ApSimon

The Total Synthesis of Natural Products

VOLUME 3

INTERSCIENCE

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Preface

Throughout the history of organic chemistry, we find that the study of natural products frequently has provided the impetus for great advances. This is certainly true in total synthesis, where the desire to construct intricate and complex molecules has led to the demonstration of the organic chemist's utmost ingenuity in the design of routes using established reactions or in the production of new methods in order to achieve a specific transformation.

These volumes draw together the reported total syntheses of various groups of natural products and commentary on the strategy involved with particular emphasis on any stereochemical control. No such compilation exists at present, and we hope that these books will act as a definitive source book of the successful synthetic approaches reported to date. As such, it will find use not only with the synthetic organic chemist but also perhaps with the organic chemist in general and the biochemist in his specific area of interest.

One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area. It is hoped that these books will act as an inspiration for future challenges and outline the development of thought and concept in the area of organic synthesis.

The project started modestly with an experiment in literature searching by a group of graduate students about nine years ago. Each student prepared a summary in equation form of the reported total syntheses of various groups of natural products. It was my intention to collate this material and possibly publish it. During a sabbatical leave in Strasbourg in 1968-1969, I attempted to prepare a manuscript, but it soon became apparent that the task would take many years and I wanted to enjoy some of the other benefits of a sabbatical leave. Several colleagues suggested that the value of such a collection would be enhanced by commentary. The only way to encompass the amount of data

collected and the inclusion of some words was to persuade experts in the various areas to contribute.

Volume 1 presented six chapters describing the total synthesis of a wide variety of natural products. The subject matter of Volume 2 was somewhat more related, being a description of some terpenoid and steroid syntheses. The present volume considers the syntheses of several classes of alkaloids. The authors originally provided me with their manucripts three years ago, and the delay in producing this volume is a result of a hope that another planned chapter would also appear in time for inclusion. Unfortunately, the author of that chapter has been unable to produce his contribution.

I have asked the authors of these chapters to provide wherever possible, an updating of their work by the use of supplementary references and addenda. The delay in producing the original work is in no way the fault of the present authors, and I apologize to them for this tardiness. However, I believe that their work is outstanding and well worth publishing. I hope the readers of this volume will find it useful as a reference work on total syntheses preformed in the alkaloid field.

I wish to express my thanks to Ms. Karen Bergenstein for preparing the index and to Karl Diedrich for preparing the illustrations to Chapter 2.

JOHN APSIMON

Ottawa, Canada
January 1977

Contents

The Total Syntheses of Isoquinoline Alkaloids

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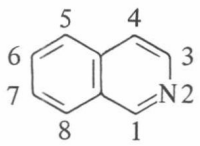
*The author is deeply indebted to Dr. Keiichiro Fukumoto and Dr. Shiroshi Shibuya, Pharmaceutical Institute, Tohoku University, for many help for suggestions, as well as for help in the preparation of this review.

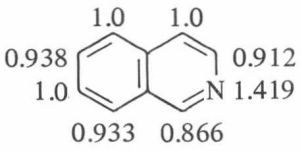
Isoquinoline or benzo[c]pyridine, an isomer of quinoline, was first obtained from coal tar by Hoogewerff and van Dorp in 1885 together with various alkylisoquinolines, and isoquinoline itself was synthesized by Gabriel in the same year. However, the natural occurrence of the isoquinoline ring system was first recognized in the opium alkaloid; papaverine, isolated as needles, m.p. 147°, $C_{20}H_{21}O_4N$, by Goldschmidt,[1] in one of the first structural determinations of alkaloids. Since Goldschmidt's recognition, efforts by chemists have been devoted to the chemistry of the alkaloids and by now about 1000 isoquinoline alkaloids are known.[2]

The numbering of isoquinoline ring system is shown as follow.

