A Modified Bischler-Napieralski Reaction. Synthesis of 2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indole Derivatives and Their Base-Catalyzed Transformation to N-Acetyl-N-[2-[1-acetyl-2-[1-(acetyloxy)-1-propenyl]-1H-indol-3-yl]ethyl]acetamides

George Bobowski

Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company,
2800 Plymouth road, Ann Arbor, Michigan 48105
Received July 19, 1982

The treatment of N-[2-(1H-indol-3-yl)ethyl]alkanamide, 1 (1), with phosphorus oxychloride under controlled conditions gave 1-alkyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol, 2. The reaction of 2 with acetic anhydride or with methyl isocyanate at room temperature resulted in the formation of amido carbinol 3 and urea carbinol 7, respectively. The former was transformed into amido ester 4 by boiling acetic anhydride. When the reaction of 3 with acetic anhydride was carried out in the presence of excess triethylamine at 105°, C-N bond cleavage of the tetrahydropyridine ring took place with concurrent bis(N-acetylation) to give the enol ester derivative 5. The structures of all compounds are consistent with chemical and spectral evidence.

A previous report (1) described the formation of 1-alkyl-4,9-dihydro-3H-pyrido[3,4-b]indoles, 8, by cyclodehydration of N-[2-(1H-indol-3-yl)ethyl]alkanamides, 1. Those results were completely consistent with that reported for similar examples when conventional Bischler-Napieralski reaction conditions were employed (3a-b). We now report, however, that an atypical outcome could be observed if the reaction is interrupted. Thus, an unstable intermediate amino carbinol, 2, could be isolated and characterized by transformations depicted in Scheme I indicating that dehydration is not a necessary consequence of cyclization during formation of 8.

The treatment of amide 1 (1) with neat phosphorus oxychloride at 110° for 3 minutes and immediate cooling of the dark solution to 0° gave the off-white precipitate in 54% yield, presumably in the form of complex A (2).

Scheme I
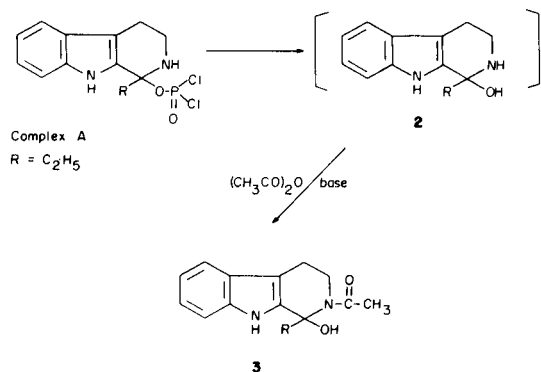
When the solid A was made basic with sodium bicarbonate to pH 8.0 at 0°, extracted with ether and treated with acetic anhydride, the resulting product was the amido carbinol 3 and not the enamido derivative 10 (1) which was obtained by acetylation of 8b.

