A STUDY OF THE
BISCHLER-NAPIERALSKI REACTION

By
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fulfillment of the requirements for the
degree of Doctor of Philosophy

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This thesis was assembled under the direction of Dr. Walter H. Hartung, whose aid was essential to its success and whose kindness will always be warmly remembered.

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These pages were typewritten by my wife, Betty, who supplied most of their inspiration.

T A B L E O F C O N T E N T S

I N T R O D U C T I O N

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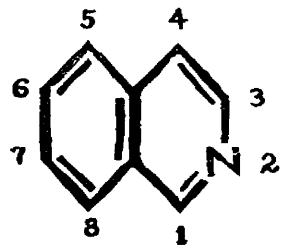
The Bischler-Napieralski reaction was published in 1893 as a method for the synthesis of isoquinoline nuclei. This very important heterocyclic residue has also been known as 2-benzazine and leucoline, and has the structure:

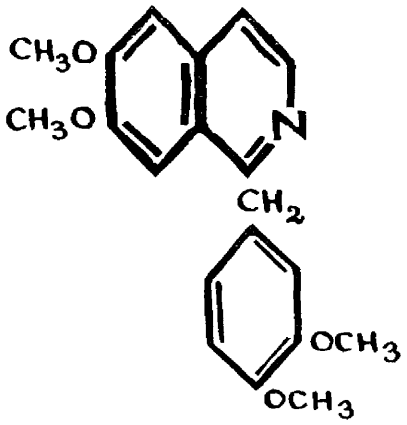


3,4-Dihydro- and 1,2,3,4-tetrahydroisoquinoline derivatives are equally important and are often the forms resulting from ring-closures. It has been shown that 1,2-dihydroisoquinolines are incapable of existence (1). The isoquinoline nucleus is present in many alkaloids (2), notably those of opium, and thus assumes a significant position in the fields of medicinal and alkaloidal chemistry.

Pharmacology of the Isoquinolines —

Synthetic isoquinolines have exhibited such discrepant and diphasic physiological activity that the data so far accumulated are quite uncongenial and only a very thorough study of the entire field can result in usefulness of these compounds as medicinals. Nonetheless, previous workers have reported findings from which some tentative generalities may be culled.

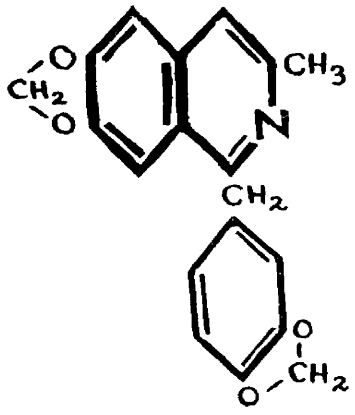
Most naturally-occurring isoquinolines possess the 1-benzyl group, as seen in the smooth-muscle relaxant, papaverine (3), though it has been shown by Bruckner and Fodor (4) that if the methylene portion of the benzyl



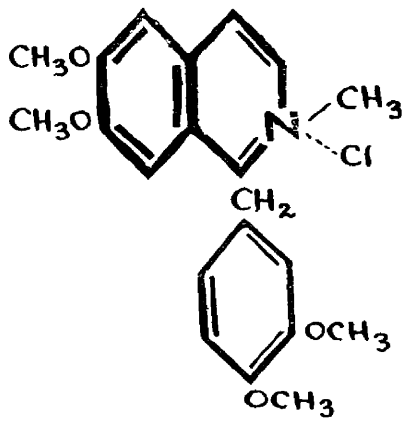
Papaverine

group be omitted, the resulting 1-phenyl compounds are equally potent pharmacologically. The same workers have also shown that a methyl group in the 3-position enhances activity while decreasing toxicity. An antispasmodic similar to papaverine has been marketed in which there is a 3-methyl group (Eupaverine)(3). The tetraethoxy analog of papaverine, known as perperine (5), is also superior to papaverine. Apparently most alkyl- and

alkoxyisoquinolines are depressants of smooth muscle (4,6, 7,8) and there are a number which possess considerable potency. On the other hand, Laidlaw (9) states that when isoquinoline is substituted in the 6,7 and 8-positions with methoxy or methylenedioxy groups the compounds are apt to be strychnine-like if the nitrogen is tertiary and to be devoid of this effect when pentavalent. Thus, papaverine exerts considerable reflex excitatory effect in the background of its antispasmodic action, while papaverine methochloride does not have any stimulatory properties. The presence of free hydroxyl groups also precludes stimulatory manifestations. It has been claimed, though, that isoquinolines containing



Eupaverine



Papaverine methochloride

free hydroxyl groups affect the central nervous system and may be emetic and analgesic (10).

The pharmacological position of 3,4-dihydroisoquinolines is very similar to that of the N-substituted tetrahydroisoquinolines, for the latter are usually distinguished as containing secondary or tertiary nitrogen.

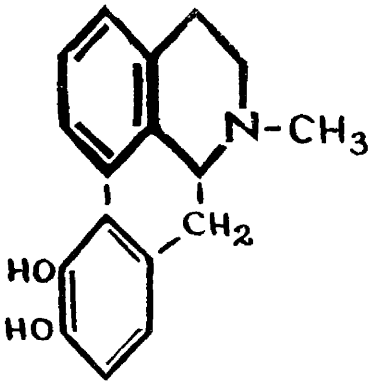
Most of the tetrahydroisoquinolines are reported as stimulatory to smooth muscle (11, 12, 13), though the presence of ethoxy groups tends to confer anticonvulsant powers, and the presence of an N-(ω-phenylalkyl) group larger than benzyl is supposed to result in papaverine-like activity (14). Dihydro and N-alkyltetrahydroisoquinolines exert a strychnine-like stimulation upon the reflexes unless there are free hydroxyl groups or a 1-keto group (9).

The interest in tetrahydroisoquinolines has centered largely upon their cardiovascular activities. Generally, it may be said that the tertiary derivatives are depressors while the secondary amines are pressors (15, 16). This is not entirely true, since the action is often diphasic (12) and is greatly modified by the presence and position of hydroxy, alkoxy and alkyl groups (11, 12, 13, 15, 17). The size of the 2-alkyl group has a marked but irregular effect upon pressor or depressor activity (11) and toxicity (18).

Quaternary ammonium derivatives of the di- and tetrahydroisoquinolines are predominantly of the pressor type (13, 19, 20), though lengthening the carbon chain on the nitrogen may at times convert them to depressors (20). Such reversal of activity upon altering chain-length is well-known among the sympathomimetic amines (21). Quaternary ammonium salts of isoquinolines tend to be devoid of any of the reflex

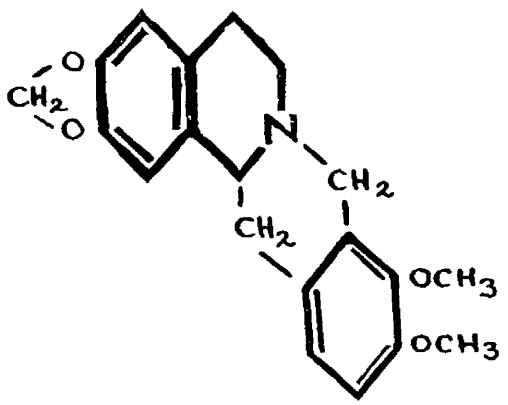
excitation noted among their trivalent antecedents (9).

Two series of naturally occurring cyclized 1-benzyltetrahydroisoquinolines are amenable to generalization (3). The compounds of the first series of which apomorphine is an example, are stimulants of smooth muscle,



Apomorphine

being emetics and spastic poisons by stimulating the motor centers of the brain (22). Other substances of analogous structure exhibiting the same physiological activity are apocodeine, corydine, corytuberine, dicentrine, glaucine and laurotetanine, all of which have the 2'-position of the 1-benzyl group attached directly to the 8-position of the isoquinoline nucleus. There are exceptions to this rule, such as bulbocapnine, but there is sufficient agreement to be significant. The compounds of the second series, which may be represented by canadine, paralyze



Canadine

the central nervous system or spinal cord, and thus have an action opposite to that of the first group even though the external symptoms be similar. Other drugs of this class are berberine, columbamine, corybulbine, corydaline, isocorybulbine and palmatine, all of which have the 2'-position of the 1-benzyl group linked through a methylene group to the nitrogen of the isoquinoline nucleus. It is interesting to note that derivatives of both series possess hypnotic activity in varying degrees, though it is usually secondary to the motor and circulatory effects noted; whereas morphine tends to produce nausea and emesis by central action, though the primary effect is hypnotic (23).

Various other physiologic effects have been recorded. For example, a number of tetrahydroisoquinolines have been examined for antianesthetic properties and showed varying effects from marked prolongation to marked shortening of the sleeping time (24). Respiration is frequently stimulated, though sometimes inhibited. Pancreatic secretion is inhibited by 2-methyl-6,7-dihydroxytetrahydroisoquinoline, probably by vaso-constriction (25).

The picture which has been painted of the pharmacology of the isoquinolines is complex and discontinuous, but it at least provides ample evidence that the isoquinolines offer a rich field of profound physiological

activity, and it suggests that many precious drugs will result when deleterious side-effects are excluded from compounds which are mainly hypnotics, cerebral stimulants, pressors, depressors, spastics or antispasmodics.

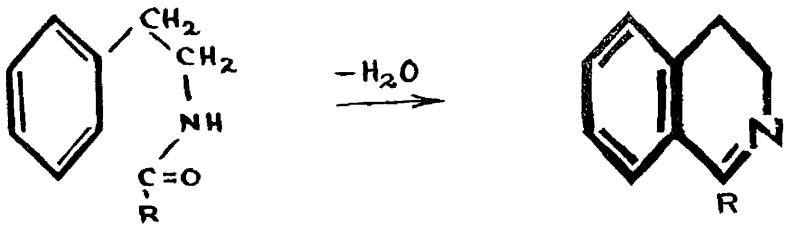
Isoquinoline Syntheses —

The system used here for presenting the various methods of synthesizing isoquinolines is that used by Hollins in his excellent treatise (26). Limited reference has been made to the recent book by Morton on heterocyclic compounds (27). The methods will be only briefly described and selected references given. Following this, the Bischler-Napieralski reaction will be discussed in considerable detail.

I. Ring Closure between the Nucleus and Carbon-1.

1. β-Arylethylamines with Acids.

Bischler and Napieralski obtained dihydroisoquinolines in poor yield by heating N-acyl-β-arylethylamines with P_2O_5 at 250° (28).

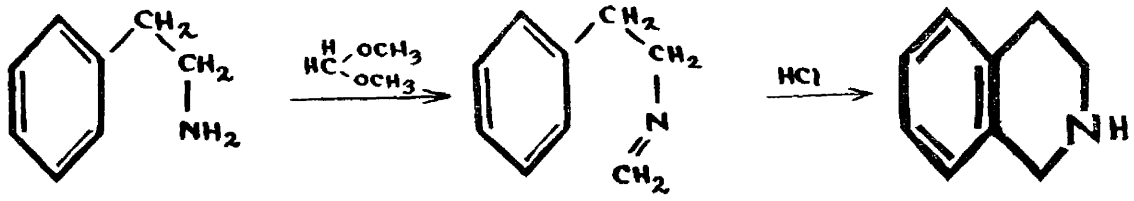


Pictet later improved the method by the milder conditions of boiling the amides with phosphorus pentoxide in toluene or xylene for fifteen minutes (29). The progress of this reaction will

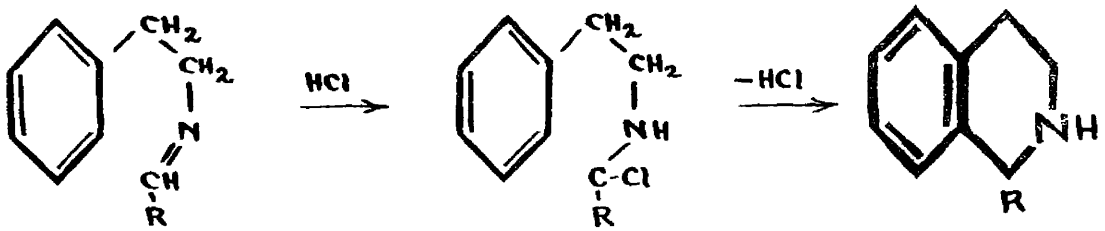
be discussed in a subsequent section.

2. β-Arylethylamines with Aldehydes.

In 1911, Pictet (30,31) prepared tetrahydroisoquinoline in 40% yield by the action of concentrated hydrochloric acid upon β-phenylethylamine and methylal at 100°. In the same manner, 7-hydroxy-



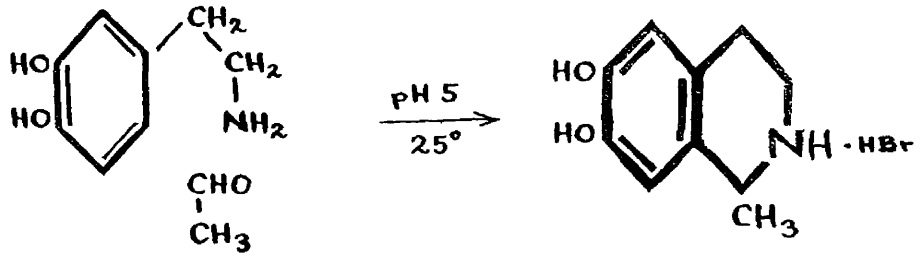
tetrahydroisoquinoline-3-carboxylic acid was synthesized from tyrosine in 75% yield. Two years later, Decker published an extension of the reaction, using higher aldehydes and isolating the intermediate Schiff's bases before effecting closure by means of hydrochloric acid (32), which formed an unstable hydrochloride of the Schiff's base, the latter spontaneously rearranging to the desired tetrahydroisoquinoline. The probable steps are:



Kondo and Ochiai repeated Pictet's work in 1933, concluding that it was unreliable and that Pictet's

theory of biosynthesis from amines and aldehydes was untenable (33). A year later, Helfer prepared 6-methoxytetrahydroisoquinoline in 80% yield by Pictet's method (34), and more recent work has also been corroborative (35).

The suggestion by Pictet that isoquinolines might be formed <u>in vivo</u> by condensation of aldehydes with β-phenylethylamines derived from proteins finally bore fruit in 1934, when Schöpf published a series of articles on the synthesis of various alkaloidal types under physiological conditions. He prepared 1-methyl-6,7-dihydroxytetrahydro-isoquinoline in 83% yield by allowing a mixture of acetaldehyde and β-(3,4-dihydroxyphenyl)-ethylamine hydrobromide (0.04 molar) to stand at 25° and pH 5 for 3 days.