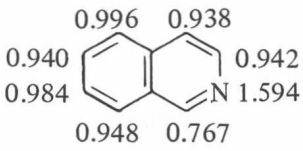


Isoquinoline is obtained as hygroscopic colorless crystals, m.p. 24.6°, $b.p._{760}$ 243.3°, $b.p._{40}$ 142° with *p*Ka 5.14 in water at 20°. The odor of isoquinoline is almost the same as that of quinoline, but the former smells somewhat likes benzaldehyde. The basicity of isoquinoline is stronger than that of quinoline, which has *p*Ka 4.85 in water at 20°. Electronically, the chief difference between naphthalene and isoquinoline is due to the fact that the latter, isoquinoline has the "lone pair" at its nitrogen atom. Furthermore, the nitrogen attracts electron density from the carbon atoms so that these carbon atoms have a deficiency of the electron charge compared with the atoms in naphthalene.[3] Quantitatively, the charge on each atom can be calculated by the valence bond method or by the method of molecular orbitals.[3]

π-Electron Densities for Isoquinoline



V. B. Method



M. O. Method

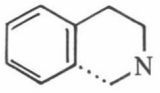
In general, it would be expected that substitution with electrophilic reagents would occur at the carbon having the greatest π-electron density and that substitution with nucleophilic reagents would occur at the position having the smallest π-electron density.

1. GENERAL METHODS

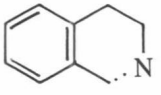
A. Introduction

The methods for the synthesis of isoquinoline ring system can be classified systematically in five ways according to the mode of formation of the pyridine ring (Chart 1-1). The first type involves ring closure between the benzene ring and

Chart 1-1.



Type 1



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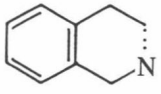

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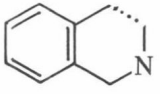

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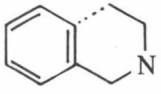
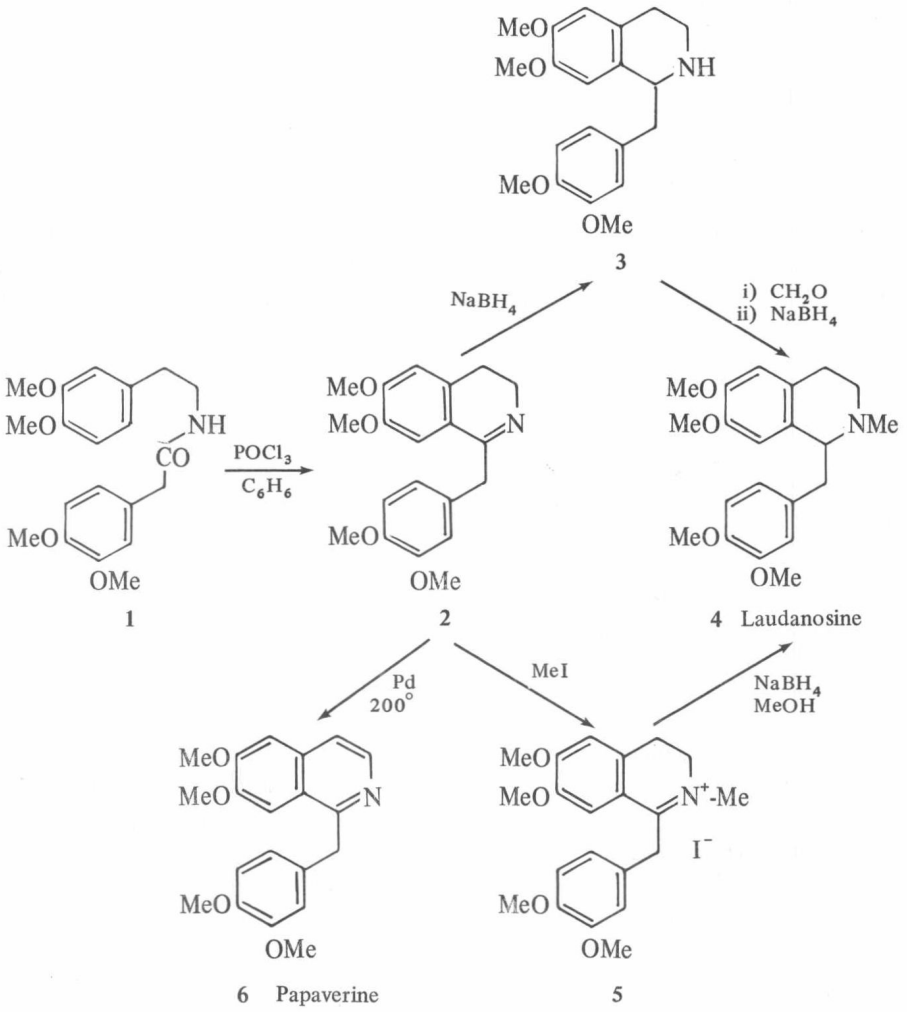


Type 5

the carbon atom, which forms the C_1-position of the resulting isoquinoline ring. The second type uses bond formation between the C_1-position and nitrogen, and the third type uses cyclization by the combination of nitrogen with the C_3-position. The fourth type is due to the formation of isoquinoline ring by ring closure between the C_3- and C_4-position. The fifth type necessitates ring closure between the benzene ring and C_4-position.