8b

10
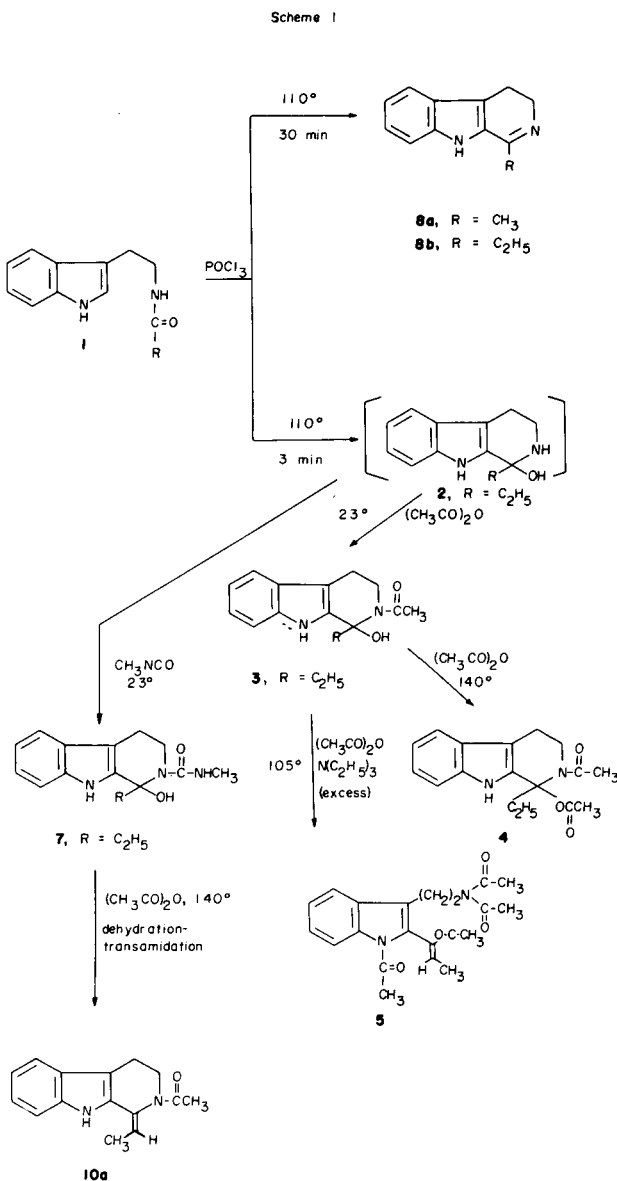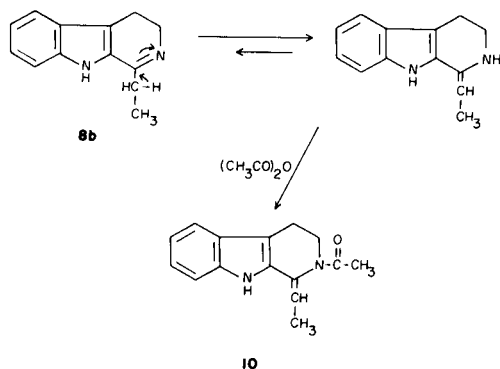
Attempts to isolate and characterize "free" amino carbinol **2** proved unsuccessful. On liberation of the free base and evaporation of the ethereal solution at low temperature (both under diminished or atmospheric pressure), compound **2** underwent elimination of water giving 4,9-dihydro-1-ethyl-3H-pyrido[3,4-b]indole, **8b** (1). In contrast to the unstable nature of **2**, the amido carbinol **3** is characterized by remarkable stability and does not change on heating with anhydrous mineral acids. Compound **3** bears some partial resemblance to 3,4-disubstituted-3,4-dihydro-4-hydroxy-2H-1,3-benzoxazin-2-ones (**12**) (4).

The compound has sharp melting point and only one spot on thin layer chromatography (tlc) using several different solvent systems. The ultraviolet spectrum of **3** [nm (ϵ) 235 (15,200), 310 (18,600)] remains unchanged on addition of acid in sharp contrast to compound **8b** (1) which undergoes considerable bathochromic shifts [235 (14,600), 315 (14,200); in the presence of acid: 245 (9900), 351 (21,400)].

The infrared absorption spectrum of **3** (potassium bromide) exhibits NH and OH bands at 3350 cm^{-1} and 3250 cm^{-1}. The proton magnetic resonance spectrum (deuteriochloroform) shows an exchangeable hydroxyl proton at δ 5.82, a methylene quartet of the ethyl group at δ 3.02, a methylene group attached to the indole nucleus (CH$_2$-4) as a multiplet at δ 3.35, and a N-methylene group (CH$_2$-3) at δ 3.55. The upfield shift of the N-methylene protons (CH$_2$-3) by about 0.3 ppm (5) could be explained by assuming that the amido carbonyl is constrained in the conformation where it forms an intramolecular six-membered hydrogen bond with the hydroxyl function in **3**. Consequently, there is considerably less deshielding influence of the carbonyl function on the neighboring methylene group (6). The relatively strong hydrogen bonding might also explain the low field resonance for the hydroxyl proton (see Experimental).
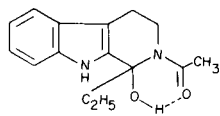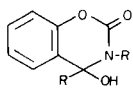

3   **12** (4)

