QUINUCLIDINE·BORANES AS INTERMEDIATES IN FORMATION AND ISOLATION OF FUNCTIONALIZED QUINUCLIDINE SYSTEMS ‡

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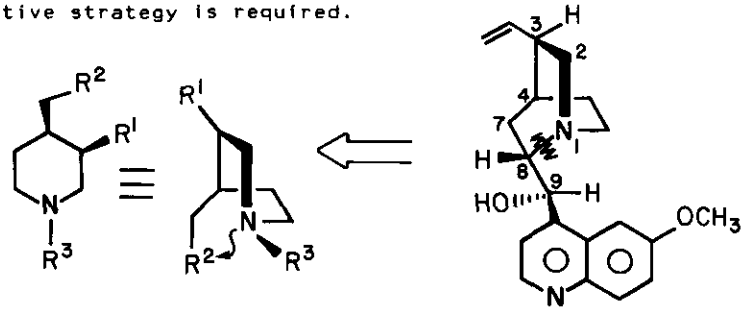
Abstract - Stable N-borane complexes of quinuclidine systems are useful both as N-protected intermediates (in alkylation and hydroboration/oxidation reactions) and as derivatives which facilitate isolation/purification and subsequent characterization. Deprotection is readily effected using acidic oxidation of hydride.

An observation made by Gilbert Stork‡ some years ago prompted the studies reported in this and the following communication. He noted in passing that, since Rabe's work of 1918,[2] no successful approach to the stereocontrolled construction of Cinchona alkaloid skeletons containing an intact, polyfunctionalized quinuclidine has utilized synthetic strategy other than a late stage closure of the substituted quinuclidine moiety (via N-1/C-8 bond formation). All total syntheses reported to date[3] have incorporated construction of a cis-3,4-disubstituted piperidine[4] as a requisite part of the strategy for generating the functionalized quinuclidine. However, methodology for enantioselection or resolution with effective recycling of the unwanted enantiomer is not readily compatible with known methods for the preparation of enantiomer-pure 3,4-disubstituted piperidines. Thus, full consideration of Professor Stork's observation logically implies that a successful strategy for completely stereocontrolled total synthesis of alkaloids containing substituted quinuclidines (such as quinine or quinidine) is presently incompatible with the classical synthetic approach. For complete stereocontrol (incorporating effective use of all synthetic intermediate species in the generation of enantiomer-pure final products), an alternative strategy is required.

Classical Synthetic Approach to Cinchona Alkaloids Containing Quinuclidine Moiety (e.g., quinine)



‡ Dedicated to Gilbert Stork on the occasion of his sixty-fifth birthday

Because of symmetry inherent in the quinuclidine (1-azabicyclo[2.2.2]octane) skeleton, we undertook an extended investigation of formation of functionalized quinuclidine systems from prochiral parent structures, with the following methodological constraints as essential elements in our strategy:

1. Demonstration of stereocontrolled synthetic methods compatible with the quinuclidine skeleton containing a readily accessible and powerfully nucleophilic nitrogen (not easily masked by commonly employed techniques for N-protection); and
2. Utilization of methodology readily compatible with enantioselection and/or resolution/recycling (requisite to an enantiocontrolled synthesis).

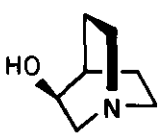
This communication describes the use of quinuclidine·borane complexes as part of solutions to three synthetic problems. First, formation of 3-alkoxyquinuclidines from 3-quinuclidinol (while maintaining the C-3 oxygen and C-3 stereochemistry) is a problem of effecting selective electrophilic attack at a hindered, secondary hydroxylic oxygen rather than at the accessible and highly nucleophilic bridgehead nitrogen. The second problem is generation and isolation of isomer-pure materials, via stereoselective conversion of 3-quinuclidinone to 3-alkylidenequinuclidines. The final problem is the hydroboration of quinuclidines containing unsaturation and the subsequent oxidation of organoborane intermediates without oxidation of the bridgehead nitrogen.

