On the Reactions of β-Ketoesters with 2,3-Diaminopyridine and its Derivatives (1)

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Studies in these laboratories and elsewhere on the condensation of β-ketoesters with unsymmetrical *o*-diamines have thus far failed to explain the factors which govern the direction of cyclization in these reactions. Various additional diamine-ketoester condensations have been studied and the results compared in an attempt to develop generalizations of predictive value regarding the direction of ring closure to form diazepinones. The following condensation reactions are described: 2,3-diaminopyridine with 2-ethoxycarbonylcyclohexanone and with ethyl α-methylacetoacetate, 5-bromo-2,3-diamino-4-methylpyridine with ethyl acetoacetate, 3-amino-2-anilinopyridine and 3-amino-2-methylaminopyridine with ethyl acetoacetate, and *N*-methyl-*o*-phenylenediamine with ethyl acetoacetate.

We earlier reported (2) that by varying the reaction conditions the condensation of 2,3-diaminopyridine (**1**) with ethyl acetoacetate could be made to give either of the two possible isomeric diazepine ring closure products. Although the mechanism by which these products were formed remains obscure, the diazepine product obtained under conditions of boiling xylene was structurally that which would result from the interaction of the more basic 3-amino group of **1** with the keto carbonyl of the β-ketoester (2). This direction of cyclization was also seen in the condensation of **1** with ethyl benzoylacetate under similar conditions (3). However, the diazepinone products from the reactions of acetoacetic ester with 3,4-diaminopyridine (4) and 4,5-diaminopyrimidine (5) appeared rather to derive from an acetoacetamide intermediate. In an attempt to gain insight into the factors which control the direction of cyclization in these reactions, we have examined and compared the condensations of several β-ketoesters with **1** and some of its derivatives. We now wish to report the results of these studies.

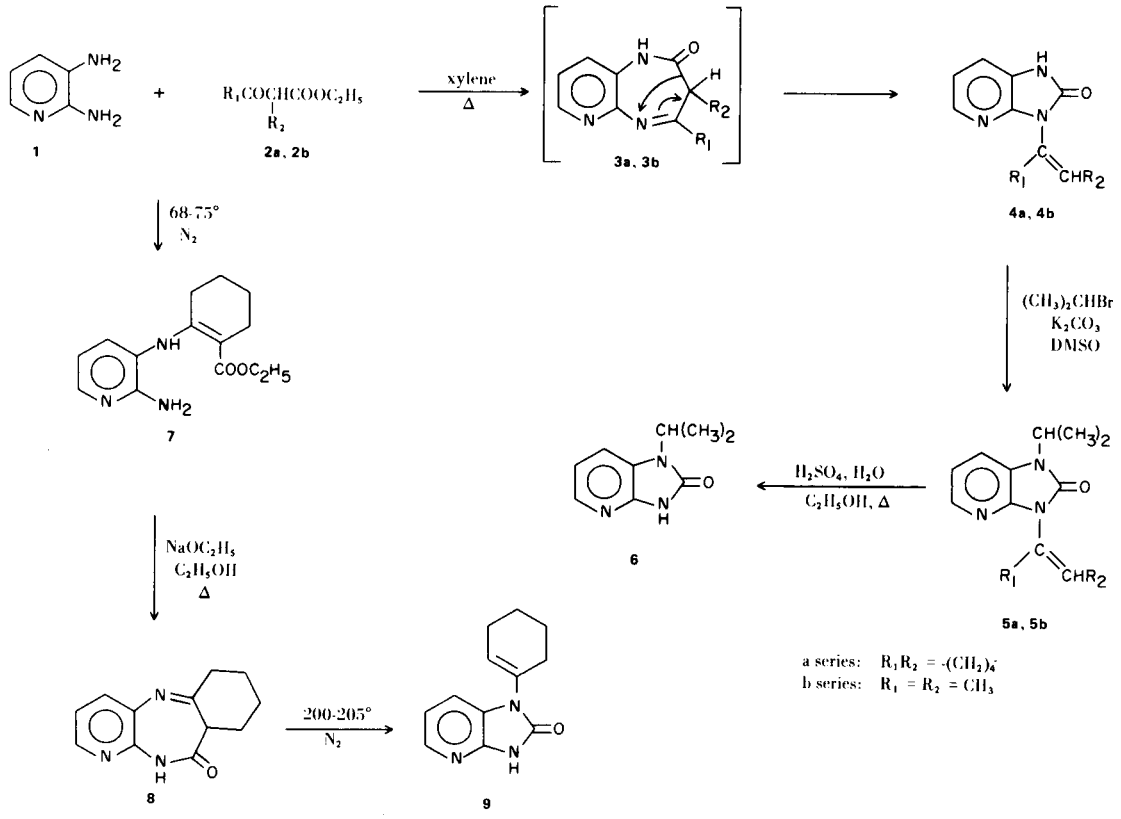
It has been reported (6) that the reaction of *o*-phenylenediamine with 2-ethoxycarbonylcyclohexanone in boiling xylene gave *N*-cyclohexenylbenzimidazolone. We have now observed that condensation of the pyridinediamine **1** with 2-ethoxycarbonylcyclohexanone (**2a**, Scheme I) in boiling xylene also gives a cyclohexenylimidazolone, as evidenced by the strong carbonyl peak at 5.88 μ in the ir and the vinyl proton multiplet centered at δ 5.94 in the nmr exhibited by the product. The identity of this material as **4a** was determined by isopropylation to **5a**, followed by hydrolysis. This sequence afforded 1-isopropyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**6**), identical in all respects with a previously (7) characterized sample.