In the Chart 1-1, the dotted lines indicate the bond formation by cyclization. Although all the types of these reactions are known, the most popular reactions are the type of 1 and 5, giving usually dihydro- or tetrahydroisoquinoline derivatives and aromatic isoquinolines can be prepared by the dehydrogenation of the corresponding dihydro- or tetrahydroisoquinolines. Among reactions of type 1 and 5, the Bischler-Napieralski, Pictet-Spengler, and Pomeranz-Fritsch reactions are especially important.

Chart 1-2.

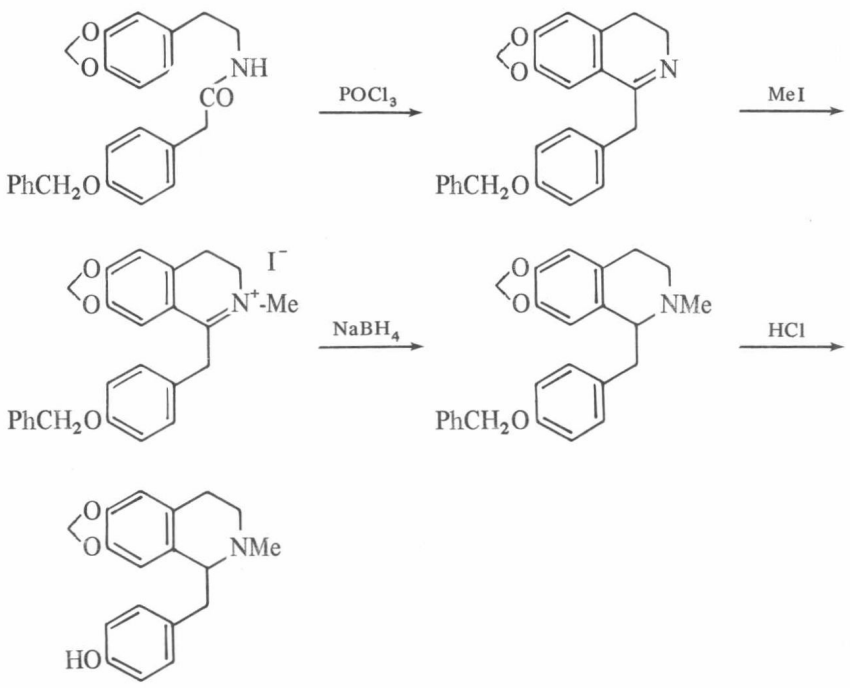


B. Type 1 Synthesis

Bischler-Napieralski Reaction[4] *(Chart 1-2)*

The Bischler-Napieralski route involves the cyclodehydration of an acyl derivative **1** of β-phenethylamine in the presence of a Lewis acid such as phosphoryl chloride or phosphorous pentoxide in an inert solvent to give a 3,4-dihydroisoquinoline **2**, which must be reduced to a 1,2,3,4-tetrahydroisoquinoline **3** since the isoquinoline alkaloids[5] exist as the tetrahydro derivatives in most cases. For this purpose, 3,4-dihydroisoquinoline hydrochloride can be directly reduced with sodium borohydride to give the tetrahydroisoquinoline derivative **3**.[6] When the *N*-methyl derivative **4** is desired, the Eschweiler-Clarke reaction of **3** with formalin and formic acid or sodium borohydride gives the expected *N*-methyl compound **4**.[7] Reduction of the methiodide **5** of a 3,4-dihydroisoquinoline with sodium borohydride to **4** is also recommended.[8] Recently, cinnamolaurine was synthesized by this method as shown Chart 1-3A.[8a] On the other hand, the mild dehydrogenation of a 3,4-dihydroisoquinoline **2** can be

Chart 1-3A.

