complete hydrolysis of the imidate. The precipitated solids were then dried and extracted with ether. Thus, another 2.4 g. of insoluble terephthalonitrile was recovered (m.p. 215°). Evaporation of the ether solution gave 4.6 g. of methyl *p*-cyanobenzoate, m.p. 59–61° (lit.[36] m.p. 62°). The yield was 61% based on unrecovered terephthalonitrile. Dimethyl terephthalate (m.p. 140°) which was expected to arise from the diimidate present at equilibrium was not found, but could conceivably have been dissolved in the discarded aqueous methanol.

(36) H. Rupe and K. Majewski, *Ber.*, **33**, 3405 (1900).

STAMFORD, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pschorr Cyclizations in the Pyridine Series. The Synthesis of Benz[*f*]- and Benz[*h*]isoquinoline[1]

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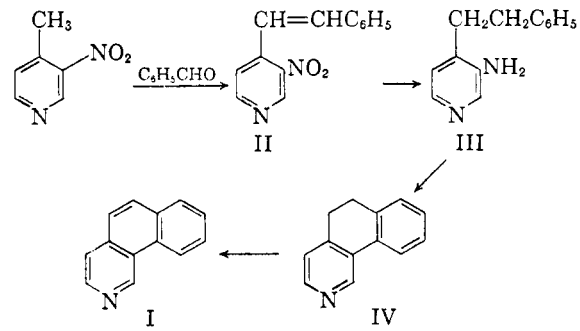
Convenient syntheses of the title compounds using the Pschorr cyclization are reported.

Dehydrogenation of diterpene alkaloids gives rise to alkylbenz[*h*]-isoquinolines[3–6] (3-azaphenanthrenes I), whose synthesis presents certain problems. Thus, several attempts to apply the Bischler-Napieralski reaction[7] to the cyclization of *N*-acyl-β-2-naphthylethylamines failed,[8] the only successful example being the conversion of a somewhat difficulty accessible oxime to 1-methylbenz[*h*] isoquinoline.[9] Koelsch and Lindquist[10] prepared I in 3% overall yield from 1,2-naphthalic anhydride, but their method does not appear to lend itself easily to the synthesis of substituted benz[*h*]isoquinolines. The Pictet-Spengler reaction[11] was successful in the two instances tried,[3,12] but again the synthesis of the requisite starting materials may be attended by difficulties.

For these reasons it was decided to study the preparation of I by the following route, which should, in theory, be adaptable to the synthesis of



many different derivatives. 3-Nitro-4-picoline was prepared in good yield by a modification of the method of Baumgarten, Su, and Krieger[13] and condensed with benzaldehyde in 44% yield. II exhibited an infrared band at 785 cm.$^{-1}$ (*trans*-ethylenic double bond); the corresponding amine would therefore not have been suitable for the Pschorr cyclization.[14] Hence, II was catalytically reduced to III which smoothly underwent the Pschorr synthesis (40% yield). It was found that the so-called Gattermann copper[14] could be successfully replaced by commercially available copper powder and that the cyclization could also be effected by warming the diazonium solution on the steam bath without catalyst, although the yield was somewhat lower.

As elementary analysis did not distinguish satisfactorily between IV and a possible by-product, 4-(β-phenethyl)pyridine,[15] the latter was synthesized from 4-picoline-1-oxide by way of 4-styrylpyridine 1-oxide.[16] Its properties clearly differentiated it from IV. Finally, IV was dehydrogenated to I, which again was different from 4-styrylpyridine, the dehydrogenation product of V.

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(2) Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1960.

(3) D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.*, 81, 2246 (1959).

(4) M. F. Bartlett and K. Wiesner, *Chem. and Ind.*, 542 (1954).

(5) K. Wiesner, Z. Valenta, S. F. King, R K. Maugdal, L. G. Humber, and Sho Ito, *Chem. and Ind.*, 173 (1957).

(6) K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Babin, F. Bickelhaupt, J. Kallos, and T. Bogri, *Tetrahedron Letters*, No. 3, 17 (1960).

(7) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 74 (1951).

(8) B. B. Dey and S. Rajagopalan, *Arch Pharm.*, 277, 377 (1939); *Current Science*, 13, 204 (1944).

(9) C. S. Gibson, K. V. Harihan, K. N. Menon, and J. L. Simonsen, *J. Chem. Soc.*, 2247 (1926).

