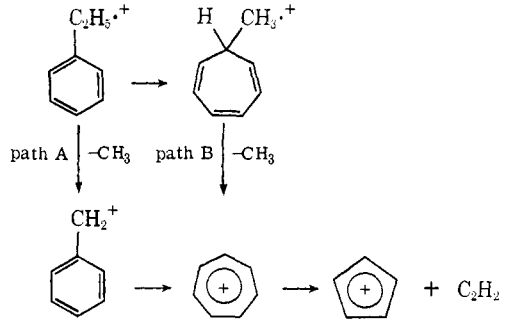
ucts with that of the authentic sample[13] is that the active species for both products is a common $C_7H_5D_2^+$ ion formed by a preferential loss of β-methyl from the original molecular ion without involving isotopic mixing between β-methyl and benzyl groups.

The methylene protium atom, however, was not detected for the nmr analysis of *N,N*-dimethylbenzylamine formed by the radiolysis of a mixture of ethylbenzene-α-d_2 (2.2 mm) and dimethylamine (3.8 mm). However, in EDPM produced from ethylbenzene-α-d_2 (5 mm) small amounts of methylene protium atom were observed and the ratio of the methylene and phenyl protium atoms of EDPM was determined to be 0.024, suggesting the occurrence of a $\sim$15% scrambling path. If the $C_7H_5D_2^+$ ion reacted after complete scrambling as proposed in mass spectrometry, the H_{CH_2}/H_{Ph} ratio would be 0.189. The present observation shows sharp contrast with the mass spectrometry of ethylbenzene in which the $C_7H_7^+$ ion formed by a loss of β-methyl can be satisfactorily represented as a tropylium ion structure. The elucidation is evidenced by the fact that all hydrogens of the $C_7H_7^+$ ion completely lose the positional identity and become equivalent in the further degradation process to the $C_5H_5^+$ ion. Scheme I has been proposed as a possible pathway from

Scheme I



the mass spectrometric investigations.[14] Though it has not been established whether path A or path B is preferable, structural information on the nondecomposing $C_7H_7^+$ ion, which comprises about 90% of the total $C_7H_7^+$ ion in ethylbenzene,[15] is not obtained by the mass spectrometry. On the other hand, the present results clearly demonstrate that the nondecomposing $C_7H_7^+$ ion is predominantly an unscrambled benzyl ion produced *via* path A which reacts rapidly with dimethylamine. Since the $C_7H_7^+$ ion reacts less rapidly with ethylbenzene, hydrogen scrambling may come to compete with the EDPM formation. The reactivity ratio of the $C_7H_7^+$ ion with dimethylamine and ethylbenzene, k_3/k_2, was calculated to be 2.7 from data shown in Figure 1.

In the radiolysis of toluene vapor a scrambling path such as path B contributed appreciably to the MDPM formation (31–33%).[1] The reason why the toluene and ethylbenzene ions behave differently is obscure, but seems to correlate with the lifetime of the molecular ion as suggested by Howe and McLafferty.[4] The ethylbenzene ion is probably more short-lived than the toluene ion[16] since the β C–C bond fission in the former occurs with greater facility; therefore the scrambling path cannot compete with the direct dissociation path. The benzyl ion thus formed is also short-lived in the presence of ethylbenzene and dimethylamine which are reactive to the ion; consequently the further reactions of the benzyl ion may proceed without involving hydrogen scrambling to a considerable extent.

Acknowledgment. We wish to thank Dr. Seung-Geon Kim for advice on the preparation of ethylbenzene-α-d_2. Thanks are also due to Mr. Yoshio Takai and Mr. Norio Kimura for measurements of nmr and mass spectra, and Mr. Tomikazu Sawai and Mr. Tamotsu Yamamoto for γ-irradiation.

(13) The mass spectra of *N,N*-dimethylbenzylamine formed by the radiolysis of a mixture of ethylbenzene-α-d_2 and dimethylamine agreed closely with that of *N,N*-dimethylbenzylamine-α-d_2 prepared by a reduction of *N,N*-dimethylbenzamide with $LiAlD_4$.

(14) P. Brown, *Org. Mass Spectrom.*, **2**, 1317 (1969).

