The Mechanism of the Bischler-Napieralski Reaction

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The Bischler-Napieralski dihydroisoquinoline synthesis was proven to occur *via* imidoyl chlorides and the corresponding nitrilium salt. The two-step process required much milder conditions (20°-50°) compared to drastic classical conditions of refluxing at 100°-200°. The Bischler-Napieralski reaction is shown to share a common intermediate with two other well-known reactions: the von Braun and the Ritter reactions.

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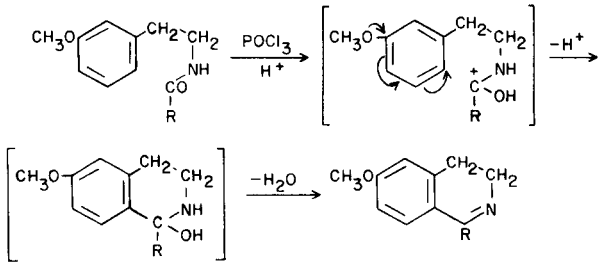
The pharmacological interest (2) attached to the isoquinoline nucleus of alkaloids led to a great deal of interest in the synthesis of isoquinolines. The Bischler-Napieralski reaction (3) is one of the methods of choice for the preparation of isoquinoline derivatives. This reaction consists of the cyclodehydration, with phosphorus oxychloride and phosphorus pentoxide, *etc.*, of an amide, derived from a substituted 2-phenethylamine to yield the corresponding 3,4-dihydroisoquinoline. Even though several hundred references (4) can be found in the literature for the use of Bischler-Napieralski reaction (further referred to as B-N reaction), the mechanism has never been studied in detail. The only early mechanistic idea (5) about the B-N reaction, as shown in Scheme 1, involved the protonation of the amide oxygen by a trace of hydrogen chloride that is present in phosphoryl chloride followed by cyclization to a 1-hydroxytetrahydroisoquinoline and ultimate dehydration to the 3,4-dihydroisoquinoline. Consequently, conversion of amide into imidoyl chloride by a Lewis acid was assumed for the B-N reaction (4). In addition, preliminary observations (6) in our laboratory support the formation of imidoyl chlorides and a possible correlation between B-N reaction and von Braun and Vilsmeier-Haack reactions in which the imidoyl chlorides are also intermediates.

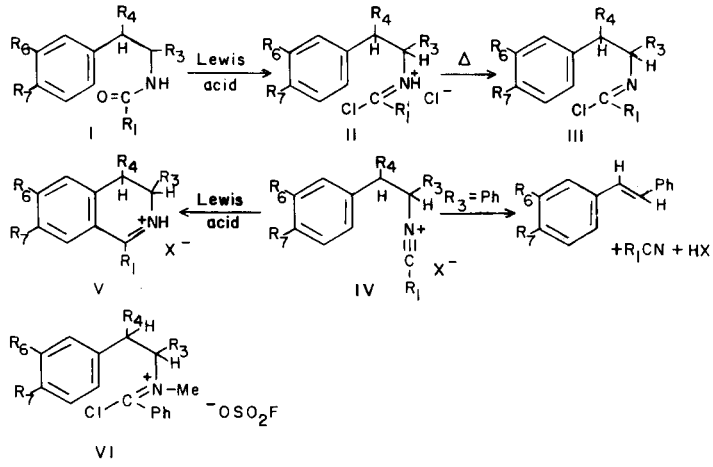
SCHEME 1



The first mechanistic concept of the Bischler-Napieralski reaction.

In contrast to the mechanism (5) in Scheme 1, we proved that a variety of 2-phenethylamides (I) give the imidoyl halides (III) or their hydrohalides under milder conditions with various reagents (phosphorus pentachloride, phosphorus oxychloride, thionyl chloride and carbonyl bromide). Thus, it is clear that dehydration or the loss of carbonyl oxygen must precede ring closure (Scheme 2). The imidoyl chlorides cyclize to yield dihydroisoquinolines. The rate of cyclization is enhanced with the addition of a Lewis acid (such as stannic chloride, zinc chloride, *etc.*). The increase in the reaction can be explained by the formation of a nitrilium salt (IV).

SCHEME 2



R_1 = Ph or Me, R_3 = H or Ph, R_4 = H or Ph, $R_{6,7}$ = H or OMe, X = Cl, $SbCl_6^{2-}$, SbF_6^{2-},