Additional confirmation of the structure of **4a** was obtained when **1** was treated with **2a** at 68-75° in a nitrogen atmosphere in the absence of solvent. This reaction afforded the aminocyclohexenylcarboxylate **7**, which, when heated with sodium ethoxide in ethanol, gave the 2,3-tetramethylenediazepine **8**. Fusion of **8** at 200-205° under nitrogen resulted in the formation of the 1-cyclohexenylimidazolone **9**, isomeric with **4a**.

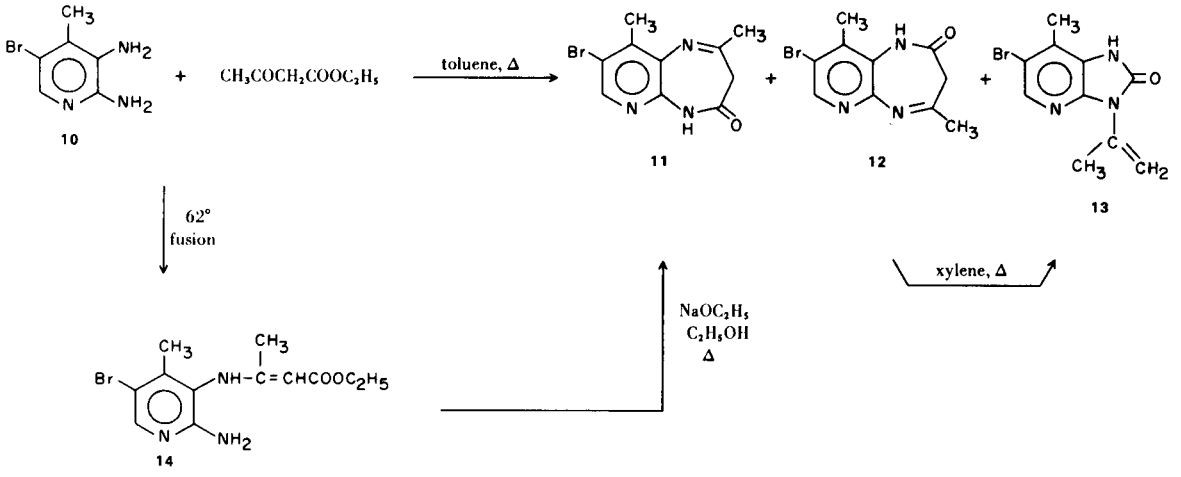
In a similar manner, the reaction of **1** with α-methylacetoacetic ester (**2b**) in xylene for 7 hours gave the 2-butenylimidazolone **4b**, together with some unchanged diamine. The identity of **4b** was again established by isopropylation and conversion of the alkylated product **5b** into **6**.

The formation of *N*-alkenylimidazolones in reactions of diamines with β-ketoesters is now understood to result from thermally-induced ring contraction of initially formed dihydrodiazepinone products (7). Thus, the isolation of **4a** and **4b** in the above described reactions presupposes the transitory existence of the corresponding diazepinones **3a** and **3b** as precursors. The presence of these diazepine products could not be detected by thin layer chromatography of the reaction mixtures, nor was it possible to observe these or other products when the condensations