(15) E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Ed., "Atlas of Mass Spectral Data," Vol. 1, Interscience, New York, N. Y., 1969.

(16) The greater $M^+:C_7H_7^+$ intensity ratio in the spectrum of toluene (0.74) than in those of ethylbenzene (0.32) may mean that the ethylbenzene ion decomposes more rapidly to $C_7H_7^+$ ion than toluene ion does (ref 15).

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A Facile Synthesis of Quinine and Related Cinchona Alkaloids

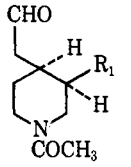
Sir:

There has been a remarkable resurgence of interest within the past few years[1–8] in developing new synthetic routes to the Cinchona alkaloids, culminating in several ingenious total syntheses of quinine (**10a**) and quinidine (**11a**) by Uskoković[2] and Gates.[3] Albeit by different routes, both groups prepared the olefin **8a** (R_3 = H) which served as the immediate precursor to a mixture of desoxyquinine and desoxyquinidine (**9a**) by intramolecular Michael addition of the piperidine nitrogen to the conjugated vinyl grouping. Subsequent base-catalyzed hydroxylation gave a mixture of quinine (**10a**) and quinidine (**11a**), along with smaller amounts of epiquinine and epiquinidine.

We have recently described[9] a new procedure for the direct introduction of alkyl and alkenyl groups into heterocyclic nuclei involving nucleophilic displacement of a suitable leaving group on the heterocycle by a Wittig reagent to provide a new heterocyclic ylide which subsequently can be either hydrolyzed (to give an alkyl-substituted heterocycle) or treated with a carbonyl compound (to give an alkenyl-substituted heterocycle). We now describe the application of this new synthetic method to the direct conversion of 4-chloro-6-methoxyquinoline (**3**) to a mixture of desoxyquinine and desoxy-

(1) M. Uskoković, J. Gutzwiller, and T. Henderson, *J. Amer. Chem. Soc.*, **92**, 203 (1970).
(2) J. Gutzwiller and M. Uskoković, *ibid.*, **92**, 204 (1970).
(3) M. Gates, B. Sugavanam, and W. L. Schreiber, *ibid.*, **92**, 205 (1970).
(4) D. L. Coffen and T. E. McEntee, Jr., *Chem. Commun.*, 539 (1971).
(5) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Amer. Chem. Soc.*, **93**, 5902 (1971).
(6) G. Grethe, H. L. Lee, T. Mitt, and M. Uskoković, *ibid.*, **93**, 5904 (1971).
(7) R. L. Augustine and S. F. Wanat, *Syn. Commun.*, **1**, 241 (1971).
(8) D. R. Bender and D. L. Coffen, *J. Heterocycl. Chem.*, **8**, 937 (1971).
(9) E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, **94**, 2874 (1972).

