Application of a Thermal Rearrangement Reaction to Questions of Structure of Condensed Dihydrodiazepinones: Synthesis and Characterization of Isomeric Dihydropyrido[3,4-*b*][1,4]diazepinones from 3,4-Diaminopyridine and Ethyl Acetoacetate (1,2)

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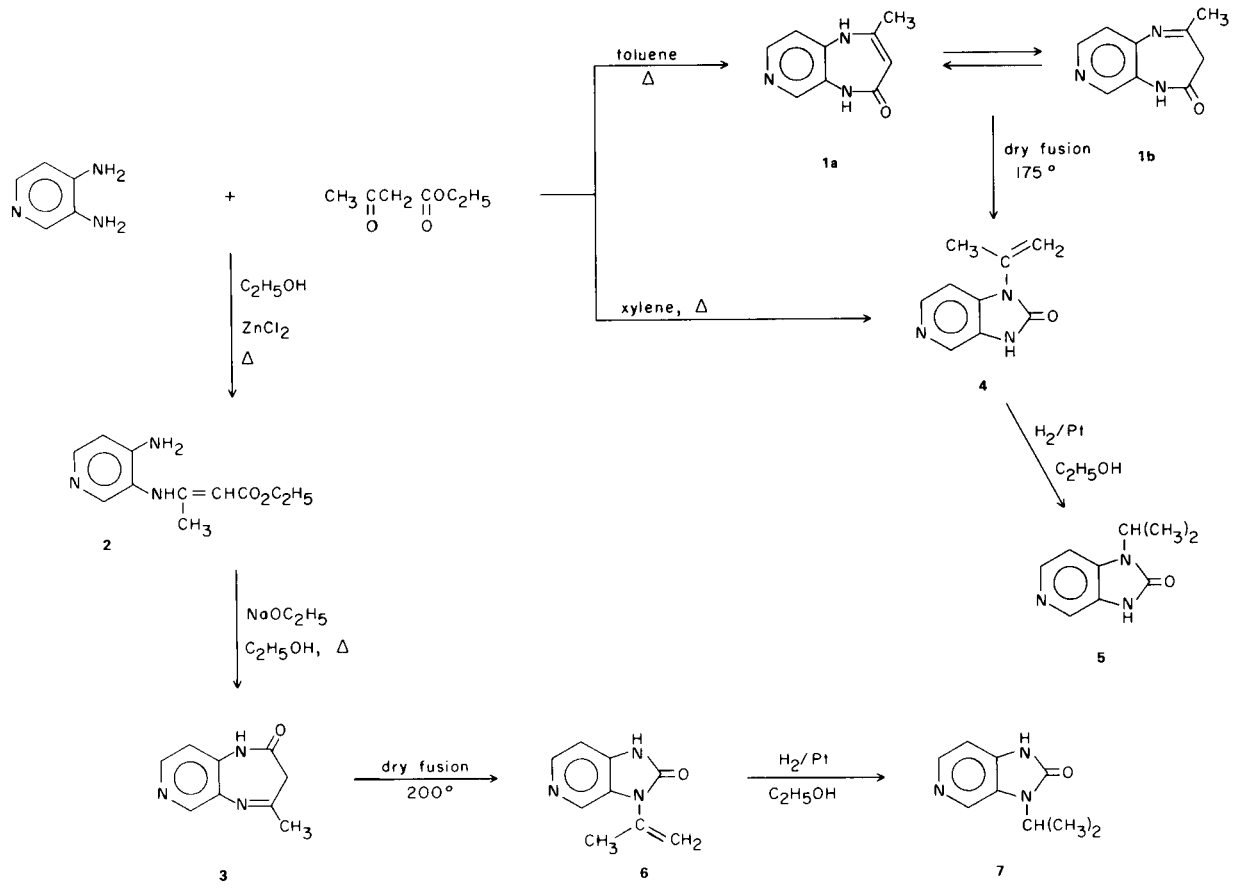
Reaction of ethyl acetoacetate with 3,4-diaminopyridine can theoretically give rise to the isomeric dihydrodiazepinones **1** and **3**. However, only one of these (compound **1**) was formed on direct condensation of the reactants in boiling toluene. The preparation of **3** required the synthesis of the pyridylaminocrotonate **2**, which cyclized under conditions of base catalysis. When subjected to dry fusion, both diazepine derivatives rearranged to give isomeric isopropenylpyridoimidazolones. The structures of these rearranged products were used to characterize the diazepines from which they were derived, according to a technique previously described (20,21). Our results contradict a recent report (17) ascribing structure **3** to the product from 3,4-diaminopyridine and ethyl acetoacetate in boiling xylene.

