Pyrido[2,3-*h*]-2,6-naphthyridines. I.
Synthesis and Thermal Reactions of the 2,2'-Bisacylazide of 3,3'-Bipyridine

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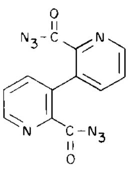
The 2,2'-bisacylazide of 3,3'-bipyridine (1) has been synthesized from the (4,7)-phenantholine-5,6-dione (**3**) and the thermal decomposition of this new bisacylazide has been shown to give rise to the Curtius rearrangement and subsequent cyclization to the pyrido[2,3-*h*]-2,6-naphthridinone ring system **8**.

Although the chemistry of a variety of aliphatic and aromatic acylazides has been introduced into the literature in the past few years (2,3), very little has appeared regarding heterocyclic acylazides and particularly heterocyclic bisacylazides. As a result of our current interest in the synthesis of various heterocyclic polyamines, we have recently examined the synthesis and thermal rearrangement of a new heterocyclic acylazide, the bisacylazide of 3,3'-bipyridine (**1**).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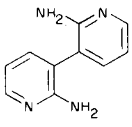
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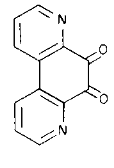
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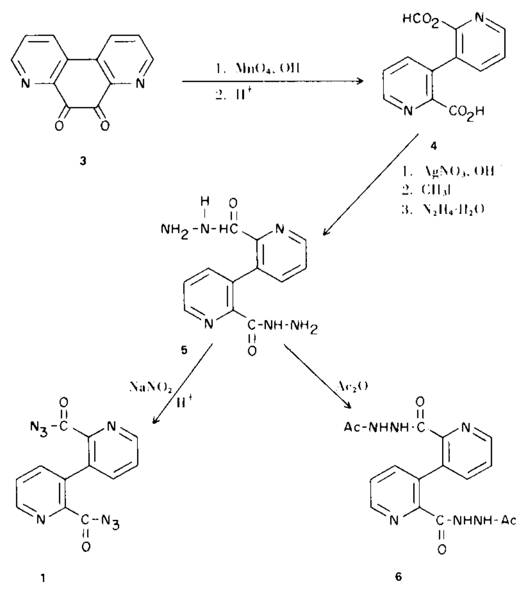
This new system was initially proposed as a means of preparing the corresponding 6,6'-diaminobipyridine (**2**) *via* the Curtius rearrangement of the acylazide moiety. However, we now wish to report that this system is subject to an unexpected cyclization reaction during the degradation.

The synthesis of the new bisacylazide **1** (Scheme I) begins with the oxidation of (4,7)-phenanthroline-5,6-dione (**3**) by a method described by Kuhn and Bauer (4). The resulting biscarboxylic acid (**4**) was then treated with excess silver nitrate to give the corresponding silver salt which could be subsequently converted to the dimethyl ester with methyl iodide in dry toluene. Treatment of this diester with refluxing hydrazine hydrate gives the bisacylhydrazide (**5**) in 87% yield. Acetylation of this bisacylhydrazide was achieved with refluxing acetic anhydride to give the bisacetamido derivative **6**.

Treatment of a solution of **5** in 1*N*, hydrochloric acid with aqueous sodium nitrite at room temperature gave an immediate precipitate of the azide **1**. The preceding new compounds have all been fully characterized by elemental analysis and spectral techniques. The newly isolated acylazide was found to be quite unstable and was observed to be slowly converted to a new substance on standing. This conversion was considerably accelerated in solution and the resulting yellow product has prompted our study of the degradation products of the acylazide **1**.

