Imino-bridged Heterocycles. II (1). Regiospecific Synthesis of the 11*H*-Benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine and 5*H*-Benzo[4,5]cyclohepta[1,2-*b*]pyridin-5,10-imine Systems

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Regiospecific synthetic pathways for two of the eight isomeric benzocycloheptapyridinimines have been developed based upon intramolecular acid catalyzed additions between an amine function and an internal olefin. The requisite amines were generated from known tricyclic ketones by ketimine formation followed by sodium borohydride reduction.

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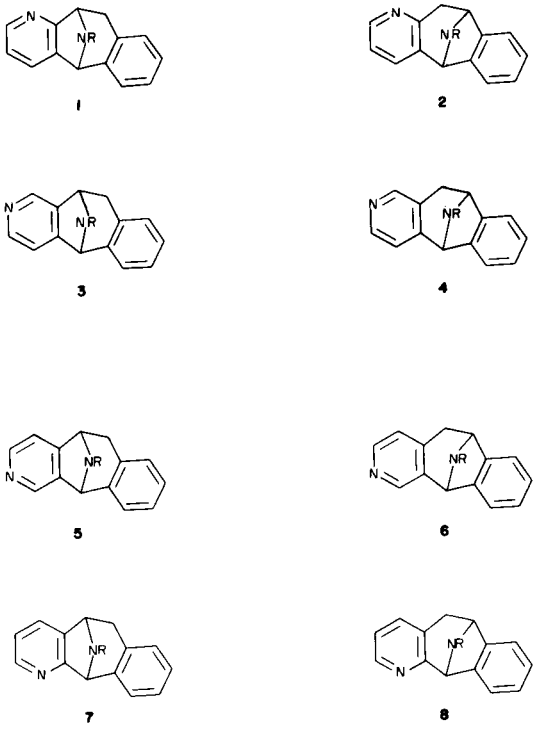
In this report we would like to describe in detail regiospecific synthetic pathways for two isomeric benzocycloheptapyridinimine systems (**2, 6**). The products correspond to two of the eight possible regio isomers depicted in Chart 1. In this class of compounds, the pyridine nitrogen may occupy any one of four non-angular positions and the imine bridge may be adjacent to the pyridine or the benzene nucleus.