SCHEME 3

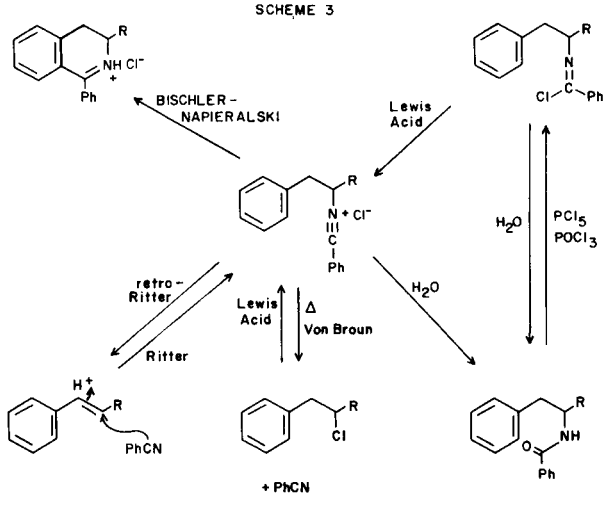


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Table 1

	Name	M.p., °C	Yield %	Formula	Calcd. % C	Calcd. % H	Found % C	Found % H	Reference
i	*N*-(2-phenethyl)benzamide	118-120	91.5	$C_{15}H_{15}NO$	79.97	6.71	79.76	6.69	4
ii	*N*-(1,2-diphenethyl)benzamide (a)	183-185	98	$C_{21}H_{19}NO$	83.68	6.36	83.71	6.34	10
iii	*N*-(1,2-diphenethyl)acetamide (b)	154-157	99	$C_{16}H_{17}NO$	80.30	7.16	80.16	7.07	10
iv	*N*-(2,2-diphenethyl)benzamide	143-145	95	$C_{21}H_{19}NO$	83.68	6.36	83.51	6.23	10
v	*N*-(2-phenethyl)phenacetamide	91-93	84	$C_{16}H_{17}NO$	80.30	7.16	80.13	7.16	10
vi	*N*-(1-benzyl-2-phenethyl)benzamide	173-176	82	$C_{22}H_{21}NO$	83.78	6.71	83.89	6.69	10
vii	*N*-(2-phenethyl)-*p*-methoxy benzamide	123-125	54	$C_{16}H_{17}NO_2$	75.27	6.71	75.15	6.66	—
viii	*N*-(1,2-diphenethyl)-*p*-methoxybenzamide (c)	194-196	90	$C_{22}H_{21}NO_2$	79.80	6.30	80.13	6.22	—
ix	*N*-(2-[3,4-dimethoxyphenyl]ethyl)-*p*-methoxy-benzamide (d)	127-129	81	$C_{18}H_{21}NO_4$	68.55	6.71	68.70	6.69	—
x	*N*-(1,2-diphenethyl)phenacetamide	189-191	82	$C_{22}H_{21}NO$	83.78	6.71	83.62	6.87	10
xi	*N*-(2,2-diphenethyl)phenacetamide	115-116	92.5	$C_{22}H_{21}NO$	83.78	6.71	83.89	6.66	10
xii	*N*-(2-[3,4-dimethoxyphenyl]ethyl)phenacetamide	110-111	83	$C_{18}H_{21}NO_3$	72.22	7.07	72.38	6.98	10
xiii	*N*-(1,2-diphenethyl)-3,4-dimethoxyphenacet-amide (e)	186-189	60	$C_{24}H_{25}NO_3$	76.70	6.71	76.15	6.74	10
xiv	*N*-(2-Phenethyl)-3,4-dimethoxyphenacetamide (f)	107-109	45	$C_{18}H_{21}NO_3$	72.22	7.07	72.04	7.13	—

(a) Calcd. for N, 4.65. Found: N, 4.55. (b) Calcd. for N, 5.85. Found: N, 5.75. (c) Calcd. for O, 9.70. Found: O, 9.80. (d) Calcd. for O, 20.29. Found: O, 20.25. (e) Calcd. for O, 12.78. Found: O, 12.65. (f) Calcd. for O, 16.03. Found: O, 16.18.