Various dihydro-1,5-benzodiazepinone derivatives have been prepared by reaction of *o*-phenylenediamines with β-ketoesters (3-14). In recent years this reaction has been extended to heteroaromatic *o*-diamines with the formation of dihydropyridodiazepinones (2,11,15,16,17) and dihydropyrimidodiazepinones (18,19). These latter reactions, however, are complicated by the possible formation of isomeric diazepine products, differentiation between which has heretofore been difficult and time consuming. During our studies on the isomeric diazepinones from 2,3-diaminopyridine and ethyl acetoacetate (15) we recognized, as a general reaction, the facile rearrangement of condensed dihydrodiazepinones into *N*-alkenylimidazolones under the influence of heat (20). Since the rearrangement proceeds without cleavage of carbon-nitrogen bonds (20), the structural relationship of the ring contracted product to the diazepinone from which it was derived provides a convenient means for determining the structure of an ambiguous dihydrodiazepinone product. We recently described an application of this thermal rearrangement reaction in the unambiguous characterization of the diazepine product arising from 2,3-diaminopyridine and ethyl benzoylacetate (21).

As part of our program on condensed diazepine derivatives, we also prepared the isomeric diazepinones **1** and **3**, which are derived from 3,4-diaminopyridine and ethyl acetoacetate. Direct condensation of the diamine with acetoacetic ester in boiling toluene was found, as described below, to give diazepinone **1** together with a small quantity of rearranged material (**4**); neither the isomeric diazepinone (**3**) nor its rearrangement product (**6**) were ever found under these conditions. However, after a preliminary report of our work had been presented (2), Nawojski (17) claimed that 3,4-diaminopyridine and ethyl acetoacetate in boiling xylene afforded diazepinone **3**, together with a small quantity of rearranged material **6**. We should like now to describe the synthesis and characterization of diazepinones **1** and **3** and to show how our results clearly indicate Nawojski's structural assignments to be incorrect.

We found that reaction of 3,4-diaminopyridine with ethyl acetoacetate in boiling toluene (Scheme I), with azeotropic removal of water, afforded a yellow colored crude product, which, upon crystallization from acetonitrile, gave a mixture of bright yellow powder and paler yellow crystals. The pale yellow crystals were separated from the yellow powder by extraction into boiling benzene. The two samples, one melting at 168-171° and the other at 180-182°, both analyzed for molecular formula $C_9H_9N_3O$ and appeared to be diazepinones. Because of differences in melting points and in infrared and ultraviolet (ethanolic solution) spectra, the two samples were at first thought to be the isomeric ring closure products **1** and **3**. However, the following evidence eventually showed these samples to be instead tautomeric forms of the same diazepinone: (1) the two samples gave identical ultraviolet spectra in aqueous *p*H 1 solution; (2) the samples were