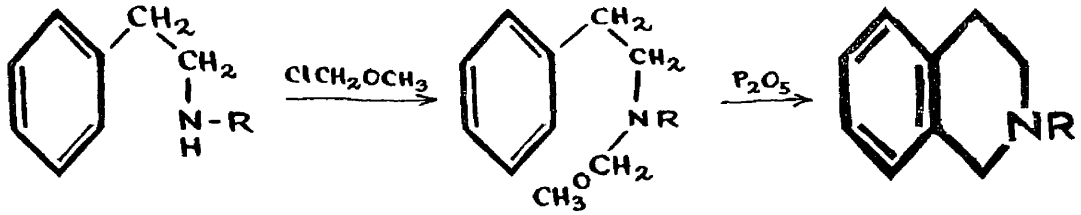


Schöpf believed that para-activation of the nuclear hydrogen by a free hydroxyl group is necessary to the reaction (36), but Hahn demonstrated that the methoxy and methylenedioxy phenethylamines will also condense, though much less completely and rapidly (37). He also succeeded in substituting

α-keto acids for aldehydes and found that the nature of the aldehyde also influenced the reaction. The work has been somewhat extended (38), though the strict dependence upon para-activation and type of aldehyde is limiting.

3. β-Arylethylamines with Chloromethyl Ether.

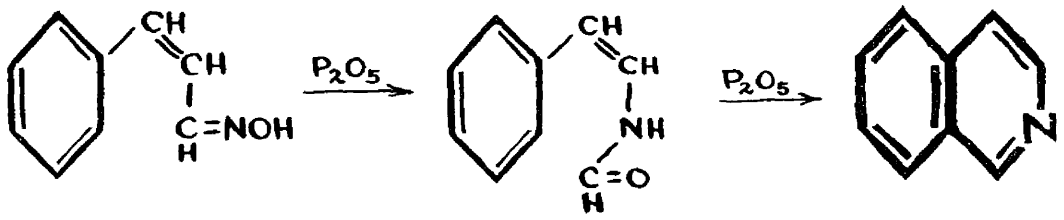
The reaction of phenethylamines with chloromethyl ether represents a special case of the previously described synthesis of isoquinolines from aldehydes. The intermediate methoxymethyl or



hydroxymethyl compound is isolated and treated with phosphorus pentoxide or 10% hydrochloric acid at 100° (39). Obviously, only tetrahydroisoquinolines unsubstituted in the 1-position can be prepared.

4. Beckmann Rearrangement of Oximes.

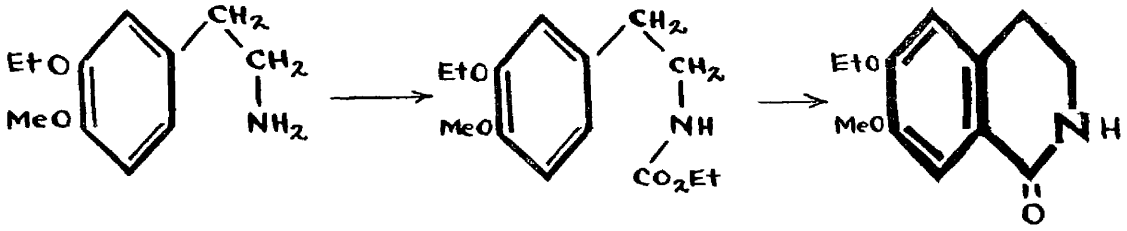
As early as 1894, Bamberger and Goldschmidt obtained isoquinoline itself from cinnamaldoxime and P_2O_5 in 10% yield (40). Pictet obtained 48%



of 1-methyl-3,4-dihydroisoquinoline from benzylacetone oxime and P_2O_5 in toluene (29). Yield of the same product from acetylphenylethylamine by the Bischler-Napieralski reaction was only 33%. The reaction has since been used sporadically by others (41).

5. Miscellaneous.

An isoquinoline may be prepared by cyclizing the urethan of a β-arylethylamine with $POCl_3$ containing a little P_2O_5 in xylene at 140° (42).

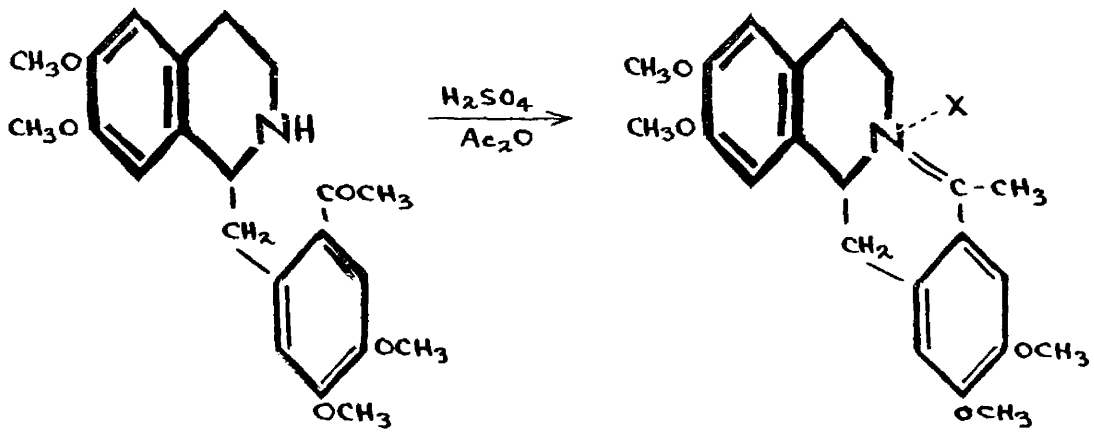


An unusual modification of the Bischler-Napieralski reaction appeared in 1927, resulting in 100% yield of 4-benzyltetrahydroisoquinoline from N-p-toluenesulfonyl-N-(β-benzyl-β-phenylethyl)-glycine and P_2O_5 in boiling xylene (43), or even in the absence of the p-toluenesulfonyl group (44).

II. Ring Closure between the Nitrogen and Carbon-1 or 3.

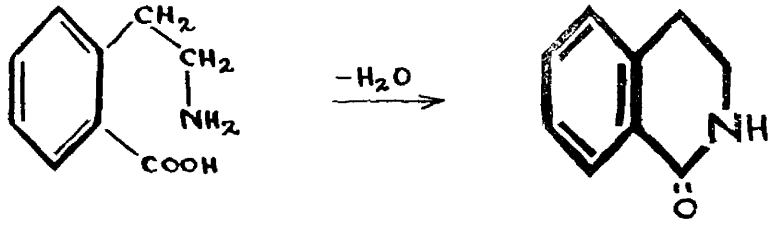
6. From o-Ketonic Arylethylamines.

No simple applications of this reaction have been noted, but it has been used by Schneider for the preparation of coralyn from acetopapaverine (26a).



7. From o-Carboxylic Arylethylamines.

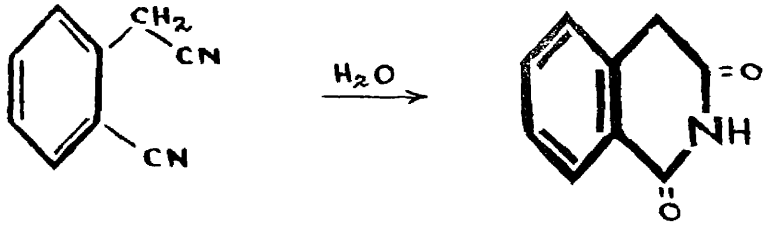
This reaction of limited utility was introduced in 1893 by Bamberger and Dieckmann (45) and



has received only occasional notice (26b).

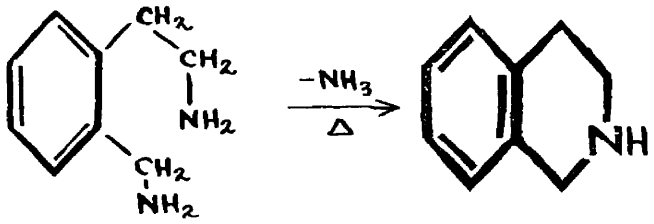
8. From o-Cyanobenzyl Cyanides.

Gabriel devised a number of reactions leading to isoquinolones, which are in reality amides. This particular synthesis leads to a homophthalimide (26c).

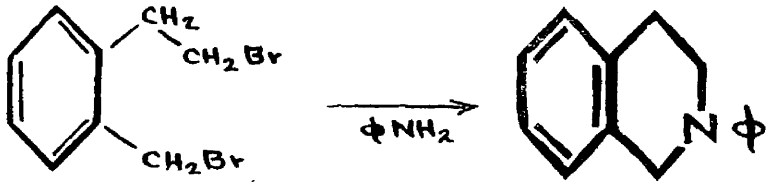


9. From Aminomethyl-arylethylamines.

Helfer published this interesting reaction in 1923, obtaining tetrahydroisoquinoline in 58% yield.

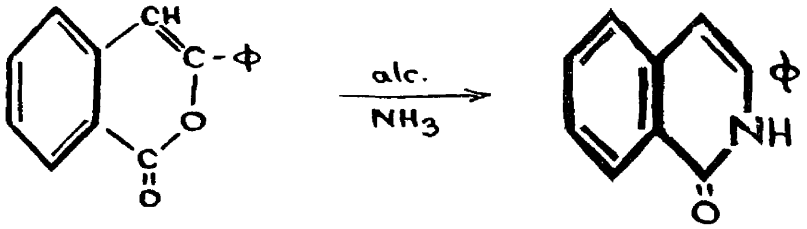


A variation producing N-substituted tetrahydroisoquinolines was also recorded in 1923 by von Braun (26d).

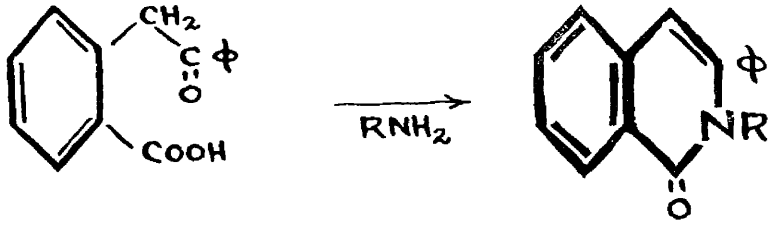


10. From Isocoumarins and Amines.

As early as 1885, Gabriel synthesized 1-isoquinolones by treating isocoumarins with ammonia or amines (26e). The reaction may also be run

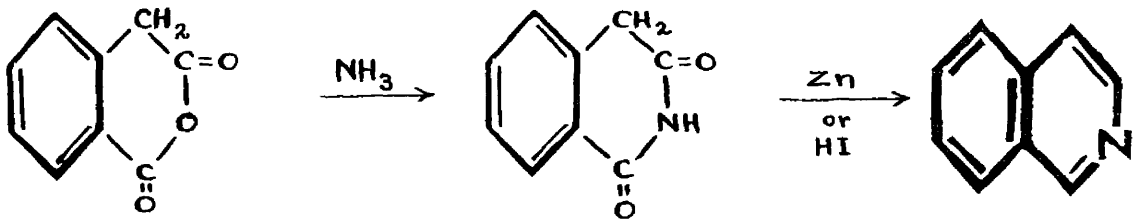


with the free ketonic acid and an amine.



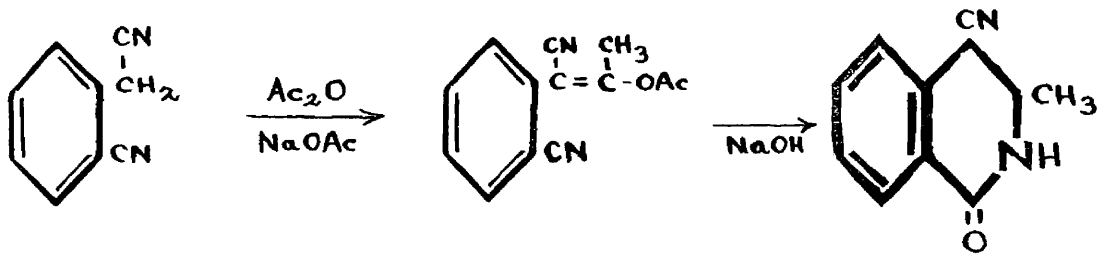
11. From Homophthalic Acids and Amines.

This reaction represents a logical development and is due also to Gabriel (26f).



12. From o-Cyanobenzyl Ketones.

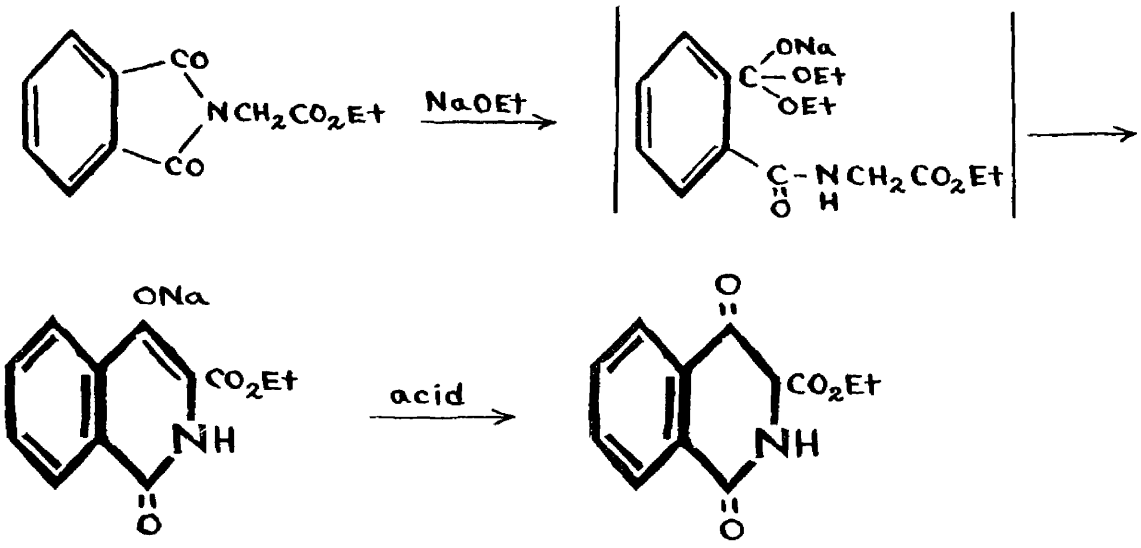
In 1892, Gabriel came forth with a very clever, and perhaps useful, modification of the isocoumarin reaction, in which o-cyanobenzyl cyanide is the starting material (26g). However, the product is an amide and requires reduction to the corresponding isoquinoline.



III. Ring Closure between Carbons-3 and 4.

13. From α-Phthalylamino Esters or Ketones.

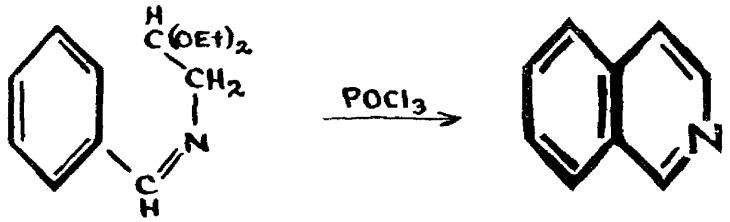
A method for the production of isoquinolones in 65-75% yield was worked out by Gabriel in 1900, based on the phthalimide of compounds in which the α-methylene group is activated, as in α-amino esters or ketones (26h).



