

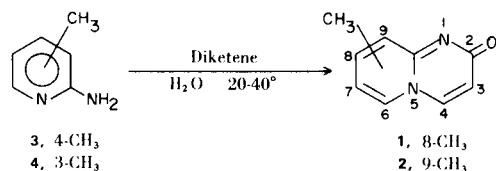
The Reactions of 2-Amino-4-picoline and 2-Amino-3-picoline
with Diketene, Ethyl Acetoacetate, and Ethyl β -Aminocrotonate

Harry L. Yale (1), Barbara Toeplitz, J. Z. Gougoutas (2), and Mohindar Puar

Squibb Institute for Medical Research, Princeton, New Jersey 08540

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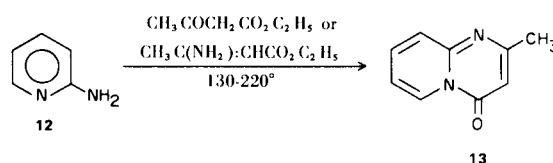
In 1969, Stöckelmann, Specker, and Riepe (3) reported the synthesis of 2,8-dimethyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (1) m.p. 120° in 97% yield, and 2,9-dimethyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (2) m.p. 73° in 90% yield, via the reactions of 2-amino-4-picoline (3), and 2-amino-3-picoline (4), with diketene, at 20-40°. This report was a significant development in view of our interest in the synthesis of derivatives of this heterocycle and the isomeric 4-one. We repeated this work precisely as described; however, our results vary significantly from those reported. The corresponding products obtained were 5, m.p. 136.0-137.5°, in 16% yield, and 6, m.p. 129-130°, in 6% yield; the recovery of unreacted 3 was 80% and of unreacted 4 was 79%. The products, 5 and 6, were identical in m.p., ir, uv, and pmr spectra, with the products 7 and 8, respectively, obtained as described by Antaki and Petrow (4) when 3 and 4 were reacted with ethyl acetoacetate (9) or ethyl β -aminocrotonate (10), at 130-220°. We have also obtained a product identical with 7 from 3 and *N,N*-dimethylacetoacetamide at 175°.



A comparison of the uv and pmr spectra of 1 (5) with the corresponding spectra of 5 and 7 in the same solvents, showed that the spectra were identical. Further identification was seen in their ir spectra; 1, in carbon tetrachloride solution, was reported (3) to show carbonyl absorption at 1697 cm⁻¹ while 5 and 7, in the same solvent, showed that absorption at 1698-1702 cm⁻¹. Finally, 5 gave a hydrobromide, 11, whose m.p., ir, and pmr spectra were identical with the hydrobromide obtained from 7.

Earlier synthetic work by Khitrick (6), Antaki and Petrow (4), and uv spectral studies by Adams and Pachter (7), had clearly established that the reaction of 2-aminopyridine (12) and 9 or 10 at 130-220°, gave 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (13). While it was reasonable to infer that 3 and 4 would react with 9 and 10, under the same conditions, to yield the corres-

ponding 4-one derivatives, no structural elucidation, either chemical or spectral, for 7 or 8 was presented by these earlier workers. The two approaches that we have employed to establish that 7 and 8, and consequently, 5 and 6 were, in fact, 4-ones involved X-ray crystallographic analysis of a single crystal of 11 and the effect of Eu(fod)₃ shift reagent (8) on the pmr spectra of 5 and 6. These results are summarized below.



X-Ray Crystallography.

Crystals of 11 grown from butyronitrile were found to be monoclinic with $a = 8.49$, $b = 6.78$, $c = 9.59$ Å, and $\beta = 102.3^\circ$. Systematically absent reflections suggested space group P2₁. The crystal density of 1.525 gm./cm³, measured by flotation in mixed hexane and carbon tetrachloride, together with the calculated unit cell volume of 552 Å³, indicated the presence of two molecules per unit cell.

Our expectation that the relatively planar molecular structure, when viewed in projection, would be sufficiently resolved to allow a differentiation between an amide carbonyl oxygen atom and a methyl group was realized through an analysis of the *hol* diffraction data.

These intensities (Cu K α) were recorded photographically and estimated by visual comparison with a reference intensity scale. One hundred forty three reflections were recorded, of which one hundred five were used in the final refinement stages. A Patterson map was used to locate the bromine atom and the other non-hydrogen atoms were located on subsequent Fourier maps. Least squares refinements gave an R factor of .13.

Consideration of the relatively greater electron density, and the projected bonding geometry of the atom attached to the 4- position compared to those associated with the 2- position, led to assignment of the amide carbonyl oxygen at the 4-, and the methyl group at the 2- positions.