Chart I

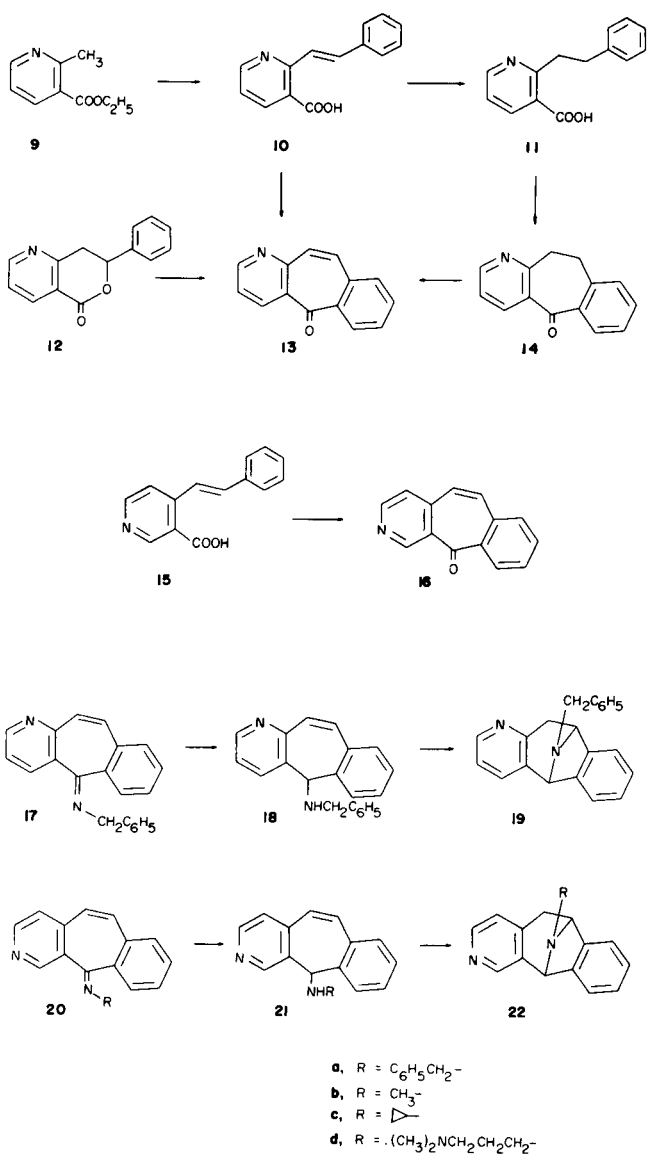


A careful analysis of the structures in Chart 1 led to the realization that structures **2** and **6** could be viewed as β-aminoethyl 2- and 4-substituted pyridines. As such, we envisaged they could be prepared by a regiospecific intramolecular addition reaction between an amine function and an olefin (Scheme 1). Levine, *et al.*, (3a-c) and Phillips (3d) have demonstrated that 2- and 4-vinyl pyridines undergo Michael-like additions at the β-carbon, especially by amines under acidic conditions. Our initial synthetic goals thus became preparation of the two amines (**18** and **21a**) from **13** and **16** for subsequent cyclization efforts.

Scheme I

In the case of **13**, the reported preparations utilized **9** as the pyridine subunit. Villani (5) converted **9** to the lactone (**12**) according to an earlier procedure and cyclized it to the desired ketone (**13**) in PPA. Another longer reported route (6) involved conversion of **9** to the unsaturated acid (**10**), reduction to the dihydro derivative (**11**), cyclization to the ketone (**14**) and reintroduction of the olefinic linkage with *N*-bromosuccinimide and benzoyl peroxide. We, likewise, decided to use **9** as our pyridine building block and found that it could be formed in satisfactory quantity and quality by the condensation of β-ethoxyacrolein diethylacetal (7) and ethyl β-aminocrotonate followed by a simple acid extraction. Treatment of this ester with benzaldehyde under strong basic conditions (*t*-BuONa, DMF) generated the *trans*-nicotinic acid analog (**10**). It is interesting to note that the ester is hydrolyzed under these conditions apparently by the water liberated during the condensation. This occurrence is similar to the observation of Villani (4), who reported conversion of a nitrile to an amide during a related reaction. We cyclized **10** directly to the desired **13** utilizing a brief treatment with hot PPA. Under these conditions, the trans acid is isomerized to the cis product prior to cyclization. The preparation of **16** generally followed the reported method, (4) and similarly involved the PPA cyclization of a *trans*-styryl pyridinecarboxylic acid (**15**).

With these ketones in hand, we began an investigation



to convert them to the desired amine derivatives and study the intramolecular cyclization. Treatment of either ketone with benzylamine in toluene in the presence of titanium tetrachloride generated the corresponding *N*-benzylketimines (**17** and **20a**). ^1H nmr and tlc examination of these products indicated they were mixtures of the possible geometric isomers. No effort was made to define or separate the materials and they were in turn reduced to the corresponding benzylamines (**18** and **21a**) with sodium borohydride in acetonitrile. Although some cyclization could be detected by ^1H nmr when **21a** was treated with acetic acid in alcohol, a better method involved treatment with an ethanolic hydrogen chloride mixture. The *N*-benzyl imino-bridged structure (**22a**) was readily confirmed by an investigation of its nmr spectrum. The olefinic absorption disappeared and two bridgehead protons, H_6 and H_{11} were observed (δ 4.33 and 4.82, respectively). The methylene protons, $H_{5\alpha}$ and $H_{5\beta}$, appeared at higher fields. The $H_{5\alpha}$ proton, attached cis to the bridgehead proton H_6, displays coupling only with its methylene component (J = 18 Hz) whereas the $H_{5\beta}$ proton couples with H_{5a} (J = 18 Hz) as well as H_6 (J = 5 Hz). The remainder of the spectrum was entirely consistent with the proposed structure (see Experimental).