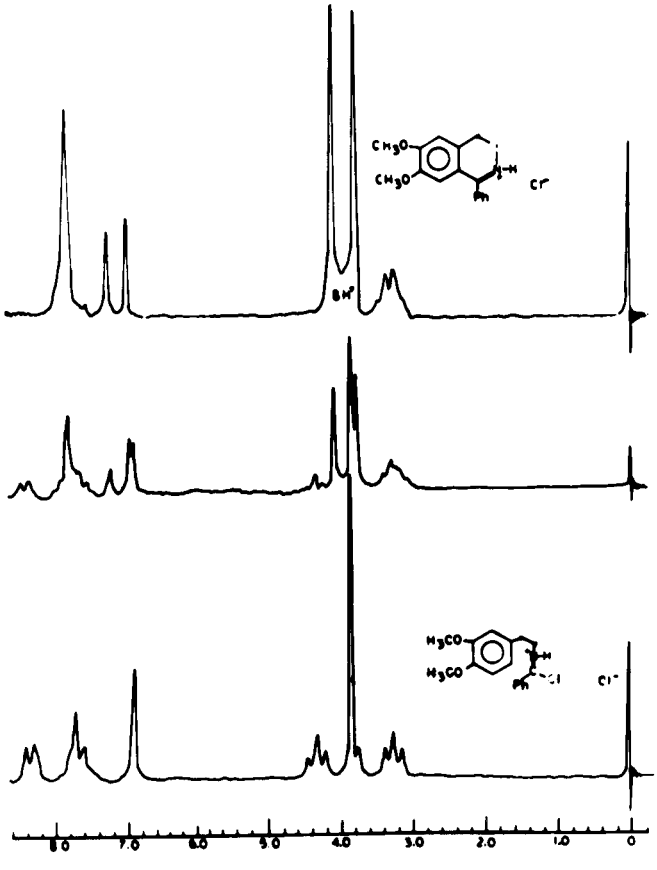


Figure 1: Cyclization of *N*-(2-[3,4-dimethoxyphenyl]ethyl)-benzimidoyl chloride, monitored by nmr.

Several amides (Tables 1 and 2) and a few imidoyl chlorides (Table 3) were prepared (7a,b) and the latter were cyclized to the corresponding isoquinoline derivatives (Table 4). The yields were in most cases significantly higher than in the classical "one-pot" reflux process of amides with phosphorus oxychloride. The *N*-(2-[3,4-dimethoxyphenyl]ethyl)benzimidoyl chloride shows a singlet at 3.82 ppm for six methoxy protons which were converted into a pair of singlets at 3.80 ppm and 4.09 ppm as the cyclization proceeds (Figure 1). The triplet for the methylene protons *alpha* to the amide group also moves first downfield and then upfield till it reaches the same position as in the cyclized product. The reaction is relatively fast, but in case of *N*-(2-phenethyl)benzimidoyl chloride (8) the cyclization did not occur unless a Lewis acid (*e.g.* stannic chloride, zinc chloride) was added. The *alpha* methylene protons moved from 4.02 ppm to 4.68 ppm as the corresponding nitrilium ion formed, and again

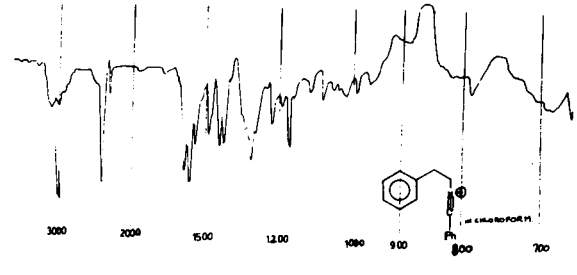
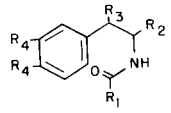


Figure 2: Ir spectrum of *N*-2-phenethylbenzonitrilium hexachlorostannate.

Table 2

Spectroscopic Data of Amides



	R_1	R_2	R_3	R_4	Ir (mull) 3500-1400 cm^{-1}	-CHR_3-	-CHR_2-	Other	Aryl Signals
i	Ph	H	H	H	3400 (s), 1634 (s), 1535 (s)	2.80 (t)	3.65 (q)	——	6.77 (m) 7.23 (s) 7.40 (m) 7.74 (m)
ii	Ph	Ph	H	H	3300 (m), 1650 (s), 1540 (m)	3.21 (d)	5.55 (t)	——	6.39 (broad) 7.08 (m) 7.45 (m)
iii	CH_3	Ph	H	H	3325 (s), 1690 (s), 1540 (s)	3.03 (d)	5.25 (v)	1.83 (s, CH_3)	7.16 (m) 7.30 (s)
iv	Ph	H	Ph	H	3300 (m), 1625 (s), 1510 (s)	——	——	——	——
v	$PhCH_2$	H	H	H	3300 (m), 1645 (s), 1550 (m)	2.68 (t)	3.37 (q)	3.42 (s, -$COCH_2$-)	6.43 (s) 7.13 (m) 7.20 (s)
vi	Ph	$PhCH_2$	H	H	3340 (m), 1625 (s), 1525 (s)	2.90 (d)	——	——	6.90 (s) 7.06 (s)
vii	CHO_3Ph	H	H	H	3340 (m), 1630 (s), 1540 (m)	2.87 (t)	3.63	3.75 (s, OCH_3)	6.87 (s) 7.60 (s) 7.72 (s) 7.20 (s)
viii	CH_3OPh	Ph	H	H	3320 (m), 1625 (s), 1525 (m)	3.18 (d)	5.43 (q)	3.78 (s, OCH_3)	6.83 (s) 7.63 (d) 7.13 (s) 7.27 (s)
ix	CH_3OPh	H	H	OCH_3	3320 (m), 1640 (s), 1530 (m)	2.82 (t)	3.67 (v)	3.76 (s, OCH_3) 3.79 (s, OCH_3)	6.71 (s) 6.87 (s) 7.67 (s)
x	$PhCH_2$	Ph	H	H	3325 (m), 1635 (s), 1520 (s)	2.97 (d)	5.03 (t)	3.33 (s, CH_2CO)	7.13 (s) (a) 7.20 (s) 7.28 (s)
xi	$PhCH_2$	H	Ph	H	3300 (m), 1645 (s), 1500 (m)	3.90 (m)	3.90 (m)	3.38 (s, CH_2CO)	7.50 (s)
xii	$PhCH_2$	H	H	OCH_3	3275 (m), 1640 (s), 1550 (m)	2.73 (q)	3.38 (t)	3.40 (s, CH_2CO) 3.78 (d, OCH_3)	6.63 (s) 7.23 (s)
xiii	$(CH_3O)_2PhCH_2$	Ph	H	H	3350 (m), 1645 (s), 1525 (s)	3.03 (d)	5.00 (t)	3.47 (s, CH_2CO) 3.87 (d, OCH_3)	6.80 (d) 7.20 (d)
xiv	$(CH_3O)_2PhCH_2$	H	H	H	3300 (m), 1640 (m), 1540 (m)	2.93 (t)	3.47 ( )	3.58 (d, OCH_3)	6.73 (s) 7.15 (s)