IV. Ring Closure between Carbon-4 and the Nucleus.

14. From Aminoacetal and Aldehydes.

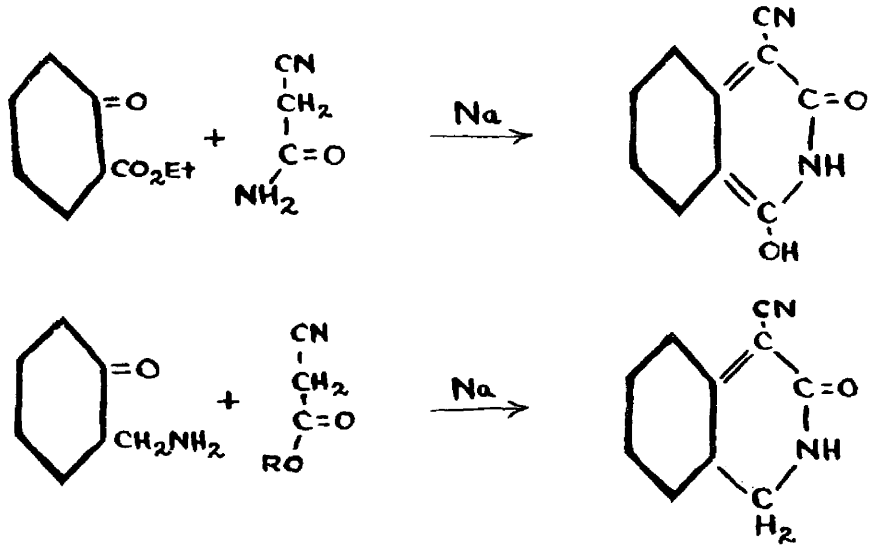
In 1893, Pomeranz and Fritsch independently published upon the fairly popular aminoacetal synthesis, in which a Schiff's base of aminoacetal is made and cyclized with a standard condensing agent (46). Isoquinoline itself may be prepared in 50% yield, whereas 1-methylisoquinoline may be prepared from acetophenone in 15% yield. As may



be expected, when a m-alkoxy group is present in the aldehyde, closure takes place para rather than ortho to the alkoxy group (47). The reaction may also be performed by starting with chloroacetal and a benzylamine.

V. Ring Closure with Cyclohexanones.

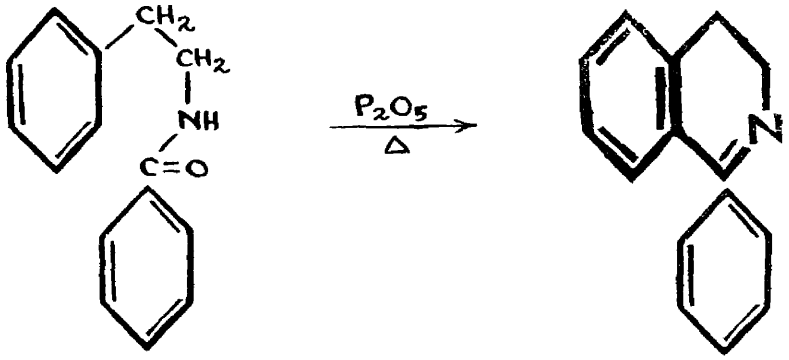
15. A novel synthesis recently accomplished by Basu (27) utilizes the following condensations to produce benzohydrogenated isoquinolones:



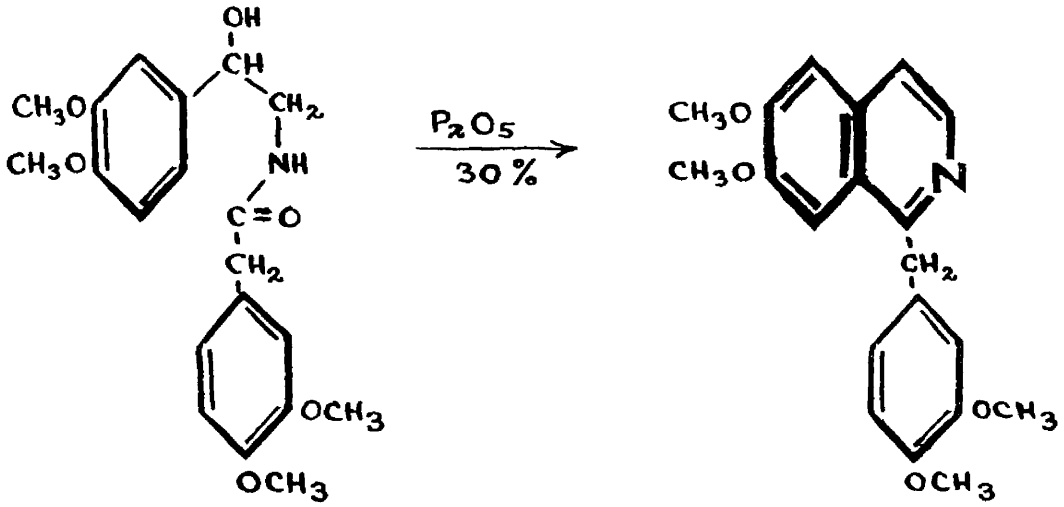
The Bischler-Napieralski Reaction —

By far, the most important and useful synthesis of isoquinolines has been the Bischler-Napieralski reaction. One reason is that the necessary phenethylamines may be prepared (though not easily) from available aromatic aldehydes which contain substituents (methoxy and methylenedioxy) corresponding to those found in the naturally occurring isoquinolines. The immediate product is an isoquinoline or dihydroisoquinoline, rather than an amide. Another reason is that the substituent in the 1-position of the isoquinoline may be changed at will — an important factor in alkaloidal syntheses. And finally, the yields are usually quite satisfactory, with some exceptions which will be noted.

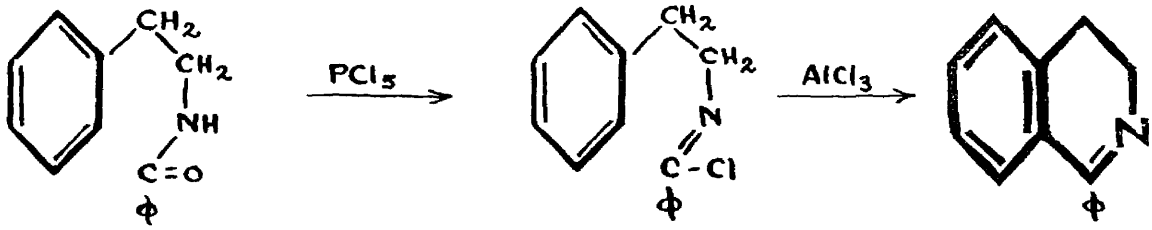
It has been seen that in 1893, Bischler and Napieralski (28) discovered the reaction which bears their names, though they conducted it rather crudely by merely heating a β-phenylethylamide and phosphorus pentoxide a few hours at 250°. The yields of dihydroisoquinolines were poor. They showed that PCl_5 would



not effect ring closure, but produced the imidochloride. Anhydrous zinc chloride closed the ring, probably in poorer yield. In 1909, Pictet improved the synthesis by running the reaction in the presence of a solvent such as toluene, which acted as a temperature moderator (29, 48). He obtained yields of 75% of the 1-phenyl and 1-benzyl derivatives, and 35% of the 1-methyldihydroisoquinoline. The great ingenuity of Pictet is emphasized by his direct synthesis of papaverine according to the equation:

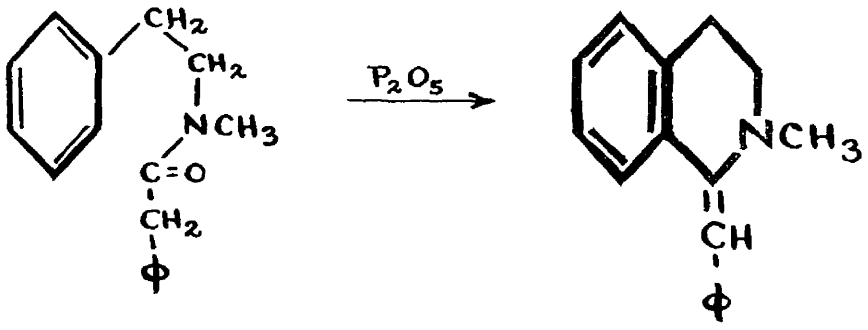


At the same time, Decker succeeded in cyclizing amides in "good yield" with PCl_5 by treating the intermediate imidochloride with anhydrous $AlCl_3$ (49).



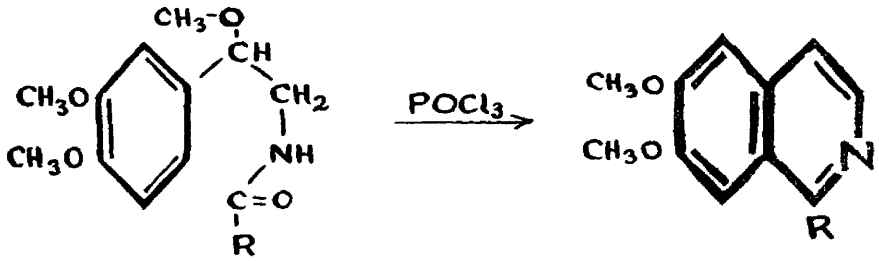
He later used PCl_5 (without $AlCl_3$) as well as $POCl_3$ for ring formation, with acceptable results (50), though he claimed that formyl-β-phenylethylamine yields only a small amount of dihydroisoquinoline and a large quantity of a complex aminomalonamide (51).

In 1916, Hamilton and Robinson showed that a di-N-substituted amide may be condensed by P_2O_5 to an alkylidene-tetrahydroisoquinoline (52), though it is not known if the α-hydrogen atoms of most acids would be active enough for such a migration.

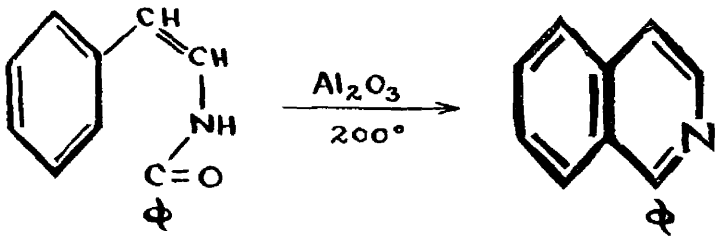


Dihydroisoquinoline-3-carboxylic esters were prepared in 1922 by condensing amides of substituted phenylalanine esters with acid condensing agents, but no yields were given (53). Similar compounds were later prepared by Harwood and Johnson (54).

Mannich (55) prepared papaverine from the methyl ether of the ethanolamine used by Pictet. He prepared



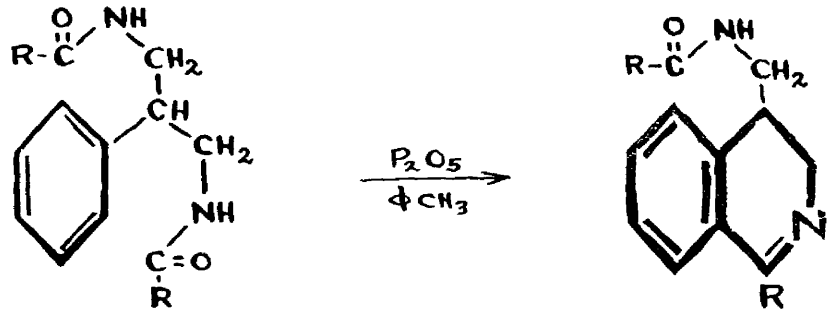
other derivatives in the same way, but stated that the reaction would not proceed if the benzene nucleus of the phenylethylamine was unsubstituted, or in other words if there was no activation of the ortho hydrogen atom. The reaction was further altered by Rosenmund (56), who cyclized N-benzoyl-β-phenylvinylamine in boiling decalin with activated alumina.



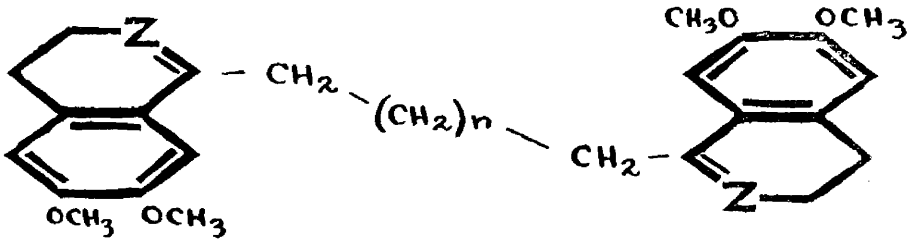
He indicated that the reaction performed by Mannich to synthesize papaverine gave only 6% yield when P_2O_5 was the dehydrating agent.

Some amides containing activating alkoxy groups para to the position of closure may be cyclized at room temperature by standing with PCl_5 in chloroform for several days,(57).

Jackson and Kenner have shown that acylamino derivatives of isoquinolines may be prepared in the usual way (58). It is interesting to note that their



compounds could have cyclized in both directions, but apparently did not. By using the diamides of dicarboxylic acids, the α,ω-bis(1-dihydroisoquinolyl)-alkanes have been prepared by Child and Pyman in about 90% yield (59).



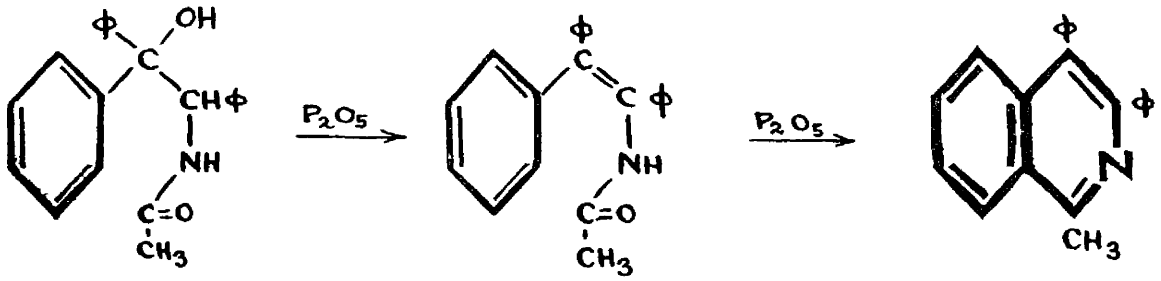
The same workers obtained dihydroisoquinolines containing 1-chloroalkyl and 1-cyanoalkyl groups in good yield, using $POCl_3$ on the corresponding amides (60).

In 1930, the use of tetralin as a solvent was advocated by Späth (61) on the basis that Pictet's method was too mild for cyclizing unactivated amides. He obtained 1-alkyldihydroisoquinolines in yields of 35%-85% and dihydroisoquinoline itself in 18% yield.

3-Methyldihydroisoquinolines containing activating alkoxy groups were reported in 1932 (62), being prepared by the action of $POCl_3$ on the amides in boiling toluene. Three years later, Bruckner (63) began his work on the direct synthesis of 3-methylisoquinolines from amides of 3-hydroxy-3-phenyl-2-aminopropanes and $POCl_3$, all of which contained o,p-directing groups. He obtained yields of about 60% (64). Yields of 60-80% of the same products were obtained by Sugasawa using amides of 3-methoxy-3-phenyl-2-aminopropanes (65).