Cyclization of **18** was effected by treatment with *p*-toluenesulfonic acid in hot ethanol. This product (**19**) was isolated as its oxalate salt and, as in the earlier case, the structure could be readily confirmed by an investigation of the nmr spectrum (see Experimental). In both cases, only a single product was generated.

Having established that the intramolecular cyclization was a viable process, it was imperative that the structure of the products be established conclusively. From a mechanistic point of view, the attachment of the amino function to the carbon β- to the pyridine ring was the expected one. However, the proton nmr should exhibit a similar spectrum regardless of the point of attachment. Therefore, an experiment was conducted in which the Nuclear Overhouser Effect of the bridgehead proton in the two carbon bridge of **22a** was determined. Irradiation of this signal had a pronounced effect on the aromatic portion of the spectrum but no effect upon the H_4-pyridine signal. This experiment would indicate that the bridgehead proton was adjacent to the benzene nucleus rather than the pyridine portion of the molecule.

It was also of further interest to explore other bridging amino substituents in a limited examination. For this purpose, the ketone isomer **16** was selected and treated with methylamine, cyclopropylamine, and 3-(dimethylamino)-propylamine as described above. The intermediate imines (**20b,c,d**) were reduced with sodium borohydride and readily cyclized by treatment with ethanolic hydrogen chloride. These products (**22b,c,d**) similarly displayed nmr spectra consistent with their structures.

We have thus demonstrated the regiospecific synthesis of two isomeric benzocycloheptapyridinimines by intramolecular acid catalyzed cyclizations. The route appears general and provides a facile means to these interesting new heterocycles for subsequent studies.

EXPERIMENTAL

Ethyl 2-methylpyridine-3-carboxylate (**9**).

A solution of β-ethoxycrolein diethyl acetal (7) (241.27 g, 1.38 moles) and ethyl β-aminocrotonate (179.5 g, 1.39 moles) was heated under reflux for 24 hours. The ethanol was removed under reduced pressure and the residue was dissoloved in 3 *N* hydrochloric acid solution. This solution was extracted with ether, made alkaline with 20% sodium hydroxide solution (10°) and reextracted with ether. The basic ether extracts were washed with saturated sodium chloride solution and dried (sodium sulfate). Evaporation of the ether after drying gave a dark oil (127.11 g) whose ^1H nmr spectrum indicated essentially no impurities and was iden-

tical to a distilled sample.

2-Styrylnicotinic Acid (**10**).

A mixture of NaH (1.32 g, 57% oil disperison, 0.055 mole), *t*-butyl alcohol (3.34 g, 0.045 mole), and DMF (30 ml) was warmed on a steam bath until gas evolution ceased then cooled to 0°. The ester **9** (2.5 g, 0.015 mole) in DMF (5 ml) was added, followed an hour later by benzaldehyde (1.91 g, 0.018 mole) in DMF (5 ml). The mixture was stirred overnight as it warmed to 25°, and added to ice water (50 ml). The cold solution was acidified with acetic acid to *p*H 6 and filtered. The air-dried solid was recrystallized from methanol, 2.45 g, mp 215-216° (lit (6) 208-211°).

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.62; H, 5.06; N, 6.11.

5,6-Dihydro-12-methylbenzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine Dihydrochloride Hydrate (**22b**).