(a) Nmr was taken in DMSO-d_6.

shifted to 4.20 ppm as the cyclization proceeded. The *N*-2-phenethylbenzonitrilium chlorostannate has been monitored by its infrared spectrum (Figure 2).

Before Fodor, *et al.* (6), the presence of nitrilium salts were not even proposed in B-N reactions. However, a two-step reaction involving an ion-pair (similar to the nitrilium salt) has been postulated (9) in the hydrolysis of imidoyl chloride. In addition, imidoyl bromides are known (8) to dissociate in liquid sulfur dioxide into nitrilium bromides.

In the original B-N reaction (3), phosphorus pentoxide was used for the cyclization. It is conceivable that an imidoyl phosphate has been formed in place of imidoyl chloride. The nitrilium salt might have formed by the elimination of the phosphate group, thus giving high

Table 3

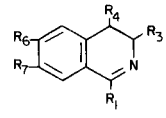
Imidoyl Chlorides (a) (III) From Amides (I) $(R_6R_7)ph\text{-}CH(R_4)\text{-}CH(R_3)\text{-}N{=}\underset{\underset{Cl}{|}}{C}\text{-}R_1$

Structure						
R_1	R_3	R_4	$R_{6,7}$	Name	Yield % (c)	M.p. or B.p.
Ph	H	H	H	*N*-(2-phenethyl)benzimidoyl chloride (IIIa)	96	138-140° 0.05 mm
Ph	Ph	H	H	*N*-(1,2-diphenethyl)benzimidoyl chloride (IIIb)	92	78°
Me	Ph	H	H	*N*-(1,2-diphenethyl)acetimidoyl chloride (IIIc)	91	— (b)
Ph	H	Ph	H	*N*-(2,2-diphenethyl)benzimidoyl chloride (IIId)	92.3	80°
Ph	H	H	OMe	*N*-(2-(3,4-dimethoxyphenyl)ethyl)benzimidoyl chloride (IIIe)	88	— (b)
$PhCH_2$	H	H	H	*N*-(2-phenethyl)phenacetimidoyl chloride (IIIf)	45	— (d)

(a) For additional physical and analytical data see Experimental. (b) Yield calculated from its hydrochloride, which was 93.5% based on the corresponding amide. (c) Based on amide. Viscous oily material, m.p. of hydrochloride **3a**, 144-148°. (d) Decomposed upon heating.

Table 4

3,4-Dihydroisoquinolines



	R_1	R_3	R_4	$R_{6,7}$	M.p.	Yield, New Method
Va	Ph	H	H	H	245° (HCl)	97% (a,b)
Vb	Ph	Ph	H	H	---	---
Vc	Me	Ph	H	H	---	---
Vd	Ph	H	Ph	H	112°	95% (b)
Ve	Ph	H	H	OMe	220° (HCl)	88% (b)
Vf	$PhCH_2$	H	H	H	---	95% (b)
Vg	Ph	$PhCH_2$	H	H	---	80% (c)
Vr	$(MeO)_2Ph$	H	H	OMe	168° (picrate)	75%

(a) Yields ranging from 26-86% were reported. The higher yields were achieved by using phosphorus pentoxide. (b) Based on the imidoyl chloride. (c) Based on the amide (own experiments).

