Anal. Calcd. for $C_{18}H_{18}$: C, 92.25; H, 7.74. Found: C, 91.81; H, 7.47.

5-(β,γ-Dibromopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (IX).—A solution of 1.39 g. of bromine in 25 ml. of chloroform was added dropwise to a solution of 2.0 g. of the diene VI in 75 ml. of chloroform at room temperature and at such a rate that the reaction mixture remained colorless. After a total of 1.28 g. of bromine had been added (the reaction mixture failed to absorb bromine further), the addition was stopped and stirring continued for 40 min. The reaction mixture was taken to dryness *in vacuo*, the residual oil dissolved in hexane, filtered through Celite, concentrated to a small volume, seeded, and chilled to yield 3.0 g. of crystalline dibromide with m.p. 92–94°; λ_{max}^{MeOH} 242.5 mμ, ε 15,300; $\lambda_{max}^{CHCl_3}$ 6.2, 6.78, 6.92, 7.36, and 8.83 μ.

Anal. Calcd. for $C_{18}H_{16}Br_2$: C, 55.12; H, 4.11; Br, 40.76. Found: C, 55.33; H, 4.29; Br, 40.80.

Reaction of the Dibromide IX with Dimethylamine.—A solution of 1.0 g. of the dibromide IX in 10 ml. of benzene saturated with dimethylamine was heated in a sealed tube at 85° overnight. The reaction mixture was taken to dryness, the residue triturated with ether, and 480 mg. (74.5%) of dimethylamine hydrobromide, m.p. 132–133.6°, was filtered off. The filtrate yielded 770 mg. of oily residue which was chromatographed over 25 g. of neutral alumina. The hexane fractions eluted 400 mg. of noncrystalline material, essentially single spot by t.l.c., which had λ_{max}^{MeOH} 280 mμ, and an n.m.r. spectrum compatible with the vinyl bromide X. This substance could not be obtained analytically pure.

5-(γ-Hydroxypropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = OH).—A solution of 2.0 g. of the diene VI in 25 ml. of dry tetrahydrofuran was treated, at 0° and under dry nitrogen, with 3.8 ml. of a 2.28 *M* solution of di-*sec*-isoamylborane[4] in 4 ml. of tetrahydrofuran and allowed to stand at 0–5° for 1 hr. Water, 2 ml., was added (at 0°) to decompose any excess di-*sec*-isoamylborane, the mixture was allowed to come to room temperature and was oxidized by the addition of 4 ml. of 2.5 *N* sodium hydroxide and 2.7 ml. of 30% hydrogen peroxide. The aqueous layer was saturated with solid, anhydrous potassium carbonate, the layers separated, and the aqueous layer extracted with 10 ml. of tetrahydrofuran. The combined organic extracts were dried over magnesium sulfate, and the solvent removed *in vacuo*. The residue, on trituration with petroleum ether (b.p. 30–60°), yielded 1.45 g. (67%) of first crop crystalline alcohol identical (mixture melting point, ultraviolet, and infrared) with a sample produced by the procedure reported previously.[2]

5-(γ-Chloropropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = Cl).—A solution of 50 mg. of the primary carbinol II (X = OH) in 3 ml. of benzene containing 1 drop of pyridine was treated dropwise with 65.6 mg. of thionyl chloride in 2 ml. of benzene at room temperature and refluxed on a steam bath for 3 hr. The reaction mixture was then evaporated to dryness *in vacuo*. The residue was triturated with benzene, the benzene solution filtered, and taken to dryness *in vacuo* to give a quantitative yield of the crystalline chloride II (X = Cl identical with a sample obtained by a previously reported method.[2]

Conversion of the Primary Carbinol II (X = OH) to 5-(γ-Dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene Hydrochloride (XI).—A solution of 400 mg. of the pirmary carbinol II (X = OH) in 5 ml. of dry pyridine, chilled to 0°, was treated with 400 mg. of *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand overnight at 0–4°. At the end of this period, the reaction mixture was poured over 15–20 ml. of crushed ice and extracted with three 10-ml. portions of chloroform. The combined extracts were washed with 5-ml. portions of cold 2.5 *N* hydrochloric acid until the last wash was acidic, then washed with 10 ml. of excess potassium bicarbonate solution, followed by 10 ml. of saturated salt solution. The solution was finally dried over magnesium sulfate and taken to dryness *in vacuo* to yield 620 mg. (96.5%) of crude, noncrystalline tosylate. This material had $\lambda_{max}^{CHCl_3}$ 6.3, 7.40, 8.45, 8.55, 9.15, and 12.29 μ.

