The Cyclocondensation of 5-Amino-1,3-dimethylpyrazole with Ethyl Acetoacetate. Synthesis of Isomeric Pyrazolopyridones

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The reaction of 5-amino-1,3-dimethylpyrazole with ethyl acetoacetate yielded two isomeric pyrazolopyridones which were identified as their corresponding tetrahydropyrazolopyridine derivatives and by their ir, pmr and ^{13}C-nmr spectral data. Additional proof was provided by a separate synthetic route involving the Friedländer reaction.

Although the cyclocondensation of ethyl acetoacetate with 1,3-disubstituted-5-aminopyrazoles **1** has been studied by several investigators (1-8), there still exists a disparity in the assignments of structures to the products **4** and **5** (Scheme I).

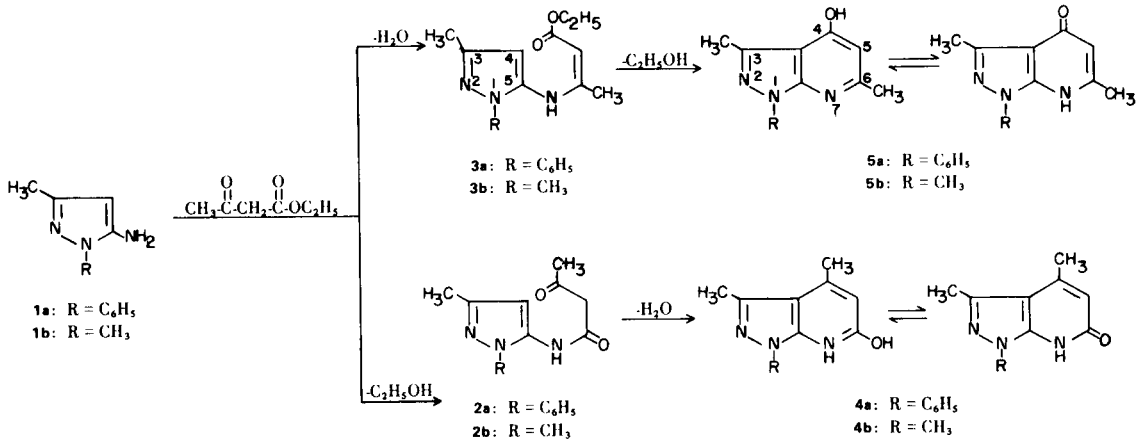
According to Bülow (1), Makisumi (2) and Dorn and Zubek (3,4), the condensation carried out in refluxing glacial acetic acid yielded pyrazolopyridones possessing the 4-pyridone structure **5**. While no explanation was offered by Bülow (1) for his assignments, the rest of the investigators (2-4) based their arguments on the fact that the isolated crotonate intermediate **3** could be cyclized to the same product **5** by heating at reflux with acetic acid, ethylene glycol or ethylene glycol monomethyl ether.

However, Tabak and coworkers (5,6) suggested the 2-pyridone structure **4a** for their product resulting from the condensation of **1a** with ethyl acetoacetate carried out under identical conditions as described in (1-4). Their findings were supported by the fact that heating the synthetic intermediate **2a** in sulfuric acid yielded a product identical to that of Bülow's pyrazolopyridone and having the structure **4a** rather than **5a**. This assumes no conversion of **2a** to **3a**. On the other hand, Tabak (6) cyclized **3a** by addition to boiling Dowtherm producing the pyrazolo-4-pyridone **5a** which was not the same as Bülow's product. Hauser and Reynolds (9) have shown that the benzenoid derivatives of the pair **2** and **3** can be interconverted, the formation of **2** being favored by acidic conditions.

