Enamines Derived from the Reactions of 2-Amino-3-(*o*-bromobenzyloxy)pyridine with Esters of Acetoacetic and β-Aminocrotonic Acids. Enamines as Intermediates in the Formation of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones (1,2)

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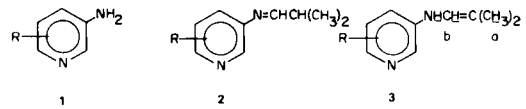
Two stable crystalline enamines, **10** and **11**, have been isolated from the reactions of 2-amino-3-(*o*-bromobenzyloxy)pyridine, **4**, with esters of acetoacetic or β-aminocrotonic acids. The formation of **10** and **11** occurred in the absence of a solvent or in diethylbenzene at 100-175°, and was always accompanied by the formation of the cyclized derivative, 9-(*o*-bromobenzyloxy)-2-methylpyrido[1,2-*a*]pyrimidin-4-one, **12**. Molecular models, ir, and pmr spectra were employed to establish the structure of the enamines and to demonstrate that in solution, **10** and **11** existed as six-membered chelate structures, with intramolecular hydrogen bonding between the NH proton and the ester carbonyl oxygen atom. The thermal cyclization of **10** and **11** to **12** occurred under a variety of conditions: (a) in diethylbenzene at 170-175°, (b) fusion at 175-180° under atmospheric pressure, or (c) heating at 175-180°/1 mm, thus suggesting that an enamine is the intermediate in cyclization reactions that lead to the formation of pyrido[1,2-*a*]pyrimidin-4-ones.

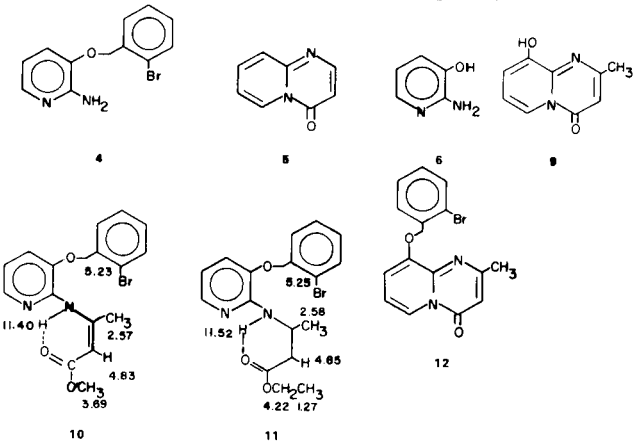
Enamines of 2-, 3-, and 4-aminopyridines are unknown. Recently, Sauleau (3a, b, c) reported that several substituted 3-aminopyridines, **1a-e**, and isobutyraldehyde, gave only the imine, **2**; others, **1f-i**, gave only the enamine, **3**, while **1j** gave mixtures of imine and enamine. In only one instance, **1h**, was the pure enamine isolated; **1h** was characterized by m.p., ir and pmr spectra but was found to be unstable (3d). With **1f**, **1g**, **1i**, and **1j**, the presence of the enamine in a crude distillate of the reaction mixture was inferred by the chemical shifts in the pmr spectra of the resonances attributable to the protons, *Ha*, *Hb*, and N*H* in **3** (4).



1 2 3

1a, R = 5-Br
1b, R = 6-CH_3O
1c, R = 4-C_2H_5O
1d, R = 2,6-$(CH_3)_2$
1e, R = 2,4,6-$(CH_3)_3$
1f, R = 2-Cl
1g, R = 2-C_2H_5O
1h, R = 2-O_2N
1i, R = 1-oxide
1j, R = 4-CH_3O

In this paper, we are reporting the isolation and characterization of several stable, crystalline enamines derived from 2-amino-3-(*o*-bromobenzyloxy)pyridine, **4**. These derivatives were obtained during a program directed toward (a) the synthesis of derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **5** (1,2), and (b) the elaboration of the mechanism by which these bicyclic heterocycles were formed. Our interest in the mechanism was stimulated by the observation that the hydroxyl group in 2-amino-3-pyridinol, **6**, greatly facilitated the cyclization reactions between **6** and either methyl or ethyl acetoacetate, **7a**,**b**, or methyl β-aminocrotonate, **8**, and gave **9**, a crystalline product of high purity, in 80-90% yield, directly from the reaction mixture (2,5). In contrast, **4**, under the same conditions, was significantly less reactive toward **7a**,**b** or **8**, and, with each reagent gave two products in low combined overall yield. These products could be separated by column chromatography on activated

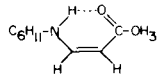


4 5 6 9

10 11 12

alumina. With benzene, the most readily eluting compounds were the enamines, **10** and **11**, followed by the somewhat slower-eluting cyclized derivative, **12**, and, finally, unreacted **4**.