Anal. Calcd. for $C_{25}H_{24}O_3S$: S, 7.92. Found: S, 7.21.

This tosylate was treated with dimethylamine in benzene in a sealed tube at 85° as described previously[2] to yield 360 mg. (77.5%) of first crop crystalline product, m.p. 191–193°, which was identical with an authentic sample of amitriptyline XI.

1,5-Naphthyridine and Some of Its Alkyl Derivatives

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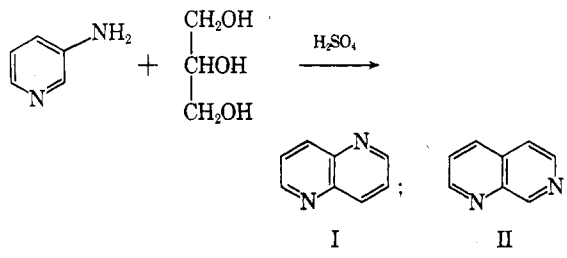
The preparation of 1,5-naphthyridine from 3-aminopyridine and glycerol in the Skraup reaction led to the isolation of 1,2,3,4-tetrahydro-1,5-naphthyridine and 3-methyl- and 3-ethyl-1,5-naphthyridine as by-products. The structures of these products were established by independent syntheses and explanations for their mode of formation are suggested. The isomeric 1,7-naphthyridine, prepared independently, was totally absent as a product of the 3-aminopyridine reaction. Oxidation of 3-ethyl-1,5-naphthyridine gave the expected 1,5-naphthyridine-3-carboxylic acid; however, 3-methyl-1,5-naphthyridine under the same conditions surprisingly gave 3-acetamidopicolinic acid. A possible mechanism for this oxidation is proposed. The infrared spectra of the various 1,5- and 1,7-naphthyridines have been correlated.

1,5-Naphthyridine (I) has appeared in the literature several times,[1-4] resulting from the Skraup reaction with 3-aminopyridine. In no instance was the isomeric 1,7-naphthyridine (II) detected, although its formation cannot be excluded rigorously, since purification was by crystallization exclusively. It seemed reasonable to expect that some of the 1,7-isomer would be formed, particularly since the analogous reaction with *m*-substituted anilines invariably gave both possible isomers.[5] For this reason, and also because we required a large quantity of pure 1,5-naphthyridine, we have examined the Skraup reaction with 3-aminopyridine in detail.



Preliminary experiments established that (1) the maximum crude yield was obtained in the presence of boric acid, and (2) this crude product, on chromatography, gave a fraction with the characteristic 1,5-naphthyridine ultraviolet spectrum and a fraction with the characteristic 3-aminopyridine spectrum. A convenient large-scale purification method then was

(1) B. Bobranski and E. Sucharda, *Ber.*, **60**, 1081 (1927).
(2) C. R. Hauser and G. A. Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).
(3) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).
(4) A. Albert, *ibid.*, 1790 (1960).
(5) M. H. Palmer, *ibid.*, 3645 (1962), and references therein.