Scheme I



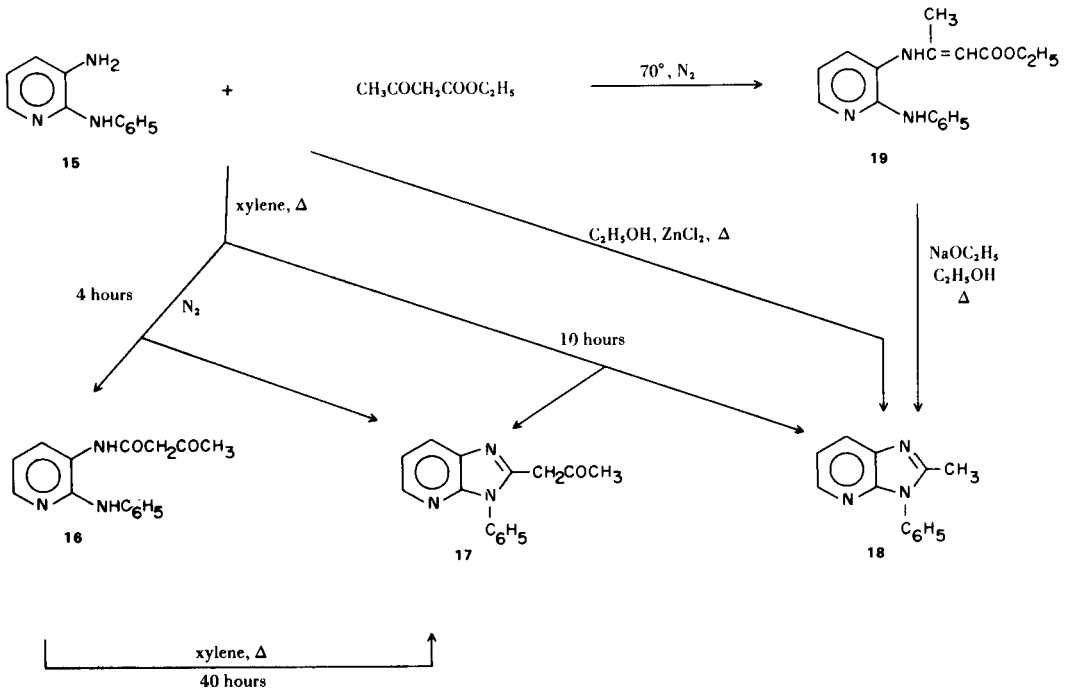
Scheme II



were run at lower temperature or for shorter periods of time. It appears, therefore, that in these reactions the exclusive, although short-lived, diazepine product was that which appeared to derive from interaction of the 3-amino group of **1** with the ester carbonyl of the β-keto-ester. The mode of cyclization seen here then is not the same as the earlier observed direction of cyclization of **1** with ethyl acetoacetate (2) and ethyl benzoylacetate (3) under similar conditions.

The reaction of the more highly substituted diamine 5-bromo-2,3-diamino-4-methylpyridine (**10**) with ethyl acetoacetate presented a less clear-cut situation. Con-

Scheme III



densation of **10** with the ketoester in hot xylene (Scheme II) afforded a mixture of three isomeric products, the two diazepinones **11** and **12** and a quantity of the isopropenylimidazolone, **13**. In hot toluene, **11**, **12**, and the imidazolone were again obtained, but **12** was present in greater yield and **13** in lesser yield than in the xylene reaction. The identity of **13** was established when a pure sample of **12** was heated in xylene for 3 hours, thereby partially converting it into **13**. The absolute identity of the **12** used in this experiment was based upon the lack of identity of the diazepinone sample with **11** prepared by cyclization of the crotonate intermediate **14**.

In an attempt to obtain by direct cyclization a dihydrodiazepinone product bearing a substituent on a nitrogen atom, 3-amino-2-anilinopyridine (**15**) was prepared and condensed with ethyl acetoacetate. In boiling xylene for 4 hours under a nitrogen atmosphere (Scheme III) the reaction gave a 55% yield of the acetoacetamide **16**, together with an 18% yield of **17**. A similar experiment allowed to proceed for 6 hours gave 22% of **16** and 36% of **17**.

The 2-acetonyl-3-phenylpyridoimidazole structure was assigned to **17** on the basis of microchemical analysis, nmr (in deuteriodimethylsulfoxide a 3 proton singlet δ 2.37 and a 2 proton singlet δ 3.38) and ir (strong carbonyl stretch at 5.93 μ) spectral data, and its derivation from **16** (**16** maintained in boiling xylene for 40 hours showed partial conversion into **17**). Additional support for the assignment of **17** was obtained from the condensation of **15** with ethyl acetoacetate in hot xylene for 10 hours. This reaction gave **17**, together with the 2-methyl-3-phenylimidazole **18** and a trace of **16**. The formation of **18** can be rationalized by a reverse Claisen reaction of **17** catalyzed by the basic diamine, although an acceptable alternate explanation might involve a reverse Claisen of the acetoacetamide **16**, followed by cyclization.