(10) C. F. Koelsch and R. M. Lindquist, *J. Org. Chem.*, 21, 657 (1956)

(11) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 151 (1951).

(12) E. Mayer and O. Schnecko, *Ber.*, **56**, 1408 (1923).

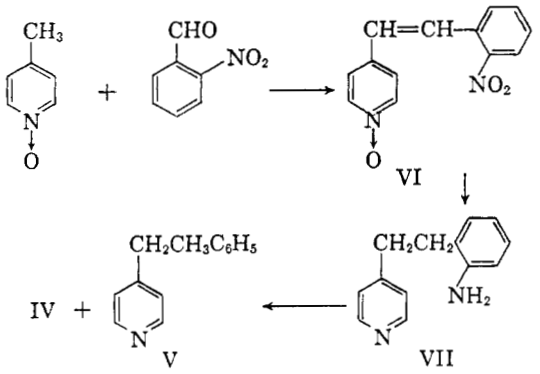
(13) H. E. Baumgarten, H. C. Su, and A. L. Krieger, *J. Am. Chem. Soc.*, **76**, 596 (1954).

(14) D. F. DeTar, *Org. Reactions*, 408 (1957).

(15) See for example, N. Kornblum, G. D. Cooper, and J. E. Taylor, *J. Am. Chem. Soc.*, 72, 3013 (1950).

(16) D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958).

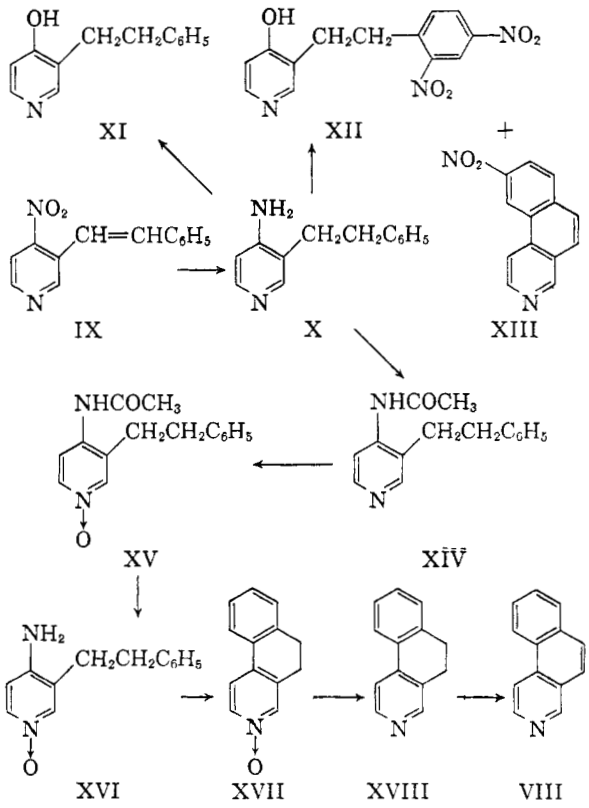
A second route to IV involving the diazotization of VII was of interest because when this study was begun there appeared to be no example of a Pschorr cyclization into the pyridine ring. As pyridine is not deactivated toward free radical attack, such cyclizations might be expected to proceed relatively smoothly.[17] Unfortunately, the condensation of 4-picoline 1-oxide with *o*-nitrobenzaldehyde, the first step of the projected synthesis, proceeded only in poor yield. Catalytic hydrogenation of the condensation product gave VII which could be cyclized to a mixture of IV and V.



Benz[*f*]isoquinoline (VIII) has not been prepared previously. Pictet and Manevitch[18] reported the successful cyclization of *N*-acetyl-β-hydroxy-β-(1-naphthyl)ethylamine to 4-methylbenz[*f*]isoquinoline, but two groups[10,19] were subsequently unable to reproduce this work. Similar cyclizations have been attempted with indifferent results[8,12,20,21]; in no instance was the synthesis of VIII accomplished. Koelsch and Lindquist[10] attempted the preparation of VIII from benzo[*c*]phthalimidoacetic acid through the intermediacy of 2-carbethoxydihydroxybenz[*f*]isoquinoline, but the main product was the isomeric 3-carbethoxy-1,4-dihydroxybenz[*h*]isoquinoline, which was converted to I.