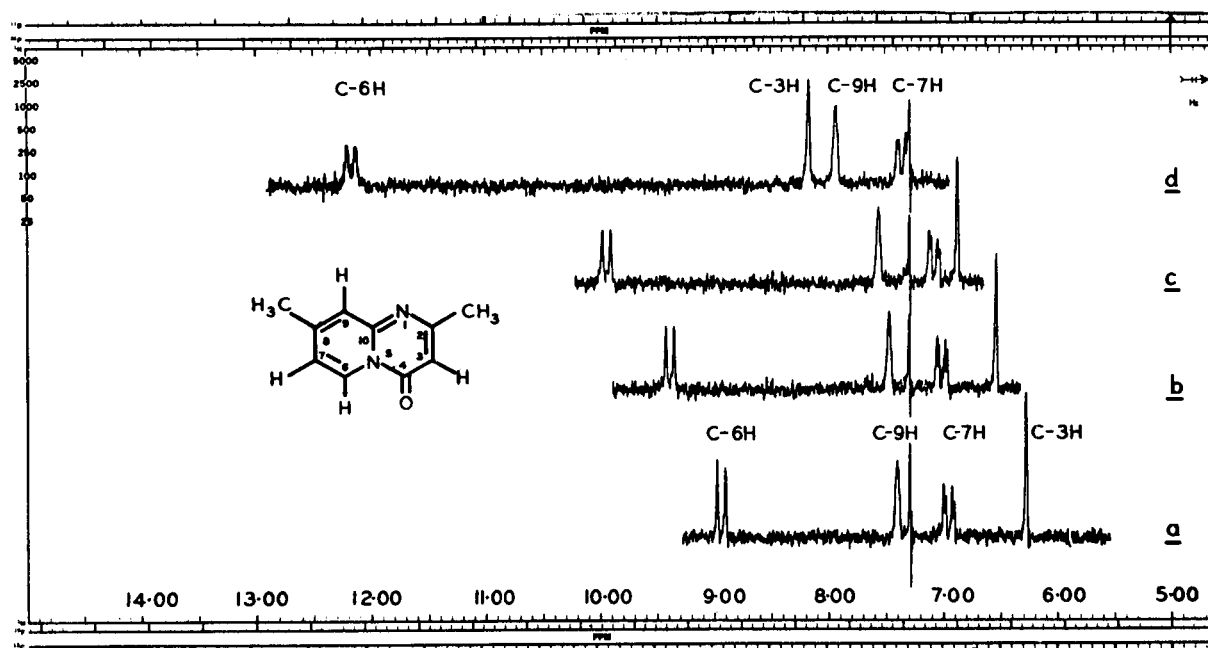


Figure 1. Effect of $\text{Eu}(\text{fod})_3$ on PMR Spectrum of 2,8-Dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Shift Reagent Proton Magnetic Resonance Spectra.

Confirmation of the structure of these pyrido[1,2-a]-pyrimidinones as the -4-ones came from observing the deshielding effects produced by $\text{Eu}(\text{fod})_3$ shift reagent (8) on the normal pmr spectrum of 7. The preferential complexing of this reagent with the carbonyl oxygen of cyclic amides has been demonstrated unequivocally by Neville (9) with several of the pyrimidinone derivatives. Thus, the complexing of the reagent, were the amide oxygen to be at position-2, would deshield predominantly the proton at position-3, while complexing with the carbonyl oxygen at position-4 would deshield predominantly the protons at positions-3 and -6.

The aromatic resonances obtained with 5 are shown in Fig. 1, a: δ 6.28 (s, 1H, H_3), δ 6.96 (q, $J = 6.0, 2.0$ Hz, 1H, H_7), δ 7.39 (d, 1H, H_9), δ 8.94 (d, 1H, H_6) (the two CH_3 resonances are seen as two 3-proton singlets at δ 2.44 and 2.48). The addition of $\text{Eu}(\text{fod})_3$, in increments, produced the progressive downfield chemical shifts seen in Fig. 1, b, c, and d; the H_3 and H_6 chemical shifts are most affected, to the extent of ca. 1.9 and 3.2 ppm, respectively, and these are significantly larger than those induced on the H_7 and H_9 protons, ca. 0.4 and 0.5 ppm.

Similar results were obtained by the use of the same shift reagent with 6. The original spectrum showed the following resonances: δ 6.33 (s, 1H, H_3), δ 6.98 (t, $J = 7.0, 7.0$ Hz, 1H, H_7), δ 7.56 (q, $J = 7.0, 1.5$ Hz, H_8), δ 8.93 (q, $J = 7.0, 1.5$ Hz, H_6) (the two CH_3 resonances are

seen as two 3-proton singlets at δ 2.47 and 2.58). The addition of $\text{Eu}(\text{fod})_3$, in increments, produced the progressive downfield chemical shifts, ca. 0.4, 0.7, 0.1, and 0.1 ppm for the H_3 , H_6 , H_7 and H_8 protons, respectively.