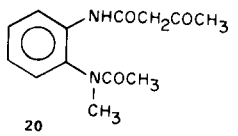
Failure to obtain a diazepinone product *via* direct condensation led us to prepare the crotonate intermediate **19** for subsequent cyclization. Attempted preparation of **19** from **15** and ethyl acetoacetate in ethanol in the presence of zinc chloride (5) gave only **18**. Fusion of **15** and the ketoester at 70° under nitrogen gave **19** as evidenced by the typical nmr pattern (2,4,5) of the aminocrotonate and by supporting microanalytical data. However, attempted diazepinone cyclization of **19** under the usual conditions of base catalysis (2,4,5,8) resulted again in reverse Claisen reaction, with the resultant formation of **18**.

In a single experiment with 3-amino-2-methylaminopyridine and ethyl acetoacetate in hot xylene, the reaction gave a mixture of 2-acetonyl-3-methyl-3*H*-imidazo[4,5-*b*]-pyridine and 2,3-dimethyl-3*H*-imidazo[4,5-*b*]pyridine, similar to the result obtained with diamine **15** and ethyl acetoacetate after 10 hours of reflux.

Although the sampling is still small, comparisons can now be made of the reactions of a single diamine, **1**, with

four β-ketoesters and also of the reactions of a single ketoester, ethyl acetoacetate, with various heteroaromatic diamines. Thus, it now seems reasonable to attempt to derive some generalizations concerning the nature and direction of cyclization products in these reactions. Firstly, for the condensations of **1** with acetoacetic, benzoylacetic, α-methylacetoacetic, and cyclohexanonecarboxylic esters, careful examination of the reaction mixture in each instance failed to reveal the presence of an intermediate which might explain the eventual cyclization product. Also, modification of reaction times and temperature proved of no value in this regard. However, since the reactions were performed on the same diamine under essentially identical conditions, observed differences in the direction of cyclization must be reflecting differences in the character of the ketoester. While acetoacetic and benzoylacetic esters (ketoesters unsubstituted at the α-position) gave diazepinone products structurally derived from keto-carbonyl interaction with the 3-amino group of **1** (2,3), ketoesters possessing an α-substituent (*i.e.* **2a** and **2b**) resulted in diazepinone cyclization in a manner suggesting an acetoacetamide intermediate. Thus, α-substitution on the ketoester appears to reduce reaction at the keto carbonyl, probably as a result of steric effects, thereby favoring reaction with the ester carbonyl. Furthermore, diazepinone derivatives with substituents at both the 2- and 3-positions appear to be more sensitive to thermally-induced ring contraction than similar monosubstituted products (7); this observation is supported by our current findings and by literature reports (6,9) on the reactions of *o*-phenylenediamine and 2-ethoxycarbonylcyclohexanone, 2-ethoxycarbonylcyclopentanone, and α-phenylacetoacetic ester in boiling xylene, which give *N*-alkenylbenzimidazolones either exclusively or as the major product.

As noted above, no *N*-substituted diazepine product from acetoacetic ester and 3-amino-2-anilinopyridine or 3-amino-2-methylaminopyridine could be obtained by direct condensation; to our knowledge no successful analogous reaction with an *N*-substituted-*o*-phenylenediamine has been achieved. Ruske and Grimm (10) reported that *N*-methyl-*o*-phenylenediamine and ethyl acetoacetate in alcohol gave the corresponding aminocrotonate. We have prepared this material in a different manner and have found that attempted cyclization of the crotonate to the diazepinone in the presence of sodium ethoxide gave only 2,3-dimethylbenzimidazole. Direct condensation of *N*-methyl-*o*-phenylenediamine with ethyl acetoacetate in hot xylene gave **20** and a small quantity of 2,3-dimethylbenzimidazole. The failure to form the seven-membered ring in these reactions appears to be due to steric factors associated with substitution on the amino function; these effects seem to be less critical in the formation of the five-membered imidazole nucleus.



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Finally, examination of the reactions of acetoacetic ester with diamine **10**, as described herein, and with **1** (2), 3,4-diaminopyridine (4), and 4,5-diaminopyrimidine (5) suggests that with different heterodiamines the location of the two amino functions relative to a deactivating substituent (*i.e.* ring nitrogen atom) is important in determining the direction of cyclization. In each instance, the more basic amino function of the diamine is located *meta* to a ring *N* atom. With **1**, wherein the less basic amino group is *ortho* to the ring *N* atom, diazepinone cyclization proceeds exclusively as though derived from a crotonate intermediate. With 3,4-diaminopyridine and 4,5-diaminopyrimidine, each of which has a ring *N* atom *para* to the less basic amino group, condensation proceeds essentially exclusively *via* the acetoacetamide pathway. Although diamine **10** is a substituted derivative of **1**, the presence of the weakly deactivating 5-bromo substituent *para* to the less basic 2-amino function results in a mixture of diazepinone cyclization products; the reactivity of diamine **10** thus appears to be intermediate between that of **1** and 4,5-diaminopyrimidine.