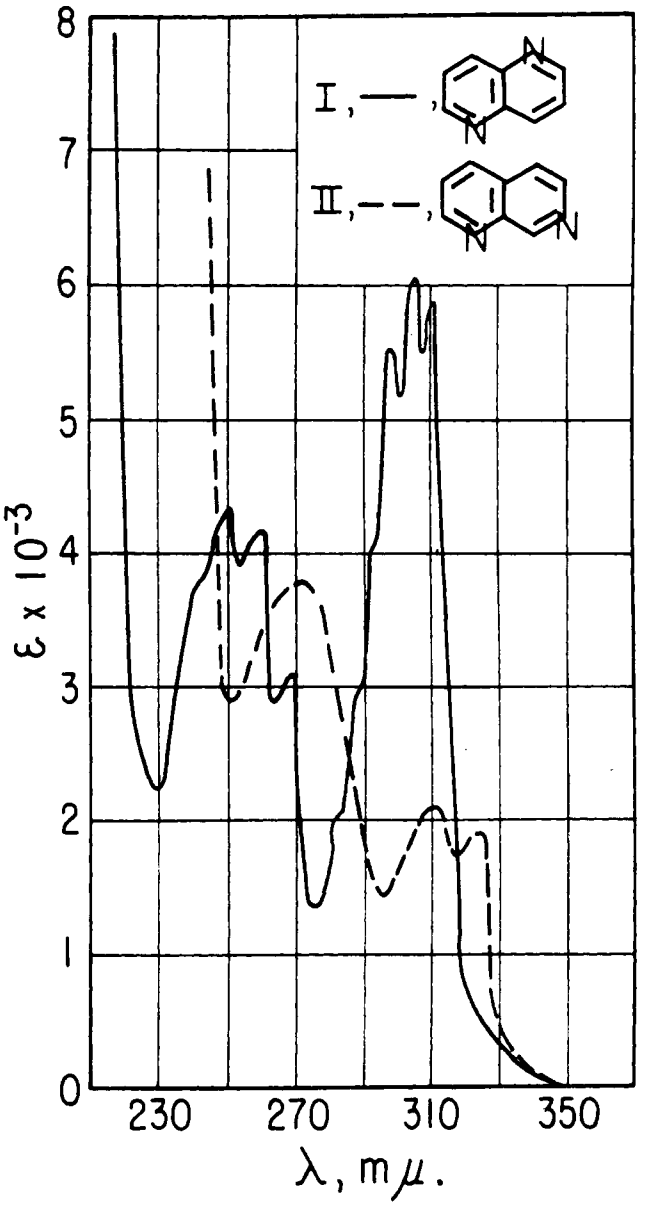


Fig. 1.—Ultraviolet absorption spectra of 1,5-naphthyridine (I) and 1,7-naphthyridine (II) in methanol.

developed by considering the differences in basicity and polarity between the naphthyridine and 3-aminopyridine fractions. Taking 1,5-naphthyridine and 3-aminopyridine as typical of the two fractions, the pK_a values were determined by partition methods and found to be 3.2 for 1,5-naphthyridine[6] and 6.0 for 3-aminopyridine.[7] Also, 1,5-naphthyridine has a partition coefficient of 0.3 between pentane and water, while that of 3-aminopyridine is less than 0.01. Thus, continuous extraction at pH 3 with pentane cleanly and completely removed the weak naphthyridine bases, and the 3-aminopyridine fraction then was extracted by ether after making the solution alkaline.

Vapor phase chromatography (v.p.c.) of the ether extract, fraction A, demonstrated the presence of two compounds, A-1 and A-2, obtained in quantity by fractional distillation. Fraction A-1 was recovered 3-aminopyridine. Fraction A-2, $C_8H_{10}N_2$, had an ultraviolet absorption very similar to that of 3-aminopyridine and was shown to be 1,2,3,4-tetrahydro-1,5-naphthyridine (III)[8] by comparison with an authentic sample prepared by catalytic hydrogenation of 1,5-naphthyridine. By extending the reaction time from six to twenty hours, the yields of A-1 and A-2 become negligible with a corresponding increase in the naphthyridine fraction.

The initial pentane fraction, N, was shown by v.p.c. to contain three components which were separable by fractional distillation. Fraction N-1, by elemental analysis and comparison of physical properties with the literature values, was obviously 1,5-naphthyridine (I) and was obtained in 31% yield.

Fraction N-2, $C_9H_8N_2$, m.p. 73–75°, was obtained in 4% yield. Its ultraviolet absorption was very similar to that of 1,5-naphthyridine, and Kuhn–Roth oxidation gave acetic acid. Thus, N-2 was probably a methyl-1,5-naphthyridine, and, since it failed to condense with benzaldehyde, the methyl group was assigned to position 3.

As confirmation, and since we wished to establish some infrared correlations (given later), all three methyl isomers were synthesized. This was conveniently done by the reaction of 3-aminopyridine with crotonaldehyde, methylacrolein, and methyl vinyl ketone, to yield 2-methyl-, 3-methyl-, and 4-methyl-1,5-naphthyridine, respectively. These isomers can be clearly distinguished by melting point, infrared absorption, and v.p.c. The 3-methyl-1,5-naphthyridine (IV) was identical with compound N-2.