In their studies on Bischler-Napieralski reaction Fodor and coworkers (7a-c) have proposed that dehydration precedes cyclization with formation of imidoyl halide, R-C(X)=N-. The imidoyl halide would equilibrate forming nitrilium salt [$^{+}$N $\equiv$ C-R]X^{-}, which would then cyclize to give 3,4-dihydroisoquinoline derivative as shown.
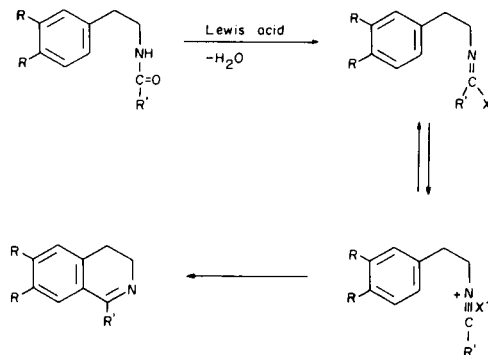
An earlier proposal (8) involved protonation of the amide oxygen by a trace of hydrogen chloride followed by cyclization to tetrahydro-1-hydroxyisoquinoline derivative and finally dehydration to give the 3,4-dihydroisoquinoline, e.g.
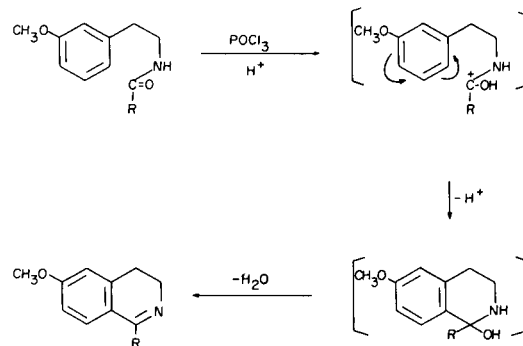
While compound **8** could have formed via an imidoyl halide, compound **3** clearly could not. It may be that only superior electron donating properties of an aromatic ring will allow ring closure to precede dehydration. Examples of this would be the phenyl ring aided by para methoxy group or the 2-position of an indole. In any case, in view of the subsequent formation of compounds **3** and **7** and the presumptive structure of "complex A", we suggest the following mechanism for our ring closure.
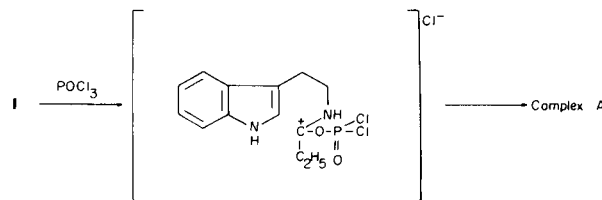
In support of the concept of cyclization preceding dehydration, the following examples can be cited in Bischler-

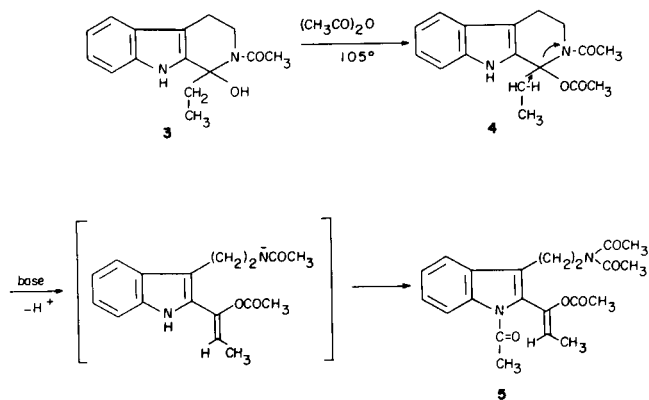Napieralski related reactions. Thus, 2-alkyltetrahydro-1-hydroxyisoquinoline derivatives (9a-f) are known to arise from cyclization of formamides of secondary amines. These *pseudo* bases are relatively stable under neutral conditions, because they lack an NH function next to the hydroxy group for easy elimination of water. In the presence of acids, these compounds such as 13 (9a) form quaternary ammonium salts.