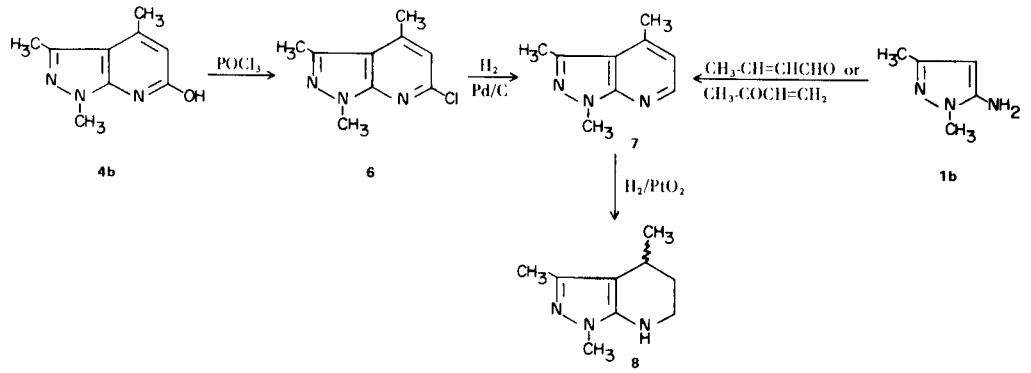
In order to establish fully the assignments of the structures of the products of this condensation, the reaction between a 5-aminopyrazole and ethyl acetoacetate was reinvestigated.

The reaction of the aminopyrazole **1b** with ethyl acetoacetate in refluxing acetic acid yielded a product which was identified as **4b** while cyclization of a synthetic sample of **3b** by gradual addition to refluxing Dowtherm, afforded the isomeric pyrazolopyridone **5b**. On the other hand, **3b**

(SCHEME I)



(SCHEME II)



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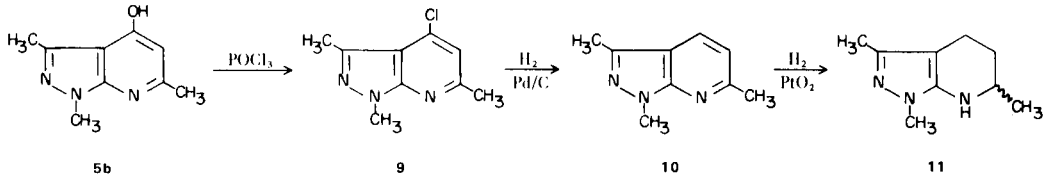
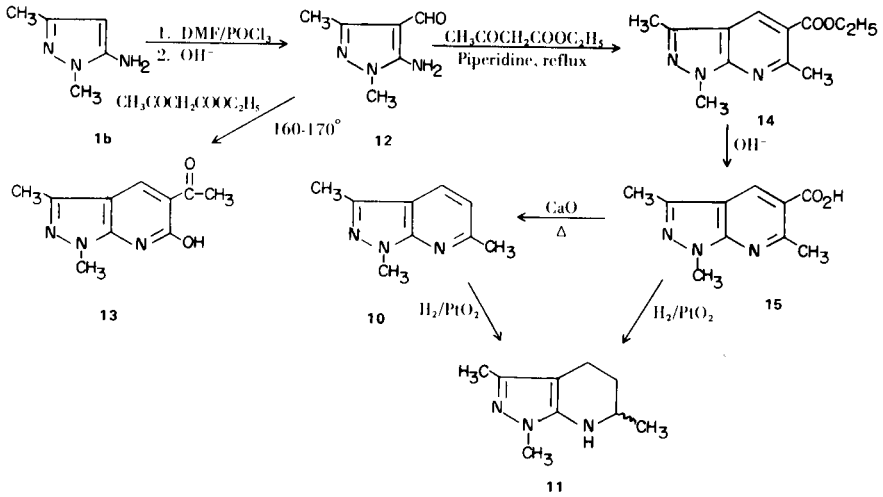


(SCHEME IV)



when heated under reflux in glacial acetic acid or in ethylene glycol monomethyl ether yielded **4b**, indicating that crotonate **3b** had been converted to **2b** prior to cyclization. These data are in full accordance with the findings of Tabak *et al.* (5,6) and Hauser and Reynolds (9).

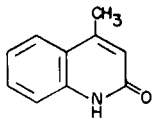
The products **4b** and **5b** were identified as their tetrahydropyrazolopyridine derivatives respectively (Schemes II, III, and IV). A sample of **4b** was converted to the chloro derivative **6**, which in turn was catalytically hydrogenolyzed to the pyrazolopyridine derivative **7** (Scheme II). The latter could also be obtained by reacting **1b** with either crotonaldehyde or methyl vinyl ketone (10). Further hydrogenation of **7** over platinum oxide yielded the tetrahydropyrazolopyridine **8** having a m.p. of 106.5-107.5°.