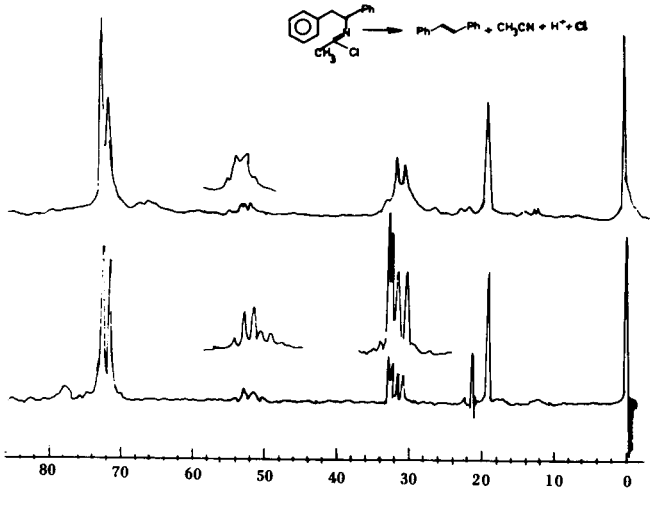


Figure 3: Decomposition of *N*-(1,2-diphenethyl)acetimidoyl chloride, monitored by nmr.

yields of the cyclized product, in spite the heterogeneity of the reaction mixture. Similarly, polyphosphoric acid (PPA) and polyphosphoric ester (PPE) may react when used in the cyclization. In order to monitor the formation of nitrilium salts, *N*-(2-[3,4-dimethoxyphenyl]ethyl)benzimidoyl pyrophosphate was prepared by reacting the corresponding amide with PPE. The cyclization resulted in high yields but the nitrilium salt could not be monitored. The PPE did not prove to be useful in cyclizing some amides (*e.g.* 2-phenethylamide).

In case of *N*-(1,2-diphenylethyl)benzimidoyl chloride the cyclization did not take place. Dey and Ramanathan (10) have reported no basic product in their experiments when the corresponding amide was used. Nitroarylamides, on the other hand, gave nitrobenzonitriles. We rationalized that failure by assuming a reversal of the Ritter reaction. This hypothesis has been substantiated by isolating the corresponding olefine and the nitrile. The imidoylchloride

is converted to corresponding nitrilium salt which immediately decomposes to give olefine and the nitrile. The "retro-Ritter reaction" was probably enhanced due to the formation of fully conjugated system in the resulting *trans*-stilbene. In order to stabilize the nitrilium ion several Lewis acids (such as antimony pentachloride, silver hexafluoroantimonate, methylfluorosulfonate, *etc.*) were used in the preparation of the nitrilium ion. In all the cases the retro-Ritter reaction predominated except when methylfluorosulfonic acid is used, in which case the *N*-methylated amide was the major product (VI).

When *N*-(1,2-diphenethyl)-acetimidoyl chloride was stored under anhydrous conditions, it decomposed even in the absence of any Lewis acid to yield new basic products that would arise from a reversal of the Ritter reaction. This decomposition could be easily followed by nmr as the singlet at 1.90 ppm of the methyl group disappears (Figure 3) and a new singlet for three protons appeared at 2.11 ppm (for acetonitrile). This additionally proves that the electronic factors in the nitrile to be formed are not a deciding factor. If this retro-Ritter reaction is more favored, we rationalized that one could not synthesize *N*-(1,2-diphenethyl)benzamide under classical Ritter reaction conditions (11a,b). Indeed, no Ritter reaction took place between *trans*-stilbene and benzonitrile in acidic medium, and unchanged stilbene was recovered.

The unsuccessful B-N cyclization in case of *N*-(1,2-diphenethyl)benzamide pointed out the relationship between the three formerly unrelated processes: the von Braun amide degradation (12), the Bischler-Napieralski reaction (3), and the Ritter (11a,b) reaction (Scheme 3). The common intermediate, of course, is the nitrilium salt, which can undergo cyclization if a sufficiently strong nucleophilic carbon is in the position to attack the nitrilium carbon atom. However, the nitrilium ion may reversibly dissociate into a nitrile and a carbonium ion. The latter, in turn, may lose a proton to give the alkene as in case of the retro-Ritter reaction. Alternatively, the halide ion from the nitrilium ion-pair can recombine with carbonium ion to yield the von Braun amide degradation products. If the conjugation is broken as in the case of *N*-(2,2-diphenethyl)benzimidoyl chloride the B-N cyclization predominates over retro-Ritter reaction. This is the first known correlation between these three reactions.

EXPERIMENTAL

Melting points were determined on a Model 1A 6304 Electrothermal apparatus and are uncorrected. Boiling points were also uncorrected. Ir spectra were recorded on Perkin-Elmer Models 137 and 137G, Beckman IR-8 or Bausch and Lomb 250 spectrophotometers. The term "solution" is used with chloroform as the solvent (unless another solvent is mentioned) and the term "mull" is used for nujol. If pellets are used, potassium bromide was put in parenthesis. The usual abbreviations (vs = very strong, s = strong, m = medium, and w = weak) were used to describe the intensities of the infrared peaks. Nmr spectra were obtained using Varian Associates Model T-60, EM-360, HA-60, using deuteriochloroform as an external solvent with reference. The values are in the δ scale (Elemental analysis by Galbraith Laboratories, Inc., Knoxville, Tennessee). All the dihydroisoquinolines were prepared by the classical procedure (4,10) and treated as authentic samples for comparison.