The successful preparation of I by the Pschorr reaction suggested that this method, applied to a suitable pyridine derivative, could also lead to VIII. 4-Nitro-3-styrylpyridine 1-oxide[16] (IX) was reduced chemically to 4-amino-3-styrylpyridine; however, the characteristic *trans*-ethylenic band at 785 cm.[-1] in the infrared spectrum of the latter compound indicated that it would be unsuitable for ring closure. IX was therefore reduced to 4-amino-3-(β-phenethyl)pyridine (X), which when subjected to the usual conditions of the Pschorr reaction gave only 4-hydroxy-3-(β-phenethyl)pyridine (XI).

This behavior was not surprising, as it is well known that 3-aminopyridine forms a stable diazonium salt, while 2- and 4-amino-pyridine give rise to the corresponding hydroxypyridines, presumably because of the destabilizing effect of the hetero atom. However, Witt[22] discovered that treatment of 4-aminopyridine with fuming nitric acid and potassium metabisulfite at low temperature resulted in a stable diazonium salt. Application of this procedure to X resulted in the formation of two substances. The major product, a yellow compound of formula $C_{13}H_{11}N_3O_5$, was 4-hydroxy-3-(β-2,5-dinitrophenethyl)-pyridine[23] (XII); the minor product, formed only after the addition of copper, is considered to be 5,6-dihydro-9-nitrobenz[*f*]isoquinoline (XIII) because of the analysis and the similarity of its ultraviolet spectrum to that of XVIII.



(17) In the interval, the decomposition of the diazonium salt of *N*-methyl-*N*-3-pyridyl-*o*-phenylenediamine to give a mixture of *N*-methyl-β- and δ-carboline has been reported, R. A Abramovitch, Abstracts, Atlantic City Meeting, American Chemical Society, p. 12 P (1959). This has recently been published, *Can. J. Chem.*, **38**, 2273(1960). Reference is made to two prior instances of a Pschorr cyclization into the pyridine nucleus, although the yields were poor, D. H. Hey and J. M. Osband, *J. Chem. Soc.*, 3164(1649); and R. A. Abramovitch, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.*, 4263 (1954).

(18) A. Pictet and B. Manevitch, *Arch. Sci. Phys. Nat.*, **35**, 40 (1913); *Chem. Abstr.*, **7**, 1713 (1913).

(19) B. B. Dey and S. Rajagopalan, *Arch. Pharm.*, **277**, 359 (1939).

(20) W. M. Whaley and W. H. Hartung, *J. Org Chem.*, **14**, 650 (1949).

(21) K. Kindler and W. Peschke, German Pat. 704,762; *Chem. Abstr.*, **36**, 1956 (1942).

(22) O. N. Witt, *Ber.*, **42**, 2953 (1909).

(23) Nitration of the pyridine ring under these circumstances which might result in the formation of 3-nitro-4-hydroxy-5-(β-4-nitrophenethyl)pyridine was considered less likely and was excluded by the results of an oxidation which led to the isolation of 2,4-dinitrobenzoic acid.

Ochiai and coworkers discovered that 4-aminopyridine 1-oxide forms a stable diaonium salt.[24] The above difficulties were therefore circumvented by converting X to XVI in the manner shown (overall yield 65%) and diazotizing the latter. Treatment with copper gave a 50% yield of XVII which was reduced and dehydrogenated to benz[*f*]isoquinoline (VIII).

Some effort was made to improve the above procedures by cyclizing appropriate cinnamonitriles or cinnamic acids.[14] However, the condensation of 4-pyridineacetonitrile with *o*-nitrobenzaldehyde proceeded in 18% yield only and the hydrolysis of the product was difficult.

Condensation of 3-pyridinealdehyde with *o*-nitrophenylacetic acid gave a 43% yield of *trans*-α-(2-nitrophenyl)-β-(3-pyridyl)acrylic acid which on chemical reduction gave 3-pyridaloxindole, synthesized independently from oxindole and 3-pyridinealdehyde. Attempts to isolate the aminoacrylic acid for purposes of cyclization proved abortive. Similarly, reduction of *trans*-α-(2-nitrophenyl)-β-(4-pyridyl)-acrylic acid, prepared from *o*-nitrophenylacetic acid and 4-pyridinealdehyde, resulted in the formation of 4-pyridaloxindole.

ADDED IN PROOF: Syntheses of the title compounds by different methods have been reported since this paper was submitted, G. Coppens, *Bull. Soc. chim. belg.*, **69**, 413 (1960); and J. N. Chatterjea and K. Prasad, *J. Ind. Chem. Soc.*, **37**, 357 (1960).