SCHEME I



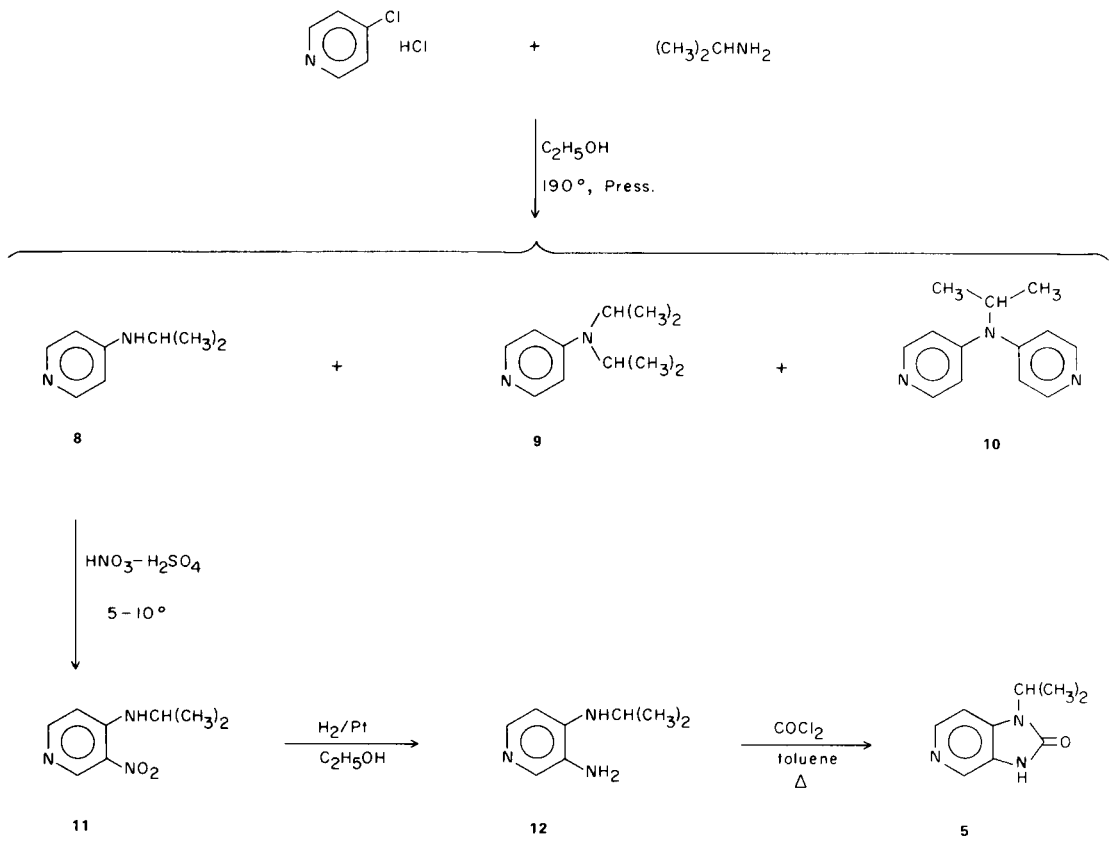
each homogeneous by thin layer chromatography and a mixture of the two could not be separated; (3) melting points and other physical characteristics of these samples differed from those of another $C_9H_9N_3O$ diazepinone product, m.p. 205-207°, obtained by cyclization of an intermediate later shown to be **2** (*vide infra*); (4) both samples afforded the same thermal rearrangement product, different from the rearrangement product formed from diazepinone m.p. 205-207°; and (5) the two samples gave the same nuclear magnetic resonance spectrum in deuteriopyridine, a spectrum which showed the presence of two tautomeric species in solution in approximately a 1:2 equilibrium.

We have previously noted that condensed dihydrodiazepinones can exist in stable prototropic forms in the solid state (15,19) and the present example appears to be another instance of this phenomenon. The pale yellow form, tautomer **1a**, with the double bond of the diazepine ring out of conjugation with the pyridine nucleus, exhibits an ultraviolet spectrum in ethanol solution equivalent to that of a simple substituted pyridinediamine (λ max 262 and 292 nm) and contributes to the nmr spectrum a vinyl proton signal (δ 4.97 ppm) *cis* to a methyl group (δ 1.82 ppm). Tautomer **1b**, with the double bond in conjugation with the pyridine moiety, shows long wavelength absorption in the uv [λ max (ethanol) 233, 262, 293, and 360 (shoulder) nm] and provides a methyl and methylene signal in the nmr (δ 2.35 and 3.32 ppm, respectively).

Samples of **1a** and **1b** underwent thermal rearrangement quite easily to give the *N*-isopropenylimidazolone **4**. Under dry fusion conditions at 175° in a nitrogen atmosphere, the yield of **4** was nearly quantitative. Indeed, diazepinone **1** rearranged so easily that, when the reaction of 3,4-diaminopyridine and ethyl acetoacetate was carried out in boiling xylene, **4** was obtained as the major product, together with a small quantity of **1**. The condensation reaction in hot toluene, on the other hand, gave only a small quantity of **4** as a companion product to the diazepine. Characterization of compound **4** and, thereby, of **1** was accomplished by comparison of the reduction product of **4** with an unambiguous sample of 1,3-dihydro-1-isopropyl-2*H*-imidazo[4,5-*c*]pyridin-2-one (**5**).