In an analogous fashion, **5b** yielded the chloro derivative **9**, pyrazolopyridine **10** and finally the tetrahydropyrazolopyridine **11**, exhibiting a m.p. of 130.5-132.0° (Scheme III).

The tetrahydro derivative **11** was also prepared by a separate route (Scheme IV) whereby **1b** was formylated by the aid of the Vilsmeier reagent and hydrolyzed under basic conditions to yield the aminoaldehyde **12** (11). The latter could not be obtained sufficiently pure and was characterized as its derivative **13** (12,13). Treatment of **12** with ethyl acetoacetate under classical base-catalyzed Friedländer conditions yielded the ester **14** which, after

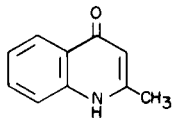
hydrolysis to acid **15** and decarboxylation, afforded **10**, identical to the one prepared from **5b** (Scheme III). Finally, the tetrahydro compound **11** was obtained from **10** or directly from **15** by hydrogenation over platinum oxide. The product obtained gave a m.p. of 130.5-132.0° and was identical to **11** prepared in Scheme III.

Additional proof for the assignment of the structures of compounds **4b** and **5b** was obtained from ^{13}C-nmr spectral data (14). By comparing the significant difference between the carbonyl chemical shifts of the isomeric models 4(2)-methyl-2(4)-quinolones (**16**,**17**) (15), assignments could be made on the basis of a similar difference observed with the isomeric pyrazole compounds **4b** and **5b**.



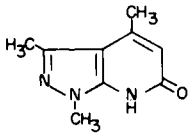
16

δ CO = 162.9 ppm



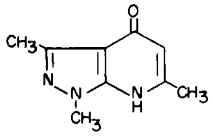
17

δ CO = 177.9 ppm



4b

δ CO = 163.2 ppm



5b

δ CO = 178.5 ppm

The observed carbonyl chemical shifts closely match those of the two model compounds and clearly support the proposed structures.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The pmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm (δ). Signals assigned to protons from NH and OH groups disappeared after exchange in deuterium oxide. The ^{13}C-nmr spectra were obtained in DMSO-d_6 solutions at 100°. A Varian XL-100 FT spectrometer was used for the two pyrazole compounds and a Bruker HFX-10 spectrometer was employed for the model compounds. Infrared spectra were recorded on a Perkin-Elmer model 521 spectrophotometer and were consistent with the structures assigned. 5-Amino-1,3-dimethylpyrazole was prepared according to the method of Taylor and Hartke (16). All solvents and chemicals were of reagent and analytical grade.

Ethyl 3-(1,3-dimethyl-5-pyrazoleamino)crotonate (**3b**).

Method A.

Based on a procedure by Reynolds and Hauser (17), a mixture of 22.2 g. (0.20 mole) of 5-amino-1,3-dimethylpyrazole, 26.0 g. (0.20 mole) of ethyl acetoacetate, 150 ml. of benzene, and 1 ml. of glacial acetic acid was refluxed under a water separator overnight, during which time the theoretical amount of water was collected. The reaction mixture was allowed to cool, filtered and concentrated *in vacuo* to a yellow oil. Residual volatiles were removed at 100° and 1 mm-Hg for 1.5 hours. The crude ester solidified upon cooling to give 40.5 g. (90%) of a yellow solid with m.p. 40-47°; pmr δ (deuteriochloroform): 10.08 (1H, broad singlet, NH), 5.79 (1H, singlet, C_4-H), 4.75 (1H, singlet, CH=), 4.08 (2H, quartet, $COOCH_2CH_3$), 3.63 (3H, singlet, N-CH_3), 2.18 (3H, singlet, C_3-CH_3), 1.88 (3H, singlet, C-CH_3), and 1.25 (3H, triplet, $COOCH_2CH_3$).

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.24; H, 7.43; N, 18.83.