EXPERIMENTAL[25]

3-Nitro-4-picoline. Commercially available 2-amino-4-picoline was converted to a mixture of 2-chloro-3-nitro-4-picoline and 2-chloro-5-nitro-4-picoline by the method of Baumgarten, Su, and Krieger.[13] The dechlorination of the mixture with copper and benzoic acid gave poor yields. The mixture was therefore hydrogenated to 3-amino-4-picoline[26] (90%) and the latter oxidized as follows. To a solution of 175 ml. of fuming (15%) sulfuric acid and 88 ml. of 30% hydrogen peroxide was added, at 10°, a solution of 10 g. of 3-amino-4-picoline in 50 ml. of concd. sulfuric acid with stirring. The mixture was warmed gradually on a steam bath until a reaction could be noticed and the flask was then cooled intermittently to moderate the vigorous reaction. After 2 hr. on the steam bath and 1 day at room temperature, the contents were heated for another hour, poured into ice, made basic with dilute sodium hydroxide solution, extracted with chloroform, dried, and the chloroform removed. Distillation furnished 9.6 g. (75%) of a pale yellow liquid, b.p. 100° (3.5 mm.).

3-Nitro-4-styrylpyridine. A mixture of 18 g. of benzaldehyde, 18.2 g. of 3-nitro-4-picoline, 6 g. of piperidine, and 30 ml. of methanol was refluxed for 8 hr. On cooling there separated 15.6 g. of product. The filtrate on concentration and refrigeration yielded an additional 4.2 g., yield 66.5%. Two recrystallizations from methanol afforded yellow needles, m.p. 114–116°.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.98; H, 4.53; N, 12.19.

3-Amino-4-(β-phenethyl)pyridine. A solution of 6.8 g. of the preceding substance in 100 ml. of ethanol was reduced catalytically with 5% palladium-charcoal. Evaporation of the solvent gave 4.8 g. (80%) of crude product, m.p. 131–134°. Three recrystallizations from ethanol-water raised the m.p. to 134.5–137°.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.95; H, 6.96; N, 14.10.

The *picrate* melted at 177–179°.

Anal. Calcd. for $C_{19}H_{17}N_5O_7$: C, 53.39; H, 4.00; N, 16.39. Found: C, 53.90; H, 3.82; N, 16.65.

5,6-Dihydrobenz[h]isoquinoline. A solution of 6 g. of III in 60 ml. of dilute (10%) sulfuric acid was cooled to 3° and a solution of 3 g. of sodium nitrite in 30 ml. of water was added dropwise with stirring at such a rate that the temperature did not rise over 5°. Stirring was continued for 15 min., 6 g. of copper powder (Baker purified, the substitution of freshly prepared Gattermann copper resulted in no increase in yield) was added, and stirring was continued for 30 min. The mixture was made basic and extracted thoroughly with ether. The dried ether extracts furnished a viscous residue which was distilled, b.p. 140° (1 mm.), wt. 1.9 g. (35%).

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.12; N, 7.73. Found: C, 85.77; H, 6.27; N, 7.72.

The *picrate* melted at 195–196°.

Anal. Calcd. for $C_{19}H_{14}N_4O_7$: C, 55.61; H, 3.44; N, 13.66 Found: C, 55.98; H, 3.33; N, 13.65.

The ultraviolet spectrum had λ_{min} 240 (log ε 3.95) and a broad maximum, λ_{max} 261 mμ (4.16). Omission of the copper from the cyclization resulted in yields averaging about 30%.

Benz[h]isoquinoline. Dehydrogenation of 1.65 g. of the dihydro derivative with 4 g. of 5% palladium charcoal in 50 ml. of boiling toluene for 36 hr. gave 1.2 g. of a basic fraction, b.p. 145° (0.5 mm.), ultraviolet spectrum λ_{max} 212 and 253 mμ (log ε 4.21 and 4.55), λ_{min} 225 mμ (4.26), shoulder at 300 mμ.

Anal. Calcd. for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.40; H, 5.10; N, 7.66.

The *picrate* melted at 223–225° (lit.[10] m.p. 219°).

Anal. Calcd. for $C_{19}H_{12}N_4O_7$: C, 55.89; H, 2.96; N, 13.72. Found: C, 56.49; H, 3.19; N, 13.95.