To a stirred solution of **16** (4) (10 g, 0.048 mole) and anhydrous methyl amine (6.2 g, 0.20 mole) in toluene (1 ℓ) was added a solution of titanium tetrachloride (3.5 ml, c. 0.03 mole) in toluene (100 ml). The resulting mixture was stirred at 25° for 24 hours, treated with anhydrous potassium carbonate and filtered through Supercel. The residual amber oil from evaporation of the solvent was dissolved in dry acetonitrile (500 ml), sodium borohydride (3.0 g) added and the mixture warmed on the steam bath for a few hours. Dilute 3 *N* hydrochloric acid was added to the cooled mixture to destroy the excess hydride and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 3 *N* hydrochloric acid (200 ml), treated with Norit and filtered. After extraction with ether, the aqueous phase was treated with 20% sodium hydroxide solution to *p*H >12 and extracted with chloroform (5 × 100 ml). The chloroform extracts were washed with 2% potassium hydroxide solution, saturated brine and dried (sodium hydroxide). The residue, after removal of the solvent, was dissolved in ethanol (50 ml) and 9 *N* hydrochloric acid in ethanol (5 ml) was added . The solvent was removed *in vacuo* and the residue was treated with a boiling mixture of methanol (375 ml) and 2-propanol (375 ml). The solution was concentrated to one-third volume and let stand. The solid that precipitated (2.16 g), mp 221-223° dec, a mixture of **21b** and **22b**, was filtered and the filtrate evaporated to dryness. The residue was dissolved in a minimum amount of cold ethanol and set aside. Filtration yielded 1.9 g, mp 211-215° of a yellow powder. An ether extract of a basic solution of this material was homogeneous on tlc (fl. silica, C_6M_1). Recrystallization of a sample from ethanol gave material of mp 215.5-217.5°. ^{1}H nmr (deuterium oxide): δ Hz (from DOH line), +98 (singlet, 3 H, -NCH_3), +70 (doublet, J = 20 Hz, 1 H, $H_{5\alpha}$), +36 (doublet of doublets, J = 20 Hz, J = 5 Hz, 1 H, $H_{5\beta}$), −45 (doublet, J = 5 Hz, 1 H, H_6), −86 (singlet, 1 H, H_{11}), −154 to −172 (multiplets, aromatic $H_{7\text{-}10}$), −189 (doublet, J = 7 Hz, 1 H, H_4), −237 (doublet, J = 7 Hz, 1 H, H_3), −254 (singlet, 1 H, H_1).

Anal. Calcd. for $C_{15}H_{14}N_2 + 2HCl + H_2O$: C, 57.52; H, 5.79; N, 8.95; Cl, 22.64. Found: C, 57.60; H, 5.34; N, 8.99; Cl, 23.26.

12-Benzyl-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine Fumarate (**22a**).

a) 11-Benzyliminobenzo[5,6]cyclohepta[1,2-*c*]pyridine (**20a**).

To a stirred mixture of **16** (6.0 g, 0.029 mole) and benzyl amine (12.84 g, 0.12 mole) in toluene (125 ml) was added a solution of titanium tetrachloride (3.42 g, 0.018 mole) in toluene (50 ml). After 1.5 hours at 25°, tlc examination indicated complete loss of ketone. Anhydrous potassium carbonate was added to the mixture and filtered. The filter cake was washed with toluene and the combined filtrates were evaporated to dryness under reduced pressure. The residue was triturated with hexane to give 5.3 g of yellow powder, mp 134.5-137.5°. Recrystallization from cyclohexane produced material with mp 136.5-138.5°.

Anal. Calcd. for $C_{21}H_{16}N_2$: C, 85.10; H, 5.44; N, 9.45. Found: C, 85.21; H, 5.49; N, 9.32.

b) 11-Benzylaminobenzo[5,6]cyclohepta[1,2-*c*]pyridine (**21a**).