EXPERIMENTAL (11)

Condensation of **1** with 2-Ethoxycarbonylcyclohexanone (**2a**). Preparation of 3-Cyclohexenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]-pyridin-2-one (**4a**).

A mixture of 4.36 g. (40 mmoles) of **1** and 10.2 g. (60 mmoles) of **2a** in 300 ml. of xylene was maintained at reflux for 6 hours with azeotropic removal of water (Dean-Stark trap). The solution was concentrated to 25 ml. and the pale yellow solid was collected. Two crystallizations from benzene afforded the analytical sample, m.p. 177-178°; 6.32 g. (74%); ir (potassium chloride): 5.88 μ; nmr (deuteriopyridine): δ 5.94 (1H multiplet) ppm.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.53. Found: C, 67.33; H, 6.24; N, 19.42.

Tlc examination of the xylene filtrate from above showed traces of **1** and **4a** and brightly fluorescent material which remained at the origin.

3-Cyclohexen-1-yl-1-isopropyl-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (**5a**).

A mixture of 1.08 g. (5 mmoles) of **4a**, 0.69 g. (5 mmoles) of potassium carbonate, 1.37 g. (10 mmoles) of isopropyl bromide and 3 ml. of dimethylsulfoxide was heated at 60° overnight with stirring. The pale yellow reaction solution was poured over ice and the resulting oil was triturated under cold water until it formed into a hard gum. The water was then decanted and the gum was allowed to air dry. Crystallization of the gum from ligroine (b.p. 65-90°) afforded a white powder, m.p. 68-71°; 930 mg. (72%).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.06; H, 7.22; N, 16.07.

A 200 mg. sample of **5a** was dissolved in 10 ml. of a sulfuric acid-water-ethanol solvent system (1:1:2 by volume) and the solution was gently warmed for 1 hour. The reaction mixture was neutralized to *p*H 8 with 5% sodium hydroxide and the product was crystallized from ligroine (b.p. 65-90°) to give material, m.p. 178-181°, identical in all respects with a previously (7) characterized sample of **6**; mixture m.p. 178-180°.

2-Amino-3-(2-ethoxycarbonylcyclohexen-1-yl)aminopyridine (**7**).

A suspension of 2.18 g. (20 mmoles) of **1** and 4.0 g. (20 mmoles) of **2a** was maintained at 68-75° for 20 hours under nitrogen. A red oil was decanted from unchanged **1** (recovery 0.56 g., 26%). Addition of ether to the oil precipitated a gray powder which was collected and air dried. The crude material was crystallized 3 times from ligroine (b.p. 65-90°) to give white crystals, m.p. 96-98°; 2.22 g. (42%); nmr (deuteriochloroform): δ 1.30 (3H, t, J = 14 Hz), 1.60 (4H, m), 1.95-2.50 (4H, broad), 3.73 (1H, s), 4.17 (2H, q, J = 22 Hz), and 4.90 (2H, broad) ppm.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.33; H, 7.34; N, 16.08. Found: C, 64.45; H, 7.15; N, 16.30.

3,5-Dihydro-2,3-tetramethylene-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one (**8**).

Compound **7** (1.53 g., 6 mmoles) was added to 100 ml. of absolute ethanol in which 140 mg. (6 mg.-atoms) of sodium had previously been dissolved. The solution was maintained at reflux for 2 hours. Water was added and, after neutralization to *p*H 6 by means of dilute hydrochloric acid, the solvent was reduced to half volume. The solid was collected and dried, then crystallized once from ethanol (charcoal) and twice from methanol; yellow needles, m.p. 199-203°; 710 mg. (55%); ir (potassium chloride): 6.10, (C=N), 6.16 (CONH) (2), and 6.25 (pyridine ring) μ.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.53. Found: C, 66.80; H, 6.18; N, 19.28.

1-Cyclohexen-1-yl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**9**).

A 180 mg. sample of **8** (0.8 mmole) was heated under a stream of nitrogen at 200-205° for 1.5 hours. The yellow solid began to shrink and then gradually turned white. Two crystallizations of the white material from toluene gave white powder, m.p. 202-204°; 150 mg. (83%); ir (potassium chloride): 5.90 (C=O) and 6.07 (C=C) μ.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.53. Found: C, 66.78; H, 6.11; N, 19.40.