4-Styrylpyridine. This compound has been prepared previously in unspecified yield by the condensation of 4-picoline and benzaldehyde with zinc chloride in a sealed tube.[27] The following procedure was more convenient. To a solution of 1 g. of 4-styrylpyridine 1-oxide[16] in 5 ml. of acetic acid was added 0.5 g. of iron powder. The mixture was heated on the steam bath and stirred for 45 min., cooled, diluted with water, made basic, and extracted with ether. From the dried ether extracts was obtained 0.6 g. of crude product which was recrystallized from ethanol-water, m.p. 127–129°, lit.,[27] m.p. 127°. The ultraviolet spectrum had λ_{max} at 227 and 308 mμ (log ε 4.13 and 4.43) λ_{min} 246 mμ (2.87).

4-β-Phenethylpyridine. Catalytic reduction of the previous substance in ethanol resulted in a product, m.p. 68°, lit.,[27] m.p. 65°. The ultraviolet spectrum had λ_{max} 256 and 290 mμ (log ε 3.2 and 2.11), λ_{min} 235 and 280 mμ (log ε 2.79 and 2.00).

The *picrate* melted at 166–167°.

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.58. Found: C, 55.21; H, 3.88; N, 13.45.

4-(2-Nitrostyryl)pyridine 1-oxide. Löwensohn[28] reported the condensation of 4-picoline and *o*-nitrobenzaldehyde in a sealed tube, but the yields were not specified. Repetition

(24) E. Ochiai and T. Teshigawara, *J. Pharm. Soc. Japan*, **65**, 435 (1945); F. Ochiai and T. Naito, *J. Pharm. Soc. Japan*, **65**, 441 (1945).

(25) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. Ultraviolet spectra were determined in 95% ethanol solution on a Beckman DU spectrophotometer, infrared spectra were run in chloroform solution on Perkin-Elmer Model 21 or infracord spectrometers.

(26) W. Herz and D. R. K. Murty, *J. Org. Chem.*, **25**, 2242 (1960).

(27) K. Friedlander, *Ber.*, **38**, 159 (1905).

(28) M. Löwensohn, *Ber.*, **40**, 4860 (1907).

of this work gave less than 5% of crude product; hence the condensation of 4-picoline 1-oxide with *o*-nitrobenzaldehyde was studied. A mixture of 10 g. of the oxide, 20 g. of the aldehyde, and 45 ml. of 5% sodium methoxide was refluxed for 5 hr. and steam distilled. The aqueous residue was concentrated to 50 ml., refrigerated, and the solid filtered and recrystallized from ethanol; yield, 2.3 g., m.p. 238–239°.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: N, 11.56. Found: N, 11.20.

When piperidine was used as the catalyst, no product could be isolated and most of the *o*-nitrobenzaldehyde was recovered. Heating of 8 g. of 4-picoline 1-oxide, 15 g. of the aldehyde, and 2 g. of fused zinc chloride in a sealed tube for 10 hr. at 130–140° gave 1.4 g. of condensation product.

4-(2-Aminophenethyl)pyridine. Catalytic hydrogenation of 1.5 g. of the preceding compound in ethanol, using 5% palladium-charcoal followed by removal of solvent, gave a viscous residue which was triturated with water. Recrystallization from ethanol-water gave white needles, m.p. 74–75°, lit.,[28] m.p. 76°; yield, 0.46 g.

The procedure used for the Pschorr cyclization of this substance was the same as the method adopted for III. From 0.45 g. there was obtained a small amount of a viscous product which was converted to a mixture of picrates, wt. 0.165 g. Fractional crystallization gave 0.06 g., m.p. 194–196°, undepressed on admixture of an authentic sample of the picrate, m.p. 195–196°, of 5,6-dihydrobenz[*h*]isoquinoline, and 0.027 g. of a fraction, m.p. 163–167°, undepressed on admixture of the picrate, m.p. 166–167°, of 4-β-phenethylpyridine.

4-Amino-3-styrylpyridine. To a solution of 7 g. of 4-nitrl-3-styrylpyridine 1-oxide[16] in 125 ml. of acetic acid was added in small portions with stirring 12 g. of iron powder, the mixture being heated in such a way that the reaction did not become too vigorous. After the completion of the addition, heating and stirring were continued for 1 hr. The mixture was cooled, diluted with water, made basic, and extracted with ether. The dried ether extracts yielded 2.2 g. of crude product, m.p. 171–176°, which was recrystallized from ethanol-water, m.p. 178–179°.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.61; H, 5.92; N, 14.10.