As anticipated, reaction of 3-quinuclidinol (from prochiral 3-quinuclidinone) with a variety of alkyl halides under near-neutral conditions led only to products of N-alkylation. Attempts to effect reversion of N-alkylation with subsequent, slow O-alkylation using methyl iodide, allyl bromide or allyl iodide failed in our hands, even in polar solvents such as DMF at elevated temperatures . Prior formation of the sodium alkoxide using NaH and subsequent reaction with methyl iodide, allyl bromide or allyl iodide in THF, THF/DMF, or DMF led exclusively to the zwitterionic, insoluble salt (by N-alkylation) and all attempts to effect thermal reversion with subsequent O-alkylation proved synthetically unacceptable in these solvent systems.

Early in our studies, we noted[5] that formation of the stable complexes of quinuclidines with borane or alkylboranes often proved useful in isolation, purification, and characterization of volatile and/or water-soluble quinuclidines. These N-borane complexes were often significantly less volatile and less water-soluble than the corresponding free bases, thus facilitating extraction from aqueous solution and subsequent removal of organic solvents without co-distillation. Furthermore, compared to the corresponding free bases, the N-borane complexes were often more likely to be crystalline and readily recrystallizable from non-polar solvents. Because of their high stability, simple quinuclidine·boranes do not readily liberate the parent amine on exposure to hydroxylic solvents (even in presence of 1 N HCl) and are stable in acetone solution in the absence of acid. However, oxidation of hydride with concomitant cleavage of the N-borane complex can be effected using strong aqueous acid or acetone/acid. N-Borane complexes were therefore used as N-protecting groups in the preparation of 3-alkoxyquinuclidines (Scheme 1).

Addition of BH_3·THF (1 mol equiv) to racemic 3-quinuclidinol (1) in THF at 0°C formed the racemic complex 2 which, after partition between brine/CH_2Cl_2, was

readily isolated from the organic phase as a stable, crystalline solid (mp 190°C, with decomposition, gas evolution) suitable for storage under N_2. Alternatively, complex 2 could be used directly in the following steps without workup or crystallization (other than removal of THF *in vacuo*) with no significant effect on overall yields. The sodium salt 3 was generated by addition of 2 to NaH (1 equiv) in DMF at room temperature (45 min, until H_2 evolution ceased) and was O-alkylated using primary alkyl halides (1.1 equiv). After 18 h at room temperature, the reaction mixture was partitioned between ether/brine, and the ethereal solution dried and evaporated. 3-Alkoxyquinuclidine·boranes 4a-c (R = methyl, ethyl, allyl) were isolated in 70-80% yields. Methyl ester 4e (mp 81-81.5°C) was prepared in 75% yield by a modification of the general procedure: Alkylation of 3 to afford a DMF solution of sodium carboxylate 4d was carried out, as above, using sodium iodoacetate (1 equiv, 18h at room temperature); and the resulting solution was directly esterified to 4e by addition of methyl iodide (2 equiv, 24 h at room temperature), followed by the normal workup.



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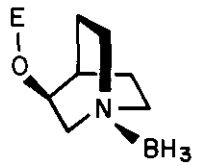
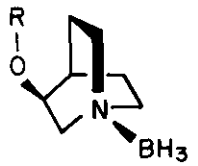
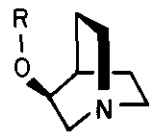


2 (E = H)
3 (E = Na)



4a (R = CH_3)
4b (R = C_2H_5)
4c (R = $CH_2CH{=}CH_2$)
4d (R = CH_2CO_2Na)
4e (R = $CH_2CO_2CH_3$)



5a (R = CH_3)
5b (R = C_2H_5)
5c (R = $CH_2CH{=}CH_2$)
5e (R = $CH_2CO_2CH_3$)