The synthesis of **5** is outlined in Scheme II. Wibaut and Broekman (22) reported that the chlorine atom of 4-chloropyridine is replaced by amines slowly and with difficulty. These workers obtained only a 0.4% yield of 4-iso-

SCHEME II



propylaminopyridine (**8**) from the reaction of 4-chloropyridine and isopropylamine in benzene at 160-170° for over 6 hours in a sealed glass tube. We treated 4-chloropyridinium chloride with isopropylamine in ethanol solution at 190° for 16 hours in an autoclave. Under these conditions, three products, 4-*N*,*N*-diisopropylpyridine (**9**), 4,4′-dipyridylisopropylamine (**10**), and the desired 4-isopropylaminopyridine (**8**), were formed; the yields were 2, 10, and 25%, respectively. Nitration of crude **8** with fuming nitric acid in the cold afforded the nitro derivative **11**, which was easily reduced catalytically to give 3-amino-4-isopropylaminopyridine (**12**). Treatment of **12** with phosgene in warm toluene afforded the authentic sample of **5**, m.p. 138-140°.

Compound **5**, obtained from **4**, was identical with the synthetic sample on the basis of all physical criteria examined. This identity then established the structure of **4** as the N^1-isopropenylimidazolone. Since **4** was obtained by thermal rearrangement of the diazepinone, the presence of the isopropenyl function at the 1-position of **4** established the structure of the diazepine product as **1** (20,21).

Reaction of 3,4-diaminopyridine with ethyl acetoacetate in ethanol in the presence of zinc chloride afforded an ethyl pyridylaminocrotonate, as evidenced by microchemical analysis and by infrared, ultraviolet, and nuclear magnetic resonance spectra; substitution could, however, theoretically occur at either the 3- or 4-amino function of the diamine in this reaction. Structure **2** was automatically assigned to this product when it was found that treatment of the pyridylaminocrotonate with sodium ethoxide afforded a diazepine product, **3**, m.p. 205-207°, similar to but not identical with **1**. Mixture melting point determination of **1** and **3** showed depression. The infrared, ultraviolet, and nuclear magnetic resonance spectra of **3** were not superimposable on those of **1**. In contrast to **1**, the low solubility of **3** in deuteriopyridine necessitated the use of time-averaging techniques in obtaining the nmr spectrum, which showed **3** to exist solely in the imine form in pyridine solution.

Since the structure of the alternate ring closure product **1** had already been established with certainty, structure **3** could be assigned directly to this new diazepine product. However, in further support of this assignment, **3** was subjected to thermal rearrangement. At 200° in the absence of solvent, **3** was converted to an isopropenylimidazolone (**6**), which, after catalytic hydrogenation, afforded an isopropylimidazolone (**7**), m.p. 197-203°. Compounds **6** and **7**, while exhibiting similarities of spectral features with **4**

and **5**, respectively, were not identical with their N^1-substituted counterparts. Thus, the isopropyl group in **7** and, consequently, the isopropenyl group in **6** were located at the 3-position of the ring system.

Nawojski (17) claimed m.p. 174-177° for the diazepinone product, incorrectly assigned structure **3**, from 3,4-diaminopyridine and ethyl acetoacetate; a companion product, incorrectly assigned structure **6**, was reported to have m.p. 122-124°. From the work we have just described, it was seen that reaction of 3,4-diaminopyridine and ethyl acetoacetate in boiling toluene gave rise to **1**, accompanied by a small quantity of **4**; in boiling xylene, **4** was the major product and **1** became the minor product. Nawojski's melting point for the diazepinone product actually falls between the melting points given by the two tautomeric forms of **1** and comes nowhere close to that of **3**, which is not formed in these direct condensation reactions. The spectral features given by Nawojski for the companion product fall close to those of our samples of **4**. However, the melting point of our analytical sample of **4** (162-165°) leads us to suspect that Nawojski's sample of companion product was never obtained in the pure state.