The *picrate* melted at 245–246°.

Anal. Calcd. for $C_{19}H_{15}N_5O_7$: C, 53.65; H, 3.55; N, 16.47. Found: C, 53.51; H, 3.56; N, 16.10.

4-Amino-3-(β-phenethyl)pyridine. A suspension of 25 g. of the preceding substance in 200 ml. of ethanol was hydrogenated with palladium-charcoal. The material gradually dissolved. The solution was filtered and the solvent removed. The residue solidified upon addition of 10 ml. of water and scratching; yield 17.5 g., m.p. 100–104°. It could not be crystallized satisfactorily and was analyzed as the *picrate*, m.p. 154.5–155.5°.

Anal. Calcd. for $C_{19}H_{17}N_5O_7$: C, 53.39; H, 4.00; N, 16.39. Found: C, 53.50; H, 3.80; N, 16.20.

4-Hydroxy-3-(β-phenethyl)pyridine. When 4-amino-3-(β-phenethyl)pyridine was dissolved in dilute sulfuric acid, cooled to 3°, and treated with sodium nitrite solution in the manner described for 3-amino-4-(β-phenethyl)pyridine, the separation of a viscous oil was noted. The solution was decanted and the oil was treated with dilute sodium bicarbonate solution to slightly basic reaction. The resulting solution was evaporated to dryness *in vacuo* and the residue extracted with absolute ethanol. Concentration of the extract gave a solid, m.p. 162°, which was recrystallized from ethanol-acetone without change in melting point.

Anal. Calcd. for $C_{13}H_{13}NO.{}^1/_2H_2O$: C, 74.97; H, 6.78; N, 6.73. Found: C, 75.05; H, 6.76; N, 6.72.

This substance was the only product isolated even when the viscous oil was treated with Gattermann copper powder or heated on the steam bath.

Treatment of 4-amino-3-(β-phenethyl)pyridine with fuming nitric acid and sodium metabisulfite. An intimate mixture of 10 g. of X and 6 g. of sodium metabisulfite was added gradually, with shaking, to 30 ml. of ice cold fuming nitric acid. The resulting solution was diluted with crushed ice. A yellow solid separated immediately which when filtered, washed with a little water, and dried gave 2.5 g. of 4-hydroxy-3-(β-2,4-dinitrophenethyl)pyridine, m.p. 183–185°. Recrystallization from water yielded yellow needles, m.p. 191–192° dec.

Anal. Calcd. for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 54.06; H, 3.93; N, 13.90.

The filtrate from the isolation of the preceding compound was treated with 3 g. of copper powder in the usual way, the temperature being maintained below 5°. After 30 min., the mixture was made basic and extracted with ether. The dried ether extracts was evaporated; the residue was dissolved in hot water and allowed to cool. There separated 0.05 g. of 5,6-dihydro-9-nitrobenz[*f*]isoquinoline, m.p. 175–178°, which was recrystallized twice from acetone, brown needles, m.p. 179–181°, λ_{max} 257 mμ (log ε 4.19), λ_{min} 249 mμ (3.70), shoulder at 277 mμ.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.83; H, 4.37; N, 12.50.

4-Acetamido-3-(β-phenethyl)pyridine and oxide. A mixture of 10.75 g. of X and 16 ml. of acetic acid was refluxed for 2 hr. The residue obtained after removal of excess acetic acid could not be induced to crystallize and decompose during distillation. Hence it was analyzed as the *picrate*, m.p. 172–174°.

Anal. Calcd. for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.08; N, 14.92. Found: C, 54.20; H, 4.17; N, 15.10.

The viscous crude product, wt. 11.5 g., was converted to the oxide by warming on the steam bath with 30 ml. of 40% peracetic acid until a vigorous exothermic reaction began. After the reaction subsided, the mixture was allowed to stand at room temperature overnight and heated again for 1 hr. The excess of acetic acid was removed *in vacuo* and the brown residue chromatographed over alumina (solvent and eluent ethanol). The pale yellow eluate was decolorized by shaking the hot solution with charcoal. The filtered solution was evaporated and the hygroscopic residue triturated with a little benzene, yield 11 g., m.p. 173–175°. Two recrystallizations from ethanol-acetone gave colorless needles, m.p. 175–176°.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.70; H, 6.22; N, 11.15.

The *picrate* melted at 157.5–158.5°.