3-(2-Buten-2-yl)-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (**4b**).

A mixture of 2.73 g. (25 mmoles) of **1** and 5.04 g. (37.5 mmoles) of ethyl α-methylacetoacetate (**2b**) in 150 ml. of xylene was heated at reflux for 7 hours with azeotropic removal of water. The xylene solution was decanted from the black tar and evaporated to dryness. Addition of ether-benzene (3:1 by volume) afforded an amber-colored solution above pale yellow solid. The solid (unchanged **1**, 13% recovery) was separated and the filtrate was taken to dryness. The residue was crystallized several times from cyclohexane to give 1.07 g. (23%) of **4b** as white powder, m.p. 122-123°; ir (potassium chloride): 5.90 μ.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.53; H, 5.88; N, 22.04.

3-(2-Buten-2-yl)-1-isopropyl-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (**5b**).

A mixture of 570 mg. (3 mmoles) of **4b**, 414 mg. (3 mmoles) of potassium carbonate, 822 mg. (6 mmoles) of isopropyl bromide, and 3 ml. of dimethylsulfoxide was warmed at 55-60° overnight with stirring. The reaction mixture was poured over ice and the resulting solid was collected. The pale yellow solid was crystallized from ligroine (b.p. 65-90°) to give white crystals of **5b**, m.p. 89-90°; 475 mg. (69%).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.49; H, 7.42; N, 18.17. Found: C, 67.61; H, 7.20; N, 18.25.

Acid hydrolysis of a sample of **5b**, as described for **4b**, afforded **6**, m.p. 177-179°; mixture melting point with authentic sample, 177-180°.

Condensation of 5-Bromo-2,3-diamino-4-methylpyridine (**10**) with Ethyl Acetoacetate in Boiling Toluene.

A mixture of 2.02 g. (10 mmoles) of **10** (12), 1.95 g. (15 mmoles) of ethyl acetoacetate, and 80 ml. of toluene was heated at reflux for 4 hours with stirring and azeotropic removal of water. When cool, the pale yellow solid was collected and air dried. Tlc on Eastman Chromagram plates with 9:1 benzene-ethanol showed 3 spots attributable to **11**, **12**, and **13**. The mixture was extracted with hot ethyl acetate. The ethyl acetate solution upon cooling deposited white crystals. These were recrystallized from ethanol to give 740 mg. (28%) of 6-bromo-3-isopropenyl-7-methyl-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (**13**), m.p. 289-292°.

Anal. Calcd. for $C_{10}H_{10}BrN_3O$: C, 44.79; H, 3.75; Br, 29.81; N, 15.68. Found: C, 45.02; H, 3.79; Br, 29.82; N, 15.79.

The ethyl acetate insoluble material (**11** + **12**) was suspended in benzene and the mixture was heated to boiling. When allowed to cool gradually, the benzene solution deposited yellow crystals, which were collected and purified by recrystallization from benzene. The product, 8-bromo-4,9-dimethyl-1,3-dihydro-2*H*-pyrido-[2,3-*b*][1,4]diazepin-2-one (**12**), when heated turned white at 210° and melted at 289-291°, the m.p. of **13**; 1.05 g. (39%).

Anal. Calcd. for $C_{10}H_{10}BrN_3O$: C, 44.79; H, 3.75; Br, 29.81; N, 15.68. Found: C, 44.91; H, 3.73; Br, 29.87; N, 15.56.

Evaporation of the benzene filtrate from above gave, after crystallization from a small volume of benzene, 500 mg. (19%) of 8-bromo-2,9-dimethyl-3,5-dihydro-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one (**11**) contaminated with traces of **12** (tlc evidence).

Ethyl 3-(2-Amino-5-bromo-4-methyl-3-pyridylaminocrotonate (**14**).

A mixture of 2.02 g. (10 mmoles) of **10** and 1.95 g. (15 mmoles) of ethyl acetoacetate was heated for 72 hours at 60-65° under a nitrogen atmosphere. The off-white crystals were collected and purified by repeated crystallization from ligroine (b.p. 65-90°). The product, 2.62 g. (83%), melted at 135-139°.

Anal. Calcd. for $C_{12}H_{16}BrN_3O_2$: C, 45.87; H, 5.13; Br, 25.43; N, 13.38. Found: C, 46.01; H, 4.95; Br, 25.68; N, 13.60.

8-Bromo-2,9-dimethyl-3,5-dihydro-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one (**11**) from **14**.