Method B.

Following again a procedure of Hauser and Reynolds (9), a mixture of 22.2 g. (0.20 mole) of 5-amino-1,3-dimethylpyrazole, 26.0 g. (0.20 mole) of ethyl acetoacetate, 70 g. of Drierite, four drops of glacial acetic acid and 75 ml. of absolute ethanol was stirred under reflux on the steam bath for 3.5 hours. The Drierite was removed by filtration, and the solvent evaporated at 40° *in vacuo*. The residue obtained, a golden colored oil, crystallized within a short time to give 40.9 g. (92%) of the crude crotonate, identical (m.m.p., ir, pmr) with the product obtained from Method A.

6-Hydroxy-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**4b**).

Method A.

Following a procedure of Dorn and Zubek (4), a mixture of 111.0 g. (1.0 mole) of 5-amino-1,3-dimethylpyrazole, 133.0 g. (1.02 mole) of ethyl acetoacetate and 500 ml. of glacial acetic acid was heated on the steam bath for 3-4 hours and later heated at reflux for 15 minutes. The reaction mixture was cooled, filtered, the harvested crystals were washed with ethanol, and finally dried *in vacuo* at 100°. The yield was 95.0 g. (53%), m.p. 285-286°; pmr δ (trifluoroacetic acid): 6.75 (1H, broad singlet, C_5-H), 4.28 (3H, singlet, N-CH_3), 2.91 (3H, singlet, C_3-CH_3), and 2.76 (3H, singlet, C_4-CH_3).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.25; N, 23.71. Found: C, 61.09; H, 6.25; N, 23.81.

Method B (4).

A solution of 11.1 g. (0.05 mole) of ethyl 3-(1,3-dimethyl-5-pyrazoleamino)crotonate (**3b**) in 50 ml. of ethylene glycol monoethyl ether was heated under reflux for 6.5 hours, cooled and concentrated *in vacuo* to a small volume. The concentrate was diluted with ether and the crystalline material collected, washed with ether, and dried. The product obtained was identical (m.m.p., ir, pmr) with that obtained from Method A. The same product was obtained upon refluxing the crotonate in glacial acetic acid for 0.5 hour.

4-Hydroxy-1,3,6-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**5b**).

A solution of 22.3 g. (0.10 mole) of ethyl 3-(1,3-dimethyl-5-pyrazoleamino)crotonate (**3b**) in 45 ml. of Dowtherm was added slowly to 45 ml. of stirred, refluxing (250-260°) Dowtherm (1:1 mixture of diphenylether-biphenyl) according to a procedure described by Hauser and Reynolds (9). Refluxing was continued for another 20 minutes, the reaction mixture allowed to cool, and diluted with 200 ml. of petroleum ether (b.p. 63-68°). The crude product was collected, washed with petroleum ether, and crystallized from 175 ml. of hot water with Norite treatment to give, after drying at 100° *in vacuo*, 9.9 g. (56%) of **5b**, m.p. 276-277°; pmr δ (trifluoroacetic acid): 6.96 (1H, singlet, C_5-H), 4.26 (3H, singlet, N-CH_3), 2.88 (6H, singlet, C_3-CH_3 and C_6-CH_3).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.25; N, 23.71. Found: C, 61.14; H, 6.36; N, 23.85.

6-Chloro-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**6**).

Using the procedure of Dorn and Zubek (4), 65.3 g. (0.36 mole) of 6-hydroxy-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**4b**), 800 ml. of phosphorus oxychloride and 18 ml. of pyridine were reacted at 160° in a sealed pressure vessel for 6 hours. After cooling to room temperature, the dark reaction mixture was concentrated *in vacuo* to remove most of the excess phosphorus oxychloride, and the residue added to an ice-water mixture. The aqueous solution was neutralized with concentrated ammonium hydroxide solution, and the crude product extracted into 2 l. of ether. The ether layer was dried over anhydrous magnesium sulfate and decolorized with Darco. Removal of the ether gave 61.0 g. (86%) of the chloro derivative as a colorless powder with m.p. 96.0-96.5°; pmr δ (deuteriochloroform): 6.85 (1H, singlet, C_5-H), 4.01 (3H, singlet, N-CH_3), 2.65 (6H, singlet, C_3-CH_3 and C_4-CH_3).