EXPERIMENTAL

The ir spectra were obtained in mineral oil mulls, or in deuteriochloroform or carbon tetrachloride solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on Perkin-Elmer R12B and Varian Associates XL-100-15 spectrophotometers. The uv spectra were determined on a Cary 15 Recording Spectrophotometer. The microanalyses were carried out by Mr. Joseph Alicino and his associates of this Institute. The melting points were determined in capillary tubes in an electrically heated oil bath and are not corrected.

2,8-Dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (7).

(a) From 2-Amino-4-picoline (3), and Ethyl Acetoacetate.

A solution of 10.0 g. (0.106 mole) of 3 and 20.0 g. (0.154 mole) of ethyl acetoacetate was heated for 8 hours by means of an oil bath maintained at 175° . The reflux condenser was removed periodically to allow vapors to escape. The reaction mixture solidified on cooling. The crude solid was triturated with 50 ml. of pentane, and filtered to give 12.0 g. of solid, m.p. $124-127^\circ$. Recrystallization from 600 ml. of cyclohexane gave 7.45 g. (40% yield) of 7, m.p. $136.0-137.5^\circ$, ν (carbon tetrachloride): 1698-1702 (s), 1650 (s), 1415 (s), (20 mg./ml., 0.2 mm. cell); λ (H_2O , 1%) 334, 325 (sh), 307 (sh), 246, 239, 233 $m\mu$ [ϵ (10^{-3}) 12.5, 11.2, 8.2, 10.0, 11.7, 11.2]; pmr (deuteriochloroform): δ 2.44 and 2.48 (two s, each 3H, two CH_3 groups), δ 6.28 (s, 1H, H_3), δ 6.96 (q, $J = 6.0, 2.0$ Hz, 1H, H_7)

δ 7.39 (d, 1H, H_9), δ 8.94 (d, 1H, H_6).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.72; N, 16.07.

(b) From **3** and *N,N*-Dimethylacetoacetamide.

(a') A solution of 10.0 g. (0.106 mole) of **3** and 20.0 g. (0.154 mole) of *N,N*-dimethylacetoacetamide were heated as in (a). The reaction mixture did not solidify, hence it was distilled collecting the fraction, b.p. 135-140° (1 mm.). This fraction solidified spontaneously. It weighed 6.0 g., m.p. 103-117°. When heated *in vacuo* at 56°, unreacted **3** sublimed; the residue from the sublimation weighed 5.0 g., m.p. 130-133°. Recrystallization from 440 ml. of diisopropyl ether gave 3.3 g. of **7** (29% yield), m.p. and mixture m.p. with (a), 136.0-137.5°. The ir and pmr spectra obtained with the product were superimposable on the same spectra obtained with the product from (a).

(b') The reaction described in (a') was repeated except that a slow stream of nitrogen gas was used to sweep through the reaction mixture and from there into an ice-cooled water scrubber. After 8 hours the water scrubber contained 0.05 mole of dimethylamine. The cooled reaction mixture was dissolved in 20 ml. of glacial acetic acid, cooled in ice, and treated dropwise with stirring with 25 ml. of 32% hydrobromic acid in glacial acetic acid. The precipitated hydrobromide was filtered and dried to give 12.5 g. of solid, m.p. >300°. This was recrystallized from 1700 ml. of acetonitrile to give 10.5 g. (39% yield) of **11**, m.p. >300°; ν (mull) 2800-2600 (broad) (s), 1735 (s), 1725 (s), 1650 (s), 1510 (s) cm^{-1} ; pmr (DMSO- d_6) δ 2.56, 2.60 (two s, each 3H, two CH_3 groups), δ 6.0 (broad m, 1H, H^+), δ 6.55 (s, 1H, H_3), δ 7.60 (q, 1H, H_7), δ 7.80 (d, 1H, H_9), δ 9.06 (d, 1H, H_6) (this pmr spectrum was run on a Varian T-60).

Anal. Calcd. for $C_{10}H_{10}N_2O \cdot HBr$: C, 47.08; H, 4.35; N, 10.98; Br, 31.33. Found: C, 47.37; H, 4.47; N, 11.13; Br, 31.25.