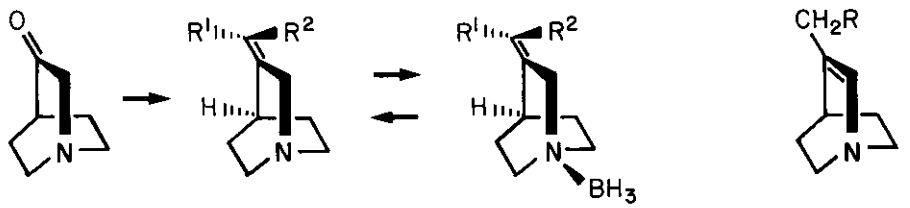
Scheme 1

The quinuclidine·boranes 4 were converted to free 3-alkoxyquinuclidines 5 by the action of either of two solutions: acetone/water/HCl (3:1 acetone/3 N HCl) or THF/acetone/water/HCl (5:1:2 THF/acetone/4 N HCl). After addition of 4 (1-2 mmol) to either acidic solution (~5 ml) at 0°C, the reaction mixture was stirred at room temperature until gas evolution ceased (~30 min). Residual aqueous acid and salts remaining after *in vacuo* removal of acetone were made basic with solid Na_2CO_3 and then partitioned between brine/CH_2Cl_2. Distillation of solvent from the dried organic phase afforded the free quinuclidine bases 5 as oils, in average yields of 70-75% after chromatographic purification.

The use of quinuclidine·boranes as crystalline derivatives for the facile purification of noncrystalline, stereoisomeric quinuclidines is illustrated by the following transformations (Scheme 2), including the facile preparation of isomer-pure E-3-ethylidenequinuclidine. No preparation of this olefin as the pure E-isomer has been previously reported.

Noncrystalline 3-methylidenequinuclidine 6[6] selectively formed its N-borane complex (without competitive hydroboration of the double bond). Slow addition of BH_3·THF (1 mol equiv) to 6 at 0°C in THF afforded, after *in vacuo* removal of

solvent, the crystalline complex 7 (mp 72-73°C from ether). This observation suggested that separation of a mixture of noncrystalline E and Z 3-ethylidenequinuclidine (8) might be effected via fractional crystallization of its N-borane complexes. Using a modification[7b] of the reported[7a] reaction of 3-quinuclidinone and ethylidenetriphenylphosphorane, 3-ethylidenequinuclidine was prepared in 93% yield as a more highly E-enriched mixture (85:15, by nmr) of stereoisomers 8a and 8b, respectively. Quinuclidine·boranes 9 were produced by slow addition of BH_3·THF (1 mol equiv) to the mixture of 8a and 8b at 0°C in THF. As with the formation of 7, no competitive addition to the double bond was observed. Removal of THF in vacuo and crystallization of the residual mixture from ether gave isomer-pure 9a (mp 44.5-45°C),[8] isolated in 70% average yield from the stereoisomeric mixture of 8. The free base was liberated as described above (for conversion 4 → 5) to afford the pure E isomer 8a in 71% yield after distillation (bp 72-75°C/19 torr). No by-products from acid-catalyzed isomerization or addition were observed.



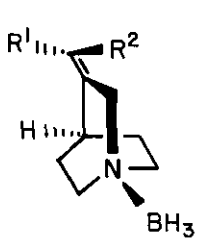
6 (R^1= R^2= H) 7 (R^1= R^2= H) 10
8a (R^1= CH_3, R^2= H) 9a (R^1= CH_3, R^2= H)
8b (R^1= H, R^2= CH_3) 9b (R^1= H, R^2= CH_3)

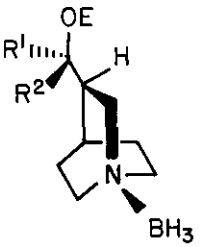
Scheme 2

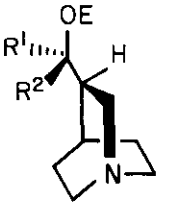
Z-3-Ethylidenequinuclidine (8b) was known[7a] to be significantly more stable than E-isomer 8a, which contains an unfavorable peri interaction between methyl and bridgehead hydrogen. Thus, under appropriate equilibrating conditions, mixtures of 8a and 8b (of any isomer ratio) can be converted to 8b (contaminated by small amounts of the endocyclic alkene isomer 10). The action[9] of catalytic sodium in HMPA (2.5 h at room temperature) smoothly effected this transformation, producing near quantitative amounts of a mixture of 8b and 10 (R=CH_3) in a ratio of~93:7 and containing no 8a, by nmr). The N-borane complex of this mixture was prepared as above but did not afford a crystalline solid.[8] However, the endocyclic contaminant did not interfere with subsequent transformations.