Anal. Calcd. for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; Cl, 18.12. Found: C, 55.53; H, 5.40; N, 21.56; Cl, 17.97.

1,3,4-Trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**7**).

Method A.

The chloro compound **6** (19.5 g., 0.10 mole) dissolved in 500 ml. of absolute ethanol, was hydrogenolyzed in the presence of 28 ml. of triethylamine and 2.0 g. of 5% palladium on activated carbon under 3 atmospheres of hydrogen pressure in a Parr hydrogenation apparatus until uptake was complete (less than 1 hour). The catalyst was removed by filtration and the solution concentrated *in vacuo*. Trituration of the residue in 100 ml. of water followed by filtration and air drying gave the dechlorinated material in a yield of 15.5 g. (96%), m.p. 56-57°; pmr δ (deuteriochloroform): 8.33 (1H, doublet, C_6-H), 6.78 (1H, doublet, C_5-H), 4.05 (3H, singlet, N-CH_3) and 2.63 (6H, singlet, C_3-CH_3 and C_4-CH_3).

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.06. Found: C, 66.87; H, 6.73; N, 26.13.

Method B.

Employing a modification of a procedure described by Badger and coworkers (10), a solution of 22.2 g. (0.20 mole) of 5-amino-1,3-dimethylpyrazole in 100 ml. of glacial acetic acid was cooled while 2 ml. of concentrated sulfuric acid was introduced with stirring. To this, a solution of 15.0 g. (0.21 mole) of anhydrous crotonaldehyde in 30 ml. of glacial acetic acid was added and the resulting mixture stirred for 0.5 hour at room temperature and then heated at reflux for another hour. The intense red colored reaction mixture was concentrated *in vacuo*, the residue dissolved in 300 ml. of water, rendered basic with 15% sodium hydroxide, and extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate and finally the solvent removed *in vacuo*. Distillation of the residue at reduced pressure gave 5.4 g. (17%) of a material boiling at 80-90° at 1.0 mm-Hg identical (m.m.p., pmr) with the product obtained in Method A.

Method C (10).

A solution of 33.3 g. (0.30 mole) of 5-amino-1,3-dimethylpyrazole in 50 ml. of glacial acetic acid was stirred while being treated dropwise at ice bath temperature with 30 g. of concentrated sulfuric acid in 100 ml. of glacial acetic acid. To the resulting solution, 23.0 g. (0.33 mole) of methyl vinyl ketone in 100 ml. of glacial acetic acid was added and the reaction mixture stirred for 0.5 hour at room temperature and then at 90° for one hour. The acetic acid was removed *in vacuo* at 70°, the residue dissolved in water and neutralized with an aqueous solution of potassium carbonate. The mixture was extracted twice with chloroform, the extracts dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Distillation of the residue at reduced pressure gave a 4.8 g. (10%) fraction with b.p. 73-83° at approximately 0.1-0.2 mm-Hg which solidified and was identical (m.m.p.) with the products obtained from Methods A and B.

4,5,6,7-Tetrahydro-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**8**).

A solution of 15.5 g. (0.0965 mole) of 1,3,4-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**7**) in 240 ml. of glacial acetic acid containing 8 ml. (one equivalent) of concentrated hydrochloric acid and 1.5 g. of platinum oxide was hydrogenated on a Parr apparatus under 3 atmospheres of hydrogen pressure until the calculated amount of hydrogen was consumed as measured by pressure drop. The solution was filtered to remove the catalyst and most of the acetic acid was removed *in vacuo* at 70°. The residue was taken up in water, the solution neutralized with 15% sodium hydroxide solution and the precipitate obtained was crystallized from petroleum ether (b.p. 63-68°) to afford 8.7 g. (55%) of the tetrahydro derivative **8**, m.p. 106.5-107.5°; pmr δ (deuteriochloroform): 3.50 (3H, singlet, N-CH_3), 3.40 (1H, broad multiplet, NH), 3.23 (2H, multiplet, C_6-CH_2), 2.75 (1H, multiplet, C_4-CH), 2.15 (3H, singlet, C_3-CH_3), 1.68 (2H, multiplet, C_5-CH_2), and 1.15 (3H, doublet, C_4-CH_3).