Sodium metal (70 mg., 2.9 mg.-atoms) was dissolved in 60 ml. of absolute ethanol and to this solution was added 910 mg. (2.9 mmoles) of **14**. The suspension was heated at reflux for 2 hours. The pale yellow solution was acidified to *p*H 2 with dilute hydrochloric acid. The resulting white precipitate was collected and crystallized from benzene to give 650 mg. (82%) of **11**, m.p. 252-255°.

Anal. Calcd. for $C_{10}H_{10}BrN_3O$: C, 44.79; H, 3.75; Br, 29.81; N, 15.68. Found: C, 44.63; H, 3.68; Br, 29.64; N, 15.53.

This material and the sample of **11** from the toluene condensation reaction were found to be essentially identical.

Condensation of 3-Amino-2-anilinopyridine (**15**) with Ethyl Acetoacetate.

2-Chloro-3-nitropyridine (Aldrich Chemical Co.) was converted into 2-anilino-3-nitropyridine in 73% yield by warming in ethanol solution with 2 equivalents of aniline. Catalytic hydrogenation of the anilinonitro compound in ethanol in the presence of 5% palladium-on-charcoal afforded diamine **15** in 82% yield; m.p. 142-143.5° [lit. (13) m.p. 141°].

To a suspension of 1.85 g. (10 mmoles) of **15** in 80 ml. of xylene was added 1.95 g. (15 mmoles) of ethyl acetoacetate and the mixture was heated at reflux for 4 hours under nitrogen with azeotropic removal of water. Tan crystals were separated from the cooled reaction mixture. These were crystallized twice from benzene to give 1.48 g. (55%) of *N*-(2-anilino-3-pyridyl)acetoacetamide (**16**) as white powder, m.p. 134-135°; ir (potassium chloride): 5.83 (C=O) and 5.99 (CONH) μ.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.89; H, 5.63; N, 15.61. Found: C, 66.80; H, 5.78; N, 15.43.

The xylene mother liquor from above was evaporated to a red oil, which was extracted with boiling ligroine (b.p. 65-90°). The ligroine solution, upon cooling, deposited pale pink needles. These were collected and purified by several crystallizations from ligroine (b.p. 65-90°) with charcoal to give 2-acetonyl-3-phenyl-3*H*-imidazo[4,5-*b*]pyridine (**17**) as small white needles, m.p. 178-181°; 452 mg. (18%); ir (potassium chloride): 5.93 (C=O) and 6.10 (C=N) μ; nmr (deuteriodimethylsulfoxide): δ 2.37 (3H, s) and 3.38 (2H, s) ppm.

A similar condensation of **15** and ethyl acetoacetate in xylene allowed to reflux for 6 hours and worked up as above gave 22% of **16** and 36% of **17**. Another condensation reaction allowed to boil for 10 hours gave 2% of **16** and 47% of **17**, together with 293 mg. (14%) of 2-methyl-3-phenyl-3*H*-imidazo[4,5-*b*]pyridine (**18**), which was isolated from the ligroine filtrate from **17** by reduction to half volume and overnight standing in the freezer. Compound **18** was crystallized from ligroine (b.p. 65-90°) to give white needles, m.p. 68-69°; the nmr spectrum (deuteriochloroform) which shows only a 3 proton singlet (δ 2.53) below 7.0 ppm, is consistent with the structure.

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.61; H, 5.30; N, 20.09. Found: C, 74.42; H, 5.30; N, 19.86.

Reaction of 1.85 g. (10 mmoles) of **15** with 1.95 g. (15 mmoles) of ethyl acetoacetate in 50 ml. of absolute ethanol containing 20 mg. of zinc chloride at reflux for 15 hours afforded, after evaporation of the solvent and crystallization of the residue from ligroine (b.p. 65-90°), 1.07 g. (51%) of **18**, identical with the above sample.

Ethyl 3-(2-Anilino-3-pyridyl)aminocrotonate (**19**).

A suspension of 3.0 g. (16 mmoles) of **15** in 5 ml. of ethyl acetoacetate was warmed at 70° for 12 hours under nitrogen. The solution was diluted with 10 ml. of ether and ligroine was added until the mixture became turbid. The mixture was placed in the freezer overnight. The product was collected and crystallized several times from ligroine (b.p. 65-90°) to give 3.11 g. (66%) of **19**, m.p. 74-75°.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.67; H, 6.52; N, 13.90.

Attempted Diazepinone Cyclization of **19**.