To a solution of 0.5 g. of sodium bicarbonate in 10 ml. of water was added 0.50 g. of **11** and the mixture stirred for 10 minutes. The solid was filtered, washed with water, and dried to give 0.36 g. of solid, m.p. 134-136°. Recrystallization from cyclohexane gave **7**, m.p. 136.0-137.5°, alone or mixed with **7** prepared as in (a). The ir and pmr spectra were identical in all respects with those obtained with the product from (a).

Neither **3** nor *N,N*-dimethylacetoacetamide, in acetic acid solution, when treated with 32% hydrobromic acid in acetic acid, gave a precipitate.

(c) From **3** and Diketene.

To a suspension of 7.1 g. (0.075 mole) of **3**, in 65 ml. of distilled water at 25°, was added dropwise 5.5 g. (0.065 mole) of diketene [distilled immediately before use, b.p. 69-70° (95 mm.); reported (10), b.p. 69.5° (99 mm)]. The temperature rose to 34° during the 30 minute addition, and dropped spontaneously to 25° during 0.5 hour. A crystalline solid began to separate after 1 hour. The mixture was cooled for 18 hours, the solid filtered, and air-dried to give 1.64 g. of solid, m.p. 134.0-135.5°. A recrystallization from 80 ml. of cyclohexane gave 1.40 g. (16% yield) of **7**, m.p. 136.0-137.5°, alone or mixed with **7** prepared in (a). The ir and pmr spectra of this product were identical in all respects with the spectra obtained with (a).

The aqueous filtrate from the above solid was concentrated to dryness *in vacuo*. The residue weighed 6.1 g. This was sublimed at 56° (0.5 mm.) to give 5.70 g. (80% recovery) of **3**, m.p. and mixture m.p. 96.0-97.5°. The residue from the sublimation was a brown tar.

2,9-Dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (**8**).

(a) From 2-Amino-3-picoline (**4**) and Ethyl Acetoacetate.

A solution of 21.6 g. (0.23 mole) of **4** and 52.0 g. (0.4 mole) of ethyl acetoacetate was heated at 170° for 4 hours and then concentrated *in vacuo* to remove excess ethyl acetoacetate. The residue was dissolved in benzene and passed through a column of 200 g. of alumina (Matheson, Coleman and Bell, 80-200 mesh, Chromatographic Grade). The eluate that collected was concentrated and the residue distilled to give 0.8 g. of solid, b.p. 105-111° (0.4 mm.). This was sublimed to give 0.70 g. of solid, m.p. 121-124° and that solid was recrystallized from 22 ml. of diisopropyl ether to give 0.36 g. (1% yield) of **8**, m.p. 129-130°; ν (deuteriochloroform): 1685-1670 (s), 1633 (m), 1462 (s), 1456 (s), 1420 (m) cm^{-1} ; pmr (deuteriochloroform), δ 2.47 and 2.58 (two s, each 3H, two CH_3 groups), δ 6.33 (s, 1H, H_3), δ 6.98 (t, J = 7.0, 7.0 Hz, H_7), δ 7.56 (q, J = 7.0, 1.5 Hz, H_8), δ 8.93 (q, J = 7.0, 1.5 Hz, H_6).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 68.74; H, 5.70; N, 16.15.

(b) From **4** and Diketene.

To 7.1 g. (0.075 mole) of **4** in 65 ml. of distilled water at 20° was added dropwise 5.5 g. (0.065 mole) of freshly distilled diketene. The addition required 30 minutes and during this period the internal temperature rose to 39°. Stirring continued as the temperature dropped spontaneously to 20°. No solid had separated after 24 hours at 20° and no crystallization could be induced by ice-cooling. The solution was concentrated to dryness *in vacuo* by means of a water bath at 40°. The semisolid residue weighed 8.4 g. All attempts to recrystallize this material were unsuccessful. Trituration with 25 ml. of diisopropyl ether gave 1.1 g. of solid, m.p. 120-123°. This was sublimed at 95° (0.5 mm.) to give 0.97 g. of a colorless solid, m.p. 124-126°. Recrystallization from 75 ml. of diisopropyl ether gave 0.77 g. (6% yield) of **8**, m.p. 129-130°, alone or mixed with the product from (a). The ir and pmr of the products from (a) and (b) were identical in all respects).

The diisopropyl ether used to triturate the crude reaction product was evaporated to remove the solvent. The residue, 5.6 g. (79% recovery) could not be induced to crystallize but its ir spectrum was identical with that of **4** [the reported m.p. of **4** is 26° (11)].

REFERENCES

- (1) To whom all correspondence should be addressed.
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- (5) Professor Stöckelmann sent us his original uv and pmr spectra of **1** in 1969. On May 10, 1972, we informed him of our findings, and asked him for a sample of his product, m.p. 120°. He has not, however, replied to that letter nor has he sent us the sample.
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