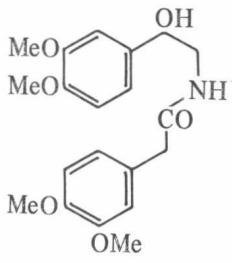


Cinnamolaurine

carried out to obtain the aromatic isoquinoline alkaloids such as papaverine **6**.[9]

One of the most important modifications of the Bischler-Napieralski reaction was introduced by Pictet and Gams.[10] This reaction gives the isoquinoline derivative instead of the 3,4-dihydro-compound by cyclization of a β-hydroxy-β-phenethylamide **7** with phosphorous pentoxide. For example, papaverine **6** was obtained directly from **7** (Chart 1-3).

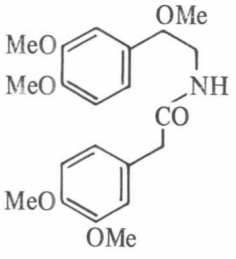
Chart 1-3.



7

Application of the Pictet-Gam's modification to β-methoxy-β-phenethylamide **7a** also gives the isoquinoline derivatives **6**, directly.[11] Therefore, the choice of the foregoing variation of the Bischler-Napieralski reaction should be made according to the availability of the starting amide (Chart 1-4).

Chart 1-4.

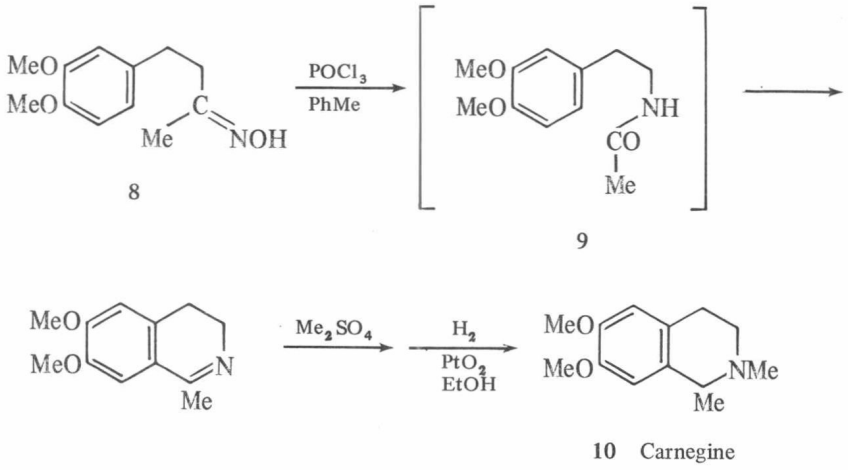


7a

Oximes **8**, which could lead to *N*-acyl-β-phenethylamide **9** by Beckmann rearrangement, are also useful as starting materials for the Bischler-Napieralski route, a method applied to the synthesis of carnegine **10**[12] (Chart 1-5).

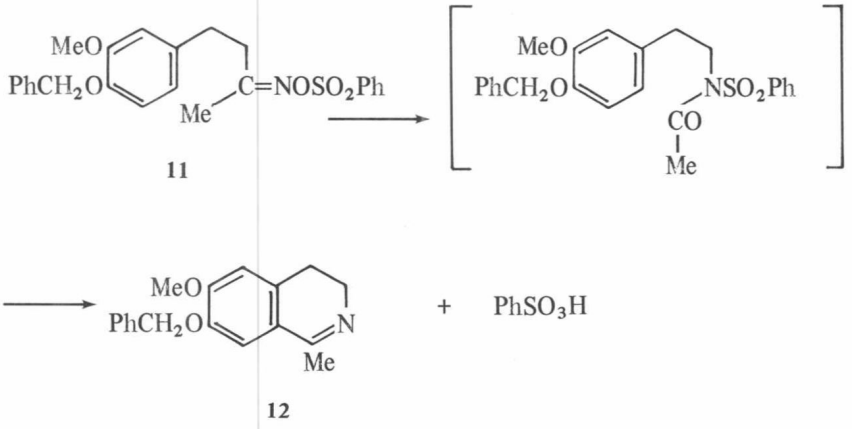
These oximes are converted into the corresponding isoquinolines or 3,4-dihydroisoquinolines without isolation of the amides formed as intermediates.[13]

Chart 1-5.