13, R' = alkyl
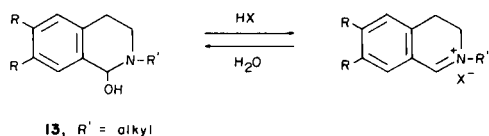
Treatment of 3 with excess acetic anhydride at 140° gave 2-acetyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]-indol-1-ol acetate (4) in 58% yield. The uv spectrum of 4 is essentially the same as that of 3 both in the neutral solution and in the presence of acid. The ir absorption spectrum shows two carbonyl bands at 1705 cm^{-1} and 1650 cm^{-1} for the ester and amido functions, respectively. The pmr spectrum (deuteriochloroform) shows a quartet of the ethyl methylene group at δ 2.98, a multiplet for CH$_2$-4 at δ 3.32 and a multiplet for CH$_2$-3 at δ 3.85. The methyl groups of both acetyl functions are equivalent and resonate at δ 2.37. In compound 4 where the N-acetyl group is no longer constrained in one conformation, there are two distinctive features apparent: the N-methylene group (CH$_2$-3) resonates at the expected field (δ 3.88) (5) (downfield shift by *ca.* 0.3 ppm as compared to 3) and the amido methyl group undergoes a downfield shift of *ca.* 0.45 ppm (see Experimental).

When the acetylation of amidocarbinol 3 was carried out in the presence of excess triethylamine at 105° for about 10 hours (until starting 3 was consumed), the isolated product analyzed for an empirical formula C$_{21}$H$_{24}$N$_2$O$_5$. The uv spectrum showed conjugated indole (10). The ir spectrum displayed carbonyl bands at 1766 cm^{-1}, 1712 cm^{-1} and 1688 cm^{-1}. The pmr spectrum showed four acetyl methyls, one allylic methyl (doublet), one vinylic proton (quartet), two methylene groups as multi-

plets and two deshielded aromatic protons as multiplets (see Experimental). The accumulated data are consistent with structure 5. Compound 5 was also obtained from amido ester 4 by heating the latter with excess triethylamine and acetic anhydride at 105°. A possible mechanism for this rearrangement is as follows: the initially formed amido ester 4, under the influence of hot organic base (triethylamine), suffered C-N bond cleavage of the tetrahydropyridine ring (11) followed by bis-acetylation to give 5.

Alternatively, cleavage of the C-N bond might have taken place prior to ester formation giving the amido ketone 6 which then under forcing conditions could enolize to 6' followed by acetylation.
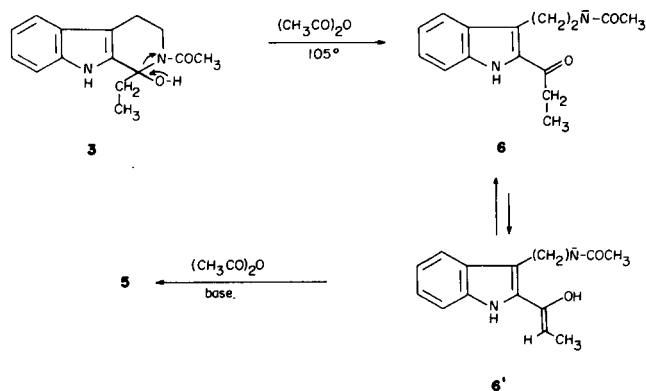
The stereochemistry was not defined rigorously, but the structure of the single isomer was presumed to be the least hindered one (as depicted).

The treatment of amino carbinol 2 with methyl isocyanate at room temperature gave urea carbinol 7. An attempt to convert compound 7 into urea carbamate 9a (R = CONHCH$_3$) with excess isocyanate at increased temperature was unsuccessful. Attempts to convert compound 7 to the urea ester 9b (in analogy to amido ester 4) by refluxing acetic anhydride was unsuccessful. The only product isolated in 62% yield was (E)-2-acetyl-1-ethylidene-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole, 10a (12). The formation of 10a from 7 appears to be inconsistent with the forma-