Nawojski's error in assigning structures derived from his assumption that the direction of cyclization of acetoacetic ester would be the same with 3,4-diaminopyridine as with 2,3-diaminopyridine. It was first shown by us (15), and later confirmed by Nawojski (16), that reaction of 2,3-diaminopyridine and ethyl acetoacetate in boiling xylene afforded a dihydrodiazepinone, the structure of which could be thought of as deriving from reaction of the more basic 3-amino group of the diamine with the keto-carbonyl of the β-ketoester. However, recently we reported that, in a related reaction, the condensation of 4,5-diaminopyrimidine with ethyl acetoacetate in boiling xylene, the major diazepinone product was that which was structurally derived from reaction of the more basic 5-amino function with the carbethoxy-carbonyl of the ketoester (19). In the present instance, the direction of cyclization of ethyl acetoacetate with 3,4-diaminopyridine more closely parallels that of 4,5-diaminopyrimidine, and not 2,3-diaminopyridine.

EXPERIMENTAL (23)

Quantitative ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers in 95% ethanol solution; where indicated, spectra at *p*H 1 were taken in 0.1 *N* hydrochloric acid. Infrared spectra were determined in potassium chloride disks, unless otherwise noted, with a Perkin-Elmer Model 137B double beam spectophotometer; significant peaks appearing between 2.5 and 8.0 μ in the spectrum are reported. Nmr spectra were obtained by means of a Varian A-60 spectrometer with tetramethylsilane as the internal standard; the solvent was anhydrous deuteriopyridine stored over Linde 4A molecular sieves, unless otherwise specified. The time averaged spectrum of **3** was obtained by means of a Japan Electron Optics Laboratory Company JRA-1 Spectrum Accumulator coupled with the nmr spectrometer. Thin layer chromatography was carried out on Eastman Chromagram plates, with 1-butanol saturated with water as the solvent system; the plates were visualized by ultraviolet light and/or in an iodine chamber. Melting points were taken by the capillary method at a rate of heating of 2°/minute in a modified Wagner-Meyer melting point apparatus (24) and are corrected. Drying of analytical samples was carried out at 70° for 17 hours *in vacuo* over phosphorus pentoxide.

Reaction of 3,4-Diaminopyridine with Ethyl Acetoacetate in Hot Toluene: Preparation of **1**.

A mixture of 2.5 g. (0.023 mole) of 3,4-diaminopyridine and 4.55 g. (0.035 mole) of ethyl acetoacetate in 180 ml. of toluene was maintained at reflux for 5 hours with azeotropic removal of water. Upon cooling, the reaction mixture deposited yellow solid (2.42 g., 60%). A mixture of bright yellow powder and paler yellow crystals resulted when the crude material was crystallized from acetonitrile. The pale yellow crystals dissolved in boiling benzene and the hot benzene solution, upon cooling, deposited light yellow crystals of 1,5-dihydro-2-methyl-4*H*-pyrido[3,4-*b*] [1,4] diazepin-4-one (**1a**), m.p. 168-171°; uv: λ max (ε) 262 (8400) and 292 (6700) nm; ir: λ max 2.88, 3.12, 3.20, 3.35, 3.45, 3.67, 5.95, 6.09, 6.32, 6.48, 6.78, 7.05, 7.17, 7.25, 7.36, 7.60, and 7.86 μ.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.69; H, 5.19; N, 23.99. Found: C, 61.90; H, 5.22; N, 23.89.

The bright yellow benzene-insoluble material from above was crystallized twice from acetonitrile and once from a mixture of ethanol and cyclohexane to give bright yellow crystals of 3,5-dihydro-2-methyl-4*H*-pyrido[3,4-*b*][1,4]diazepin-4-one (**1b**), m.p. 180-182°; uv: λ max (ε) 233 (14,900), 262 (16,500), 293 (2800) and 360 shoulder (500) nm; ir: λ max 2.92 (shoulder), 2.99 (shoulder), 3.05, 3.25 (shoulder), 5.98, 6.10, 6.22, 6.48, 6.67, 7.08, 7.18, 7.55, and 7.80 μ.

Anal. Found: C, 61.64; H, 5.22; N, 23.83.

The two stable tautomeric forms of **1** in *p*H 1 solution showed the same instantaneous uv absorption curve (λ max 213 and 266 nm). Each was homogeneous, as indicated by a single spot on thin layer chromatography, and the two samples exhibited the same R_f value. Both samples gave the same nmr spectrum, a pattern which indicated a mixture of the two tautomers in solution; integration showed this mixture to consist of approximately 33% of **1a** and 67% of **1b**; nmr: δ 1.82 (methyl group with fine splitting) and 4.97 (poorly resolved vinyl proton splitting pattern) ppm; **1b**: δ 2.35 ($C-CH_3$) and 3.32 ($-CH_2-$) ppm.