From the preceding observations, it is apparent that hydroboration of a double bond in unsaturated quinuclidine systems requires prior formation of an N-borane complex before hydroboration of the pi system can be effected. Indeed, standard reaction conditions for hydroboration/oxidation of N-borane complex 7 (1.1 equiv BH_3·THF in THF at 0°C, followed by 1 h at room temperature; excess basic H_2O_2 for 10 min; standard workup) afforded solid 3-(hydroxymethyl)quinuclidine-N-borane (11) in 94% yield, (mp 71-72.5°C after recrystallization from ether and subsequent sublimation at 68°C/0.01 torr). Identical results were obtained directly from

quinuclidine 6 (using 2.2 equiv BH_3·THF) without isolation of intermediate 7. It is significant that the N-borane complex was stable to these oxidation conditions and served to protect the nitrogen from competitive oxidation to its N-oxide, even in the presence of excess H_2O_2. Complex 11 was further characterized by near-quantitative acetylation to 12 (mp 58-59°C), using methyllithium (1.1 equiv at 0°C in THF for 10 min) followed by acetic anhydride (5-fold excess added to resulting alkoxide solution at 0°C with normal work-up after 15 min). Quinuclidine·borane complexes are, therefore, also stable to anhydrides (at least for brief exposure). The free base, 3-(acetoxymethyl)quinuclidine (14), was liberated as described above (for conversion 4 → 5) and isolated as an oil in 81% yield after distillation (bp 83-84°C/0.1 torr). 3-(Hydroxymethyl)quinuclidine (13) was obtained from either 11 or 12, using an alternative deprotection procedure. Exposure of either N-borane complex to moderately strong aqueous HCl (8 N, 18 h) at room temperature, basification of the resulting solution with KOH at 0°C, and subsequent continuous extraction (ether, 42 h) afforded 13 (mp 59-61°C)[10] in ~90% yield.







7
9a
9b

11 (R^1= R^2= E = H)
12 (R^1= R^2= H, E = $COCH_3$)
15a (R^1= CH_3, R^2= H, E = H)
15b (R^1= H, R^2= CH_3, E = H)
16a (R^1= CH_3, R^2= H, E = $COCH_3$)
16b (R^1= H, R^2= CH_3, E = $COCH_3$)

13 (R^1= R^2= E = H)
14 (R^1= R^2= H, E = $COCH_3$)
17a (R^1= CH_3, R^2= H, E = H)
17b (R^1= H, R^2= CH_3, E = H)

Scheme 3

Hydroboration/oxidation of 9a [or 9b] using 1.1 equiv BH_3·THF or 8a [or 8b] using 2.2 equiv BH_3·THF, as described above, gave the corresponding alcohol 15a [or 15b]. However, substantial contamination (>30%) by a tertiary alcohol was observed. Apparently, the complexed, allylic nitrogen induced reversely-polarized hydroboration to this extent. The difficulty was overcome by replacing BH_3·THF with thexylborane·THF[11] (1.1 equiv for 40 h) as the hydroboration agent in the general procedure described above. From 9a and 9b were prepared, respectively, threo and erythro 3-(α-hydroxyethyl)quinuclidine-N-borane (15a) and (15b). To facilitate purification by facile recrystallization from ether, each alcohol was acetylated, as described above. From 9a was prepared threo-3-(α-acetoxyethyl)quinuclidine-N-borane (16a) (mp 106.5-107.5°C) in >75% after recrystallization; and from 9b was prepared erythro-3-(α-acetoxyethyl)quinuclidine-N-borane (16b) (mp 100.5-102.5°C) in 70-75% after recrystallization. Hydrolysis of acetylated quinuclidine·boranes 16 was effected, as above, in yields >90% after distillation (using 8 N HCl, pH