SCHEME I



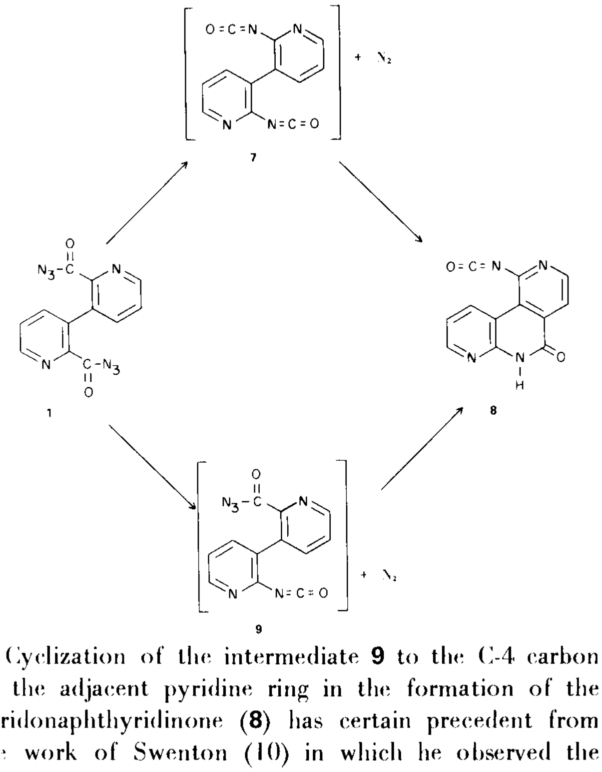
Thermolysis of **1** in dry dimethylacetamide of 60-70° produced a bright yellow solid **8** which gave the correct analysis for $C_{12}H_6N_4O_2$ and exhibited a weak isocyanate peak in the infrared spectrum at 2030 cm^{-1}. While this analysis and the isocyanate absorption are in agreement with a diisocyanate structure such as **7**, the infrared spectrum of this new material also exhibited a strong amide carbonyl at 1705 cm^{-1} together with a broad N-H peak at 3450 cm^{-1}.

This infrared data together with the nmr spectrum of compound **14**, which is not suggestive of a simple 3,3′-bipyridyl system, have led to the structural assignment for this thermal product as the 1-isocyanopyrido[2,3-*h*]-2,6-naphthyridin-5-one (**8**). The intermediacy of the diisocyanate **7** has not been demonstrated; however, the present structural assignment of **8** would require either a concerted Curtius rearrangement or a step-wise degradation of **1** leading eventually to structure **8**, Scheme 2.

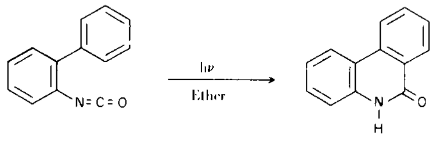
Such a step-wise degradation can be envisioned as giving rise to the isocyanate-acylazide intermediate **9** which then undergoes cyclization and further degradation to give the pyridonaphthyridinone (**8**).

Similar step-wise degradations have been observed by a number of authors in which a bisacylazide underwent partial conversion to an isocyanate-acylazide intermediate. Lindermann and co-workers (8) have described the step-wise thermolysis of phthalyl bisacylazide in benzene to give the corresponding isocyanate-acylazide while heating of the bisacylazide in alcohol gives the corresponding *N*-carbomethoxyanthranilic azide. Meyer (9) has also described a similar conversion in the thermal degradation of the 2,5-bisacylazide of pyridine.

SCHEME 2



Cyclization of the intermediate **9** to the C-4 carbon of the adjacent pyridine ring in the formation of the pyridonaphthyridinone (**8**) has certain precedent from the work of Swenton (10) in which he observed the formation of the phenanthridone (**11**) during the photolysis of the biphenylisocyanate (**10**).