9a, R = CONHCH$_3$
9b, R = COCH$_3$

10a (12)
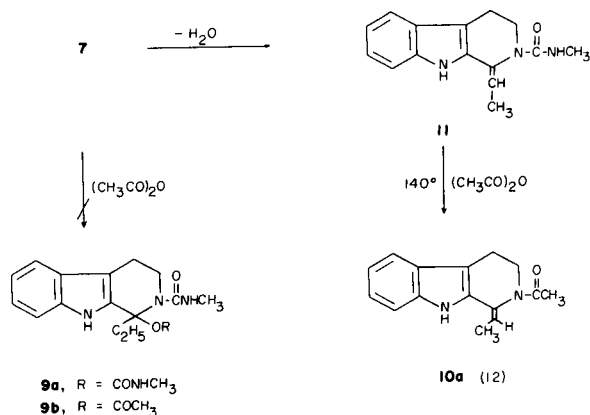
tion of **4** from **3** when the latter was also treated with hot acetic anhydride. The results can be rationalized by assuming dehydration allowed formation of **11** which preceded displacement of the carbamoyl substituent by an acetyl function as shown below.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet (uv) and infrared (ir) spectra were obtained, respectively, with a Cary 118 UV-Visible Recording spectrophotometer and a Digilab FT-IR spectrometer. The proton magnetic resonance (^{1}H-nmr) spectra were recorded with a Varian EM390 and with a Bruker WH90 spectrometers with tetramethylsilane as an internal reference. The mass spectra were recorded on a Finnigan 1015 Quadrupole mass spectrometer. Thin layer chromatography (tlc) was carried out on silica gel G (Stahl) using acetone, toluene and heptane or acetonitrile, methanol and 2-propanol in varying proportions, as the eluent. The chromatograms were developed in an iodine chamber.

A Modified Bischler-Napieralski Reaction to Obtain Latent 1-Ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol (**2**).

A solution of 8.6 g (0.04 mole) of N-[2-[1H-indol-3-yl]ethyl]propanamide (**1**) (1) in 25 ml of phosphorus oxychloride was refluxed for 3 minutes and then immediately cooled to 0°. After 4 hours, the light yellow salt complex A was collected, washed first with phosphorus oxychloride and then with dichloromethane giving (after drying in vacuo over phosphorus pentoxide) 7.2 g (54% yield) of product, mp 185-186°.

Anal. Calcd. for $C_{13}H_{15}Cl_2N_2O_2P$: C, 46.80; H, 4.81; N, 8.40; Cl, 21.22; P, 9.32. Found: C, 46.74; H, 4.62; N, 8.37; Cl, 20.89; P, 9.37.

To a suspension of the above solid in ice-water was added sodium bicarbonate to pH 8.0 and the product was immediately extracted with 300 ml of diethyl ether. The ether solution, containing carbinol 2 was used as such for subsequent transformations.

2-Acetyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol (**3**).

To a solution of 0.02 mole of crude **2** in 300 ml of ether was added 6.0 g (0.06 mole) of acetic anhydride and 5 drops of triethylamine. After 20 hours at room temperature, the resulting white crystals of **3** (2.9 g) of analytical purity were collected, mp 193-194° dec. The filtrate was made basic with aqueous ammonia (pH 8.0), the organic phase was washed, dried over sodium sulfate and concentrated to a low volume giving 0.7 g (total yield: 70%) of additional crop of 2-acetyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol (**3**), mp 192-193° dec; uv (methanol): λ max nm (ε) 235 (15,200), 310 (18,600); (methanol, hydrochloric acid): 235 (15,200) 310 (18,570); ir (potassium bromide): 3350, 3250 (OH, NH), 1651 (C=O) cm^{-1}; ir (chloroform): 3460 (NH, OH), 1667 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, CH_3CH_2, 3H, J = 7.0 Hz), 1.90 (s, CH_3CON, 3H), 3.02 (q, CH_3CH_2, 2H, J = 7.0 Hz), 3.35 (m, CH_2-4, 2H), 3.55 (m, CH_2-3, 2H), 5.80 (broad, OH, deuterium oxide-exchangeable, 1H), 7.20-7.75 (m, 4 aromtic protons), 8.82 (indole NH, 1H); (DMSO-d$_6$): δ 1.10 (t, CH_3CH_2, 3H, J = 7.0 Hz), 1.72 (s, CH_3CON, 3H), 2.98 (q, CH_3CH_2, 2H, J = 7.0 Hz), 6.95-7.70 (4 aromatic protons), 7.90 (broad, OH, 1H), 11.40 (indole NH, 1H).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.66; H, 7.00; N, 10.66.

2-Acetyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol Acetate (**4**).

A solution of 1.2 g (0.0046 mole) of **3** in 10 ml of acetic anhydride was heated for 2 hours at 140° and subsequently evaporated in vacuo. The colorless solid residue was recrystallized from 2-propanol giving 0.8 g (58% yield) of an amido ester **4** as white crystals, mp 160-161°; uv (methanol): λ max nm (ε) 17,200), 310 (18,300); ir (potassium bromide): 3340 (NH), 1705 (ester C=O), 1650 (amide C=O) cm^{-1}; ^{1}H-nmr deuterio-chloroform): δ 1.28 (t, CH_3CH_2, 3H, J = 7.0 Hz), 2.42 (s, CH_3CON and

CH_3COO, 6H), 3.03 (q, CH_3CH_2, 2H, J = 7.0 Hz), 3.35 (m, CH_2-4, 2H), 3.88 (m, CH_2-3, 2H), 7.10-7.80 (m, 4 aromatic protons), 8.95 (indole NH, 1H).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.07; H, 6.83; N, 9.35.