Krabbe contributed significantly to the theory of the reaction in 1936, when he proved that an N-acylvinylamine is the intermediate in all ring-closures of the

Pictet-Gams type, in which an isoquinoline is produced directly from an acylated phenylalkanolamine or its methyl ether (66). By using an amount of P_2O_5 insufficient for cyclization, Krabbe isolated the intermediate N-acylvinylamines in excellent yield. Upon increasing the amount of P_2O_5 he obtained nearly quantitative yields of isoquinolines substituted in the 3- and 4-positions with phenyl radicals, even though there were no alkoxy groups in the benzo-ring.



Some of the more unusual isoquinolines (or hydrogenated isoquinolines) which have been prepared by the Bischler-Napieralski reaction contain groups such as 1-furylvinyl (80% yield) (67); 1-phthalimidomethyl (87% yield) (68); 1-α-picolyl (50% yield) (69); 1-β-pyridyl (70); 5,6- and 6,7-benz (71); 1-cyclohexyl, 1-cyclohexylmethyl, 1-cyclohexenyl (72); 1-α-furyl, 1-(7-methoxy-2-coumaronyl), 1-(9-phenanthryl) (73); 1-(2-quinolyl), 1-(N-methyl-β-piperidyl), 1-piperidino-

methyl (74); 4,5-trimethylene (75); 6-benzoylamino (76).

The significant facts contained or inferred in the historical survey just presented may be briefly summarized as follows:

1. N-Acyl-β-phenylethylamines may be condensed by dehydrating agents to form 3,4-dihydroisoquinolines. The usual condensing agents are P_2O_5, $POCl_3$, and PCl_5. The application of heat is often required.

2. N-Acyl-β-hydroxy-β-phenylethylamines are dehydrated to N-acyl-β-phenylvinylamines upon treatment with dehydrating agents and upon further treatment condense to isoquinolines. This stepwise sequence has been demonstrated with amides which were unsubstituted in the benzene nucleus.

3. There is no recognized limit to the variety of substituents which may be placed upon the nucleus. Nearly all types of radicals have appeared in the 1-position. The 3- and 4-positions have largely been limited to phenyl radicals, methyl groups and carboxyl groups. The benzo-ring has been substituted usually with alkoxy groups (including the methylenedioxy), acyloxy groups and hydroxy groups.

4. The synthesis of isoquinolines or dihydroisoquinolines having a phenolic function (or derivative)

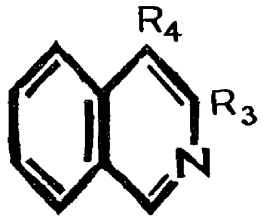
in the 6-position is markedly easier than the synthesis of those not having such para-activation of the abduced hydrogen. No isoquinolines have been prepared in which the benzo-ring carries a meta-directing substituent, and it is doubtful if such a synthesis could be effected.

5. Yields approaching quantitative are obtained from amides having para-activation. When the latter is lacking, condensation is more difficult and ranges around 50-75%. The direct formation of isoquinolines from acylated phenylethanolamines is also more difficult, and it has been stated to be unprofitable in the absence of para-activation (55), though it was effected in unknown yield by Pictet (77).

6. Though not discussed in the literature, the mechanism of ring-closure of N-acyl-β-hydroxy-β-phenylethylamines containing powerful activating groups may not be necessarily that shown by Krabbe for the non-activated amides. Ring-closure is so facile when there is a meta hydroxyl group that closure could easily take place before formation of the vinylamine by loss of water in the 3,4-positions.

Intent of the Thesis —

The previous work of Hartung and his co-workers upon phenylalkanolamines intended for the study of pressor-activity, made available a route to the direct synthesis of isoquinolines having alkyl residues in the 3-position, no alkyl radicals other than methyl having

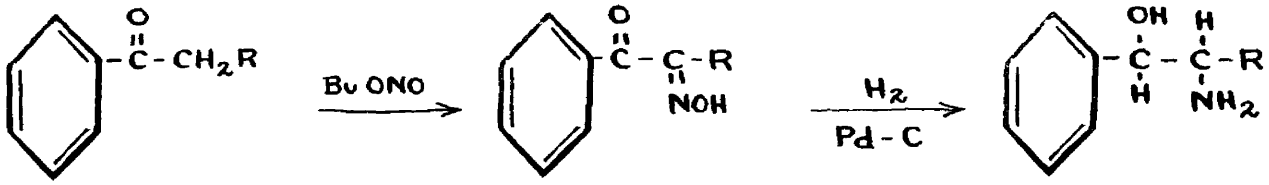


been previously attained. It was determined also to seek an equally navigable route to isoquinolines substituted in the 4-position, and to study the effect of such groups upon the ease of ring-closure in compounds not possessing substituents in the benzo-ring.

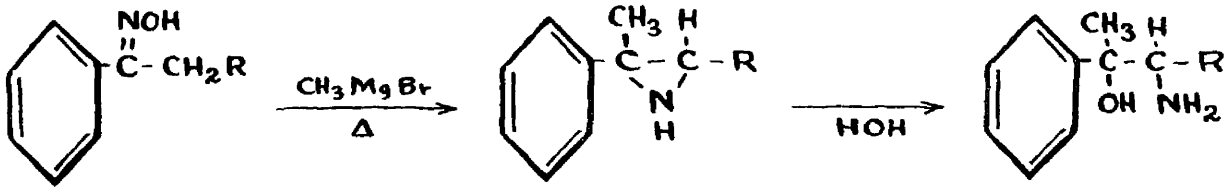
This thesis, then, represents a limited study of the Bischler-Napieralski reaction, with particular interest centering upon the production of isoquinolines having alkyl radicals in the 3,4-positions. The ultimate purposes of the work were to further our knowledge of the particular synthetical method and to permit more extensive pharmacological evaluation of structural variations in the isoquinoline series.

E X P E R I M E N T A L

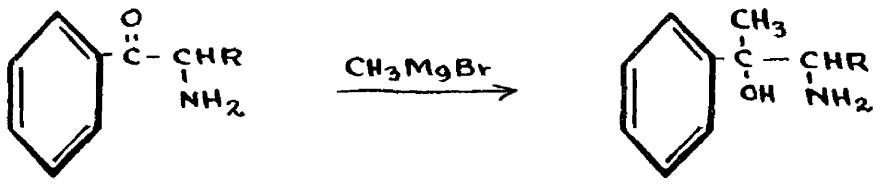
The alkanolamines used for synthesizing 3-alkylisoquinolines were prepared by the method of Hartung (78, 79, 80), as illustrated in the reactions:



The reactions usually proceed easily and efficiently, so that the end-products may be considered as quite available. Branched-chain alkanolamines necessary for preparation of 4-alkylisoquinolines were prepared by the method of Hoch (81) and Campbell (82, 83, 84, 85), utilizing a very unusual Grignard reaction with oximes according to the following scheme:



where R may be H. This particular method has not yet been properly evaluated and is not entirely reliable as used in this thesis. However, it makes important compounds available from inexpensive intermediates and deserves attention. It is also possible, though less convenient, to prepare the branched-chain alkanolamines by the action of a Grignard reagent upon the corresponding α-aminoketone (86, 87).



Preparation of the amides was by the ordinary techniques, the only question being that of possible O-acylation rather than N-acylation. It is well corroborated by previous workers, however, that the nitrogen is more easily acylated than the oxygen in most cases, and if prepared, the O-acyl derivatives tend to isomerize into the corresponding amide (88, 89, 90).

Ring closure of the various amides to isoquinolines and dihydroisoquinolines was studied by using various condensing agents and conditions of treatment, the results of which are discussed in a succeeding portion of this thesis.

The boiling points given are uncorrected; and the melting points were taken on a calibrated Fisher-Johns apparatus modified to deliver up to 50 volts to the heating

element depending upon the melting point range desired. The apparatus was calibrated against Anschütz thermometers checked by the National Bureau of Standards.

THE SYNTHESIS OF INTERMEDIATES

OXIMES AND OXIMINOKETONES-

Acetophenone oxime: A solution of 60 g. (0.5 mole) of acetophenone in 60 cc. of methanol was mixed with a solution of 60 g. (0.85 mole) of hydroxylamine hydrochloride and 60 g. (0.75 mole) of anhydrous sodium acetate in 100 cc. of water. The mixture was allowed to stand 6 weeks in the refrigerator, then the large, white crystals were filtered off and dried. Yield: 58g. (86%) of a product melting at 58-59°. (Accepted m.p. 59° (91). This method of preparing oximes, though sometimes slow, is supposed to be applicable to ketones which are difficult to oximinate. It is claimed that the pH of the buffer system employed is of primary importance (92), though it is to be doubted that there is much buffering capacity with a deficiency of sodium acetate.

A more rapid method of preparing acetophenone oxime was tried, in which the reaction was accomplished in an alkaline medium (5). Sixty grams (0.5 mole) of acetophenone, 42 g. (0.6 mole) of hydroxylamine hydrochloride (dissolved in 50 cc. of water) and 200 cc. of 95% alcohol were mixed in a one-liter flask and slowly treated, while cooling, with a solution of 97 g. (2.4 moles) of sodium hydroxide in 200 cc. of water. The hot solution was cooled, diluted with an equal volume of water and made acid with concentrated HCl.

Upon cooling with ice, the solution deposited a lumpy solid which was filtered off and dissolved in warm alcohol. The alcoholic solution was chilled and diluted with ice, whereupon a thick suspension of white crystals resulted. The filtered product was dried over P_2O_5 in vacuum and melted at 57-58°. Yield: 55 g. (82%).

Propiophenone oxime: A mixture of 67 g. (0.5 mole) of propiophenone, 250 cc. of 95% alcohol and 42 g. (0.6 mole) of hydroxylamine hydrochloride (dissolved in 50 cc. of water) was slowly treated with a solution of 97 g. (2.4 moles) of sodium hydroxide in 200 cc. of water, while cooling. After refluxing for one hour on the steam-bath, the solution was cooled, diluted to one liter with water, made acid with concentrated HCl and extracted twice with benzene. The benzene extract was dried over anhydrous $MgSO_4$ and distilled. The product distilled at 108-110°/2.7 mm. (bath 135°) and solidified upon standing. The white solid melted at 40-45° and weighed 49 g. The product was recrystallized from petroleum ether as large, white crystals melting at 47-53°. Yield: 45 g. (60%). A solid product could not be obtained without distillation. Propiophenone oxime has been reported (93) as melting at 52-53° and boiling at 165°/38 mm.

Oximinoacetophenone: A solution of 23 g. of sodium in 500 cc. of absolute alcohol was treated while cooling with 120 g. (1 mole) of acetophenone and 103 g. (1 mole) of butyl

nitrite. The red mixture was allowed to stand in the refrigerator for five days, after which time 300 cc. of ether was added and the heavy, red sodium salt filtered off and sucked dry. The salt was dissolved in 300 cc. of water, cooled to 5° and treated with 60 g. (1 mole) of glacial acetic acid. The light-yellow crystals were collected and dried in vacuum over P_2O_5. Yield: 65.5 g. (44%) of a product melting around 110°. Upon recrystallization from dilute alcohol the yellow needles melted at 127-128°. Oximinoacetophenone is somewhat soluble in water, an excess of which must be avoided. It is decomposed by boiling water. The method used is that of Claisen (94), who obtained a product melting at 136-138°. Oximination of acetophenone in the presence of hydrogen chloride is very unsatisfactory (79). The use of commercial sodium methoxide in place of sodium was not as satisfactory in the one run made, yielding only 30% of crude product.

α-Oximinopropiophenone: When prepared by the method used for oximinoacetophenone, only 34% of product melting at 112-113° was obtained. Another attempt with the same method, but allowing it to stand one night, refluxing one hour and then isolating the product gave 58% of a rather impure isolate. Recrystallization from toluene yielded white crystals melting at 113-115°. It has been reported as melting at 106° (78). The method of Hartung (78) as described here gave much better results. In a two-liter,

three-necked, round-bottomed flask equipped with a stirrer, reflux-condenser and gas delivery tube were placed a solution of 134 g. (1 mole) of propiophenone and 800 cc. of ether. Hydrogen chloride from a commercial tank was slowly bubbled through the solution while stirring and 1 mole of butyl nitrite was added slowly in small portions, allowing the red color to disappear after each addition. The reaction was mildly exothermic and required one hour. The hydrogen chloride was allowed to bubble through for another 10 minutes, then air was blown through overnight. The next morning only the solid product remained in the flask. It was recrystalized from toluene and ligroin to yield 126 g. (77%) of a product melting at 112-115°. If the reaction was run in benzene rather than ether, it tended to lag until the boiling point of benzene was reached, then proceed with violence. The yield was 105 g. (64%), m.p. 112-114°. The reaction would not proceed at all in glacial acetic acid without hydrogen chloride or with 20% phosphoric acid in ether, nor would it in the absence of any condensing agent over a period of ten days. A variation of the method is known in which methyl nitrite is substituted for the butyl nitrite (96).

<u>α-Oximinobutyrophenone</u>: By the hydrogen chloride method, this compound was obtained as a soft, brown solid which was purified by extracting from toluene with 10% NaOH

and reprecipitating as an oil with concentrated HCl. After some time in the refrigerator a 74% yield of tan product melting at 40-45° resulted. The accepted m.p. is 49°(79). It was found that a small quantity of α-oximinobutyrophenone could be distilled at 106°/0.15 mm. (bath 144°), but a large run exploded upon attempted distillation and the idea was abandoned.

Nitrosation of butyrophenone in the presence of sodium ethoxide by Claisen's method (94) resulted in 105 g. of a mixture melting at 90-115°. Upon recrystallization the m.p. rose to 118-121°. The product was proved to be benzoic acid by reacting it with thionyl chloride, followed by aniline, yielding benzanilide, m.p. 162-164°. (Accepted m.p. 163° (91)). By extraction of an ethereal solution with sodium carbonate solution, followed by acidification, it was shown that the mixture contained 90% of benzoic acid, indicating almost complete oxidation of the ketone.

α-Oximinovalerophenone: This compound was prepared by Hartung's method (78), but was not obtained pure, the 34% of discolored product being used directly in the reductions which will be described. It was found that purification by alkaline extraction resulted in some splitting to benzoic acid. This is in agreement with previous findings on oximino-ketones (93).

α-Oximinocaprylophenone: One hundred grams (0.7 mole) of n-octanoic acid was dissolved in 300 cc. of benzene and

refluxed for 2 hours with 180 g. (1.5 moles) of thionyl chloride, the evolved gases being absorbed in water. Most of the benzene and excess thionyl chloride were removed by vacuum distillation. The residue was then refluxed thirty minutes with another 90-g. portion of thionyl chloride, and again concentrated by vacuum distillation.