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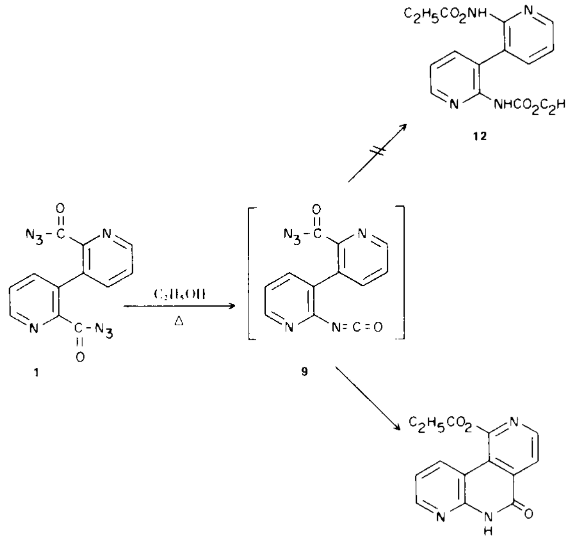
This particular cyclization of the isocyanate function of **9** is presumably quite rapid since the thermolysis of the bisacylazide (**1**) in the presence of a nucleophile such as ethanol does not give the expected diurethane (**12**) but rather produces the corresponding ester (**13**) in 75% yield, Scheme 3.

The formation of **13** lends further support to the proposed intermediacy of the isocyanate-acylazide structure (**9**), which apparently undergoes cyclization to the pyridonaphthyridinone with subsequent displacement of the azide function by ethanol. Such reactivity with regard to the nucleophilic displacement of an azide function by alcohol has been described earlier by Curtius and co-workers (7).

This type of displacement reportedly occurred in the solvolysis of certain acylazides whose decomposition temperatures were found to be higher than the boiling point of the alcohol. In these cases, the acylazide was often converted to the corresponding ester with the loss of the elements of hydrazoic acid.

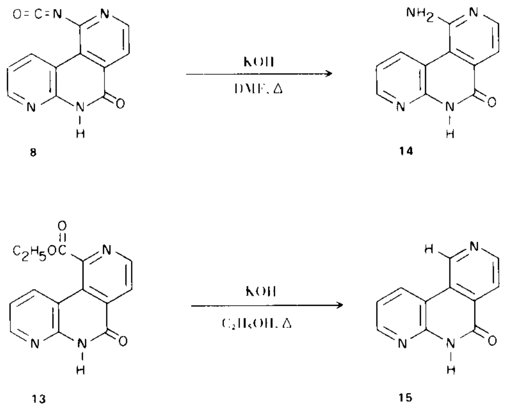
SCHEME 3



The structural assignments for both the ester **13** and the original isocyanate **8** are adequately supported by infrared and nmr spectral data as well as further chemical transformations for each species.

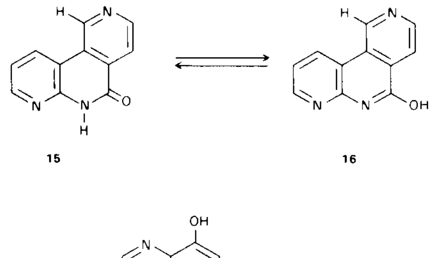
Hydrolysis of the isocyanate **8** with a solution of potassium hydroxide in dimethylformamide gave the corresponding amine **14** in 90.3% yield, while treatment of the ester **13** with alcoholic potassium hydroxide gave the unsubstituted [2,3-*h*]-2,6-pyridonaphthyridinone (**15**) in 79% yield, Scheme 4.

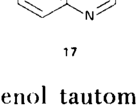
SCHEME 4



The infrared spectrum of these particular systems has proven to be quite interesting and deserves further discussion at this time. The major absorption peaks for the amine **14** were found at 3500, 3350, and 3200 and 1665 cm^{-1}. The peaks at 3500 and 1665 cm^{-1} have been assigned to the amide -NH and carbonyl respectively while the sharp doublet at 3350 and 3200 cm^{-1} is attributed to the free amine function in **14**.

The infrared spectrum of **15** exhibited three major peaks at 3500, 1670, and 2900 cm^{-1}. The first two peaks are assigned to the amide -NH and amide carbonyl respectively. The strong absorption at 2900 cm^{-1} is unique to this system and has been attributed to some contribution from the corresponding enol form **16** of this unsubstituted ring system.