A mixture of **20a** (5.0 g, 0.017 mole), sodium borohydride (0.65 g, 0.017 mole) and dry acetonitrile was heated under reflux for 0.5 hours. Tlc examination indicated a complete conversion of imine to product. Dilute (6 *N*) hydrochloric acid was added to the cooled mixture to destroy excess hydride and the mixture was evaporated to dryness. The residue was dissolved in 3 *N* hydrochloric acid (150 ml), extracted with ether (4 × 150 ml) and rendered strongly alkaline by the addition of 40% sodium hydroxide solution. The basic solution was extracted with ether and the combined organic extracts were washed with water (2 × 300 ml), saturated brine (2 × 250 ml) and dried (sodium sulfate). Filtration and removal of the solvent *in vacuo* left a viscous yellow oil, 3.65 g; ^{1}H nmr (deuteriochloroform): δ 2.1 (singlet, 1 H, -NH), 3.48 (singlet, 2 H, -NCH_2-), 4.72 (singlet, 1 H, >C*H*-N<), 6.77-8.17 (multiplets, 7 H, aromatic, vinyl, H_4), 8.43 (doublet, J = 5 Hz, 1 H, H_3), 8.6 (singlet, 1 H, H_1).

To a solution of **21a** (2.6 g) in ethanol (50 ml) was added 9 *N* ethanolic hydrochloric acid to completely convert it to the hydrochloride salt. The resulting solution was heated under reflux for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in water (100 ml). After extraction with ether, the aqueous solution was rendered alkaline by the addition of 40% sodium hydroxide solution and extracted with ether (4 × 100 ml). The basic extracts were combined, washed with water, saturated brine and dried (sodium sulfate). Filtration and removal of the dried solvent *in vacuo* gave a viscous amber oil (3.0 g) that was chromatographed over silica gel (100 g). After elution of some extraneous material with chloroform, the product was eluted with 50% ethyl acetate-chloroform. The appropriate fractions were combined and the solvent was removed to give 2.6 g of a pale yellow oil. The product was converted to its fumarate salt by treatment with a solution of fumaric acid (1.01 g) in boiling acetone (100 ml). The white crystalline material was collected and dried, 2.27 g, mp 148-150° dec with effervescence. Recrystallization from 2-propanol produced a white powder, mp 151-152.5° dec effervescence; ^{1}H nmr (DMSO-d_6): δ 2.52 (doublet, J = 18 Hz, 1 H, $H_{5\alpha}$), 3.32 (doublet of doublets, J = 18 Hz, J = 5 Hz, 1 H), $H_{5\beta}$, 3.60 (singlet, 2 H, -$NCH_2C_6H_5$), 4.33 (doublet, J = 5 Hz, 1 H, H_6), 4.82 (singlet, 1 H, H_{11}), 6.67 (singlet, 2 H, fumaric acid olefinic), 7.00 (doublet, J = 5 Hz, H_4), 7.10-7.53 (multiplets, 9 H, aromatic), 8.29 (doublet, 1 H, J = 5 Hz, 1 H, H_3), 8.37 (singlet, 1 H, H_1).

Anal. Calcd. for $C_{21}H_{18}N_2 + C_4H_4O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.54; H, 5.48; N, 6.57.

11-[3-(Dimethylamino)propylimino]benzo[5,6]cyclohepta[1,2-*c*]pyridine (**20d**).

Following the procedure described for **20a** and using 3-(dimethylamine)propylamine (12.26 g, 0.12 mole), 6.85 g of a viscous yellow oil was obtained. ^{1}H nmr (deuteriochloroform): δ 2.13 (singlet, 6 H, -$N(CH_3)_2$).

11-[3-(Dimethylamino)propylamino]benzo[5,6]cyclohepta[1,2-*c*]pyridine (**21d**).

The procedure for the preparation of **21a** was followed to give 5.72 of a viscous amber colored oil, tlc homogeneous, Fl. silica, chloroform (saturated with concentrated aqueous ammonia); ^{1}H nmr (deuteriochloroform): δ 2.13 (singlet, 6 H, -$N(CH_3)_2$), 8.67 (singlet, 1 H, H_1).

5,6-Dihydro-12-[3-(dimethylamino)propyl]benzo[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine bis-Fumarate (**22d**).