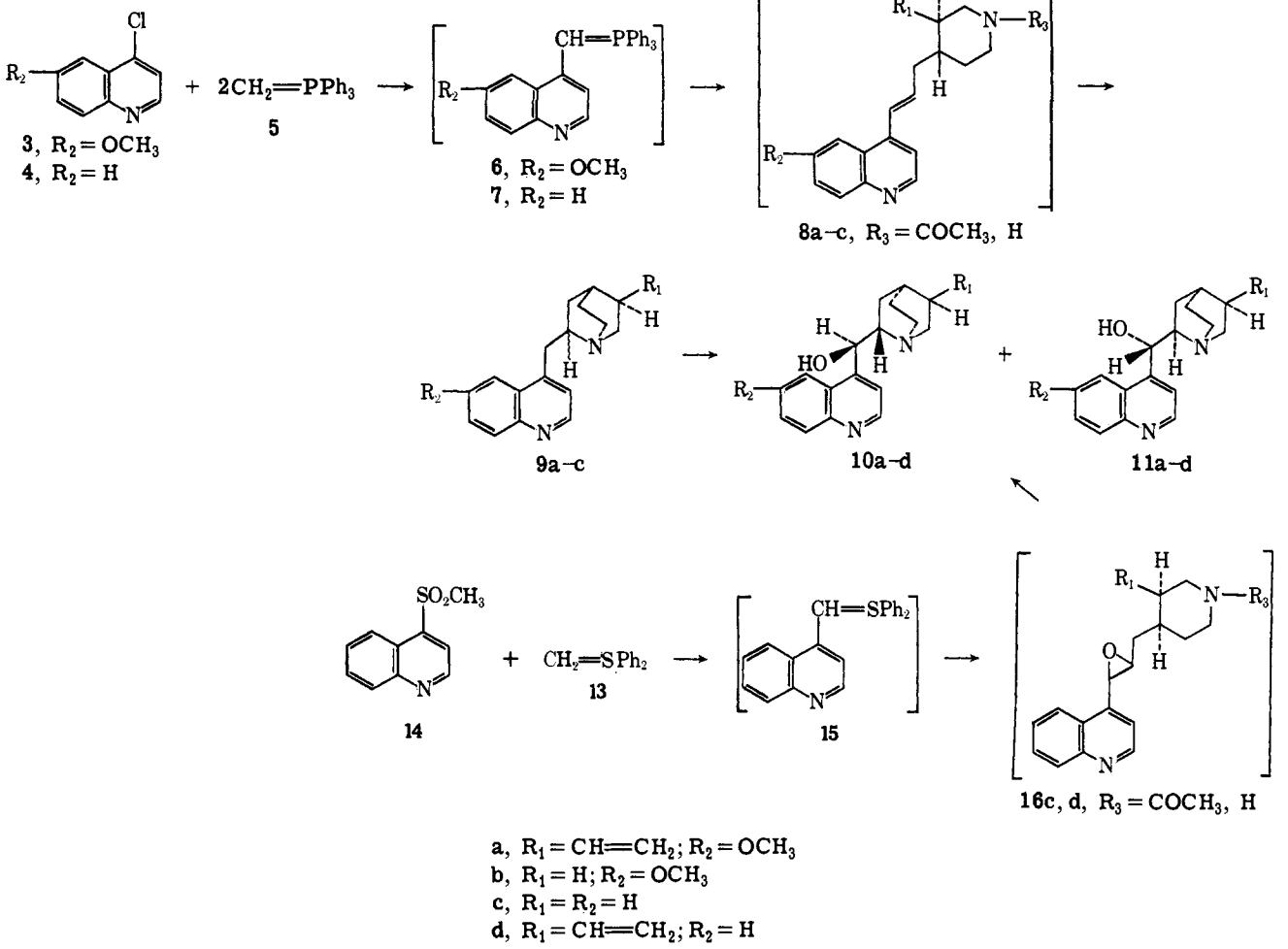
quinidine (**9a**) *via* the *in situ* formation of the olefin **8a**. Furthermore, as described below, this procedure for what is, in effect, the direct attachment of the quinu-



1, $R_1 = CH{=}CH_2$
2, $R_1 = H$

clidine moiety to the quinoline ring has also been exploited for the total syntheses of *rac*-6-methoxyruban (**9b**) and *rac*-ruban (**9c**) from 4-chloro-6-methoxyquinoline (**3**) and 4-chloroquinoline (**4**), respectively, without isolation of any of the intervening intermediates.

Thus, ylide **6**, which was prepared by treatment of 4-chloro-6-methoxyquinoline (**3**) with 2 equiv of methylenetriphenylphosphorane (**5**), was treated directly with *N*-acetyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde[9a] (**1**) to give the olefin **8a** (R_3 = $COCH_3$) (see scheme below). Removal of the *N*-acetyl group *in situ* by hydrolysis to **8a** (R_3 = H) was followed by spontaneous, intramolecular Michael addition to give a mixture of desoxyquinine and desoxyquinidine (**9a**) (38%) which was converted by base-catalyzed hydroxylation[2,3] to quinine (**10a**) (33%), quinidine (**11a**) (30%), and a mixture of epiquinine and epiquinidine (10%). Treatment of **6** with *N*-acetyl-4-piperidineacetaldehyde (**2**) gave the olefin **8b** (R_3 = $COCH_3$) which was converted by a similar sequence of operations to *rac*-6-methoxyruban (**9b**) (35%). Base-catalyzed hydroxylation, as before, afforded a mixture of *rac-erythro*- (**10b**, **11b**) and *rac-threo*-6-methoxyrubanol (*ca.* 5:1 ratio, 71% overall yield). Finally, the Wittig reaction of **2** with the heterocyclic ylide **7**, produced *in situ* from 4-chloroquinoline (**4**) and 2 equiv of **5**, gave the intermediate *N*-acetylaminovinylquinoline **8c** (R_3 = $COCH_3$) which, after hydrolysis to **8c** (R_3 = H), cyclized directly to *rac*-ruban (**9c**) in 36% overall yield. Subsequent oxidation gave a mixture of *rac-erythro*- (**10c**, **11c**) and *rac-threo*-rubanol (*ca.* 5:1 ratio, 67% overall yield).