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A similar keto-enol tautomerism has been studied by Bailey and co-workers (11) for 4-hydroxy-1,5-naphthridine (**17**) which apparently exists predominately in the enol form only in nonpolar solvents. Other hydroxy naphthyridine systems have been examined by Mason (12) and Rossotti (13); however, no definite and general position has been established regarding such keto-enol equilibria. The pyridonaphthyridinone (**15**) appears quite unique in this respect in that it exhibits a rather strong infrared absorption in the region normally associated with such systems as 3-hydroxypyridine, 3-hydroxy, and 5-hydroxyquinoline and various other hydroxy substituted heterocycles (11). This particular absorption peculiar to **15** is under further investigation in an effort to establish the extent of enolization for this species.

The parent bisacylazide (**1**) is currently being examined with regard to its photolytic decomposition.

EXPERIMENTAL (1)

Melting points were determined on a Thomas-Hoover or Mel-Temp apparatus. The infrared spectra were recorded on either a Perkin-Elmer model 137 or model 521 spectrophotometer. The nmr spectra were determined with a Varian T-60 using tetramethylsilane as an internal reference.

Interpretation of nmr data: δ chemical shift ppm (multiplicity, number of protons). s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan.

4,7-Phenanthrolin-5,6-dione (**3**).

This compound was generously donated by Ciba, Geigy and Company, Basel Switzerland. Further purification of this compound was not needed as indicated by its melting point of 293°; ν max (potassium bromide) 3070 and 1695 cm^{-1}.

2,2′-Biscarboxylic Acid of 3,3′-Bipyridine (**4**).

This compound was prepared by the method of Kuhn and Bauer (4). A solution of 25 g. (0.119 mole) of **3** in 500 ml. of 10 percent aqueous potassium hydroxide was treated dropwise with a solution of 8.75 g. (0.055 mole) of potassium permanganate in 187.5 ml. of water. The solution was then heated for one hour at 50° to 60° and the resulting black mixture was filtered to remove the precipitated manganese dioxide. The filtrate was further diluted with 65 ml. of water and acidified with 2*N* hydrochloric acid. This solution was then treated with 20 g. (0.157 mole) of cupric chloride in 25 ml. of water. The resulting blue copper complex was filtered off and suspended in 500 ml. of water. The mixture was heated for six hours at 70° and then thoroughly saturated with hydrogen sulfide gas. The cupric sulfide precipitate was filtered from solution while hot and then discarded. After standing for 24 hours at approximately 10° in the refrigerator, crystals of **4** precipitated from the mother liquid. The crude acid was washed with methanol and finally with anhydrous ether. The crystals were crushed and dried at 50° under vacuum for two hours to give 13.50 g. of the 2,2′-biscarboxylic acid of 3,3′-dipyridine (**4**). Concentration of the filtrate *in vacuo* afforded another 9.10 g. of **4** (77.9%). Recrystallization of **4** from DMSO/water gave fine, white crystals, m.p. 220° (lit. m.p. 219°) (4); ν max (potassium bromide) 3450 (-OH), 3010 (-C-H), and 1680 (>C=O) cm^{-1}.

Silver Salt of the 2,2′-Biscarboxylic Acid of 3,3′-Bipyridine.

A 5 g. (0.02 mole) sample of **4** was dissolved in a minimum amount of dilute aqueous sodium hydroxide solution. A solution of 13.6 g. (0.08 mole) of silver nitrate in 200 ml. of distilled water was then added dropwise to the above solution. The silver salt which separated from the solution was filtered and washed repeatedly with water. The resulting light rose-colored powder was dried at 100° under vacuum for 12 hours to give 8.86 g. (98%) of the silver salt (**5**) of the 2,2′-biscarboxylic acid of 3,3′-bipyridine (**4**), m.p. 310°; ν max (potassium bromide) 3008 (-C-H), 2300 (>C=O), and 1620 (>C=O) cm^{-1}.

Dimethyl Ester of the 2,2′-Biscarboxylic Acid of 3,3′-Bipyridine (14).