N-Acetyl-N-[2-[1-acetyl-2-[1-(acetyloxy)-1-propenyl]-1H-indol-3-yl]ethyl]-acetamide (**5**).

A solution of 1.3 g (0.005 mole) of 2-acetyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-ol (**3**) and 4 ml of acetic anhydride in 15 ml of triethylamine was refluxed under nitrogen for 10 hours, and subsequently the solution was evaporated in vacuo. The dark solid residue was taken up with dichloromethane and filtered through silica gel G. The filtrate was evaporated and the residue recrystallized from isopropyl ether-ethyl acetate giving 0.8 g (42% yield) of pure **5** as white crystals, mp 134-135°; uv (methanol): λ max nm (ε) 240 (15,700), 280 (12,200), 293 sh (10,980), 303 sh (9450); ir (potassium bromide): 1766 (vinyl ester), 1712 [N(COCH$_3$)$_2$], 1688 (CH$_3$CON-1) cm^{-1}; ^{1}H-nmr deuteriochloroform): δ 1.77 (d, $CH_3CH=$, 3H, J = 7.0 Hz), 2.10 (s, CH_3COO, 3H), 2.42 [s, $(CH_3CO)_2N$, 6H], 2.64 (s, CH_3CON-1), 3.10 (m, CH_2-indole, 2H), 3.88 [m, $CH_2N(COCH_3)_2$, 2H], 5.73 (q, $CH_3CH=$, 1H, J = 7.0 Hz), 7.18-7.35 (m, H-5, H-7, 2H), 7.82 (m, H-6, 1H), 7.82 (m, H-8, 1H); ms, m/e 384.

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.23; N, 7.37.

1-Ethyl-1-hydroxy-N-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxamide (**7**).

A solution of 0.005 mole of crude 1-ethyl-2,3,4,9-tetrahydro-1H-pyrido-[3,4-b]indol-1-ol (**2**), 0.6 ml of methyl isocyanate and 2 drops of triethyl-amine in 75 ml of anhydrous ether was allowed to stand at 23° for 20 hours. Methanol (0.5 ml) was added to destroy excess isocyanate and the solution was evaporated to dryness in vacuo. The solid residual cake was crystallized from ethyl acetate giving 1.1 g (80% yield) of pure **7** as white crystals, mp 172-173° dec; uv (methanol): λ max nm (ε) 234 (15,600), 310 (19,100); ir (potassium bromide): 3420, 3360, 3220 (OH, NH), 1640, 1572, 1532 (CONH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, CH_3CH_2, 3H, J = 7.0 Hz), 2.70 (d, CH_3NH, 3H, J = 5.0 Hz), 3.00 (q, CH_3CH_2-, 1H, J = 7.0 Hz), 3.35 (m, CH_2-4 and CH_2-3, 4H), 4.36 (s, OH, 1H), 4.55 (q, CH$_3$NH, 1H, J = 5.0 Hz), 7.00-7.75 (m, 4 aromatic protons), 8.88 (indole NH, 1H); ms, m/e 273.

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.85; H, 6.76; N, 15.37.

Reaction of 1-Ethyl-1-hydroxy-N-methyl-1,3,4,9-tetrahydro-2H-pyrido-[3,4-b]indole-2-carboxamide (**7**) with Hot Acetic Anhydride. (E)-2-Acetyl-1-ethylidene-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**10a**).