Evaporation of the original toluene mother liquor yielded a small but variable quantity of **4**.

When xylene was used as solvent in place of toluene, an identical reaction afforded only 6% of **1** but 72% of **4**.

Ethyl 3-(4-amino-3-pyridylamino)crotonate (**2**).

A solution containing 1.09 g. (0.01 mole) of 3,4-diaminopyridine and 1.95 g. (0.015 mole) of ethyl acetoacetate in 25 ml. of absolute ethanol was heated at reflux for 18 hours in the presence of 0.05 g. of zinc chloride. The yellow solution was then evaporated and the resulting oil was triturated under ether to dissolve the product and solidify the remaining zinc salts. After the oil had hardened, the solid was separated and discarded. The ether filtrate was partially evaporated and cooled in the freezer. The pale yellow powder which separated was crystallized once from ligroine (b.p. 60-95°) and four times from ether containing a small quantity of petroleum ether. The purified material, small white crystals, 0.71

g. (32%), melted at 105-107.5°; uv: λ max 246 and 287 nm; ir: λ max (deuteriochloroform) 2.90, 3.10, 3.35, 6.04 (shoulder), 6.09, 6.24, 6.60, 6.74, 7.00, 7.25, 7.40, and 7.87 μ; nmr (deuteriochloroform): δ 2.97 (3H triplet, J = 15 Hz), 3.48 (3H singlet), 4.22 (2H quartet, J = 21 Hz), 4.70 (broad 2H peak), 4.85 (1H poorly resolved quartet), and 5.84 (broad 1H peak) ppm.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.70; H, 6.85; N, 18.99. Found: C, 59.75; H, 6.88; N, 19.37.

1,3-Dihydro-4-methyl-2*H*-pyrido[3,4-*b*][1,4]diazepin-2-one (**3**).

A sample of 0.42 g. (2 mmoles) of ethyl 3-(4-amino-3-pyridylamino)crotonate (**2**) was dissolved in 30 ml. of absolute ethanol containing 2 mmoles of sodium ethoxide. The pale yellow solution was held at reflux for 4.5 hours. After cooling, the reaction mixture was neutralized to *p*H 6 with dilute aqueous hydrochloric acid. The solution was evaporated to dryness and the product was redissolved in a small volume of warm absolute ethanol. Sodium chloride was removed by filtration, and the solution, upon cooling, precipitated yellow powder, m.p. 205-207° (0.24 g., 67%); uv: λ max 253, 261 (shoulder), and 380 nm; ir: λ max 2.90 (shoulder), 3.00 (shoulder), 3.09, 3.22, 3.31, 3.40 (shoulder), 5.99, 6.40, 6.60, 6.78, 7.08, 7.12, 7.62, and 7.76 μ; nmr (time averaged): δ 2.40 (C-CH_3) and 3.43 (-CH_2-) ppm.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.69; H, 5.19; N, 23.99. Found: C, 61.71; H, 5.19; N, 23.84.

1,3-Dihydro-1-isopropenyl-2*H*-imidazo[4,5-*c*]pyridin-2-one (**4**).

A sample of compound **1** (0.42 g., 2.4 mmoles) was finely ground and placed in a test tube which was plunged into a silicone oil bath preheated to 175°. The diazepinone immediately melted into a black oil. After 45 minutes heating, the sample was cooled and the black mass was dissolved in absolute ethanol. Upon addition of ligroine (b.p. 65-90°) to the ethanol solution, an off-white colored product precipitated. Crystallization of this material from cyclohexane afforded a near quantitative yield of **4** as white needles, m.p. 162-165°; uv: λ max 275 nm (ε = 6100); ir: λ max 2.85, 3.30, 3.38, 3.50, 3.60, 3.71, 5.80, 6.06, 6.21, 6.72, 7.23, 7.59, 7.87, and 8.00 μ; nmr: δ 2.30 (3H quartet, J = 4 Hz) and 5.28 (2H multiplet, J = 3 Hz) ppm.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.69; H, 5.19; N, 23.99. Found: C, 61.63; H, 5.32; N, 24.33.

1,3-Dihydro-1-isopropyl-2*H*-imidazo[4,5-*c*]pyridin-2-one (**5**).