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.30; H, 9.16; N, 25.24.

4-Chloro-1,3,6-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**9**).

This compound was prepared from **5b** in the same manner as **6** and was obtained as a cream-colored solid in a yield of 78%, m.p. 66.5-67.5°; pmr δ (deuteriochloroform): 6.85 (1H, singlet, C_5-H), 4.00 (3H, singlet, N-CH_3), 2.65, 2.58 (6H, singlets, C_3-CH_3 and C_6-CH_3).

Anal. Calcd. for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; Cl, 18.12. Found: C, 55.22; H, 5.06; N, 21.57; Cl, 18.25.

1,3,6-Trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**10**).

Method A (18).

The finely pulverized potassium salt of acid **15** (29.7 g., 0.14 mole) was thoroughly mixed with 105 g. of calcium oxide and the mixture heated in a copper flask, fitted for distillation, over the full flame of a Meker burner. The decarboxylation product was collected as an orange colored distillate in a yield of 14.8 g. (66%). This sample was dissolved in ether, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to afford **10**, pmr δ (deuteriochloroform): 7.70 and 6.80 (2H, 2 doublets, C_5-H and C_4-H), 4.01 (3H, singlet, N-CH_3), 2.61 (3H, singlet, C_6-CH_3) and 2.46 (3H, singlet, C_3-CH_3).

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.06. Found: C, 66.82; H, 7.12; N, 25.90.

Method B.

The chloro compound **9** (13.7 g., 0.07 mole) was hydrogenolyzed in a manner identical to that described for compound **7**. After removal of the catalyst and solvent, the residue was taken up in 200 ml. of ether and the triethylamine hydrochloride removed by filtration. Evaporation of the solvent left 9.0 g. (79%) of golden colored oil identical (pmr, ir) with the product obtained in Method A.

4,5,6,7-Tetrahydro-1,3,6-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**11**).

Method A.

A solution of 34.3 g. (0.167 mole) of acid **15** in 500 ml. glacial

acetic acid containing 13.0 ml. hydrochloric acid and 3.4 g. platinum oxide was hydrogenated under 3 atmospheres hydrogen pressure until uptake was complete. The catalyst was removed by filtration and the filtrates concentrated *in vacuo*. The colorless syrupy residue was taken up in a small volume of water, rendered alkaline to *p*H 11.0 with sodium hydroxide solution, and the alkaline solution extracted several times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue, a colorless solid, was crystallized from petroleum ether (b.p. 63-68°)-benzene (10:1) to give 22.2 g. (79%) of the tetrahydro compound as colorless needles, m.p. 130.5-132.0°; pmr δ (deuteriochloroform): 3.53 (3H, singlet, N-CH_3), 3.35 (2H, broad signal, NH, C_6-H), 2.45 (2H, multiplet, C_4-CH_2), 2.11 (3H, singlet, C_3-CH_3), 1.65 (2H, multiplet, C_5-CH_2) and 1.25 (3H, doublet, C_6-CH_3).

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.38; H, 9.13; N, 25.23.

Method B.

To a solution of 7.8 g. (0.048 mole) of **10** in 150 ml. glacial acetic acid containing 4 ml. concentrated hydrochloric acid, 0.75 g. platinum oxide was added and the mixture hydrogenated under 3 atmosphere hydrogen pressure until the calculated amount of hydrogen was consumed. After removal of the catalyst by filtration, the acetic acid was removed *in vacuo* at 70°. The residue was dissolved in a small volume of water and alkalinized with 15% aqueous sodium hydroxide solution to *p*H 11.0. A cream-colored solid was collected and dried at 70° *in vacuo*. The yield of the tetrahydro compound was 6.4 g. (81%), identical (m.p., m.m.p.) with the product obtained from Method A.

5-Amino-1,3-dimethyl-4-formylpyrazole (**12**) (11).