adjustment, and multiple ether extractions in place of the continuous extraction required for 13). From 16a was prepared threo-3-(α-hydroxyethyl)quinuclidine (17a) (mp 81-83°C) after distillation (bp 98-101°C/0.01 torr); and from 16b was prepared erythro-3-(α-hydroxyethyl)quinuclidine (17a) (mp 63.5-64.5°C) after distillation (bp 105-107°C/0.02 torr). Overall yields of diastereomer-pure alcohols 17 are ~50% from 3-quinuclidinone.

All chemical sequences described above are clearly compatible with the first methodological constraint we originally defined. However, it may appear that our generation of racemic materials is not compatible with the second constraint, compatibility with exercise of complete stereocontrol). Thus, our convenient use of racemic 1 in the sequence 1 ⟶ 5 (Scheme I) necessarily formed racemic 5 (despite the employment of reactions which preserved the C-3 oxygen and its stereochemistry). Additionally, we have described no enantioselection in the production of 11 through 17 (Scheme 3). Nevertheless, the sequences are formally compatible with the second criterion: the precursor of all chiral materials is prochiral 3-quinuclidinone; and alkenes 6 and the stereoisomerically pure 8a and 8b are also prochiral. It is significant that all reactions which introduce chirality (reduction of 1 and hydroboration of N-boranes derived from 6 and 8) are compatible with use either of chiral induction methods or of resolution/recycling sequences.[12,13]

From these examples, it should be evident that quinuclidine·boranes are useful intermediates in the preparation and manipulation of functionalized quinuclidine systems. In the following communication, we report the use of alcohols 13 and 17 in an intramolecularly stereocontrolled preparation of quinuclidines having functionalization on two bridges. Such systems should prove suitable as intermediates in a completely stereocontrolled Cinchona alkaloid synthesis, which utilizes no 3,4-disubstituted piperidine intermediates.

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REFERENCES AND NOTES

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1e. Current address: The University of Texas at San Antonio.

1f. Current address: Texas Christian University.

2. P. Rabe and K. Kindler, Ber., 1918, 51, 466.

3. For additional description of our synthetic approach to quinine and for leading references to reported total syntheses of quinine, see:
P.L. Stotter, M.D. Friedman, and D.E. Minter, J. Org. Chem., 1985, 50, 29.

4. For a diastereospecific, although non-enantioselective, approach to C-3/C-4 3-functionalized 7-quinuclidinones (quinine numbering) which does not require synthesis of specifically cis-3,4-disubstituted piperidines, see:
D.L. Coffen and T.E. McEntee, Jr., J. Chem. Soc., Chem. Commun., 1971, 539.

5a. A number[5b] of other methods for cleavage of the various quinuclidine·boranes encountered in this study included attempted displacement using nucleophiles (i.e., phosphines, alcoholic hydroxide and/or cyanide) and acidic decomposition under well-known conditions for liberation of amines even from moderately stable amine·boranes (i.e., 1-2 N HCl or H_2SO_4 for 16-20 h). The stability of these quinuclidine·boranes to acid-free carbonyl systems is discussed in the text.

5b. M.D. Friedman, PhD Dissertation, The University of Texas at Austin, 1978; and P.L. Stotter, M.D. Friedman, and D.E. Minter, unpublished results.

6a. Application of Corey's modification[6b] of the Wittig reaction to the reported[6c] formation of 6 from methylidenetriphenylphosphorane and 3-quinuclidinone proved superior: methylsulfinylmethylsodium[6b] in DMSO was used instead of sodium amide in ammonia (also see note 7).

6b. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 1962, 84, 866; 1965, 87, 1345, 1353; J. Org. Chem., 1963, 28, 1128.