A mixture of 100 cc. of benzene and 100 cc. of carbon disulfide was placed in a one-liter flask and 106 g. of anhydrous $AlCl_3$ was added. The slurry was stirred and cooled to below -5° with the aid of dry ice and then the crude octanoyl chloride was dropped in fairly rapidly. The temperature was allowed to rise to room-temperature while stirring and then the reaction was allowed to stand overnight, after which it was poured into 100 cc. of concentrated HCl and 500 g. of cracked ice. The resultant mixture was extracted several times with ether; the ethereal extract was dried and distilled. Yield: 112 g. (78% on two reactions) of caprylophenone, boiling at 128°/1.25 mm. (bath 148°). It has been reported as boiling at 140-145°/5 mm. (79).

The caprylophenone was nitrosated by the method of Hartung (78), but the product was not isolated, being dissolved in isopropanol for reduction to 1-phenyl-2-amino-1-octanol (q.v.).

AMINES-

1-Phenyl-2-aminoethanol (Ethadrin): It was not found possible to prepare this compound by catalytic reduction of oximinoacetophenone by the method of Hartung (80), using three equivalents of methanolic hydrogen chloride, 10% palladium-charcoal catalyst and hydrogen at 400 p.s.i. The intermediate aminoketone was not isolated, either. This fact also corroborates the work of Hartung (79), who succeeded in preparing the compound by a two-stage reduction. About 3.5 g. of 1-phenyl-2-aminoethanol hydrochloride was obtained from Dr. Hartung and used for the subsequent reactions.

1-Phenyl-2-aminopropanol (Propadrin): α-Oximino-propiophenone was reduced by Hartung's method, using 24.5 g. (0.15 mole) of the oximinoketone, 260 cc. of methanol or isopropanol, 42 cc. (0.5 mole) of concentrated HCl, 10 g. of 10% palladium-charcoal catalyst and 400-500 p.s.i. of hydrogen. With pure reactants the reaction would sometimes be completed in 15 minutes. If the methanolic-HCl was prepared in advance from dry hydrogen chloride it would turn pink and poison the catalyst. One poisoned catalyst was regenerated by heating to 500° and was found to possess its original activity.

The reduction mixture was filtered to remove the catalyst,

which could be used many times. The filtrate was concentrated under reduced pressure, then distilled azeotropically with benzene or isopropanol to remove the water so the product could be completely precipitated by addition of ligroin. The product was filtered off and dried in vacuum over P_2O_5. Yields ranged from 52-86%. The hydrochloride melted at 193-195°; it has been reported as melting at 191° (78). The free base could be quantitatively obtained from the hydrochloride by shaking the latter with 20% NaOH and ether, followed by evaporation of the ether to yield white crystals melting at 100°. (Recorded m.p. 103° (78)).

1-Phenyl-2-amino-1-butanol (Butadrin): The hydrochloride was prepared in the same manner as the previous compound in yields of 36 to 47% of a white, crystalline product melting at 252-253° (Recorded m.p. 242° (79)). It was found that if the reduction is carried out at 80° some NH_4Cl is formed.

1-Phenyl-2-amino-1-pentanol (Pentadrin): Prepared in the usual way in 31% yield, the white crystalline hydrochloride melted at 227-228° (Reported m.p. 222° (79)).

1-Phenyl-2-amino-1-octanol (Octadrin): The isopropanolic solution of α-oximinocaprylophenone obtained as described under the preparation of that compound was reduced as usual (but at 80°), yielding 30% (calculated on both reactions) of the hydrochloride melting at 150-155°. (Reported m.p. 157.5° (79). About 5 g. of NH_4Cl was recovered from the reaction.

The splitting of aminoalcohols by hot hydrochloric acid has been used in one method of assaying ephedrin (97).

2-Phenyl-1-amino-2-butanol: The compound was prepared by Campbell's method (see page 26) except that dibutyl ether was used instead of using diethyl ether for preparing the Grignard reagent and then replacing it with toluene. Dibutyl ether is claimed to give nearly as good yields as diethyl ether in Grignard reactions (98). In a one-liter, three-necked flask equipped with stirrer, condenser, thermometer and dropping-funnel were placed 24.3 g. (1 g.-atom) of magnesium turnings and 20 cc. of a solution of 110 g. (1 mole) of ethyl bromide in 100 cc. of dibutyl ether (dried over sodium, then redistilled). Stirring was started and the flask heated gently to start the reaction, which was vigorous and required cooling with a water-bath. One hundred cc. of dibutyl ether was added and then the rest of the alkyl halide over a period of 2 hours, keeping the temperature below 40° to prevent loss of ethyl bromide. The black solution was heated to 65° (white fumes) for a half-hour to dissolve nearly all of the magnesium. Very slowly 27 g. (0.2 mole) of powdered acetophenone oxime was added, while the flask was cooled with cold water. There was considerable frothing due to evolution of ethane. After the addition was complete the temperature was held at 90-95° for a half-hour, then the mixture was cooled and poured into 500 g. of cracked ice and 150 g. of NH_4Cl. The resultant layers were

separated and the organic layer was extracted three times with 4N-HCl. By boiling the acid extract 5 minutes the ethyleneimine was hydrolyzed; the solution was then cooled and neutralized with NaOH. The red oil was extracted with benzene, dried over anhydrous $MgSO_4$ and treated with hydrogen chloride, yielding crystals which were purified by recrystallization from isopropanol-ligroin. Yield: 23 g. (57%) of white hydrochloride melting at 185° (Reported m.p. 181° (85)).

2-Phenyl-3-amino-2-butanol: The reaction described just previously was adapted to this synthesis, utilizing propiophenone oxime and methylmagnesium iodide. Only 2.5% of the hydrochloride was obtained; it melted at 241-243°. (Reported m.p. 244° (86)).

1,1-Diphenyl-2-aminoethanol: The hydrochloride of 1,1-diphenyl-2-aminoethanol was prepared by the action of phenylmagnesium bromide on acetophenone oxime in the usual manner, though the reaction temperature was 135-140°, since Campbell stated that more drastic conditions are necessary when aromatic Grignard reagents are used. The yield in this case was 6% of white crystals melting at 196° (Reported m.p. 192-193° (99)).

AMIDES-

N-Acetyl-β-phenylethylamine: In a 500-cc. Erlenmeyer flask were placed 20 cc. of 20% NaOH (0.1 mole) and 150 cc. of alcohol-free ether, which were cooled and treated successively with 12.1 g. (0.1 mole) of β-phenylethylamine and 11.9 g. (0.15 mole) of acetyl chloride. The resultant mixture was extracted with ether and evaporation yielded an oil which would not crystallize. It was distilled at 135°/0.15 mm. (bath 160°) to give 8 g. (50%) of a white, crystalline product melting at 49-51°. (Accepted m.p. 42-44° (28); 51° (100)).

While cooling in ice, 24.2 g. (0.2 mole) of β-phenylethylamine was treated with 25 cc. of acetic anhydride (redistilled at 137-140°), the reaction being violent. After a half-hour the solution was poured into water and the oil extracted with ether and distilled at 135°/0.15 mm. (bath 160°) to yield 28 g. (86%) of white crystals, m.p. 49-51°.

N-Butyryl-β-phenylethylamine: A mixture of 20 cc. of 20% NaOH (0.1 mole), 150 cc. of alcohol-free ether and 12.1 g. (0.1 mole) of β-phenylethylamine was cooled and treated slowly with 16 g. (0.15 mole) of butyryl chloride. Two clear layers resulted; the upper one was evaporated to give 18.5 g. (97%) of light-yellow crystals, m.p. 42-45°. The product was recrystallized from dilute alcohol as white plates m.p. 45-47°. (Accepted m.p. 49-50° (61).

N-Benzoyl-β-phenylethylamine: A mixture of 40 cc. of 20% NaOH (0.2 mole), 150 cc. of alcohol-free ether and 24.2 g. (0.2 mole) of β-phenylethylamine was cooled and treated slowly with 28.2 g. (0.2 mole) of benzoyl chloride. The entire mixture was evaporated and then recrystallized from dilute alcohol. After drying in vacuum over P_2O_5 the white crystals melted at 113-115° and weighed 39 g. (87%). (Reported m.p. 113-114° (28); 116° (100)).

N-Phenylacetyl-β-phenylethylamine: A solution of 68 g. (0.5 mole) of phenylacetic acid and 90 g. (0.75 mole) of thionyl chloride in 300 cc. of benzene was refluxed for one hour, the evolved gases being absorbed in water. Vacuum distillation yielded 68 g. (88%) of phenylacetyl chloride boiling at 94°/15 mm. (bath 130°). By the same method used for N-benzoyl-β-phenylethylamine, the amide was prepared in 83% yield, m.p. 91-92°. (Reported m.p. 95° (29)).

N-Benzoyl-β-phenylpropylamine: Prepared in 98% yield by the method used for N-benzoyl-β-phenylethylamine, this compound melted at 93-94°. (Reported m.p. 85° (101); 94° (102)). The β-phenylpropylamine was acquired through the generosity of Dr. J. M. Sprague of Sharp & Dohme.

N-Benzoyl-β-phenylisopropylamine: Prepared in 80% yield by the method used for N-benzoyl-β-phenylethylamine, this compound melted at 130°. (Reported m.p. 159-160° (103); 128° (104)). The β-phenylisopropylamine (benzedrin) was generously supplied by Dr. F. Nabenhauer of Smith, Kline

and French.

N-Benzoylethadrin: A mixture of 10 cc. of 20% NaOH (0.05 mole), 50 cc. of alcohol-free ether and 3.5 g. (0.02 mole) of ethadrin-hydrochloride (page 35) was shaken to liberate the free base and then was cooled while being treated with 2.8 g. (0.02 mole) of benzoyl chloride. After ten minutes the ether was evaporated by a stream of air and the resultant solid was recrystallized from dilute alcohol as 4.3 g. (90%) of white crystals, m.p. 110-115°. Upon recrystallization from dilute alcohol and drying in vacuum over P_2O_5 the m.p. was 112-113°. Further purification gave gleaming white crystals which melted at 112-114°. (Reported m.p. 149° (89, 100)). Despite the discrepancy in melting points, the amide gave excellent yields of 1-phenylisoquinoline.

N-Acetylpropadrin: The method used for N-benzoylethadrin (page 41) yielded 52% of N-acetylpropadrin, m.p. 130°. Substitution of acetic anhydride for the acetyl-chloride resulted in 34-58% of a product melting at 133-135°. (Reported m.p. 135° (88, 106)).

A mixture of 3.7 g. (0.02 mole) of propadrin hydrochloride (page 35), 2.0 g. of anhydrous sodium acetate and 10 cc. of acetic anhydride was allowed to stand for a half hour at room temperature, then heated to boiling, cooled and treated with water. The turbid solution was extracted with ether and evaporated to an oil, 1.7 g. (44%), which slowly crystallized forming light-yellow crystals, m.p. 130-

135°. The compound was distilled at 150°/0.4 mm. (bath 190°) as a white liquid which cooled to a glass, then crystallized, m.p. 130-135°. After recrystallization from isopropanol-ligroin the m.p. of the white, salt-like crystals was 133°. Repetition with larger quantities yielded 98% of a white liquid boiling at 135°/0.08 mm. (bath 185°), which tended to form a glass on cooling and would crystallize only when warmed (to increase molecular mobility?), yielding a solid melting about 100°. It is believed, however, that this product was quite pure.

N-Butyrylpropadrin: The general method used to prepare N-benzoylethadrin (page 41) yielded 79% of this compound as fluffy, white plates, m.p. 93-94°.

N-Benzoylpropadrin: Benzoylation of propadrin was accomplised by the method used for N-benzoylethadrin, 92% of a white compound melting at 146° being obtained. Recrystallization from dilute alcohol and drying raised the m.p. to 151-152°. (Reported m.p. 142° (105)). Use of impure propadrin hyarochloride and lack of care in the recrystallization sometimes resulted in yields as low as 65-70% of white product. Substitution of pyridine for the NaOH was very unsatisfactory as to yield and purity of the amide.

N-(Phenylacetyl)-propadrin: The method described for N-benzoylethadrin (page 41) yielded 74-78% of N-(phenylacetyl)-propadrin as white crystals, m.p. 117-119°.

N-(Phenylacetyl)-pseudopropadrin: A mixture of 6 g. of pseudopropadrin (the diastereoisomer of propadrin, obtained from Dr. Hartung) and 5.5 g. of phenylacetic acid

was heated to 180° for two hours, then cooled. A thick gel resulted which solidified after standing several months, the yellow product melting at 80-90°. After recrystallization from isopropanol and ligroin, the white crystals melted at ca. 105°.

N-Benzoylbutadrin: The N-benzoylethadrin method gave 82-98% of this amide, m. p. 156-157°, in the form of fluffy, white needles. The yield depended largely upon the purity of the butadrin hydrochloride used.

2-Phenyl-1-benzoylamino-2-butanol: This amide was obtained in 99% yield by the action of benzoyl chloride upon the corresponding amine, as described in the preparation of N-benzoylethadrin. The white crystals melted at 117°. (Reported m. p. 115° (85)).

2-Phenyl-3-benzoylamino-2-butanol: By the N-benzoylethadrin method, 81% of small, white needles, m. p. 150-151°, was obtained.

N-Benzoylpentadrin: The N-benzoylethadrin method yielded 93-95% of the benzamide from pentadrin hydrochloride. The fluffy, white needles melted at 150-151°.

N-Benzoylhexadrin: Hexadrin hydrochloride (obtained from Dr. Hartung) was benzoylated by the method used for N-benzoylethadrin (page 41), yielding 74% of fluffy, white crystals, m. p. 151-152°.

N-Benzoyloctadrin: The usual method yielded 77-86% of N-benzoyloctadrin from the amine hydrochloride. The fine,

white needles melted at 77-78°.

1,1-Diphenyl-2-benzoylaminoethanol: Prepared in 74% yield by the general method (page 41), the white needles melted at 183-185°. (Reported m. p. 182° (107)).

1,2-Diphenyl-2-benzoylaminoethanol: This amide was prepared from 1,2-diphenyl-2-aminoethanol hydrochloride (obtained from Dr. Hartung) by the general method in 88% yield, m. p. 225-230°. The white solid was recrystallized from dilute acetone and melted at 242°. (Reported m. p. 235-236° (108); 236-237° (109)).

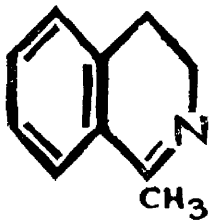
1-(α-Naphthyl)-2-benzoylaminopropanol: Prepared in the usual way from the corresponding amine hydrochloride (obtained from Dr. Hartung) in 83% yield and recrystallized from methyl cellosolve, the white needles melted at 172-173°.

α-Benzoylaminopropiophenone: The amine hydrochloride (obtained from Dr. Hartung) was benzoylated by the general method, yielding 92% of light-yellow crystals, m. p. 102-103°. Recrystallization from dilute alcohol gave white plates, m. p. 104-105°. (Reported m. p. 103° (110)).