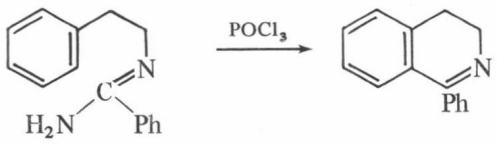
The benzenesulfonyl ester **11** of an oxime undergoes cyclization to give the 3,4-dihydroisoquinoline derivative **12** by heating alone without any other reagent[14] (Chart 1-6). In some cases, the amidine, instead of the amide, is used

Chart 1-6.



for cyclization to give the phenanthridine derivatives in good yields.[15] Short and Brodrich[16] synthesized 3,4-dihydro-1-phenylisoquinoline **13** from amidine **14** by treatment with phosphoryl chloride (Chart 1-7).

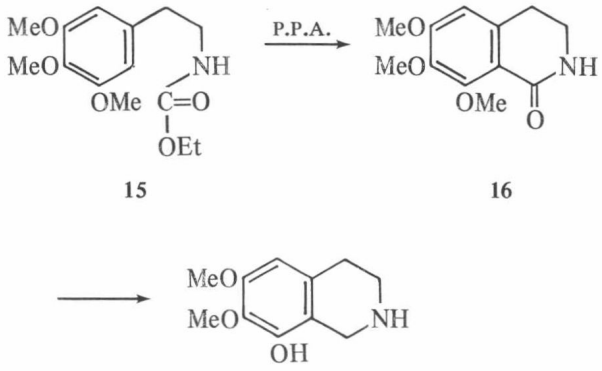
Chart 1-7.



14 **13**

N-β-Phenylethylurea and urethane derivatives are also useful for the syntheses of 3,4-dihydroisoquinolines having an amino or hydroxyl group at the C_1-position.[17] For example, an urethane **15** yields 3,4-dihydro-1-hydroxy-6,7,8-trimethoxyisoquinoline **16**,[18] which was converted into anhalamine **17** by Brossi[18] (Chart 1-8).

Chart 1-8.



15 **16**

17 Anhalamine

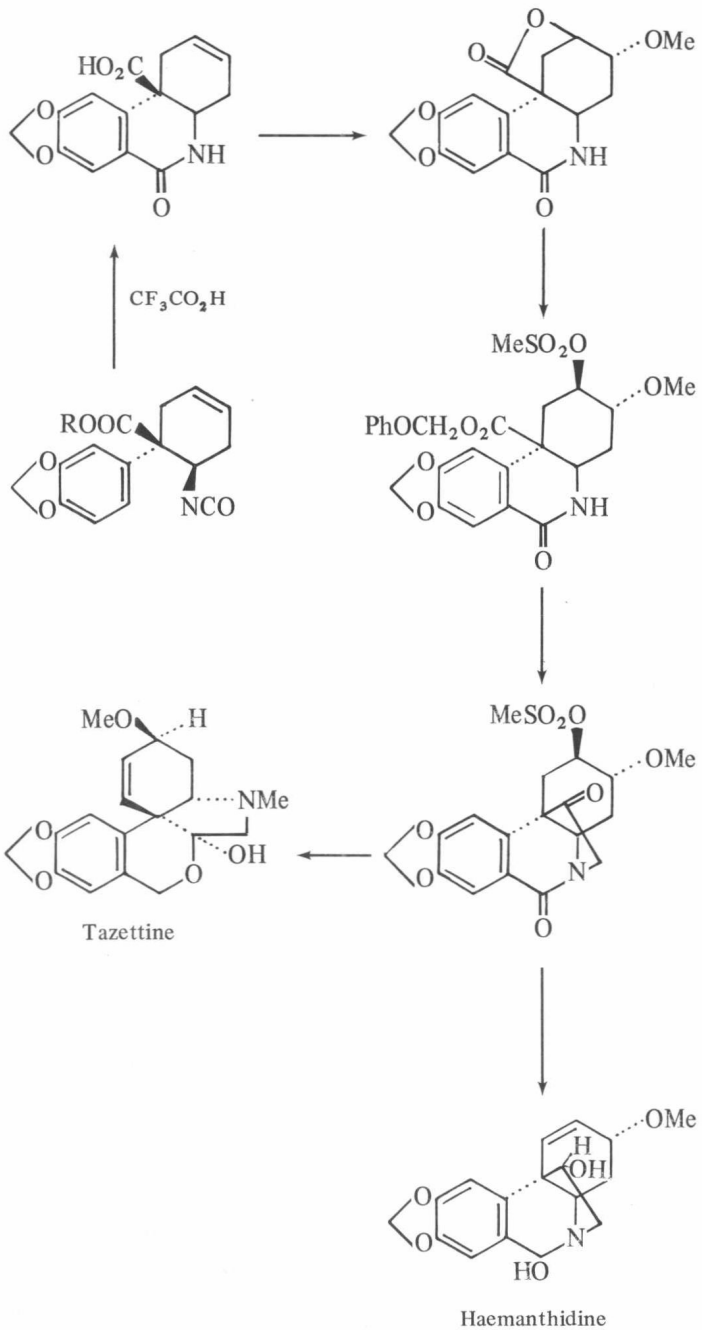
Similarly, the isocyante was converted into the isocarbostyril, which was transformed into haemanthidine and tazettine[18a] (Chart 1-8A).