The highly hygroscopic nature of almost all of the intermediates (imidoyl chlorides, nitrilium salts, and pyrophosphates) made it essential to carry out most of the experiments in nitrogen atmosphere and in a "Hydrovoid" dry box (Air Control, Inc., Norristown, PA).

This unit is clear plexiglass with 360° visibility. The dry box was fitted with an airlock and special armports (with highly flexible rubber gloves) and entrance doors will provide access while maintaining precisely controlled atmosphere within the box.

This atmosphere control system was also equipped with a desiccant system that maintains anhydrous conditions. Dry nitrogen was continuously introduced from a cylinder with ultrapure nitrogen, instead of the recirculator. The nitrogen used was bubbled through a concentrated sulfuric acid and then through a three foot drying tube filled with Drierite (8 Mesh). A large dish of phosphorus pentoxide was kept in the box for an extra precaution as well as the moisture monitor. Aluminum foil was used for the manipulation of the solids.

When introducing equipment (like a small magnetic stirrer, balance and other equipment was needed) into the dry box, the airlock was flushed with nitrogen for several minutes. A small ringstand and clamp (both were specially made with aluminum) were always maintained inside the box. The aspirator (fitted with a trap and a 3-way stop-cock) was connected, through a drying tube filled with drierite, to the vacuum inlet of the dry box. This vacuum inlet gas cock, in turn, connected to the internal part that was connected to the sidearm for the suction flask, through a 2-way stop-cock. All other equipment such as flasks, that was introduced, was previously dried in an electric oven for a predetermined time. An antistatiomaster was found very helpful whenever introducing solids into bottles inside the dry box.

General Procedure for Preparing the Amides.

To a suspension or an emulsion of the 2-phenethylamine (0.369 mole) in 15% sodium hydroxide (150 ml.), the corresponding acid chloride (0.41 mole) was added dropwise over a period of 45 minutes with efficient stirring. The bath temperature was maintained at 0° throughout the reaction. The reaction was stirred for an additional hour, and the reaction mixture was cooled and poured onto ice and the precipitate was suction filtered, washed with 15% sodium hydroxide and water. The resulting solid was recrystallized from 85% ethanol to yield 92% of the product.

N-(2-phenethyl)benzimidoyl Chloride Hydrochloride.

To a suspension of phosphorus pentachloride (10.43 g., 0.05 mole) in dry benzene, *N*-benzoyl-2-phenethylamine (5.63 g., 0.025 mole) was added slowly using a solid addition apparatus under nitrogen atmosphere over a period of 60 minutes at 0°. The resulting precipitate was suction filtered in the dry box and washed with anhydrous petroleum ether. The yield of the resulting imidoylchloride hydrochloride was 93-94% which melted at 50-52° dec.; ir (neat): 2980 (m, CH), 2850 (m, CH), 2550 (broad, m, =N-H), 1650 (s, C=N), 1470 (s), 1430 (s), 1230 (s, broad), 1165 (m, broad), 985 (m), 865 (s, broad), 755 (s, broad), 690 (s, broad) cm^{-1}; nmr: 3.30 (t, 2H, J = 7 Hz, $C_6H_5CH_2$-), 4.30 (t, 2H, J = 7 Hz, $=NHCH_2$), 7.35 (s, 5H, $C_6H_5CH_2$-), 7.70 (m, 3H, C_6H_5C=N-), 8.23 (m, 2H, C_6H_5C=N), 11.8 (broad s, 1H, C=HN).

The above imidoyl chloride hydrochloride was gently heated to about 50° (0.1 mm) for about 60 minutes. The evolution of hydrogen chloride was vigorous to give 5.34 g. (96%) of an oily *N*-(2-phenethyl)benzimidoyl chloride, b.p. 138-140° (0.050 mm); ir (neat): 3067 (w), 3055 (w), 2920 (w), 1662 (vs, -C=N-), 1490 (w), 1450 (w), 1350 (w), 1220 (m), 1015 (m), 875 (s), 760 (s), 696 (s) cm^{-1}; nmr: 3.08 (t, 2H, J = 7 Hz, $C_6H_5CH_2$-), 4.02 (t, 2H, J = 7 Hz, -C=NCH_2-), 7.30 (s, 3H, $C_6H_5CH_2$-), 7.42 (m, 3H, C_6H_5C=N-), 8.06 (m, 2H, C_6H_5C=N-).

General Procedure for Cyclization of Imidoyl Chlorides to Dihydro-

isoquinolines.

The distilled *N*-(2-phenethyl)benzimidoyl chloride (8.11 g., 0.033 mole) was dissolved in anhydrous chloroform to which stannic chloride (11 g., 0.042 mole) was dropwise added in the dry box. Aliquots were drawn at different intervals and the reaction was monitored by nmr and ir spectra.