A solution of 55.5 g. (0.50 mole) of 5-amino-1,3-dimethylpyrazole in 146 g. (2.0 mole) of dimethylformamide was treated at 80° with 321 g. (2.1 mole) of phosphorus oxychloride in a dropwise fashion over a period of 1.5 hours with stirring. The mixture was stirred at 80-90° for an additional 2 hours, and then allowed to remain at room temperature overnight. After pouring it onto ice, the reaction mixture was neutralized with 50% sodium hydroxide solution. The red oily layer which separated was extracted with several portions of chloroform. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, concentrated and distilled at 0.1-0.3 mm-Hg to give 67.7 g. (70%) of the dimethylaminomethylene derivative as an oil which slowly solidified, b.p. 133-140°; m.p. 51-55°.

Anal. Calcd. for $C_9H_{14}N_4O$: C, 55.65; H, 7.26; N, 28.84. Found: C, 55.88; H, 7.44; N, 29.14.

A mixture of 57.9 g. (0.29 mole) of the above dimethylaminomethylene derivative, 300 ml. of 20% aqueous sodium hydroxide solution and 200 ml. ethanol was stirred at reflux temperature for 2 hours. Two layers separated while the solution was hot. The hot ethanolic layer was separated, concentrated, the residue triturated in a minimum amount of water, and the crude aminoaldehyde collected as a solid of uncertain purity (m.p. 55-85°). This material was used in subsequent reactions without further purification.

5-Acetyl-1,3-dimethyl-6-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine (**13**).

A mixture of 13.9 g. (0.10 mole) of 5-amino-4-formyl-1,3-dimethylpyrazole (**12**) and 150 ml. of ethyl acetoacetate was heated for one hour in an oil bath maintained at 160-170° (12,13). The solid obtained upon cooling was washed with ethanol and crystallized from dimethylformamide. The product was washed with ethanol and dried at 90° *in vacuo* to give 6.8 g. (33%) of the ketone with m.p. 243-244°, pmr δ (deuteriochloroform): 13.35 (1H, singlet, OH), 8.43 (1H, singlet, C_4-H), 3.97 (3H, singlet, N-CH_3), 2.74 (3H, singlet, $COCH_3$), 2.54 (3H, singlet, C_3-CH_3).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.47. Found: C, 58.58; H, 5.43; N, 20.32.

5-Carbethoxy-1,3,6-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**14**).

A stirred mixture of 13.9 g. (0.10 mole) of 5-amino-1,3-dimethyl-4-formylpyrazole (**12**), 19.6 g. (0.15 mole) of ethyl acetoacetate and 150 ml. of piperidine was heated at reflux for 3 hours, filtered while hot, and allowed to cool. Upon concentration, a pale yellow substance separated. Crystallization from petroleum ether (b.p. 63-68°) afforded 10.6 g. (46%) of the ester as colorless needles, m.p. 134.5-135.0°; pmr δ (deuteriochloroform): 8.58 (1H, singlet, C_4-H), 4.42 (2H, quartet, $COOCH_2CH_3$), 4.06 (3H, singlet, N-CH_3), 2.95 (3H, singlet, C_6-CH_3), 2.57 (3H, singlet, C_3-CH_3), and 1.45 (3H, triplet, $COOCH_2CH_3$).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 62.06; H, 6.35; N, 18.08.

1,3,6-Trimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (**15**).

A mixture of 43.4 g. (0.186 mole) of ester **14**, 100 ml. of 6*N* potassium hydroxide solution, and 300 ml. of ethanol was stirred at reflux temperature for two hours, cooled and acidified with 6*N* hydrochloric acid. The crude acid was collected, washed with water, and crystallized from dimethylformamide. After drying *in vacuo* at 90°, the yield of the acid was 34.3 g. (90%); m.p. 293-296°; pmr δ (dimethylsulfoxide-d_6): 11.50-14.00 (1H, broad singlet, COOH), 8.55 (1H, singlet, C_4-H), 3.96 (3H, singlet, N-CH_3), 2.85 (3H, singlet, C_6-CH_3), 2.50 (3H, singlet, C_3-CH_3).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.47. Found: C, 58.77; H, 5.68; N, 20.47.

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