Syntheses of β-Arylethylamides

Since the syntheses of *N*-acylarylethylamines are very important as starting materials for Bischler-Napieralski reaction, and representative synthetic methods to the amides are described as follows.[19,20]

Schotten-Baumann Reaction (Chart 1-9). This reaction involves an acylation of amines by treatment with an acyl chloride under ice-cooling in dilute alkaline solution. In the case of substances labile to strong alkali, weaker alkaline reagents such as sodium carbonate, bicarbonate, or triethylamine can be used. In some cases, an excess of amine is used to remove the resulting hydrogen chloride

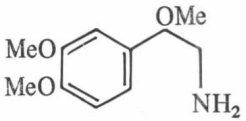
Chart 1-8A.



Tazettine

Haemanthidine

Chart 1-9.



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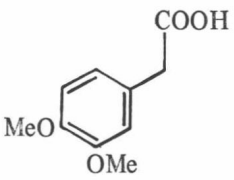
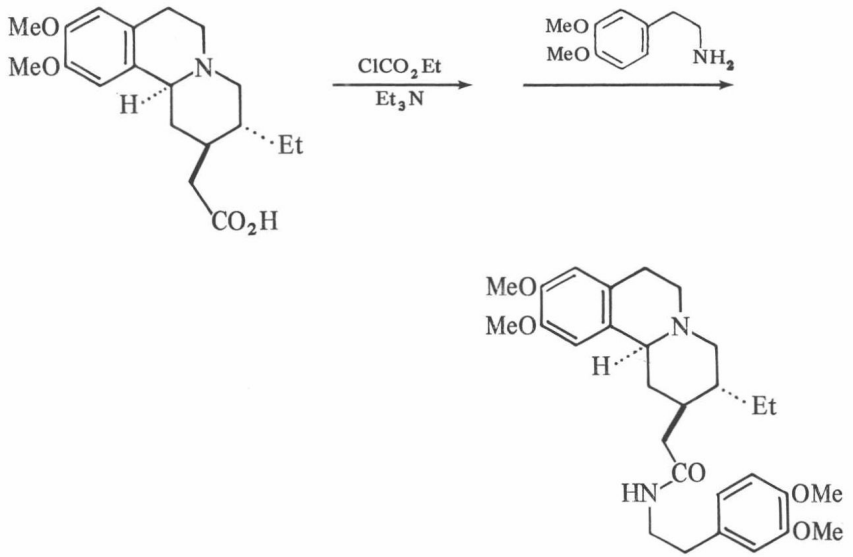


19

as its hydrochloride. Acylation with acid chloride in anhydrous pyridine also gives the amide in good yield. Sugasawa directly synthesized papaverine **6** by heating a mixture of the amine **18** and carboxylic acid **19**, without the isolation of the corresponding amide, in the presence of phosphoryl chloride.[21] The modification of this method was carried out by Battersby as follows.[21a] The carboxylic acid was treated with ethyl chlorocarbonate in the presence of triethylamine in dimethylformamide at $-5°$, and the resulting mixed anhydride, without isolation, was condensed with the homoveratrylamine at $-5\sim0°$ to afford the amide (Chart 1-10).

Chart 1-10.



The Condensation of a Carboxylic Acid with an Isocyanate (Chart 1-11). Amides, which are difficult to prepare by the Schotten-Baumann or other reactions, can often be obtained by the condensation of isocyanates with car-