A. Synthesis from 3-Amino-4-isopropylaminopyridine.

To a suspension of 1.5 g. (0.01 mole) of 3-amino-4-isopropylaminopyridine (**12**) in 10 ml. of toluene was added 20 ml. of toluene previously saturated with phosgene. The reaction mixture was heated at reflux for 4 hours. The crude product, a white hydrochloride salt, was collected and dried. The material was dissolved in water and the aqueous solution was adjusted to a *p*H of 10 by the addition of dilute sodium hydroxide. The product was extracted from the alkaline solution into chloroform. The chloroform extract was evaporated to dryness, leaving a gummy residue, which was hardened by trituration under ligroine. The solid material was crystallized three times from cyclohexane to give a white microcrystalline powder (1.33 g., 75%), m.p. 138-140°; uv: λ max (ε) 236 (5100) and 275 (6500) nm; ir: λ max 2.88, 3.15 (shoulder), 3.23 (shoulder), 3.31, 3.38, 3.48, 3.60, 3.71, 5.82, 6.15, 6.25, 6.79, 6.80 (shoulder), 7.20, 7.35, 7.54, 7.62, 7.70, and 7.80 μ; nmr: δ 1.48 (6H doublet, J = 7 Hz) and 4.78 (1H multiplet, J = 30 Hz) ppm.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.73. Found: C, 60.93; H, 6.47; N, 23.93.

B. Reduction of **4**.

A sample of 0.19 g. (1.1 mmoles) of **4** was dissolved in absolute ethanol and the solution was shaken under hydrogen for 48 hours in the presence of platinum oxide catalyst; hydrogenation was interrupted after 24 hours for the addition of fresh catalyst. At the end of the reaction, the catalyst was separated and the ethanol solution was evaporated to dryness. The gummy residue was hardened under ligroine and the resulting solid was crystallized twice from cyclohexane to give white powder, m.p. 134-137°.

Anal. Found: C, 60.44; H, 6.35; N, 23.43.

This material was identical in all respects with that prepared by procedure A. Mixture melting points of products prepared *via* procedures A and B: 135-138°.

1,3-Dihydro-3-isopropenyl-2*H*-imidazo[4,5-*c*]pyridin-2-one (**6**).

A sample of **3** (0.86 g., 5 mmoles) was placed in a test tube which was immediately plunged into an oil bath preheated to 200°. The powder melted into a brown tar and the melt was held at 200° for 30 minutes. Upon cooling the material hardened into a black solid. Treatment of this material with ethanol effected partial dissolution and loosened the remainder of the sample from the wall of the test tube. Addition of heptane to the ethanolic suspension precipitated the balance of the product. Crystallization of the combined solids three times from toluene gave a near quantitative yield of small white needles, m.p. 166-168°; uv: λ max 276 nm (ε = 5200); ir: λ max 2.84, 3.18, 3.30, 3.35 (shoulder), 3.50, 3.70, 3.85 (shoulder), 5.80, 6.04, 6.17, 6.24, 6.65, 6.75, 6.90, 7.23, 7.35, 7.58, 7.82, and 8.00 μ; nmr: δ 2.28 (3H quartet, J = 4 Hz), 5.22 (1H quartet, J = 2 Hz) and 5.30 (1H quartet, J = 4 Hz) ppm.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.69; H, 5.19; N, 23.99. Found: C, 62.00; H, 5.37; N, 23.55.

1,3-Dihydro-3-isopropyl-2*H*-imidazo[4,5-*c*]pyridin-2-one (**7**).

A solution containing 0.14 g. (0.8 mmole) of **6** in 30 ml. of absolute ethanol was shaken under hydrogen on a Parr apparatus for 48 hours in the presence of platinum oxide catalyst. Fresh catalyst was then added and the hydrogenation was allowed to continue for an additional 24 hours. Evaporation of the ethanol under reduced pressure, after removal of the catalyst, left a gummy residue, which was crystallized from toluene to give white microcrystalline solid, 99 mg., (70%), m.p. 197-203° dec.; uv: λ max (ε) 230 shoulder (5700) and 276 (5800) nm; ir: λ max 2.88, 3.12 (shoulder), 3.21, 3.30, 3.50, 3.67, 5.86, 5.98 (shoulder), 6.18, 6.24, 6.68, 6.91, 7.20, 7.40, 7.48, 7.73, and 7.90 μ; nmr: δ 1.48 (6H doublet, J = 7 Hz) and 4.83 (1H multiplet, J = 29 Hz) ppm.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.73. Found: C, 60.84; H, 6.31; N, 23.42.