The structures of the enamines, **10** and **11** were established by their elemental analyses and by their ir and pmr spectra. In their ir spectra, the intramolecularly bonded NH stretching band of **10** was seen, in carbon tetrachloride solution at a concentration of 30 mg./ml., as a weak absorption at *ca.* 3280 cm^{-1}; the position of this band remained unchanged when the solution was diluted to 6 mg./ml., and then to 1 mg./ml. In addition, the carbonyl absorption of **10**, again in carbon tetrachloride solution, was seen at 1660 cm^{-1}. These data are significant since Huisgen (6) has reported that in the ir spectrum of **13** (*cis*-form), the *intra*molecularly hydrogen-bonded NH absorption was seen at 3312 cm^{-1} while **14** (*trans*-form) showed the intermolecularly hydrogen-bonded NH absorption at 3442 cm^{-1}. In addition, the carbonyl absorption of **13** was seen at 1660 cm^{-1} while the same absorption was seen in **14** at 1682 cm^{-1}.



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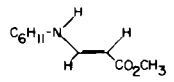

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In a similar manner, the pmr spectrum of **10**, in deuteriochloroform solution, was unaffected as a whole, or, in particular, as to the chemical shift of the NH proton, when the original spectrum solution, at a concentration of 44 mg./ml., was diluted to a concentration of 4.4 mg./ml.; the NH resonance was shifted *ca.* 0.2 ppm upfield in DMSO-d_6 and *ca.* 0.4 ppm downfield in perdeuteriopyridine (7). These pmr data on dilution studies in the same solvent must be considered confirmatory evidence for the existence of strong intramolecular hydrogen-bonding in that compound between the NH proton and the carbonyl oxygen atom. The similarity of the chemical shifts of the several structurally significant protons in **10** and **11**, suggested, also, that the latter compound, likewise, had an NH proton that was hydrogen-bonded intramolecularly to the carbonyl oxygen atom.

Thus, both **10** and **11** are best represented by the six-membered chelate structure shown for them. From another point of view, since Dreiding models of these structures reveal no steric interference with such a six-membered chelate ring formation (8), the stereochemistry of the methyl and hydrogen substituents on the carbon-carbon double bond is again established as *cis*. Again, it would be anticipated from the Dreiding models that the resonances of the protons of the methyl group would be coupled to the resonances of the adjacent vinyl proton. This was demonstrated by observing the Nuclear Overhauser Effect (NOE) produced by saturating the resonance of the methyl protons at δ 2.71 in the DMSO-d_6 solution; the result of this procedure was a marked enhancement (*ca.* 90%) and sharpening of the vinyl proton signal at δ 4.83 (8, 9).

The isolation of **10** and **11** from reactions that also yielded **12**, did not, of itself, establish the enamines as precursors to the cyclic compound. That the enamines were, in all probability, intermediates, was shown by heating pure, crystalline **11** in diethylbenzene at 170-175°; a mixture of **11** and **12** was obtained. Again, fusion of pure **11** at 175-180° also gave a mixture of **11** and **12**. When pure **10** was heated at 130-135°/1 mm, it remained unchanged, but when heated at 175-180°/1 mm, while some of the **10** sublimed, the non-volatile residue was shown to be **12**. These experiments offer evidence that support the concept that the invariable formation of pyrido[1,2-*a*]-pyrimidin-4-ones by the reaction of 2-aminopyridines with **7a,b** or **8** must involve the intermediate formation of an enamine (10).

EXPERIMENTAL

The ir spectra were obtained on 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.

Reaction of 2-Amino-3-(*o*-bromobenzyloxy)pyridine, **4**, with Ethyl Acetoacetate, **7b**. Formation of Ethyl 3-[3-[(*o*-Bromobenzyl)-oxy]-2-pyridyl]amino]crotonate, **11**, and 9-[(*o*-Bromobenzyl)oxy]-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **12**.