A solution of 1.4 g (0.005 mole) of **7** in 15 ml of eacetic anhydride was refluxed for 3 hours. The tlc (ethyl acetate-acetonitrile, 5:1) showed absence of **7** (Rf = 0.25), the new product having faster mobility (Rf = 0.5). After the solution was evaporated in vacuo, the solid residue was crystallized from 2-propanol giving 0.75 g (62% yield) of (E)-2-acetyl-1-ethylidene-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**10a**) of analytical purity as white crystals, mp 242-243° dec [ref (1), the mp of cis-isomer (**10b**) is 219-220° dec; Rf = 0.4]; uv (methanol): λ max nm (ε) 228 (23,800), 304 (19,900), 310 (19,900); ir potassium bromide): 3410, 3240 (NH), 1672 (C=C-NCO), 1638 (C=O) cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 1.79 (d, $CH_3CH=$, 3H, J = 7.0 Hz), 1.96 (s, CH$_3$C=O, 3H), 5.97 (q, vinylic, 1H, J = 7.0 Hz), 6.98 (m, 2 aromatic protons), 7.30 (m, 2 aromatic protons), 11.08 (1H, indole NH).

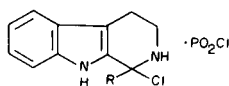*Anal.* Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.71; H, 6.70; N, 11.48.

REFERENCES AND NOTES

(1) G. Bobowski, Manuscript in Press.

(2) It is conceivable that the salt complex might exist as a chloride-phosphorus dioxychloride moiety,

prior to treatment with cold water to give intermediate 2.

(3a) A. Bischler and B. Napieralski, *Ber.*, **26**, 1903 (1893); (b) for a review of the Bischler-Napieralski reaction see: M. Whaley and T. R. Govindachari, "Organic Reactions", Vol. **6**, John Wiley and Sons, Inc., New York, NY, 1951, pp 74-150.

(4) The amido carbinol 3 shows remarkable stability towards acids. It did not change on standing in ethanol solution containing concentrated hydrochloric acid for one week at 25°. Chemically it is somewhat similar to compound 12. For details see: G. Bobowski and J. Shavel, Jr., *J. Org. Chem.*, **32**, 933 (1967).

(5) G. Bobowski, *J. Heterocyclic Chem.*, **18**, 1179 (1981). The *N*-methylene group (CH₂-3') in compound 16, resonates as triplet (J = 5.5 Hz) at δ 3.73.
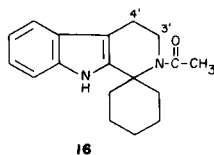
(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press Inc., New York, NY, 1962, p 124.

(7a) G. Fodor, J. Gal and B. A. Phillips, *Angew. Chem., Int. Ed. Engl.*, **11**, 919 (1972); (b) G. Fodor and S. Nagubandi, *Tetrahedron*, Vol. **36**, 1279-1300 (1980); (c) S. Nagubandi and G. Fodor, *J. Heterocyclic Chem.*, **17**, 1457 (1980).

(8) F. Ritchie, *Proc. Roy. Soc., N. S. Wales*, **78**, 147 (1945); *Chem. Abstr.*, **40**, 877 (1946).

(9a) R. D. H. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1448 (1925); (b) H. Decker and P. Becker, *Ann. Chem.*, **395**, 328 (1913); (c) K. Kindler and O. Giese, *ibid.*, **431**, 228 (1923); (d) K. Kindler and O. Giese, *Archiv. Pharm.*, **265**, 411 (1927); (e) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945); (f) W. O. Kermack and R. H. Slater, *J. Chem. Soc.*, **32**, (1928); (g) S. N. Chakravarti, R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 2275 (1927).

(10) R. Goutarel, M. M. Janot, V. Prelog and W. I. Taylor, *Helv. Chem. Acta*, **33**, 150-164 (1950).

(11) G. Bobowski, Manuscript submitted to *J. Heterocyclic Chem.* A somewhat similar cleavage of C-N bond was observed when a β-ketomide 14 was treated with sodium alkoxide in hot alcohol giving the α,β-unsaturated ketone derivative 15 shown below.
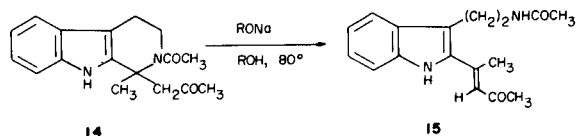
(12) Ref. 1. Amide 10a is obviously a thermodynamically controlled product in contrast to a kinetically controlled stereoisomer 10b [which is of *cis (Z)* configuration] obtained from 8b and acetic anhydride at room temperature. The *cis* isomer (10b) could be converted into *trans* (10a) by heating with triethylamine for 10 hours at 105° or with refluxing acetic anhydride for 3 hours.