Isopropylamination of 4-Chloropyridinium Chloride.

A mixture of 30.0 g. (0.2 mole) of 4-chloropyridinium chloride and 70.8 g. (1.2 moles) of isopropylamine in 75 ml. of absolute ethanol was heated at 190° for 16 hours in a stainless steel autoclave with internal agitation. Ethanol and excess isopropylamine were then removed by evaporation under reduced pressure and the residual brown oil was redissolved in water. The aqueous solution was neutralized by addition of dilute sodium hydroxide, and the organic material was extracted into chloroform. The chloroform extract was dried over sodium sulfate and evaporated leaving a brown oily residue, which was triturated under ether. With freezing and continued trituration, the oil hardened to a tan powder. The tan solid was collected and purified by precipitation several times from chloroform-carbon tetrachloride to give white crystals of

4-*N*,*N*'-diisopropylaminopyridine (9) hydrochloride, m.p. 289-290° dec. (0.76 g., 2%).

Anal. Calcd. for $C_{11}H_{19}N_2Cl$: C, 61.52; H, 8.92; N, 13.05; Cl, 16.51. Found: C, 61.63; H, 9.02; N, 13.35; Cl, 16.36.

The ether filtrate from above, after separation of **9** hydrochloride, was evaporated and the residual oil was dissolved in absolute ethanol. Anhydrous hydrogen chloride was passed into the ethanol solution with cooling. Upon addition of a small volume of ether, a hygroscopic hydrochloride salt precipitated. This material was crystallized from ethanol to give white crystals of the dihydrochloride salt of 4,4'-dipyridylisopropylamine (10), m.p. 234-234.5° dec. (2.74 g., 10%).

Anal. Calcd. for $C_{13}H_{17}N_3Cl_2$: C, 54.55; H, 5.99; N, 14.69; Cl, 24.77. Found: C, 53.93; H, 6.25; N, 14.41; Cl, 24.38.

The ethanol-ether filtrate from above, after removal of **10** hydrochloride, was evaporated to dryness. The remaining yellow oil (8.5 g., 25%) was shown by nmr and by its conversion in high yield to **11** to be the hydrochloride salt of the desired 4-isopropylaminopyridine (**8**). The product could not be induced to solidify either as the hydrochloride salt or the free base (25) and was used for the nitration reaction without purification.

3-Nitro-4-isopropylaminopyridine (**11**).

Crude 4-isopropylaminopyridine hydrochloride (8.5 g., 0.05 mole) was dissolved in 60 ml. of cold concentrated sulfuric acid. The resulting brown solution was maintained at 5° during the dropwise addition of 2.65 ml. (0.05 mole) of fuming nitric acid (about 20 minutes). The red-orange reaction mixture was stirred at 5-10° for 45 minutes, then permitted to warm to room temperature. The reaction mixture was poured over crushed ice and neutralized to *p*H 6 with aqueous ammonia. A dark yellow powder precipitated and was separated. The product was crystallized once from hot water and once from ligroine (b.p. 60-95°) to give yellow needles (7.63 g., 86%), m.p. 66-67°; uv: λ max 236 and 375 nm; nmr (deuteriochloroform): δ 1.33 (6H doublet, J = 12 Hz), 3.90 (1H broad multiplet), 6.70 (1H doublet, J = 6 Hz), 8.27 (1H doublet, J = 6 Hz), and 9.18 (1H singlet) ppm.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.02; H, 6.12; N, 23.20. Found: C, 52.88; H, 6.02; N, 23.27.

3-Amino-4-isopropylaminopyridine (**12**).

A sample of **11** (1.0 g., 5.5 mmoles) in 30 ml. of absolute ethanol was shaken under hydrogen in the presence of 150 mg. of 5% palladium-charcoal catalyst for 1 hour. The catalyst was separated by filtration and the colorless filtrate was evaporated to dryness under reduced pressure. The resulting light gray crystals were crystallized three times from toluene to give 0.61 g. (76%) of small white needles, m.p. 157-159°.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.66; N, 27.80. Found: C, 63.80; H, 8.68; N, 28.05.

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