Compound **19** (2.4 g., 8.9 mmoles) was added to 100 ml. of ethanol in which 200 mg. (8.9 mg.-atoms) of sodium had been previously dissolved. The mixture was heated at reflux for 4.5 hours, then reduced to 10 ml. on the rotary evaporator. Water was added and the solution was neutralized to *p*H 5 by the addition of dilute hydrochloric acid. The aqueous solution was extracted with 3 x 50 ml. portions of chloroform. Crystallization of the residue after evaporation of the dried, decolorized chloroform solution gave 1.26 g. (68%) of **18**, identical with the previously characterized sample. Tlc examination of the aqueous *p*H 5 solution prior to chloroform extraction revealed only the presence of **18** and unchanged **19**.

Condensation of 3-Amino-2-methylaminopyridine with Ethyl Acetoacetate.

A 6.68 g. sample of 2-methylamino-3-nitropyridine (43 mmoles) was reduced catalytically on the Parr apparatus in ethanol solution in the presence of 10% palladium-on-charcoal; reduction required 1 hour. The catalyst was separated and the ethanol filtrate was evaporated to dryness. To the crude diamine were added quickly 200 ml. of xylene and 8.3 ml. (64 mmoles) of ethyl acetoacetate and the mixture was heated at reflux for 4 hours with azeotropic removal of water. The deep red reaction solution was decanted from the black tar and was evaporated to near dryness. The residue was dissolved in ether and ligroine was added until turbidity appeared. The mixture was placed in the freezer overnight. The solid was collected and crystallized repeatedly from cyclohexane with charcoal to give 3.17 g. (39%) of 2-acetonyl-3-methyl-3*H*-imidazo[4,5-*b*]pyridine, m.p. 129-133°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.81; H, 5.66; N, 21.95.

Addition of a large volume of ligroine to the ether-ligroine filtrate from above resulted in the precipitation of pale pink powder. This product was collected and purified by two crystallizations from ligroine (b.p. 65-90°), once with charcoal, to give 2.02 g. (32%) of 2,3-dimethyl-3*H*-imidazo[4,5-*b*]pyridine as white crystals, m.p. 112-114°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.56. Found: C, 65.49; H, 6.25; N, 28.27.

Ethyl 3-(*o*-*N*-methylaminophenyl)aminocrotonate.

A mixture of 2.6 g. (21 mmoles) of freshly prepared *N*-methyl-*o*-phenylenediamine and 2.8 g. (21 mmoles) of ethyl acetoacetate in 10 ml. of benzene was refluxed for 4 hours with azeotropic removal of water. The benzene was evaporated and the oily residue was treated with 1:1 ether-ligroine. The solid was collected and crystallized from cyclohexane to give 1.08 g. (22%) of product, m.p. 68-70° [lit. (10) m.p. 70.5-71.5°]; nmr (deuteriochloroform): δ 1.26 (3H, t, J = 14 Hz, CH_2CH_3), 1.75 (3H, s, C-CH_3), 2.57 (1H, s, NH), 2.82 (3H, s, NCH_3), 3.67 (1H, s, NH), 4.13 (2H, q, J = 22 Hz, CH_2CH_3), and 4.70 (1H, s, =CH-) ppm.

Condensation of *N*-Methyl-*o*-phenylenediamine with Ethyl Acetoacetate in Boiling Xylene.

A mixture of 1.2 g. (10 mmoles) of *N*-methyl-*o*-phenylenediamine and 1.96 g. (15 mmoles) of ethyl acetoacetate in 25 ml. of xylene was heated at reflux for 70 minutes with azeotropic removal of water. The solvent was evaporated and the residual oil was extracted with ether. Addition of ligroine (b.p. 65-90°) to the ether extract resulted in the precipitation of 1,2-dimethylbenzimidazole, which after crystallization from hexane melted at 111-112° [lit. (14) m.p. 112°]; 0.66 g. (45%); nmr (deuteriochloroform): δ 2.48 (3H, s), 3.53 (3H, s), and 7.07-7.75 (4H, multiple peaks) ppm.

The ether-insoluble residue was triturated under ether until it hardened. At this time it showed a single spot on tlc. The product, m.p. 129-131°, was characterized as *N*-acetyl-*N*-methyl-*N'*-acetoacetyl-*o*-phenylenediamine, **20**, on the basis of microchemical analysis and spectral considerations; 410 mg. (17%); ir (potassium chloride): 5.70, 5.85, 5.95, 6.04, and 6.20 μ; nmr (deuteriochloroform): δ 2.07 (3H, s), 2.25 (3H, s), 3.19 (3H, s), and 3.40 (2H, s); mass spectrum (70 ev): 248 (M^+), 191, 190, 164, 149, 148, 147.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.49; N, 11.28. Found: C, 62.78; H, 6.53; N, 11.27.

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