3, $R_2 = OCH_3$
4, $R_2 = H$
5
6, $R_2 = OCH_3$
7, $R_2 = H$
8a–c, $R_3 = COCH_3$, H
9a–c
10a–d
11a–d
12
13
14
15
16c, d, $R_3 = COCH_3$, H

a, $R_1 = CH{=}CH_2$; $R_2 = OCH_3$
b, $R_1 = H$; $R_2 = OCH_3$
c, $R_1 = R_2 = H$
d, $R_1 = CH{=}CH_2$; $R_2 = H$

(9a) Prepared from *N*-benzoylmeroquinene methyl ester[1] by a procedure analogous to that described for the preparation of the corresponding *N*-benzoyl compound (see ref 6).

Uskoković has described an alternative synthetic approach to the Cinchona alkaloids involving the construction of the epoxide **12** which, when subjected to reductive debenzoylation, underwent intramolecular, nucleophilic ring opening of the epoxide to give quinine and quinidine directly.[2] In view of the general success of the phosphorus ylide approach for the functionalization of heterocycles with alkyl and alkenyl groups, we have examined the possible utility of sulfur ylides for the direct introduction of epoxy substituents into heterocyclic nuclei.[10] The potential applicability of this approach to the synthesis of the Cinchona alkaloids is illustrated by the following reactions. Thus, 4-methylsulfonylquinoline (**14**) was treated with 2 equiv of diphenylmethylenesulfurane (**13**) in 1,2-dimethoxyethane at −30° to give the sulfur ylide **15** which, without isolation, was treated with **2**. The *N*-acetylamino epoxide **16c** (R_3 = $COCH_3$) thus formed was hydrolyzed directly to **16c** (R_3 = H) which underwent spontaneous, intramolecular cyclization to a mixture of *rac-erythro*-rubanol (**10c**, **11c**) (12%), *rac-threo*-rubanol (<1%), and approximately 9% of products arising from solvolysis of the intermediate amino epoxide **16c** (R_3 = H). It should be noted that the entire sequence of reactions commencing with 4-methylsulfonylquinoline and terminating with **10c** and **11c** was executed without the isolation of a single intermediate.

Similarly, ylide **15** was treated directly with **1** to give the *N*-acetylamino epoxide **16d** (R_3 = $COCH_3$). Hydrolytic removal of the *N*-acetyl group *in situ* to **16d** (R_3 = H) was followed by intramolecular cyclization to provide a mixture of cinchonidine (**10d**) (10%) and cinchonine (**11d**) (8%).[11] Unfortunately, 4-methylsulfonyl-6-methoxyquinoline proved to be unreactive toward diphenylmethylenesulfurane, but we are currently investigating the possible utilization of other, more stable ylides in an attempt to extend the above concepts to a one-step synthesis of quinine and quinidine.

Acknowledgment. We are deeply grateful to Dr. Milan Uskoković of Hoffmann-La Roche for many stimulating discussions and a generous gift of *N*-benzoylmeroquinene.

(10) E. C. Taylor, M. L. Chittenden, and S. F. Martin, manuscript in preparation.

(11) Small amounts of epicinchonine and epicinchonidine (<2%) and some 12% of solvolysis products arising from the intermediate amino-epoxide **16d** (R_3 = H) were also formed in this reaction sequence.

(12) NIH Predoctoral Fellow, 1969–1972.