THE SYNTHESIS OF ISOQUINOLINE DERIVATIVES

DIHYDROISOQUINOLINES-

1-Methyl-3,4-dihydroisoquinoline:



70%

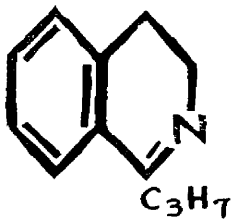
(Method I) A mixture of 10.0 g. of N-acetyl-β-phenylethylamine, 40 g. of P_2O_5 and 150 cc. of toluene in a 500-cc. flask was shaken and then refluxed a half-hour, though the mixture turned black after ten minutes. After cooling, the contents of the flask were treated with ice to destroy the excess condensing agent. The mixture was made alkaline, then acid to congo red, separated and washed with benzene, discarding the organic layers. The aqueous portion was made strongly alkaline with 20% NaOH and extracted with benzene, after which the benzene solution was dried over anhydrous magnesium sulfate and treated with hydrogen chloride. The oil obtained was crystallized from isopropanol and ligroin, yielding 1.1 g. (11%) of product melting at 195-200°. The white hydrochloride was recrystallized from isopropanol-ligroin, m. p. 198°. (Reported m. p. 160° (29)). The picrate melted at 193° (Reported m. p. 188-190° (29)).

A repetition of the experiment, using 5.0 g. of amide,

20 g. of P_2O_5 and 75 cc. of benzene resulted in 10% of tan crystals, m. p. ca. 150°.

(Method II) Five grams of N-acetyl-β-phenylethylamine, 10 g. of P_2O_5, 10 g. of $POCl_3$ and 75 cc. of dry xylene were refluxed one hour. After decomposing the condensing agents with ice, the layers were separated, the aqueous layer (after washing with benzene) was made strongly alkaline with 20% NaOH and extracted with benzene. The benzene extract was dried over anhydrous magnesium sulfate and treated with hydrogen chloride from a commercial cylinder. The oily mixture was concentrated and the hydrochloride crystallized from isopropanol-ligroin as 3.5 g. (70%) of lemon-yellow needles, m. p. 196-198°.

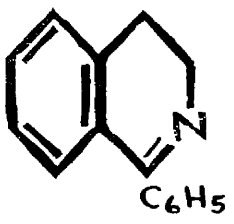
1-Propyl-3,4-dihydroisoquinoline:



?%

Attempts to cyclize N-butyryl-β-phenylethylamine by methods I and II resulted in a dark, oily hydrochloride which could not be crystallized, though ring-formation had probably occurred.

1-Phenyl-3,4-dihydroisoquinoline:



100%

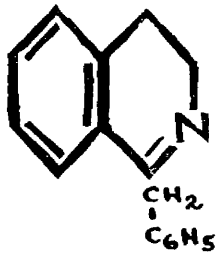
A mixture of 15 g. of N-benzoyl-β-phenylethylamine, 60 g. of P_2O_5 and 200 cc. of toluene was condensed by method I (page 45) in three hours, yielding 12.5 g. (83%) of white, crystalline hydrochloride, m. p. 230-235°. After recrystallization from isopropanol and ligroin the comound melted at 240-242°. (Reported m. p. 223° (29); 225° (50a)). The picrate melted at 178° (Reported m. p. 163° (29), 175° (49)). Substitution of anhydrous aluminum chloride for the phosphoric anhydride in this reaction resulted in much tar and no product.

Three grams of N-benzoyl-β-phenylethylamine and 20 g. of activated alumina (powdered Harshaw Puralox) were sealed into a ten-inch, thick-walled Pyrex tube at 0.25 mm. absolute pressure. The tube was placed in a 1" x 12" iron pipe having perforated screw-caps, and placed in a furnace heated to 350°. After 25 minutes the glass tube exploded, but the reaction mixture was recovered and worked up as in method I. No hydrochloride was isolated.

Three grams of amide, 100 cc. of decalin and 30 g. of Puralox alumina (previously pulverized and heated to 700°) were refluxed fourteen hours. The alumina was filtered out and most of the decalin evaporated under reduced pressure. Crystals of the original amide, m. p. 116°, were recovered, weighing 1.0 g. The filtrate was converted into the hydrochloride as in method I, yielding only about 0.2 g. of the impure salt.

Three grams of N-benzoyl-β-phenylethylamine, 10 g. of P_2O_5 and 10 g. of $POCl_3$ in 25 cc. of dry xylene were refluxed three hours and then treated as in method II, yielding 3.0 g. (100%) of fine, white crystals, m. p. 245-248°.

1-Benzyl-3,4-dihydroisoquinoline:



80%

Five grams of N-(phenylacetyl)-β-phenylethylamine, 15 g. of P_2O_5 and 30 cc. of toluene were refluxed for 1.5 hours, then the excess phosphoric anhydride was decomposed with ice, the mixture made strongly alkaline and extracted with toluene. The extract was dried over anhydrous sodium sulfate and distilled, collecting the product at 130°/0.25 mm. (bath 181°). Yield: 3.0 g. (60%) of a yellow, viscous oil giving a picrate, m. p. 176-178° (Reported m. p. 174-175° (29), 182° (50a), 173-175° (61)), and a hydrochloride, m. p. 227-229°. (Reported b. p. 196°/12 mm. (29), 130-140°/35 mm. (50a)).

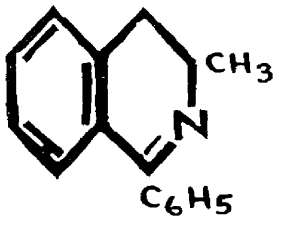
An attempt to close the ring by refluxing 5.0 g. of amide, 20 g. of $POCl_3$ and 30 cc. of toluene for 1.5 hours was unsuccessful, as was an attempt to cyclize by allowing the amide to stand one month at room temperature with $POCl_3$. It was thought that heat alone might effect cyclization, but the amide distilled unchanged at 145°/0.022 mm. (bath 215°)

and melted at 92-93°.

Cyclization was not effected by warming 10.0 g. of N-(phenylacetyl)-β-phenylethylamine with 11 g. of PCl_5 on the steam bath for 6 minutes (liquefaction occurred), then removing the $POCl_3$ by suction and refluxing the residue with 6 g. of anhydrous aluminum chloride in 100 cc. of ligroin for 6 hours. Neither was closure accomplished by treating a benzene solution of the amide with boron trifluoride for fifteen minutes at room temperature.

Refluxing 5.0 g. of N-(phenylacetyl)-β-phenylethylamine, 15 g. of P_2O_5 and 30 cc. of toluene for two hours as in method I (page 45) resulted in 1.2 g. (24%) of the hydrochloride. However, when 5.0 g. of amide, 20 g. of P_2O_5 and 100 cc. of xylene were refluxed 3.5 hours and the product worked up in the manner of method II (page 46), there resulted 4.0 g. (80%) of tan crystals, m. p. 220-225°.

1-Phenyl-3-methyl-3,4-dihydroisoquinoline:



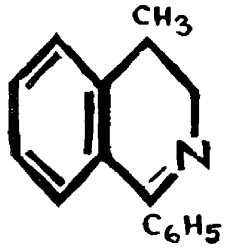
24%

Reaction of 2.0 g. of N-benzoyl-β-phenylisopropylamine with 20 g. of P_2O_5 according to method I yielded 12-19% of tan crystals, m. p. 205-210°.

Cyclodehydration of 5.0 g. of amide with 50 g. of P_2O_5 and 50 g. of $POCl_3$ in 150 cc. of dry xylene by refluxing

three hours according to method II gave 0.9 g. (13%) of the tan hydrochloride, m. p. 205-210°. Repetition using only 25 g. of P_2O_5 with 50 g. of $POCl_3$ resulted in 1.2 g. (24%) of product, the whole reaction being lighter in color.

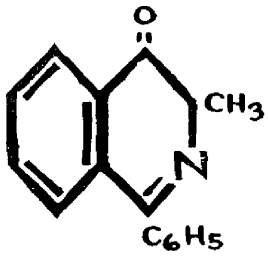
1-Phenyl-4-methyl-3,4-dihydroisoquinoline:



92%

Treatment of 5.0 g. of N-benzoyl-β-phenylpropylamine with 20 g. of P_2O_5 in 100 cc. of toluene according to method I gave 4.6 g. (92%) of white, crystalline hydrochloride, m. p. 193°; picrate m. p. 152°.

1-Phenyl-3-methyl-4-keto-3,4-dihydroisoquinoline:

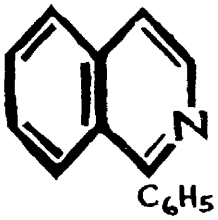


0%

Ring-closure by refluxing 5.0 g. of α-benzoylaminopropiophenone, 40 g. of P_2O_5 and 125 cc. of xylene for three hours was unsuccessful, as was an attempt according to method II (page 46).

ISOQUINOLINES-

1-Phenylisoquinoline:

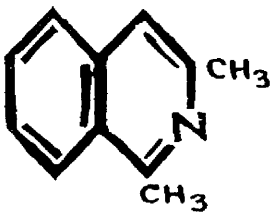


91%

Two grams of N-benzoylethadrin, 20 g. of P_2O_5 and 75 cc. of toluene were refluxed three hours, then worked up as in method I (page 45), yielding 1.62 g. (81%) of white, crystalline hydrochloride, m. p. 237-239°. (Reported m. p. 235-236° (48a)).

Refluxing 1.00 g. of amide with 5 g. of P_2O_5 and 10 g. of $POCl_3$ in 25 cc. of xylene for three hours and then treating the mixture as in method II (page 46), resulted in the isolation of 0.91 g. (91%) of white, microcrystalline hydrochloride, m. p. 233-236°; picrate m. p. 174° (Reported m. p. 164° (29)).

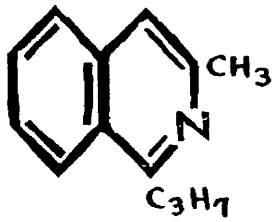
1,3-Dimethylisoquinoline:



37%

According to method I, 2.70 g. of N-acetylpropadrin, 15 g. of P_2O_5 and 50 cc. of toluene were refluxed three hours, then converted to the hydrochloride, giving 1.10 g. (37%) of white crystals, M. p. 150-160°. After recrystallization from isopropanol-ligroin the product melted at 168°.

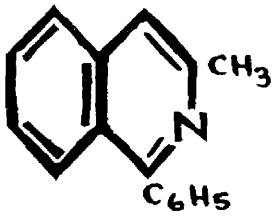
1-Propyl-3-methylisoquinoline:



35%

Two grams of N-butyrylpropadrin, 10 g. of P_2O_5 and 20 g. of $POCl_3$ in 50 cc. of dry xylene were refluxed three hours and treated as in method II (page 46), yielding 0.7 g. (35%) of white powder, m. p. 165°.

1-Phenyl-3-methylisoquinoline:



50%

(Method III) One gram of N-benzoylpropadrin in 30 cc. of toluene was refluxed one hour with 5 g. of P_2O_5, then one hour with the addition of 5 g. of fresh P_2O_5 and finally a third hour with another 5-g. portion. After decomposing the excess P_2O_5 with ice, the mixture was made alkaline, then acid to congo red and separated, discarding the organic layer and washings. The aqueous portion was made alkaline with 20% NaOH and extracted with ether, the extract being dried over anhydrous magnesium sulfate and evaporated to dryness. A colorless oil resulted which crystallized *in vacuo* over NaOH pellets to 0.27 g. (31%) of a white solid, m. p. 115-120°. Recrystallization from ligroin raised the melting point to 123-125° for the free base.

Two grams of N-benzoylpropadrin in 100 cc. of xylene was successively refluxed one-half hour with three 10 g. portions of P_2O_5, then refluxed two hours longer after standing overnight. The excess P_2O_5 was hydrolyzed with ice, the mixture was made strongly alkaline and extracted with benzene. After drying over anhydrous magnesium sulfate the benzene extract was treated with hydrogen chloride, concentrated and treated with ligroin and isopropanol to give 0.24 g. (12%) of a white hydrochloride, m. p. ca. 210°; picrate m. p. 188°.

A mixture of 75 cc. of toluene and 20 g. of P_2O_5 was refluxed fifteen minutes, then 2.00 g. of N-benzoylpropadrin was added and refluxing continued 45 minutes, by which time the P_2O_5 had formed a thick cake, as is usual in these reactions. Five grams of P_2O_5 was added and refluxing continued one hour, after which the mixture was treated as in the preceding experiment, yielding 0.4 g. of fluffy, white hydrochloride, m. p. 228°. The mother-liquor gave 0.78 g. of substance melting at 110° which was recrystallized as 0.44 g. of white crystals, m. p. 226-229°. Total yield: 0.84 g. (42%). Recrystallization from isopropanol and ligroin yielded white microcrystals, m. p. 229°.

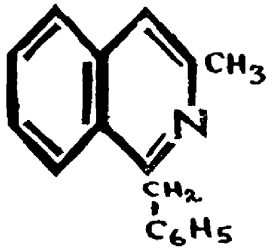
Attempts to cyclize N-benzoylpropadrin with concentrated sulfuric acid or sulfuric acid containing P_2O_5 were unsuccessful. Heating the amide without a solvent with ten parts of P_2O_5 for one hour at 250° yielded only 8% of a tan powder melting poorly around 200°. Refluxing the amide in toluene

with ten parts each of P_2O_5 and P_2S_5 for three hours did not produce any amine. Neither did refluxing the amide in dry xylene with ten parts of PCl_5 for ten hours. A mixture of 75 cc. of purified tetralin, 2.0 g. of N-benzoyl-propadrin and 20 g. of P_2O_5 was refluxed for one hour, then treated as in method II (page 46), yielding 0.7 g. (35%) of light-yellow hydrochloride, m. p. 200-220°. It was found that practical tetralin (Eastman) reacts with P_2O_5 upon being heated, forming a dark, intractable solid, whereas redistilled tetralin (80°/10 mm.) does not react with P_2O_5.

(Method IV) Two grams of N-benzoylpropadrin, 20 g. of P_2O_5 and 20 g. of $POCl_3$ in 50 cc. of dry xylene were refluxed 2.5 hours and converted to the hydrochloride of 1-phenyl-3-methylisoquinoline as in method II. One gram (50%) of white product was obtained, m. p. ca. 205°.

Treatment of the amide in xylene with $POCl_3$ alone (20 parts) under the same conditions yielded 45% of an inferior product which was tan and melted gradually up to 180°.

1-Benzyl-3-methylisoquinoline:



20%

Cyclodehydration of 2.00 g. of N-(phenylacetyl)-propadrin

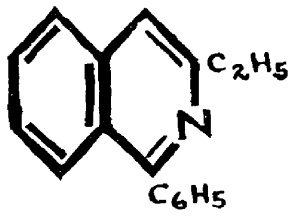
as in method III (page 52) yielded an oil which was converted to 0.21 g. (10%) of the corresponding hydrochloride, recrystallized from isopropanol-ligroin as white microcrystals, m. p. 175-177°.

A mixture of 75 cc. of purified tetralin, 2.0 g. of amide and 20 g. of P_2O_5 was refluxed fifteen minutes, then 10 g. of fresh P_2O_5 was added and refluxing continued for 45 minutes. Working up the product by method II (page 46) gave 0.4 g. (20%) of tan crystals, m. p. 207°d.