At the end of the reaction (90-100 hours later), the mixture was poured onto ice water and basified with 10% sodium hydroxide solution. The sodium stannate was vacuum filtered and the resulting dihydroisoquinoline was extracted with chloroform, dried over sodium sulfate and the solvent was evaporated. When dry hydrogen chloride was passed into the solution of the above isoquinoline derivative, and the 1-phenyl-3,4-dihydroisoquinoline hydrochloride was precipitated as white solid which was suction filtered, m.p. 242-245° dec., yield 95.5%; ir (mull): 3040 (s), 3000 (s), 2525 (broad, m, =N-H), 1630 (m), 1560 (w), 1540 (w), 1460 (w), 1440 (m), nmr: 3.18 (t, 2H, J = 7 Hz, $C_6H_5CH_2$-), 4.15 (t, 2H, J = 7 Hz, -C=NCH_2-), 7.60 (s), 7.73 (m).

Preparation of an Authentic Sample of 1-Phenyl-3,4-dihydroisoquinoline.

The following modified procedure was adopted, from Whaley and Hartung (13).

To a magnetically stirred suspension containing *N*-(2-phenethyl)-benzamide (5 g., 0.022 mole) in anhydrous xylene (90 ml.) phosphorus pentoxide (25.69 g., 0.180 mole) and phosphoryl chloride (57.22 g., 0.378 mole) were added slowly and the reaction mixture was refluxed for about 3 hours. After cooling the flask, the reaction mixture was poured onto crushed ice. The organic layer was separated, and the aqueous layer was extracted once with benzene. The water layer was made strongly alkaline, with 5*N* sodium hydroxide and was extracted with benzene (2 × 50 ml.) and dried over anhydrous sodium sulfate. An oily material was obtained upon the evaporation of benzene. Dry hydrogen chloride was passed through the above oil in anhydrous ether. The isoquinoline derivative precipitated out as white crystals, m.p. 240-242° dec., yield 90%.

Attempts to Prepare 1,3-Diphenyl-3,4-dihydroisoquinoline *via* the Classical Bischler-Napieralski Reaction.

The Dey and Ramanathan (10) procedure was used with some modifications. A solution of *N*-(1,2-diphenethyl)benzamide (3.01 g., 0.01 mole) in anhydrous toluene (100 ml.), was added to phosphorus pentoxide (5.0 g., 0.02 mole). To the above mixture phosphoryl chloride (15.12 g., 0.1 mole) was slowly added and the reaction mixture was refluxed, with continuous stirring, for about 3 hours. At the end of the reaction, the mixture was then poured onto crushed ice. The organic layer was separated and the aqueous layer was extracted with toluene (50 ml.) and the extracts were combined and dried over anhydrous sodium sulfate. The aqueous layer was made alkaline with 5N sodium hydroxide solution and the resulting basic solution was extracted with chloroform (2 × 30 ml.). The chloroform layers were separated, combined and dried over anhydrous sodium sulfate. *trans*-Stilbene was isolated when toluene was evaporated, m.p. 124-125°, identical with commercial *trans*-stilbene.

A very small amount of yellow oily material was obtained upon the evaporation of chloroform which was later identified as benzonitrile.

Preparation of *N*-(1,2-Diphenethyl)benzimidoyl Chloride.

The following procedure has been used as the general procedure for imidoyl chlorides. Solid *N*-(1,2-diphenethyl)benzamide (3.01 g., 0.01 mole) was slowly added under nitrogen atmosphere, to a magnetically stirred suspension of phosphorus pentachloride (2.50 g., 0.012 mole) in anhydrous benzene. After 1.5 hours, dry acetone (10 ml.) was added. Imidoyl chloride was isolated on evaporation of the solvent, yield 92%, m.p. 76-78°; nmr: 3.20 (d, 2H, J = 7 Hz, $C_6H_5CH_2$-), 5.23 (t, 1H, J = 7 Hz, C_6H_5CH-), 7.11 (s), 7.31 (m), 7.95 (m).

Anal. Calcd. for $C_{21}H_{18}ClN$: C, 78.85; H, 5.6; N, 4.38; Cl, 11.09. Found: C, 79.03; H, 5.77; N, 4.32; Cl, 10.88.

Attempts to Isolate the *N*-(1,2-Diphenethyl)benzonitrilium Chlorostannate.

To a solution of *N*-(1,2-diphenethyl)benzimidoyl chloride (2.42 g., 0.076 mole) in dry benzene, stannic chloride (2.08 g., 0.008 mole) was dropwise added in the dry box. Immediately after the addition, the reaction mixture showed the presence of nitrile peak (2320 cm^{-1}). The reaction mixture was stirred at 50° for 100 hours; made alkaline (10% sodium hydroxide). Sodium stannate was vacuum filtered and the organic layer dried over anhydrous sodium sulfate and solvent was evaporated to isolate the retro-Ritter reaction products along with a trace of corresponding amide. The nitrile appeared at the beginning of the reaction was indeed the benzonitrile and all attempts to isolate the nitrilium salt were unsuccessful. The nitrilium salt decomposes as soon as it is formed. The amide was separated as insoluble material in petroleum ether and was identical with the authentic sample. The benzonitrile was separated from *trans*-stilbene on a column (Silica gel, 10% ether-petroleum ether). Similar results were obtained when the reaction was carried out in liquid sulfur dioxide.