Anal. Calcd. for $C_{21}H_{19}N_5O_9$: C, 51.96; H, 3.95; N, 14.43. Found: C, 52.25; H, 4.02; N, 14.40.

4-Amino-3-(β-phenethyl)pyridine 1-oxide. A solution of 10 g. of the preceding compound in 300 ml. of 10% sulfuric acid was refluxed for 24 hr., cooled, made basic, and evaporated to dryness *in vacuo*. The residue was extracted with absolute ethanol and the extract passed through an alumina column. The eluate was evaporated. Trituration of the gummy residue with a little acetone gave solid material, wt. 4.5 g., which was recrystallized from ethanol-acetone, m.p. 184–186°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.04; H, 6.57; N, 13.10.

The *picrate* melted at 155–156°.

Anal. Calcd. for $C_{19}H_{17}N_5O_8$: C, 51.47; H, 3.86; N, 15.80. Found: C, 51.80; H, 3.65; N, 15.80.

In subsequent work, this substance was prepared in 65% overall yield from X without isolation of the intermediates as follows. A mixture of 30 g. of X and 36 ml. of acetic anhydride was refluxed for two hours, excess anhydride was removed *in vacuo* and the residue was warmed with 60 ml. of 40% peracetic acid until reaction started. When the reaction subsided, heating was continued for an hour, acetic acid removed, the residue refluxed with 900 ml. of dilute sulfuric acid and worked up as described. This resulted in 21 g. of pure XVI.

5,6-Dihydrobenz[f]isoquinoline-3-oxide. A solution of 5.7 g. of XVI in dilute sulfuric acid (15 g. of concd. sulfuric and 50 ml. of water) was cooled to 3° and heated dropwise with

sodium nitrite solution (1.5 g. in 20 ml. of water) over a period of 40 min. Stirring was continued for 5 min. and then 5 g. of freshly prepared Gattermann copper was added in small portions with stirring. A solid began to precipitate. After stirring for an additional 20 min., the mixture was heated, filtered while hot, and refrigerated overnight. There precipitated 2.8 g. of colorless product, m.p. 103°. Chloroform extraction of the basic filtrate gave intractable resinous material. The product was recrystallized from water, m.p. 103–104°.

Anal. Calcd. for $C_{13}H_{11}NO.{}^1/_2H_2O$: C, 75.70; H, 5.87; N, 6.79. Found: C, 76.10; H, 6.01; N, 7.05.

The picrate melted at 172–173.5°.

Anal. Calcd. for $C_{19}H_{14}N_4O_8$: C, 53.52; H, 3.31; N, 13.14. Found: C, 53.43; H, 3.33; N, 12.78.

5,6-Dihydrobenz[f]isoquinoline. Catalytic hydrogenation of 2 g. of the oxide in ethanol with 5% palladium-charcoal followed by evaporation of solvent and distillation gave 1.6 g. of material, b.p. 137° (0.5 mm.), ultraviolet absorption λ_{max} 268 mμ (log ε 4.16), λ_{min} 239 mμ (3.37), shoulders at 250 and 280 mμ.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.16; H, 6.12; N, 7.73. Found: C, 86.01; H, 6.27; N, 7.65.

The *picrate* melted at 210–211°.

Anal. Calcd. for $C_{19}H_{14}N_4O_7$: C, 55.61; H, 3.44; N, 13.66. Found: C, 55.41; H, 3.43; N, 13.70.

Benz[f]isoquinoline. A solution of 1.3 g. of the dihydro derivative in 50 ml. of toluene was refluxed for 36 hr. with 5 g. of 5% palladium-charcoal, filtered, and evaporated. The solid residue was purified by vacuum sublimation, yield 0.8 g., m.p. 92–94°. The ultraviolet spectrum had more sharply pronounced peaks than that of benz[*h*]-isoquinoline, λ_{max} 250, 274, and 292 mμ (log ε 4.70, 3.92, and 3.91), λ_{min} 223, 270, and 285 mμ (3.10, 3.89, and 3.62).

Anal. Calcd. for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.37; H, 5.06; N, 7.60.

The *picrate* melted at 250°.

Anal. Calcd. for $C_{19}H_{12}N_4O_7$: C, 55.89; H, 2.96; N, 13.72. Found: C, 56.50; H, 3.25; N, 13.45.