(Method V) Refluxing 2.0 g. of N-(phenylacetyl)-propadrin, 10 g. of P_2O_5 and 20 g. of $POCl_3$ in 50 cc. of dry xylene for three hours, then treatment as in method II, resulted in 0.32 g. (16%) of white powder, m. p. 180-190°.

Application of method V to the cyclodehydration of N-(phenylacetyl)-pseudopropadrin yielded an oil which could not be crystallized, preventing any comparison of ease of cyclization of the two diastereoisomers of propadrin.

1-Phenyl-3-ethylisoquinoline:

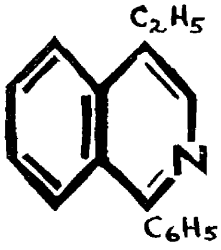


26%

Cyclization of N-benzoylbutadrin (2.0 g.) by method III (page 52) yielded 0.07 g. (3.5%) of a hydrochloride, m. p. 190-195° and 0.37 g. of a neutral, insoluble substance, m. p. 205° (N, found: 4.30, 3.94%).

Application of method IV (page 54) to the condensation of N-benzoylbutadrin yielded 1.3 g. (26%) of nearly white hydrochloride from 5 g. of amide, the salt melting at ca. 210°.

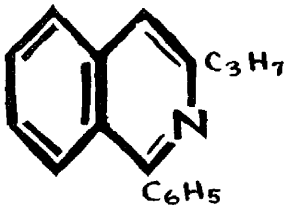
1-Phenyl-4-ethylisoquinoline:



10%

Five grams of 2-phenyl-1-benzoylamino-2-butanol, 50 g. of P_2O_5 and 150 cc. of toluene (or xylene) were refluxed three hours, then treated as in method I (page 45), giving 0.25-0.5 g. (5-10%) of tan hydrochloride, m. p. 110-113°. The product was recrystallized from isopropanol and ligroin as white needles, m. p. 113-115°; picrate m. p. 165°.

1-Phenyl-3-propylisoquinoline:



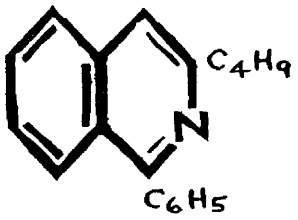
20%

Four grams of N-benzoylpentadrin, 32 g. of P_2O_5 and 100 cc. of xylene were refluxed three hours, then worked up by method I, giving 0.12 g. (3%) of tan powder, m. p. ca. 100°. Similar treatment in decalin with 20 parts of P_2O_5 gave only a red oil.

Cyclization of 2.0 g. of amide by method IV (page 54)

yielded 0.4 g. (20%) of white hydrochloride, m. p. 180-190°. Recrystallization from isopropanol-ligroin did not alter the melting point.

1-Phenyl-3-butylisoquinoline:

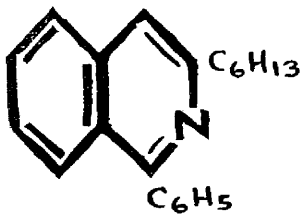


1%

Two grams of N-benzoylhexadrin, 16 g. of P_2O_5 and 50 cc. of xylene were refluxed three hours and the product converted to its hydrochloride by method I (page 45), producing only 0.012 g. (0.5%) of tan crystals.

Treatment of 2.5 g. of the amide according to method V (page 55) gave 0.033 g. (1%) of tan crystals, m. p. ca. 130°.

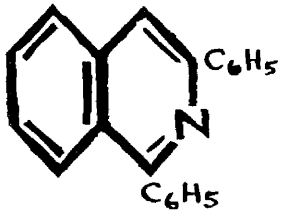
1-Phenyl-3-hexylisoquinoline:



0%

The methods used for 1-phenyl-3-butylisoquinoline were useless for the preparation of 1-phenyl-3-hexylisoquinoline, as was an attempt to close the ring with 10 parts of P_2O_5 in boiling tetralin.

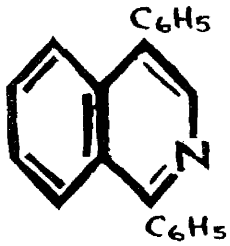
1,3-Diphenylisoquinoline:



20%

Two grams of 1,2-diphenyl-2-benzoylaminoethanol, 16 g. of P_2O_5 and 75 cc. of dry xylene were refluxed three hours then treated as in method II (page 46), yielding 0.4 g. (20%) of tan crystals, m.p. 175-180°. (Reported m.p. 123-127° (111)). A repetition of the reaction according to method V resulted in only 5% of white powder, m.p. ca. 185°; picrate m.p. 185° (Reported m.p. 185° (111)).

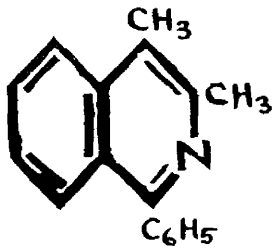
1,4-Diphenylisoquinoline:



0%

One gram of 1,1-diphenyl-2-benzoylaminoethanol, 10 g. of P_2O_5 and 10 g. of $POCl_3$ in 25 cc. of dry xylene were refluxed 3 hours and worked up by method II (page 46), yielding 0.4 g. (40%) of nearly white crystals, m.p. 129-130°. The product was insoluble in hot water and failed to give a picrate; it probably was N-benzoyl-2,2-diphenylvinylamine, which is reported as melting at 132-134° (66a).

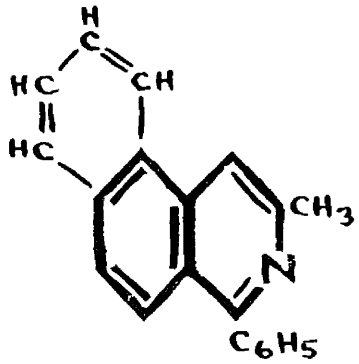
1-Phenyl-3,4-dimethylisoquinoline:



0%

One gram of 2-phenyl-3-benzoylamino-2-butanol, 5g. of P_2O_5 and 10 g. of $POCl_3$ in 30 cc. of dry xylene were refluxed three hours, then treated by method II (page 46), yielding no product.

1-Phenyl-3-methyl-5,6-benzisoquinoline:



12%

Five grams of 1-(α-naphthyl)-2-benzoylaminopropanol, 25 g. of P_2O_5 and 50 g. of $POCl_3$ in 100 cc. of dry xylene were refluxed three hours, then treated by method II (page 46), yielding 0.6 g. (12%) of yellow powder, m.p. 180-190°. The product was recrystallized from isopropanol and benzene as a white powder, m.p. 235°d.

D I S C U S S I O N

The most outstanding fact evident in the investigations just described is that the Bischler-Napieralski reaction is not universally suitable for the production of isoquinoline derivatives. Structural variations in the amide to be cyclized have a marked effect upon the yield of the final product, as seen in Table I.

TABLE I

ISOQUINOLINE DERIVATIVES

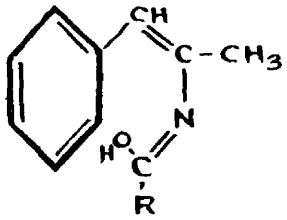
Experimental values			Literature values		
Substituents	% yield	m.p. HCl	% yield	m.p. HCl	Ref.
1-methyldihydro	70	198	35	160	29
			83	---	61
1-phenyldihydro	100	248	75	223	29
			67	---	61
1-benzyldihydro	80	229	65	---	61
			80	---	50a
1-phenyl-3-methyl-dihydro	24	210	--	---	--
1-phenyl-4-methyl-dihydro	92	193	--	----	--
1-phenyl-3-methyl-4-ketodihydro	0	---	--	---	--
1-phenyl	91	239	---	236	48a
1,3-dimethyl	37	168	--	---	--
1-propyl-3-methyl	35	165	--	---	--
1-phenyl-3-methyl	50	229	--	---	--
1-benzyl-3-methyl	20	207	--	---	--
1-phenyl-3-ethyl	26	210	--	---	--
1-phenyl-4-ethyl	10	115	--	---	--
1-phenyl-3-propyl	20	190	--	---	--
1-phenyl-3-butyl	1	130	--	---	--
1-phenyl-3-hexyl	0	---	--	---	--
1,3-diphenyl	20	180	50	127	111
1,4-diphenyl	0	---	80	---	36a
1-phenyl-3,4-dimethyl	0	---	--	---	--
1-phenyl-3-methyl-5,6-benz	12	235	--	---	--

It is apparent from these data that it is nearly as easy to cyclodehydrate an N-acylalkanolamine as the corresponding acylalkylamine, which is contrary to the reports of Mannich (55). Thus, 1-phenylisoquinoline and 1-phenyldihydroisoquinoline were both prepared in good yields. However, it is obvious that amides of secondary carbinamines are much more difficult to cyclize to 3-alkylisoquinolines and the adverse effect is proportional to the chain-length of the substituent. On the other hand, a potential 4-methyl group does not hinder the preparation of a dihydroisoquinoline whereas a potential 4-ethyl group hinders the preparation of an isoquinoline, and the phenyl radical is less undesirable than an alkyl radical. The ultimate conclusion enforced by this work is that it is impractical to synthesize by present methods isoquinolines and dihydroisoquinolines substituted in the 3- or 4-position with an alkyl radical larger than methyl, and possibly excluding the phenyl radical.

For obvious reasons it is important that the theoretical aspects of the reaction mechanism be examined in search of some explanation of the extreme variations in yield resulting from relatively minor structural changes. A starting-point for the explanation is found in the demonstration by Krabbe (66) that the first step in cyclizing simpler N-acylalkanolamines is their conversion into acylvinylamines by loss of one molecule of water. Keeping this in mind, better insight

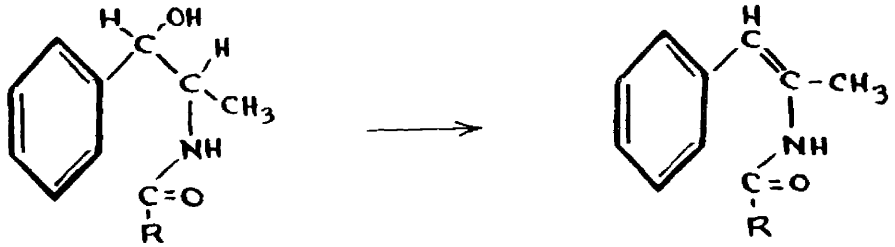
into the mechanism is perhaps gained, though, by starting with the second step, or the conversion of an acylvinylamine into an isoquinoline, and working backward from there.

In cyclizing tautomeric acylvinylamines of the type:

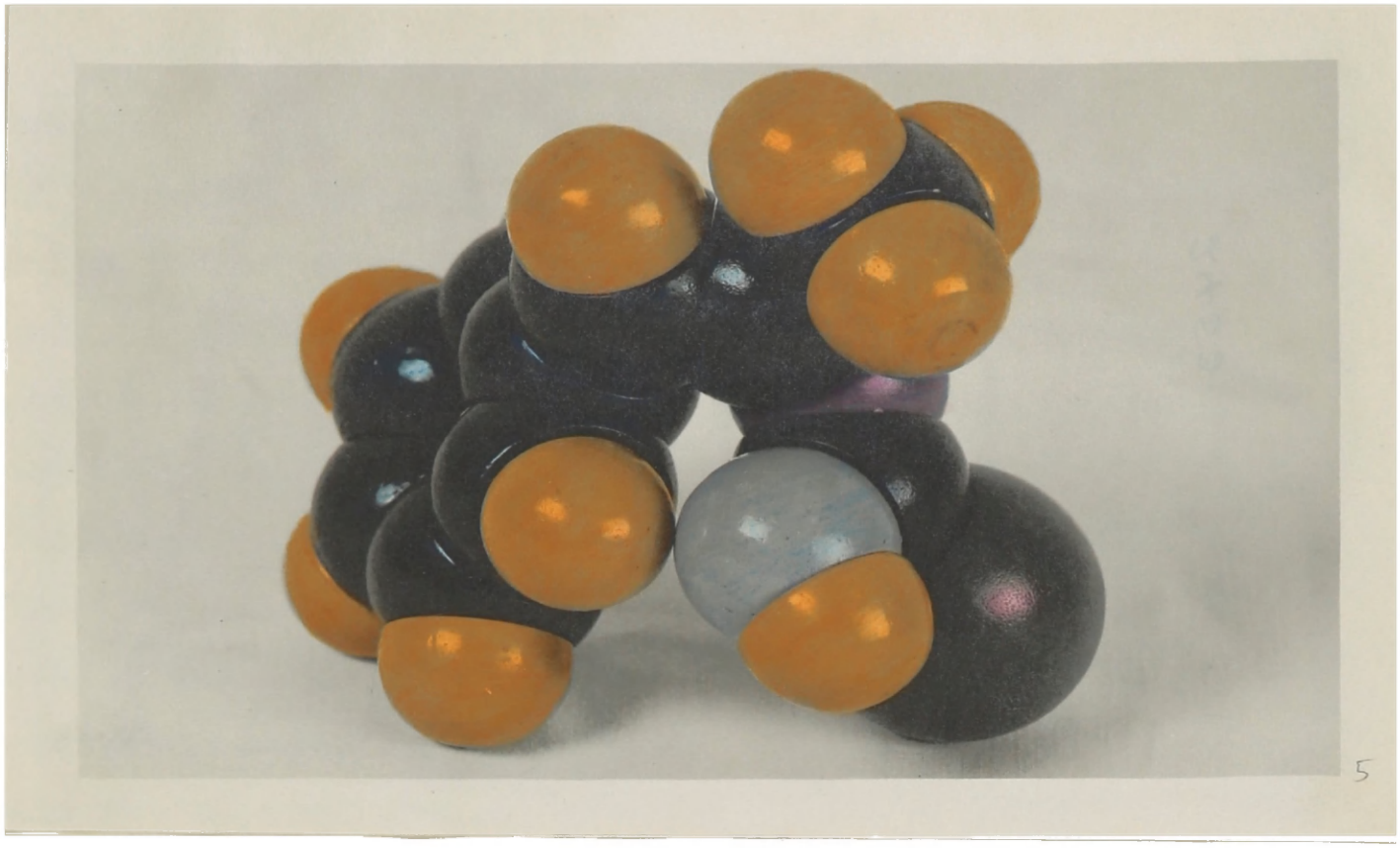


if the phenyl radical and amido group are <u>trans</u> it can be shown with scale models of the molecules that the nuclear-hydrogen and the hydroxyl group can not approach within several Angstrom units of each other, whereas if the phenyl radical and amido group are <u>cis</u> it is easily shown that the nuclear hydrogen and the hydroxyl group can approach as closely to each other as is desired, and can thus unite to form a water molecule, closing the ring in consequence.