A solution of 2.80 g. (0.01 mole) of **4** and 12.00 g. (0.09 mole) of **7b** was heated in an oil bath maintained at 100° for four hours and then concentrated, *in vacuo*, to give 3.90 g. of a dark colored gum. The gum was dissolved in 50 ml. of benzene and chromatographed on a column of 25 g. of activated alumina (Mathieson, Coleman, Bell, Chromatographic Grade, 80-200 mesh) prepared in benzene. Concentration of the first 75 ml. of benzene eluate gave 0.80 g. of a pale yellow solid that was recrystallized from 55 ml. of pentane to give 0.52 g. (13% yield) of the enamine, **11** m.p. 87-89°; ir (deuteriochloroform): ν 3262 (w), 1650 (s), 1620 (s), 1590 (s), 1563 (m), 1500 (w), 1458 (s), 1435 (s), 1420 (s) cm^{-1}; uv λ max (ethanol): 278 (sh), 284, 329 mμ (ε, 6850, 7900, 30,000); pmr (deuteriochloroform): δ 1.27, t (J = 7 Hz), 3H, CH_3CH_2, 2.58 (m, 3H, $=CCH_3$), 4.22 [q (J = 7 Hz), 2H, CH_3CH_2], 4.85 (m, 1H, =CH), 5.25 (s, 2H, *o*-$BrC_6H_4CH_2$), 6.68-8.16 (m, 7 Ar-H), 11.52 [broad s, 1H, NH (exchanges with deuterium oxide)].

Anal. Calcd. for $C_{18}H_{19}BrN_2O_3$: C, 55.29; H, 4.90; N, 7.17. Found: C, 55.42; H, 5.06; N, 7.14.

The second 50 ml. of benzene eluate was concentrated to give 0.80 g. of residue. This was extracted with 55 ml. of boiling pentane, the insoluble material, 0.50 g., m.p. 138-140°, was recrystallized from 35 ml. of cyclohexane to give 0.32 g. (9% yield) of **12**, m.p. 148-149°. The ir, uv, and pmr spectra of **12** were identical in all respects with the spectra previously reported (2).

Anal. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12; Br, 23.15. Found: C, 55.92; H, 3.85; N, 7.93; Br, 23.49.

Reaction of **4** with **8**. Formation of **10** and **12**.

A solution of 9.20 g. (0.033 mole) of **4** and 4.20 g. (0.038 mole) of **8** in 150 ml. of diethylbenzene was heated for 9.5 hours by means of an oil bath so that the internal temperature remained at 175°. The diethylbenzene was then distilled *in vacuo* to give 12.10 g. of a brown oil. This was dissolved in 150 ml. of benzene and poured on a column of 80 g. of activated alumina (M., C., B., Chromatographic Grade, 80-200 mesh) prepared in benzene. The first two benzene eluates (100 ml., combined) yielded only traces of diethylbenzene. The following two benzene eluates (100 ml., combined) gave 3.0 g. of a yellow solid; this material was recrystallized from 200 ml. of pentane to give 1.40 g. (11% yield) of **10**, m.p. 97-98°, ir ν (carbon tetrachloride): 3280 (w), 1660 (s), 1650 (s), 1640 (s), 1595 (s), 1520 (s), 1500 (s), 1460 (s), 1440 (s), 1425 (s) cm^{-1} (c, 30 mg./ml.; the absorption at 3280 cm^{-1} remained unchanged at 6 mg./ml., and at 1 mg./ml.); uv λ max (ethanol): 223 (sh), 284, 329 mμ (ϵ, 15,600, 7650, 23,900); pmr (deuteriochloroform): δ 2.57 (m, 3H, -CC*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 4.83 (m, 1H, -C*H*), 5.23 (s, 2H, *o*-BrC$_6$H$_4$C*H*$_2$), 6.75-8.05 (m, 7 Ar-*H*), 11.42 [broad s, 1H, N*H* (exchanges with deuterium oxide)] (c, 44.0 mg./ml.; at 4.4 mg./ml., the resonances were δ 2.58 4.84, 3.70, 5.24, 11.41); (DMSO-d$_6$), δ 2.71, 4.83, 3.57, 5.25, 11.23 (c, 23.4 mg./ml.); (perdeuteriopyridine): δ 2.63, 5.03, 3.68, 5.25, 11.77 (c, 24.0 mg./ml.).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_3$: C, 54.13; H, 4.55; N, 7.43. Found: C, 54.33; H, 4.71; N, 7.72.