An ethanolic hydrogen chloride solution (100 ml) of **21d** (5.7 g) was treated as described for **22a** and the product (4.2 g) in acetone (50 ml) was treated with a boiling solution of fumaric acid (3.32 g) in acetone (350 ml). The white solid that precipitated, 6.4 g, was a mixture of **21d** and **22d**, mp 140-144°. Repeated recrystallization from 2-propanol followed by acetonitrile gave the homogeneous product, 1.7 g, mp 151-153° dec with effervescence; ^{1}H nmr (DMSO-d_6): δ 2.67 (singlet, 6 H, -$N(CH_3)_2$), 4.41 (doublet, J = 5 Hz, 1 H, H_6), 4.92 (singlet, 1 H, H_{11}), 6.6 (singlet, 4 H, fumaric acid olefinic), 6.90-7.50 (multiplets, 5 H, aromatic, H_4), 8.28 (doublet, J = 5 Hz, 1 H, H_3), 8.40 (singlet, 1 H, H_1).

Anal. Calcd. for $C_{19}H_{23}N_3 + 2C_4H_4O_4$: C, 61.70; H, 5.95; N, 8.00. Found: C, 61.42; H, 5.75; N, 7.84.

11-Cyclopropyliminobenzo[5,6]cyclohepta[1,2-*c*]pyridine (**20c**).

Following the procedure described for **20a**, and using cyclopropylamine (6.85 g, 0.12 mole), there was obtained a viscous oil, 5.88 g; ^{1}H nmr (deuteriochloroform): δ 0.6-1.27 (multiplets, 4 H, cyclopropyl), 2.9-3.27 (multiplets, 1 H, *t*-cyclopropyl H), 6.53-7.70 (multiplets, 7 H, benzene, olefin, H_4), 8.47 (doublet, J = 5 Hz, 1 H, H_3), 8.73 (singlet, 1 H, H_1).

11-Cyclopropylaminobenzo[5,6]cyclohepta[1,2-*c*]pyridine (**21c**).

As described for **20b**, sodium borohydride reduction of **21c** produced fine white crystals from petroleum ether, mp 71.5-73°; ^{1}H nmr (deuteriochloroform): δ 0.30 (singlet, 2 H, cyclopropyl), 0.38 (singlet, 2 H, cyclopropyl), 2.3 (singlet, 1 H, *t*-cyclopropyl H), 4.93 (singlet, 1 H, H_{11}), 6.8-7.63 (multiplets, 7 H, benzene, olefin, H_4), 8.53 (doublet, J = 5 Hz, 1 H, H_3), 8.73 (singlet, 1 H, H_1).

12-Cyclopropyl-5,6-dihydro[5,6]cyclohepta[1,2-*c*]pyridin-6,11-imine (**22c**).

An ethanolic solution (50 ml) of **21c** (3.5 g) was treated as described for **22a**. After 40 hours, the hot mixture was filtered to give 2.33 g of off-white solid. Another 0.78 g was obtained from the filtrate. The sample was washed with cold ethanol and dried. ^{1}H nmr indicated ethanol still present, mp >205° dec; ^{1}H nmr (deuterium oxide): δ 1.0-1.47 (multiplets, 4 H, cyclopropyl), 2.77-3.20 (multiplets, 1 H, *t*-cyclopropyl), 3.63 (doublet, J = 20 Hz, $H_{5\alpha}$), 4.20 (doublet of doublets, J = 20 Hz, J = 5 Hz, 1 H, $H_{5\beta}$), 5.71 (doublet, J = 5 Hz, 1 H, H_6), 6.40 (singlet, 1 H, H_{11}), 7.43-7.87 (multiplets, 4 H, benzene), 7.99 (doublet, J = 5 Hz, H_4), 8.78 (doublet, J = 5 Hz, 1 H, H_3), 9.07 (singlet, 1 H, H_1).

Anal. Calcd. for $C_{17}H_{16}N_2$ + 2 HCl + 0.25 C_2H_5OH: C, 63.16; H, 5.91; N, 8.42; Cl, 21.31. Found: C, 63.01; H, 5.83; N, 8.34; Cl, 21.14.

Benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (**13**).

The acid **10** (41.8 g, 0.165 mmole) was added portionwise to hot (220°) PPA (800 g). The temperature of the stirred reaction mixture was maintained at 220-225° for 0.75 hours then cooled to 100°. The dark reaction mixture was poured slowly into 4 ℓ of water with stirring and a dark brown solid that formed was filtered. The filtrate was made alkaline by the addition of 20% sodium hydroxide solution and the beige precipitate that formed was filtered, washed with water and air-dried, 40.78 g, mp 82-90°. Recrystallization from hexane gave 25.2 g of light yellow solid, mp 95-97° (lit (5,6) mp 96-97°).

5-Benzylimino[4,5]cyclohepta[1,2-*b*]pyridine (**17**).

Following the procedure described for **20a** and using **13** (4.7 g, 0.023 mole), benzylamine (9.44 g, 0.088 mole) and titanium tetrachloride (2.51 g, 0.0132 mole) in toluene (300 ml), there was obtained a pale yellow solid, 5.0 g, mp 101-115°. Recrystallization from hexane did not change the mp. Tlc examination indicated that two equal intensity components corresponding to two geometrical isomers: ^{1}H nmr (deuteriochloroform) displayed doubling of all peaks.

Anal. Calcd. for $C_{21}H_{26}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.72; H, 5.59; N, 9.10.

5-Benzylaminobenzo[4,5]cyclohepta[1,2-*b*]pyridine (**18**).

A mixture of **17** (5.7 g, 0.01 mole) and sodium borohydride (0.76 g, 0.02 mole) in acetonitrile (150 ml) was warmed on the steam bath for 24 hours. The reaction mixture was worked up as described for **20b** to give 4.7 g of an amber oil. This material was used directly in the next step with no further purification.

12-Benzyl-10,11-dihydro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5,10-imine (**19**).

A solution of **18** (4.7 g, 0.0158 mole) and *p*-toluenesulfonic acid hydrate (3 g, 0.0158 mole) in ethanol (100 ml) was heated under reflux for 24 hours. The solvent was removed *in vacuo* and the residue was treated with 4% sodium hydroxide solution (100 ml). The basic solution was extracted with ether and the ether extracts were washed (water, saturated brine), and dried (sodium sulfate). After filtration and removal of the solvent the residue (4.6 g) was chromatographed over silica gel (400 g) eluting with dichloromethane (95):2-propanol (5). The fractions containing the product were combined and stripped to a pale yellow oil, 1.15 g. This material was dissolved in ethyl acetate (40 ml) and converted to its oxalate salt by treatment with a solution of oxalic acid (0.90 g) in ether (10 ml). The white solid that precipitated was collected, washed with ether then recrystallized from ethyl acetate, mp indefinite below 100° (ethyl acetate present). ^{1}H nmr (DMSO-d_6): δ 2.82 (doublet, J = 18 Hz, 1 H, $H_{11\alpha}$), 3.55 (doublet of doublets, J = 18 Hz, J = 5 Hz, 1 H, $H_{11\beta}$), 3.87 (singlet, 2 H, benzylic), 4.75 (doublet, J = 5 Hz, 1 H, H_{10}), 5.17 (singlet, 1 H, H_5), 7.0-7.6 (multiplets, 10 H, aromatic, H_3), 7.70 (doublet of doublets, J = 8 Hz, J = 2 Hz, 1 H, H_4), 8.35 (doublet of doublets, J = 6 Hz, J = 2 Hz, 1 H, H_2).

Anal. Calcd. for $C_{21}H_{18}N_2 + 2C_2H_2O_4 + \frac{1}{2}C_4H_4O_2$: C, 62.06; H, 5.02; N, 5.36. Found: C, 62.11; H, 4.88; N, 5.42.

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(1) For paper No. 1 in this series, see; W. Halczenko and K. L. Shepard, *J. Heterocyclic Chem.*, **19**, (1982).

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