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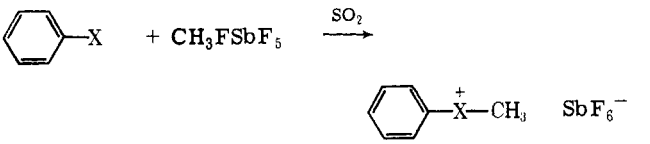
Onium Ions. III.[1] Alkylarylhalonium Ions

Sir:

Diphenylhalonium ions have been known for many years.[2,3] We have more recently reported the preparation of dialkylhalonium ions and suggested their possible importance in Friedel–Crafts alkylation reactions.[1,4] The possibility that alkylarylhalonium ions could also play a role in Friedel–Crafts reactions has led us to an investigation of the existence of these ions. When a SO_2 solution of iodobenzene is added to a SO_2 solution of the CH_3F–SbF_5 complex[5] (methyl fluoroantimonate) at −78°, a clear slightly colored solution results. The pmr spectrum of this solution at −80° shows in addition to the excess methyl fluoroantimonate a methyl singlet at δ 3.80 and a multiplet aromatic region (7.7–8.3) with a peak area ratio of 3:5. The aromatic signals show the same coupling pattern as that of iodobenzene in SO_2 but are deshielded by approximately 0.5 ppm. The fluorine-19 nmr spectrum of the solution shows only a very broad absorption centered around ϕ 112 (from CF_3CCl_3) which is characteristic of the SbF_6^- counterion. We suggest that the species that accounts for the nmr data is the methylphenyliodonium ion, $CH_3I^+C_6H_5$ (**1-I**). When bromobenzene and other aryl bromides or iodides are added in the same manner to methyl fluoroantimonate in SO_2, analogous spectra are obtained indicating the formation of the corresponding methylarylhalonium ions (**1-X**).



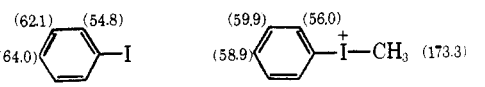
1-X

X = Br or I

Likewise, the reaction of aryl bromides and iodides with ethyl fluoroantimonate[5] in SO_2 results in the formation of ethylarylhalonium ions.

The pmr data of the alkylarylhalonium ions studied are summarized in Table I. The pmr chemical shifts of the methyl and ethyl protons are in good agreement with those reported for dialkylhalonium ions.[4]

The cmr chemical shift of the methyl carbon in the methylphenyliodonium ion, **1-I**, occurs at $\delta_{^{13}C}$ 173.3 (from CS_2) which agrees with that reported for the dimethyliodonium ion ($\delta_{^{13}C}$ 184.3).[4b] The C-1 chemical shift occurs at $\delta_{^{13}C}$ 87.4 compared to 97.0 in iodobenzene.[6] The ^{13}C chemical shifts of $C_{2,6}$, $C_{3,4}$, and C_6 in ion **1-I** are not appreciably different from the analogous carbons in iodobenzene. This indicates that there is not any appreciable charge delocalization due to resonance into the aromatic ring in the methylphenyliodonium ion.



The reaction of chlorobenzene and fluorobenzene, respectively (with methylfluoroantimonate), in SO_2 does not result in the formation of alkylarylhalonium ions **1-Cl** or **1-F** but instead sulfinylmethylation occurs exclusively at the para position forming the corresponding methyl sulfinylates. Methyl fluoroantimonate is apparently methylating SO_2 and the aromatic rings of

(1) Parts I and II are considered, respectively: G. A. Olah and J. R. DeMember, *J. Amer. Chem. Soc.*, **91**, 2113 (1969); **92**, 718 (1970).

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(4) G. A. Olah and J. R. DeMember, *J. Amer. Chem. Soc.*, **92**, 2562 (1970).

(5) G. A. Olah, J. R. DeMember, and R. H. Schlosberg, *ibid.*, **91**, 2112 (1969); G. A. Olah, J. R. DeMember, R. H. Schlosberg, and Y. Halpern, *ibid.*, **94**, 156 (1972).

(6) P. C. Lauterbur, *J. Chem. Phys.*, **38**, 1406 (1963).