The following five benzene eluates (250 ml. combined) yielded 1.70 g. of material. This was extracted with 50 ml. of boiling pentane, and the pentane insoluble material was recrystallized from 40 ml. of cyclohexane to give 0.60 g. (5% yield) of **12**, m.p. 148-149°; a mixture m.p. with **12** prepared as described (2) was 148-149° and their ir and pmr spectra were identical.

Anal. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.49; H, 3.93; N, 8.37.

Continuation of the elution with 2-propanol resulted in a recovery of 2.50 g. (27% yield) of **4**.

Reaction of **4** with **7a**. Formation of **10** and **12**.

A solution of 4.10 g. (0.016 mole) of **4** and 3.50 g. (0.03 mole) of **7a** in 75 ml. of diethylbenzene was heated at 160-170° for 9 hours. Workup as described above gave 0.065 g. (1% yield) of **10**, m.p. 97-98°, 0.20 g. (3% yield) of **12**, m.p. 148-149°, and 1.50 g. (36% recovery) of **4**. Both **10** and **12** gave ir and pmr spectra that were identical with those obtained with **10** and **12** in the reaction between **4** and **8** as described aobe.

Cyclization Reactions.

(a) Heating at 175-180° under Atmospheric Pressure.

Compound **11**, 0.10 g., was placed in a small open test tube and heated in an oil bath maintained at 175-180° for 2 hours. The melt solifidied on cooling; a m.p. taken at this point was 128-138°. Recrystallization from cyclohexane gave 0.40 g. (45% yield) of **12**, m.p. 148-149°.

(b) Heating in Diethylbenzene at 170-175°.

To 10 ml. of diethylbenzene, preheated to 165°, was added 0.12 g. of **11** and the mixture heated for five hours at an internal temperature of 170-175°. The diethylbenzene was removed *in vacuo*, and the residual oil, 0.30 g., was chromatographed on 15 g. of activated alumina (M., C., B., Chromatographic Grade, 80-200 mesh) prepared in benzene. The recovery of **12**, m.p. 148-149°, was 0.027 g. (25% yield).

(c) Heating at 170-175°/1 mm.

In the preliminary experiment, 0.10 g. of **10** in an open test tube was heated in an Abderhalden drying apparatus at 1 mm over refluxing xylene. The colorless solid formed a yellow melt under these conditions, but after two hours of heating was shown to be essentially unchanged **10**, m.p. 94-96°.

The xylene was replaced by diethylbenzene and the same sample was heated by the refluxing diethylbenzene. A colorless solid sublimed during the one and one-half hours of heating, but a yellow, non-volatile residue, 0.20 g. remained in the test tube. Recrystallization from cyclohexane gave 8 mg. of **12**, m.p. and mixture m.p. 148-149°.

The sublimed material was shown to be unchanged **10** by m.p. and mixture m.p.

REFERENCES

(1) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, 10, 123 (1973). See, also, T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, 20, 142 (1972).

(2) H. L. Yale and J. T. Sheehan, *J. Heterocyclic Chem.*, 10, 143 (1973).

(3a) A. Sauleau, *Bull, Soc. Chim. France*, 2823 (1973); (b) *idem., ibid.*, 2828 (1973); (c) *idem., ibid.*, 2832 (1973); (d) Personal Communication from Dr. A. Sauleau. A paper has just come to our attention: L. Achremowicz and J. Mlochowski [*Rocz. Chem.*, 47, 1383 (1973)], have reported the first preparation of ethyl 3-[[3-pyridyl]amino]crotonate as well as the 3-[2-methyl-3-pyridyl]-, 3-[2,6-dimethyl-3-pyridyl]-, and 3-[[2,5,6-trimethyl-3-pyridyl]amino]crotonate homologs. All of the compounds are crystalline, stable solids which in the ir show NH absorption at 3250-3260 cm^{-1} and CO absorption at 1660-1665 cm^{-1} (potassium bromide) and in the pmr show NH resonance at δ 9.97-10.36 (carbon tetrachloride).