α-(3-Pyridyl)-β-(2-nitrophenyl)acrylonitrile. A mixture of 2 g. of 3-pyridineacetonitrile,[27] 3 g. of *o*-nitrobenzaldehyde, 0.8 g. of piperidine, and 5 ml. of methanol was refluxed on the steam bath for 6 hr., concentrated, and refrigerated. The crystalline yellow solid was filtered, washed with a little methanol, and dried, wt. 0.9 g., m.p. 137–139°. Recrystallization from ethanol-acetone raised the m.p. to 138–140°.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.92; H, 3.61; N, 16.73. Found: C, 66.42; H, 3.77; N, 16.70.

The *picrate* melted at 204.5–205.5°.

Anal. Calcd. for $C_{20}H_{12}N_6O_9$: C, 50.01; H, 2.52; N, 17.50. Found: C, 49.76; H, 2.49; N, 17.66.

Hydrolysis of 0.7 g. of this substance with 2 g. of 75% sulfuric acid followed by dilution with water and addition of base gave 0.2 g. of the amide, m.p. 205–206°. Recrystallization from ethanol gave greenish-yellow needles, m.p. 208–209°.

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.67. Found: C, 61.90; H, 4.29; N, 15.83.

Hydrolysis with base caused reversal of the aldol condensation.

trans-α-(2-Nitrophenyl)-β-(3-pyridyl)acrylic acid. A mixture of 23 g. of the sodium salt of *o*-nitrophenylacetic acid, 11.5 g. of 3-pyridinealdehyde, 80 ml. of acetic anhydride, and 2 g. of fused zinc chloride was heated on the steam bath for 20 hr., cooled, diluted with 350 ml. of water, and chilled. The solid was filtered, washed with cold water, and suspended in 300 ml. of acetic acid to remove tarry impurities. The residual yellow solid was filtered, washed with water, and purified by reprecipitating from an ammoniacal solution; yield, 13 g. (43%). Two recrystallizations from ethanol gave yellow needles, m.p. 245°.

Anal. Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.73. Found: C, 62.07; H, 4.00; N, 11.14.

The *picrate* melted at 203–204°.

Anal. Calcd. for $C_{20}H_{13}N_5O_{11}$: C, 48.20; H, 2.83; N, 16.86. Found: C, 48.02; H, 2.66; N, 16.92.

3-Pyridaloxindole. A solution of 1.25 g. of the preceding compound in 4 ml. of ammonium hydroxide and 8 ml. of water was added to 8.5 g. of ferrous sulfate, 25 ml. of water, and 21 ml. of ammonium hydroxide at 80–90°. After 20 min. at this temperature, the mixture was filtered, the filtrate was cooled, and neutralized gradually with dilute hydrochloric acid. There separated 0.6 g. of an orange-yellow solid which was recrystallized from alcohol-water, m.p. 187–188°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.61; H, 4.41; N, 12.47.

This compound was also prepared by refluxing 0.30 g. of 3-pyridinealdehyde, 0.33 g. of oxindole, 0.15 g. of piperidine, and 2 ml. of methanol for 5 hr. The mixture was chilled and the solid, wt. 0.53 g., recrystallized from ethanol-water, m.p. 187–188°. A mixed melting point was not depressed.

An effort was made to isolate *trans-α-*(2-aminophenyl)-*β-*(3-pyridyl)acrylic acid from the ferrous sulfate reduction by neutralizing with acetic acid in the cold. A colorless solid separated which on standing in air or during attempts at recrystallization was converted to the oxindole. When an attempt was made to diazotize the crude solid, treatment with dilute acid caused cyclization to the oxindole also.

trans-α-(2-Nitrophenyl)-β-(4-pyridyl)acrylic acid. Condensation of 11.5 g. of 4-pyridinealdehyde with sodium *o*-nitrophenylacetate in the manner described for 3-pyridinealdehyde gave 5.5 g. of yellow product, m.p. 258–262°. Recrystallization from ethanol raised the m.p. to 266–267° dec.

Anal. Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73. Found: C, 61.87; H, 4.00.

4-Pyridaloxindole. Reduction of 0.3 g. of the above with ferrous sulfate gave 0.1 g. of orange-red solid which was recrystallized from ethanol-water, m.p. 225°. An authentic sample, made in 90% yield by condensation of oxindole with 4-pyridinealdehyde, m.p. 225°, did not depress the melting point.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.46; H, 4.59; N, 12.88.

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(27) S. Okuda and M. M. Robison, *J. Am. Chem. Soc.*, **81**, 740 (1959).