readily converted into 2-(dimethylaminomethyl)cyclohexanone hydrochloride. The salt, dissolved in water, was added to tetrahydrofuran containing the organoborane. Then methyl iodide and aqueous potassium carbonate were added and the reaction was allowed to proceed. Triethylborane produced 2-*n*-propylcyclohexanone in a yield of 85% (eq 2). Similarly, tri-*sec*-butylborane and tricyclopentylborane produced 2-(2-methylbutyl)cyclohexanone (eq 3) and 2-(cyclopentylmethyl)cyclohexanone (eq 4) in isolated yields of 58 and 85%.

The generality of the reaction is indicated by the observation that the Mannich bases from cyclopentanone and norbornanone also readily undergo the reaction (eq 5, 6). The results are summarized in Table I.



(5)



(6)

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(1) A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić, and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 5708 (1967).

(2) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **89**, 5709 (1967).

(3) H. C. Brown, G. W. Kabalka, M. W. Rathke, and M. M. Rogić, *ibid.*, **90**, 4165 (1968).

(4) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

(5) J. H. Brewster and E. L. Elid, *ibid.*, **7**, 99 (1953).

The following procedure for the conversion of cyclohexanone to 2-(cyclopentylmethyl)cyclohexanone is representative. A dry 1-l. flask equipped with a water condenser, septum inlet, pressure-equalizing dropping funnel, and magnetic stirrer was flushed with nitrogen and then maintained under a static pressure of the gas. The preparation of tricyclopentylborane was achieved by the dropwise addition of 100 ml of a 2 *M* solution of borane (0.2 mol) in tetrahydrofuran to the flask containing a solution of 53.2 ml (0.06 mol) of cyclopentene in 100 ml of tetrahydrofuran. The solution was stirred for 1 hr at room temperature, and then 100 ml of a water solution containing 19.2 g (0.1 mol) of 2-(dimethylaminomethyl)cyclohexanone hydrochloride was added. Quaternization was achieved by adding 14 ml (0.22 mol) of methyl iodide, followed by the addition of 33.3 ml of 3 *M* solution of potassium carbonate (0.1 mol). The reaction mixture was stirred at room temperature for 24 hr to complete the reaction. *n*-Octane was added as an internal standard. Glpc analysis indicated a 90% yield. The tetrahydrofuran layer was separated and washed once with water saturated with sodium chloride. The residual organoboranes were oxidized[6] by the addition of 66 ml of 3 *M* sodium hydroxide followed by dropwise addition of 55 ml of 30% hydrogen peroxide, while the temperature was maintained under 40°. Distillation at reduced pressure gave 16 g (85%) of 2-(cyclopentylmethyl)cyclohexanone, bp 78° (0.5 mm).

Many types of organic molecules with reactive $\alpha$ positions are readily converted into Mannich bases.[4,5] This suggests the possibility that the present reaction may make it possible to achieve the alkylation of many other such derivatives *via* organoboranes. We continue to explore these developments.

[6] This conversion of the dialkylborinic acid to boric acid and the alcohols greatly simplified the distillation to isolate the product.

[7] National Science Foundation Postdoctorate Fellow at Purdue University, 1967–1968.

[8] Graduate research assistant on Grant GM 10937 from the National Institutes of Health.

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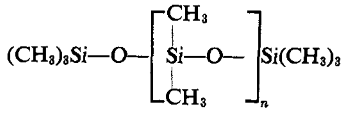
## Far-Ultraviolet Optical Activity of Crystals in Mulls. I. Cystine[1]

*Sir:*

In studying the correlation of the screw sense of aliphatic disulfides with the signs of their circular dichroic bands, we have measured the untraviolet circular dichroism (CD) spectra of several forms of crystalline cystine to 190 m$\mu$.

Several papers have reported ORD and CD spectra of cystine and derivatives of cystine in solution,[2–4] but the interpretation of results in terms of inherent or induced asymmetry has been hindered by uncertainty concerning rotational equilibration about the disulfide bond. A recent report by Carmack and Neubert on disulfides stereospecifically constrained within rings has shown that the longest wavelength CD band was oppositely signed in rings having opposite disulfide handedness.[5] The crystalline materials were examined because X-ray diffraction studies show that, while hexagonal L-cystine crystallizes with the disulfide as a left-handed screw,[6,7] the dihydrochloride has opposite chirality.[8,9] Corresponding bands due to inherent asymmetry of the two materials should, therefore, have opposite signs.

The method requires that samples be suspended in a chemically inert medium having little or no ultraviolet absorption and no optical activity of its own. These requirements are met by a silicon polyether called SE-30,[10] which has the formula



$$(CH_3)_3Si{-}O{-}\left[\begin{matrix}CH_3\\ |\\ Si{-}O{-}\\ |\\ CH_3\end{matrix}\right]_n Si(CH_3)_3$$

The technique involves placing a small amount (50–75 mg) of mulling matrix on a glass surface; an overturned beaker is suitable. If necessary, the material is pressed flat with a spatula, and the sample of crystals (2–10 mg) is spread onto it. The mixture is then alternately rolled and kneaded with the spatula until a uniform distribution of crystals is obtained. It is next rolled into a ball if possible and placed at the center of the outer window of an involuted cylindrical cell. A second cell is now pressed onto the first, squeezing the mixture out into a thin, flat layer between them. The whole assembly is finally placed in the appropriate instrument.

Microscopic examination showed that the crystals were often oriented in a nonrandom manner. Linear dichroism artifacts arising from this were tested for by pulverizing the samples with an agate mortar and pestle; the very small crystals that resulted were oriented more randomly when made into mulls. These mulls, however, scattered so much of the input light that measurements at short wavelengths became impossible. The scattering was reduced by mixing 60% spectroanalyzed dodecane ($n$-$C_{12}H_{26}$) with 40% SE-30. The mixture is prepared by dissolving 0.4 g of silicone in spectroanalyzed methylene chloride or spectroanalyzed chloroform, pipetting in 0.6 g of dodecane, and, after mixing, removing solvent in a stream of dry nitrogen. When as much of it has been removed as seems possible by this method, the mixture is evacuated at room temperature for about 5 min. Care must be taken to avoid loss of dodecane through excessive exposure to low pressure. Solvent removal is considered complete when no odor of it is detected after brief, gentle warming followed by a few minutes of standing.

The materials whose spectra are reported in Figures 1 and 2 are hexagonal plates of D- and L-cystine, L-cystine dihydrochloride, which crystallizes as long white

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[1] This work was supported in part by grants from the U. S. Public Health Service (Research Grant No. GM 10576) and from the National Science Foundation (Research Grant No. GB 7128).

[2] E. Iizuka and J. T. Yang, *Biochemistry*, 3, 1519 (1964).

[3] S. Beychok, *Proc. Nat. Acad. Sci. U. S.*, 53, 999 (1965).

[4] D. L. Coleman and E. R. Blout, *J. Amer. Chem. Soc.*, 90, 2405 (1968).

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[7] B. M. Oughton and P. Harrison, *ibid.*, 12, 396 (1959).

[8] A. F. Corsmit, A. Schuyff, and D. Feil, *Koninkl Ned. Akad. Wetenschap, Proc.*, B59, 470 (1956).

[9] L. K. Steinrauf, J. Petersen, and L. H. Jensen, *J. Amer. Chem. Soc.*, 80, 3835 (1958).

[10] The substance is marketed as a stationary phase in gas chromatography by the Pierce Chemical Co., Rockford, Ill.