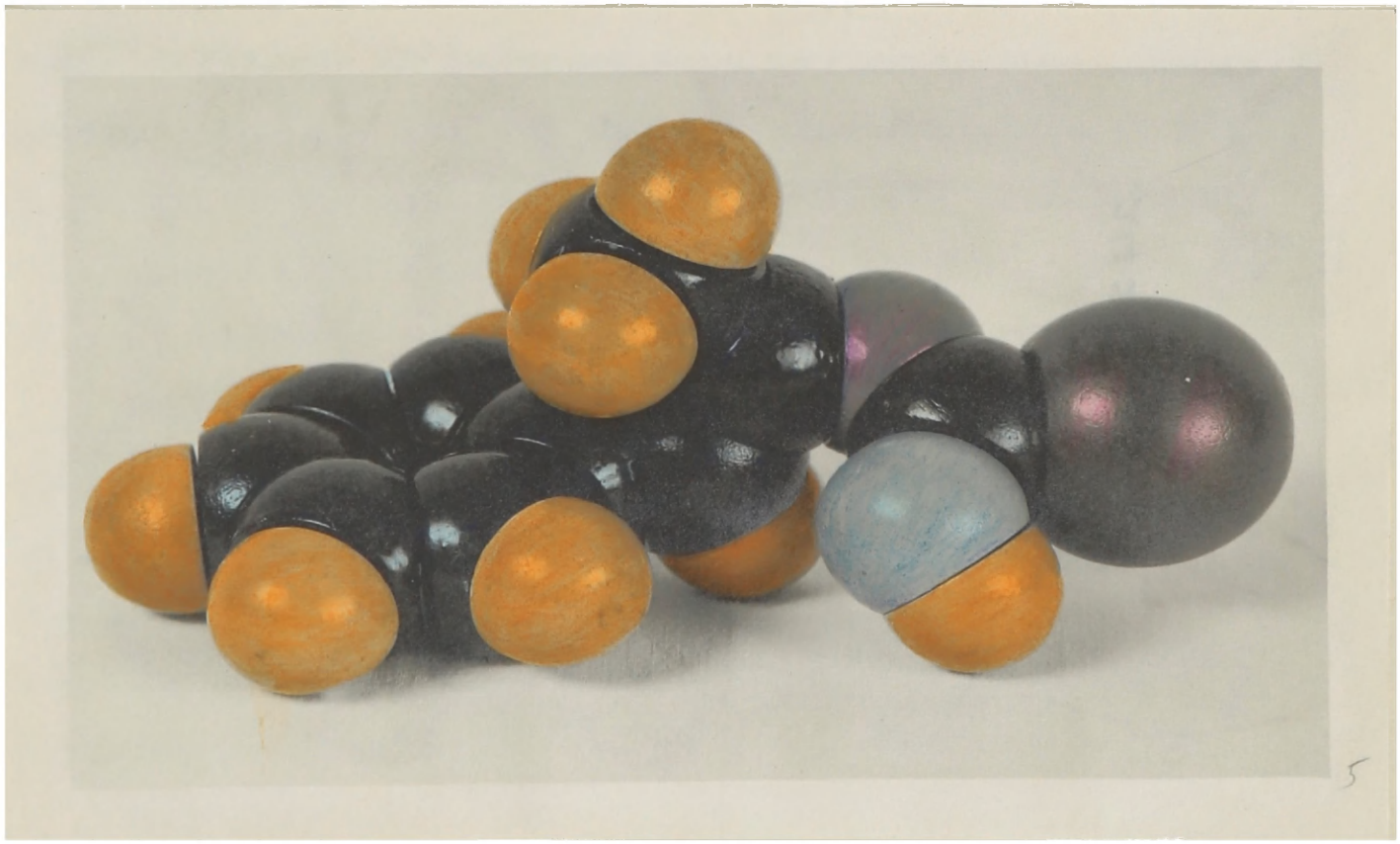
The <u>cis</u> or <u>trans</u> form shown on page 63 is produced during dehydration of the acylpropanolamine to the acylvinylamine, and it would appear that this first dehydration is the key to the success of the ring-closure:



However, it can be shown that one diastereoisomer naturally



cis form



trans form

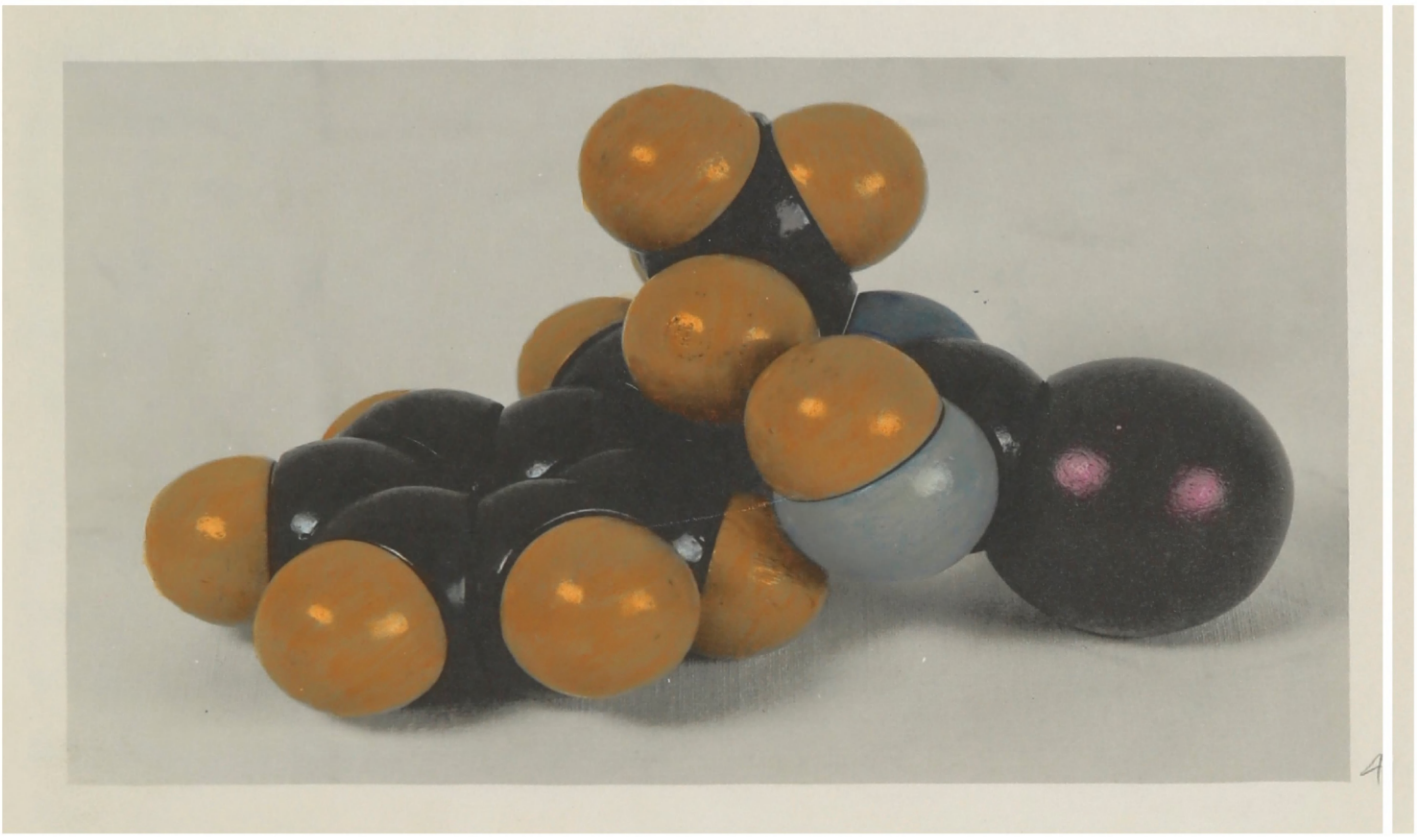
exhibits the cis form when the hydrogen and hydroxyl group of the alpha and beta carbons are in greatest proximity, while the other diastereoisomer exhibits the trans form under the same conditions. It might be expected that propadrin or its diastereoisomer (pseudopropadrin (112)) would yield the cis form upon dehydration and the other diastereoisomer would yield the trans form, with the result that the amides of one isomer would cyclize much more easily than the other. The one attempt to cyclize N-(phenylacetyl)-pseudopropadrin did not give conclusive results and the theory remains untested. Lack of proof at this point, though, does not remove the necessity for considering the geometrical isomerism of the N-acylvinylamines, since their existence as intermediates is undisputed. There is, however, the possibility of inter-isomerization of the two forms under the drastic conditions of the cyclization, analogous to the formation of maleic anhydride from fumaric acid at elevated temperatures.

As pointed out in the Introduction (page 24), it is quite conceivable that with nuclear-activated amides cyclization takes place before formation of the double bond in the 3,4-position. This possibility, along with the increased lability of the hydrogen atom, could explain the better yields reported for 3-methylisoquinolines having 6-methoxy groups.

Such reasoning will not explain why 2-phenyl-1-benzoylamino-2-butanol is difficultly cyclized while N-benzoyl-

ethadrin condenses easily, since they both contain only one asymmetric carbon atom. Neither will it explain why increasing the length of side-chains further decreases the yield, or why there is difficulty in condensing N-benzoyl-β-phenylisopropylamine. For these examples it seems permissible to rely upon ordinary steric hindrance. It may be demonstrated with models that whereas the oxygen of N-benzoyl-β-phenylethylamine may approach the ring with facility from any direction, the oxygen of N-benzoyl- -phenylisopropylamine is definitely restricted in direction and ease of approach. (See the photograph on page 66). It should be pointed out that such a simple explanation can not apply to the acylvinylamines, in which a single methyl group is prevented from interfering sterically in the <u>cis</u> form by the rigidity of the double bond. In the <u>trans</u> form which is postulated, a group larger than methyl can be visualized as furthering the difficulties already present.

The somewhat lessened hindering value of the phenyl radical as seen in the cyclization of 1,2-diphenyl-2-benzoylaminoethanol may have some connection with the fact that the phenyl radical is electron-attracting, while alkyl radicals are electron-repulsive. However, the electronic implications of the Bischler-Napieralski reaction are as yet unknown. It is notable, too, that the 1-phenyl derivatives were more easily formed than the 1-alkyl derivatives.



N-acyl-β-phenylisopropylamine

Aside from the significance of geometrical and spacial relationships in this work, the results obtained illustrate nicely the surprising importance of minor alkyl groups in some reactions. To give a few examples, halogen reactivity is forty times as great in bromoacetic acid as in α-bromopropionic acid, even though the latter compound has a secondary bromine atom (115). n-Butyl bromide reacts very efficiently in the acetoacetic ester condensation, but isobutyl bromide reacts hardly at all (113). Methyl groups have a high degree of effectiveness in restricting rotation when placed in the ortho positions of diphenyl (114).

In a somewhat more practical light, there are a number of general deductions which may be made from the reactions described in the Experimental section of this thesis. The most efficient methods of synthesizing isoquinolines and dihydroisoquinolines have been those utilizing the following formulations:

Dihydroisoquinolines: The amide was refluxed with 2 parts each of P_2O_5 and $POCl_3$ in 15 parts of dry xylene for one hour.

Isoquinolines: The amide was refluxed with 5 parts of P_2O_5 and 10 parts of $POCl_3$ in 25 parts of dry xylene for three hours.

The P_2O_5 formed a plastic mass in the bottom of the flask which could not be stirred, and was orange to black in color depending on the amide used. The addition of $POCl_3$ caused

the reactions to be much lighter as well as to give better yields in most cases. At the completion of the reaction, the isoquinoline derivatives were best isolated by conversion to their hydrochlorides and crystallization of the salts from isopropanol-ligroin. Large volumes of water were necessary in the extractions to keep in solution the Na_3PO_4 and NaCl formed when the mixtures were made strongly alkaline. A two-liter separatory funnel was necessary to isolate the product from five grams of acylalkanolamine. It was found in isolating quantities of amine less than one gram that the hydrochlorides were too soluble for precipitation from benzene or ether and usually had to be recovered from a very small quantity of almost pure ligroin, containing just enough isopropanol to hold the tars in solution. Frequently long storage in the refrigerator was necessary for isolation. It was also found very difficult to purify the compounds by recrystallization, the best products being produced from the cyclizations showing least tar and color. When obtained in the pure state, the hydrochlorides were soluble in distilled water, but formed turbid mixtures with tapwater.

When tetralin was used it had to be particularly pure, since practical tetralin resinified with P_2O_5. No such difficulty was encountered with decalin.

The condensing agents used in this work may be grouped

as follows:

Good: A mixture of P_2O_5 and $POCl_3$ in boiling xylene.

Fair: P_2O_5 in a boiling hydrocarbon.

Poor: P_2O_5 with no solvent, Al_2O_3 in boiling decalin, $POCl_3$ in a boiling solvent.

No Good: $AlCl_3$, PCl_5, BF_3, H_2SO_4, P_2S_5, heat alone.

ANALYTICAL DATA

AMIDES

Name	Formula	Nitrogen % Calcd.	Found
N-Benzoylethadrin	$C_{15}H_{15}NO_2$	5.81	6.24*
N-Butyrylpropadrin	$C_{13}H_{19}NO_2$	6.33	6.56
N-Benzoylpropadrin	$C_{16}H_{17}NO_2$	5.49	5.50
N-Phenylacetylpropadrin	$C_{17}H_{19}NO_2$	5.20	5.27
N-Benzoyloutadrin	$C_{17}H_{19}NO_2$	5.20	5.39
2-Phenyl-3-benzoylamino-2-butanol	$C_{17}H_{19}NO_2$	5.20	5.40
N-Benzoylpentadrin	$C_{18}H_{21}NO_2$	4.94	5.10
N-Benzoylhexadrin	$C_{19}H_{23}NO_2$	4.71	4.93
N-Benzoyloctadrin	$C_{21}H_{27}NO_2$	4.30	4.37
1-(α -naphthyl)-2-benzoylaminopropanol	$C_{20}H_{19}NO_2$	4.59	4.73

ISOQUINOLINE HYDROCHLORIDES

Substituents	Formula	Nitrogen % Calcd.	Found
1-Methyldihydro	$C_{10}H_{12}NCl$	7.71	7.92
1-Phenyldihydro	$C_{15}H_{14}NCl$	5.75	6.03
1-Benzyldihydro	$C_{16}H_{16}NCl$	5.44	5.58
1-Phenyl-3-methyldihydro	$C_{16}H_{16}NCl$	5.44	5.61
1-Phenyl-4-methyldihydro	$C_{16}H_{16}NCl$	5.44	5.61
1-Phenyl	$C_{15}H_{12}NCl$	5.80	5.59
1,3-Dimethyl	$C_{11}H_{12}NCl$	7.23	7.06
1-Phenyl-3-methyl	$C_{16}H_{14}NCl$	5.48	5.26
1-Benzyl-3-methyl	$C_{17}H_{16}NCl$	5.19	5.32
1-Phenyl-3-ethyl	$C_{17}H_{16}NCl$	5.19	5.13
1-Phenyl-4-ethyl	$C_{17}H_{16}NCl$	5.19	5.48
1-Phenyl-3-propyl	$C_{18}H_{18}NCl$	4.94	4.39*
1,3-Diphenyl	$C_{21}H_{16}NCl$	4.41	4.32
1-Phenyl-3-methyl-5,6-benz	$C_{20}H_{16}NCl$	4.58	4.45

*Not considered corroborative.

Microanalyses by Oakwold Laboratories, Alexandria, Va.

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