(4) In his papers and his Personal Communication, Dr. Sauleau offered no rationalization for these divergent substituent effects on imine *vs.* enamine formation and no rationalization is evident to the present author. The pmr spectra are not discussed and there appear to be some inconsistencies in the data. Finally, there is no mention of the use of deuterium exchange to identify the NH proton.

(5) Dr. H. Jacobson of this Institute has determined that **6** and **9** are amphoteric substances with pK_{a_1} and pK_{a_2}, respectively, of 5.99 and 9.40 and 3.63 and 7.79; the *p*H of 0.01 *M* solutions of **6** and **9** are 7.66 and 5.73, respectively. It would seem reasonable to assume that the weakly acidic properties of **6** do not contribute to its enhanced reactivity in forming the pyrido[1,2-*a*]pyrimidin-4-one structure.

(6) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 99, 2526 (1966).

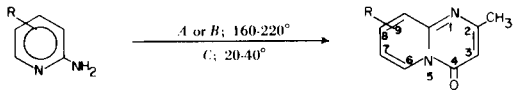
(7) These studies were carried out by Dr. M. Puar of this Institute.

(8) D. L. Ostercamp, *J. Org. Chem.*, 35, 1632 (1970) has evoked the generalization that unless there is sufficient steric resistance to the formation of a six-membered chelate ring, it is the intramolecularly hydrogen bonded structure that is favored.

(9) J. H. Nogel and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, 1971. There authors have shown, by example on pp. 174-176, that the intensity of the NOE observed is a measure of how close two substituents are in a *cis* configuration. Thus, an increase of 31% in the intensity of the

signal of a methine proton was seen when the methyl protons *cis* to that proton, were saturated.

(10) The ambiguity that has existed in the literature as to the structure of the bicyclic heterocycle obtained by the reactions between *2-aminopyridines* and (a) a large excess of either ethyl acetoacetate, *A*, or ethyl β-aminocrotonate, *B*, at 160-220° and (b) a molar equivalent amount of diketene, *C*, in water, at 20-40°, has recently been resolved by the use of X-ray crystallography and pmr shift reagent studies (1). All of these products are derivatives of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and *not* of the isomeric -2-one system. There is lacking, however, an adequate explanation for a mechanism by which these two strikingly different procedures give products that arise by the same mode of cyclization, *i.e.*, the cyclic amide linkage that is formed involved the pyridine nitrogen

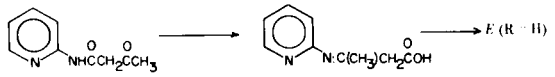


D *E*

D, R = H, 3-CH_3, or 4-CH_3 *E*, R = H, 9-CH_3, or 8-CH_3

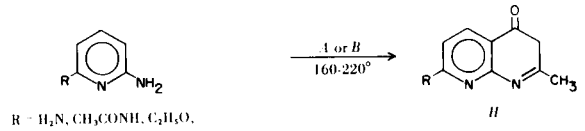
atom and the ester carbonyl group. There is a need to emphasize that is the early literature, the cyclization products obtained at 160-220° were not isolated directly; instead, the reaction mixtures were distilled *in vacuo* to give the crude product as a distillate that was repeatedly recrystallized to obtain the final product. Few yields were reported and the isolation of any other products was not disclosed.

There is adequate evidence that the high temperature reaction did not proceed *via* an intermediary *2-acetoactamido derivative;* thus, while *D*, R = H and either *A* or *B* at 160-220° gave *E* (R = H), 2-acetoacetamidopyridine, *F*, formed from *D* (R = H) and *A* at 100°, failed to give *E* (R = H) under "all conditions tried;" the exception was concentrated sulfuric acid in which *F* gave E (R = H), in $< 10\%$ yield. The suggested explanation, without proof, was that, except in concentrated sulfuric acid, *F* did not rearrange, presumably to *G*, and it was the latter that cyclized to give *E* (R = H). In addition, while 2-aminopyridines having methyl substituents in the 3- and 4-positions or bromine or chlorine in the 5-position



F *G*

gave the corresponding *E* derivatives at 160-220°, 2-aminopyridines carrying an amino, acetamido, ethoxy, or methyl substituent at position-6 gave naphthyridine derivatives, *H*.



R = H_2N, CH_3CONH, C_2H_5O, CH_3 *H*