Attempts to Prepare the *N*-(1,2-Diphenethyl)benzonitrilium Salt with Silver Hexafluoroantimonate.

To a solution of *N*-(1,2-diphenethyl)benzimidoyl chloride (3.19 g., 0.01 mole) in anhydrous nitromethane (30 ml.), solid silver hexafluoroantimonate (3.78 g., 0.011 mole) was added in the dry box at room temperature. At the end of 26 hours, the precipitated silver chloride was suction filtered under anhydrous conditions. The nitromethane was evaporated to give an oily material, which was identified as a mixture of *trans*-stilbene, benzonitrile and some unchanged amide.

Attempts to Synthesize 1-Methyl-3-phenyl-3,4-dihydroisoquinoline.

Stannic chloride (3.90 g., 0.015 mole) was slowly added to the *N*-(1,2-diphenethyl)acetimidoyl chloride (2.5 g., 0.01 mole), in the dry box. After 4 hours, 20% sodiumhydroxide solution (30 ml.) was added and the precipitated sodium stannate was filtered. The filtrate was extracted with chloroform (2 × 35 ml.) and the extracts were combined and dried. An oily material was obtained on removal of the solvent, which later was identified as a mixture of *trans*-stilbene and acetonitrile.

Attempts to Synthesize *N*-(1,2-Diphenethyl)benzamide from *trans*-Stilbene by the Ritter Reaction.

This technique was adopted from Ritter and Kalish (11b). Glacial acetic acid (200 ml.) was added to a 0.5 liter, 3-necked flask carrying a stirrer, dropping funnel and a reflux condenser attached to a trap containing 20% sodium hydroxide solution. The flask was kept at 20° while stirred. To the acetic acid, benzonitrile (5.67 g., 0.055 mole) was added over a period of 25 minutes. A pre-cooled solution of concentrated sulfuric acid (60 ml.) in glacial acetic acid (50 ml.) was dropwise added. The cooling was removed and *trans*-stilbene (9.01 g., 0.05 mole) was slowly added over a period of 30-45 minutes. The stirring was continued for 24 hours at room temperature, and nitrogen was passed through the mixture for two hours. The reaction mixture was poured onto crushed ice and the solution was neutralized with aqueous 15% sodium carbonate. The precipitate was suction filtered and identified as unchanged *trans*-stilbene.

Cyclodehydration with Polyphosphoric Ester (PPE). (General Procedure).

The reagent was prepared according to Fieser and Fieser (14) and characterized by spectral data; ir (mull): 3000 (m), 2320 (w, broad), 1400 (m), 1345 (m), 1275 (vs, broad), 1160 (s), 1000 (vs, very broad), 800 (s) cm^{-1}. This reagent has been used for isoquinoline synthesis by Kanaoka, *et al.* (15). While their procedure required prolonged heating to reflux temperatures, from 70 to 120°, particularly for amides with no electron releasing group in the ring, we successfully used much milder conditions, (25-30°).

Method A.

A stirred solution of the amide (1 mole) and PPE (5 mole) in anhydrous chloroform (20 ml.) was maintained at room temperature for 40-60 hours. The chloroform was removed and water (100 ml.) was added to the remaining syrupy liquid, and was made alkaline with either sodium carbonate or potassium hydroxide. The reaction mixture was then extracted with chloroform (2 × 25 ml.) and extracts were combined, dried over

anhydrous sodium sulfate. A thick oil obtained, on evaporation of chloroform, was triturated with petroleum ether to obtain the corresponding isoquinoline derivative.

Method B.

Procedure A was modified by using the following quantities of reagents: amide 1 (mole), PPE (1 mole), anhydrous chloroform (20 ml.), and phenyl sulfide (1 mole). After the reaction mixture was stirred for 60 hours at room temperature, the solvent was evaporated, and water (100 ml.) was added. Then the reaction mixture was basified and was extracted with either chloroform or ether (2 × 50 ml.). The isoquinoline derivative precipitated on addition of petroleum ether.

Retro-Ritter Reaction of *N*-(1,2-Diphenethyl)benzamide with PPE.

A mixture of *N*-(1,2-diphenethyl)benzamide (1 g., 0.0033 mole), PPE (7.18 g., 0.0166 mole) and anhydrous chloroform (20 ml.) was stirred for 50 hours. 100 ml. of water was added to the reaction mixture and extracted with ether (2 × 25 ml.). Work up as in Method A above yielded the *trans*-stilbene and the mother liquor contained benzonitrile.

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