6c. L.N. Yakhontov, L.I. Mastafanova, K.F. Turchin, T.D. Pervacheva, and M.V. Rubtsov, Khim. Geterosikl. Soedin., Akad. Nauk. Latv. SSR, 1968, 881.

7a. G. Van Binst, J.C. Nouls, J. Stokoe, C. Danheux, and R.H. Martin, Bull. Soc. Chim. Belges, 1965, 74, 506; J.C. Nouls, G. Van Binst, and R.H. Martin, Tetrahedron Lett., 1967, 4065.

7b. In DMSO (as in note 6a), substitution of ethyltriphenylphosphonium iodide for the bromide gave 85:15 E:Z ratio; under similar conditions, use of the bromide gave 70:30 E:Z ratio, as reported.[7a] In benzene using phenyllithium as base, reaction gave 1:1 E:Z ratio.

8. The facile, high-yield recovery of 9a by crystallization (from the 85:15) mixture is a serendipitous consequence of the different physical properties of 9a and 9b. E-isomer 9a is a low-melting crystalline solid; 9b could not be induced to crystallize. However, after isomerization of mixture 8 to 8b (containing ~7% 10), a crystalline complex of 8b could be readily formed by complexation with thexylborane.[11] Although recrystallization of this complex provided a suitable method of purification (to remove 10), this step did not appreciably affect yields in hydroboration/oxidation.

9a. In our hands, application of an alternative procedure[9b] for isomerization of hydrocarbon alkenes proved to be reproducibly superior for the isomerization of 8 than the reported use[7a] of sodium on alumina. It is likely that the

isomerization of 8a to 8b proceeds via 10 (R=CH_3), probably mediated by deprotonation/reprotonation (with dimethylamide from decomposition of HMPA radical anion as base), since similar isomerization of 6 led to a mixture containing a much higher proportion of endocyclic alkene 10 (R=H). In general, best results for a number of different isomerizations were obtained when the alkene was first exposed to freshly-cut sodium overnight and then transferred to a blue solution of sodium in dried HMPA (prepared at least 40 min prior to addition of alkene and containing ~10 mol% sodium per mol alkene). Reaction is held at room temperature until equilibrium has been reached; and product may be isolated either by direct distillation from the reaction mixture or, after quenching, by ether/water partition. After such isomerizations have reached equilibrium, product distributions of regio- and/or stereoisomeric alkenes apparently reflect thermodynamic stabilities of the respective alkene components and not kinetic or thermodynamic characteristics of allylic anion intermediates. Additional details and other examples of this isomerization method will be published elsewhere.

9b. See, for example: A. Schriesheim and C.A. Rowe, US Patent No. 3,217,050, 1965.

10a. Previous reports[10b] of preparation of 13 indicate a lower mp (47-50°C).

10b. L.I. Mastafanova, L.N. Yakhontov, and M.V. Rubtsov, Khim. Geterosikl. Soedin., Akad. Nauk. Latv. SSR, 1965, 858; and C.A. Grob and E. Renk, Helv. Chim. Acta, 1954, 37, 1689.

11. Thexylborane (or t-hexylborane) is the commonly used name for 1,1,2-trimethylpropylborane, the monohydroboration product of 2,3-dimethyl-2-butene. For trivial nomenclature, preparation, and use as a regioselective hydroboration reagent, see: H.C. Brown and G. Zweifel, J. Am. Chem. Soc., 1960, 82, 3222, 3223; 1961, 83, 1241.

12. We have not as yet attempted chiral induction methods for enantioselective preparation of these systems; nor have attempts been made to resolve new alcohols 17.

13. Dehydration of chiral alcohols 13, 17a and 17b was anticipated as a suitable method for regenerating the prochiral substituted alkenes (for recycling after resolution). We have partially confirmed this hypothesis, without regeneration of 17a. The tosylates derived from racemic 13, 17a and 17b were each subjected to E-1 elimination conditions in DMF, regenerating 6 from 13 and 8b from both isomers of 17, in good yield.

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