A suspension of 8.86 g. (0.019 mole) of **5** in 150 ml. of dry toluene and 5.7 ml. (0.94 mole) of methyl iodide was heated for two hours at 60° to 70° and then at 100° for three hours. The black-olive solution was then filtered to remove the precipitated silver iodide and refrigerated for 12 hours at approximately 10° to give light green crystals of the diester. The crude product was crushed and washed with methanol, then dried at 50° under vacuum for three hours to yield 1.12 g. of the methyl ester of the 2,2′-biscarboxylic acid of 3,3′-bipyridine. Concentrating the toluene fraction gave an additional 0.46 g. for an overall yield of 1.58 g. (52.7%), m.p. 150° to 151°. The ester was recrystallized twice from methanol to give white crystals, m.p. 156° to 157°; ν max (potassium bromide) 1710 (>C=O) and 1300 (C-O-C) cm^{-1} nmr δ (DMSO) 8.7 (m, 2), 7.9 (m, 4), 3.5 (s, 6) ppm.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.41; N, 10.29. Found: C, 61.64; H, 4.29; N, 10.18.

2,2′-Bisacylhydrazide of 3,3′-Bipyridine (**5**).

A 1 g. (0.0037 mole) sample of the dimethyl ester in 1.11 ml. (0.222 mole) of hydrazine hydrate was heated for 1 hour at 200°. The mixture was cooled, and the crude product was filtered and washed repeatedly with ethanol to remove the residual excess hydrazine hydrate. The crude solid 0.87 g. (87%) was recrystallized from ethanol to give fine white crystals of **5**, m.p. 217°; ν max (potassium bromide) 3460, 3300 (-NH, -NH_2 stretch), 1665 (>C=O), and 1650 (-NH_2 bending) cm^{-1}: nmr δ (DMSO) 9.65 (broad s, 2), 8.64 (m, 2), 7.62 (m, 4), 4.33 (broad s, 4) ppm.

Anal. Calcd. for $C_{12}H_{12}N_6O_2$: C, 52.94; H, 4.41; N, 30.88. Found: C, 52.88; H, 4.27; N, 30.18.

N,N′-Diacetyl Derivative of the 2,2′-Bisacylhydrazide of 3,3′-Bipyridine (**6**).

A 0.2 g. (0.00084 mole) sample of **5** was refluxed in 10 ml. of acetic anhydride for one hour. The mixture was cooled, and the product was filtered and washed repeatedly with water to remove the residual excess acetic anhydride. The resulting white crystals were dried at 80° for three hours to give, in nearly quantitative yield, the diacetyl derivative **6** of the 2,2′-bisacylhydrazide of 3,3′-bipyridine, m.p. dec. 312° to 318°; ν max (potassium bromide) 3300 (-NH), 1710 (acetyl >C=O), and 1640 (amide >C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.49; N, 23.60. Found: C, 53.73; H, 4.50; N, 23.72.

2,2′-Bisacylazide of 3,3′-Bipyridine (**1**).

A 0.3 g. (0.0011 mole) sample of **5** was dissolved in 8 ml. of 1*N* hydrochloric acid and carefully treated with a solution of 0.4 g. (0.006 mole) of sodium nitrite at room temperature to give a 0.22 g. (68%) of **1**, m.p. (explodes) 96°; ν max (potassium bromide) 2165 (-N=N=N) and 1710 (>C=O) cm^{-1}: nmr δ (CF_3CO_2D) 9.25 (m, 2), 8.65 (m, 4) ppm.

Anal. Calcd. for $C_{12}H_6N_8O_2$: C, 48.97; H, 2.04; N, 39.09. Found: C, 48.85; H, 1.96; N, 37.87.

1-Isocyanopyrido[2,3-*h*]-2,6-naphthyridin-5-one (**8**).

A solution of 0.2 g. (0.00068 mole) of **1** in 5 ml. of dry dimethylformamide was heated for one-half hour at 60° to 65° while being purged with nitrogen gas. At the end of this time, a yellow solid had precipitated from the solution. The product was filtered and washed, with ethanol and then with anhydrous ether. It was air-dried for two hours to give 0.16 g. (98.8%) of the 1-isocyanopyrido[2,3-*h*]-2,6-naphthyridin-5-one (**8**), m.p. dec. 358° to 360°; ν max (potassium bromide) 3450 (-NH), 2030 (-N=C=P), and 1705 (>C=O) cm^{-1}: nmr δ (CF_3CO_2D) 9.9 (d, 1), 9.6 (d, 1), 9.6 (s, 1), 9.2 (m, 1), 8.8 (m, 1), 8.22 (m, 1) ppm.

Anal. Calcd. for $C_{12}H_6N_4O_2$: C, 60.50; H, 2.52; N, 23.53. Found: C, 60.58; H, 2.47; N, 23.59.

1-Carboethoxypyrido[2,3-*h*]-2,6-naphthyridin-5-one (**13**).

A suspension of 0.2 g. (0.00068 mole) of **1** in 5 ml. of freshly distilled ethanol was refluxed for one and one-half hours. When cooled, the solution yielded 0.128 g. (75%) of the 1-carboethoxypyrido[2,3-*h*]-2,6-naphthyridin-5-one (**13**), which was recrystallized twice from ethanol, m.p. 200° to 201°; ν max (potassium bromide) 3500 (-NH), 1750 (ester >C=O), 1665 (amide >C=O), and 1300 (C-O-C) cm^{-1}: nmr δ (DMSO) 8.95 (m, 2), 8.8 (s, 1), 8.1 (d, 1), 7.4 (m, 1), 7.1 (m, 1), 4.4 (q, 2), 1.3 (t, 3) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.08; N, 15.61. Found: C, 62.48; H, 3.99; N, 15.57.

1-Aminopyrido[2,3-*h*]-2,6-naphthyridin-5-one (**14**).

A solution of 0.2 g. (0.00068 mole) of the freshly prepared acylazide (**1**), in 5 ml. of wet dimethylformamide containing 0.2 g. of solid potassium hydroxide, was heated for one-half hour at 75°. The yellow solid **8** which had precipitated from the solution was not isolated but the temperature was slowly raised and the mixture was allowed to reflux for two hours. The yellow solid gradually went into solution and, upon cooling to room temperature, gave 0.13 g. (90.3%) of the 1-aminopyrido[2,3-*h*]-2,6-naphthyridin-5-one (**14**), m.p. 278° to 279°. The amine was recrystallized from hot water to give white crystals, m.p. 280° to 281°; ν max (potassium bromide) 3500 (-NH), 3350, 3200 (-NH_2), 3000 (C-H), and 1665 (>C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_4O_1$: C, 62.26; H, 3.77; N, 26.41. Found: C, 62.31; H, 3.43; N, 26.14.

Pyrido[2,3-*h*]-2,6-naphthyridin-5-one (**15**).

A suspension of 0.2 g. (0.00074 mole) of **13** in a solution of 0.5 g. of potassium hydroxide in 20 ml. of 95 percent ethanol was refluxed for 48 hours. The mixture was allowed to cool at room temperature and then concentrated *in vacuo* to give a white solid. The crude product was washed, with water and then with methanol, and dried at 50° under vacuum for three hours to give 0.115 g. (78.5%) of pyrido[2,3-*h*]-2,6-naphthyridin-5-one (**15**), m.p. 360° to 361°; ν max (potassium bromide) 3500 (-NH), 2900 (-OH), and 1670 (>C=O) cm^{-1}: nmr δ (CF_3CO_2D) 9.5 (d, 1), 8.5 (m, 2), 8.5 (s, 1), 8.1 (d, 1), 7.8 (m, 1), 6.8 (t, 1) ppm.

Anal. Calcd. for $C_{11}H_7N_3O_1$: C, 67.01; H, 3.55; N, 21.31. Found: C, 67.23; H, 3.45; N, 21.31.

Acknowledgements.

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