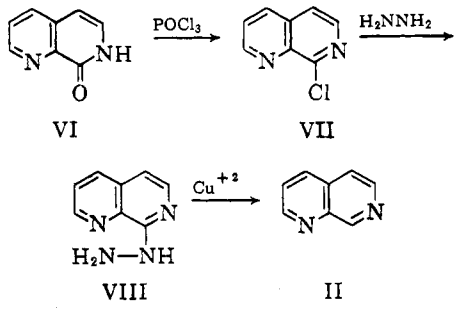
Compound N-3, $C_{10}H_{10}N_2$, also was obtained in 4% yield as a colorless liquid. Its ultraviolet absorption was almost identical with that of N-2, and it contained one C-methyl group, indicating that the additional two carbons represented an ethyl substitutent, rather than two methyl groups, on the 1,5-naphthyridine nucleus. Since the infrared absorption (given later) of N-3 in the 700–900-cm.$^{-1}$ region was quite similar to that of N-2, the former was assumed to be 3-ethyl-1,5-naphthyridine. To synthesize this compound, we followed the example provided by the synthesis of 3-ethylquinoline[9] in which 2-hydroxymethyl-2-methyl-1,3-propanediol was used and may be considered as a source of ethylacrolein, generated *in situ*. When this triol and 3-aminopyridine were treated under conditions of the Skraup reaction, 3-ethyl-1,5-naphthyridine (V) resulted. It was identical with compound N-3 in ultraviolet and infrared absorption and by v.p.c.

Thus, the various products isolated from the reaction of 3-aminopyridine and glycerol were: 1,2,3,4-tetrahydro-1,5-naphthyridine (III), 1,5-naphthyridine (I), 3-methyl-1,5-naphthyridine (IV), and 3-ethyl-1,5-naphthyridine (V). Although we had not found any 1,7-naphthyridine (II), it conceivably might have been formed to a very slight extent and have been a contaminant among the products above. To settle this question, we synthesized 1,7-naphthyridine and established its behavior in our isolation scheme and its limit of detection in the several fractions.

An improved synthesis of 1,7-naphthyridine[4,10] was developed, starting with the readily prepared 1,7-

(6) Reported pK_a 2.91 in ref. 4.
(7) Reported pK_a 6.1 [J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954)] and 6.6 [H. Tropsch, *Monatsh. Chem.*, **35**, 777 (1914)].
(8) K. Miyaki, *J. Pharm. Soc. Japan*, **62**, 257 (1942).
(9) R. W. Brown and G. Dougherty, *J. Am. Chem. Soc.*, **69**, 2232 (1947).
(10) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 401 (1958).

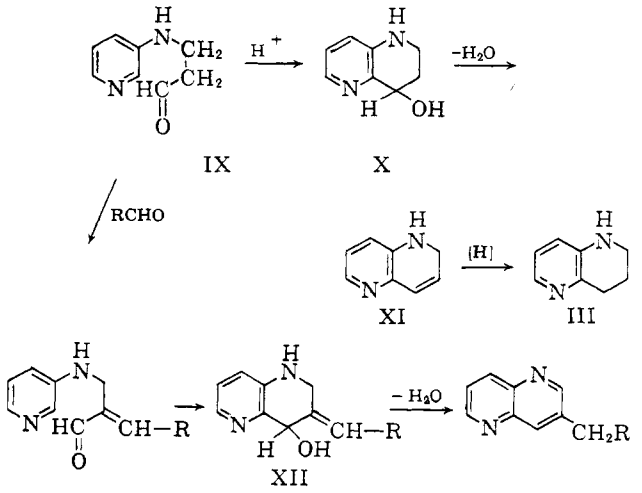
naphthyridin-8(7*H*)-one (VI).[11] Treatment with phosphorus oxychloide gave the 8-chloro compound (VII). Although hydrogenolysis of the chloro compound could not be effected without concurrent hydrogenation of the naphthyridine nucleus, the 8-hydrazino compound (VIII) was easily prepared and with cupric ion this was reduced to 1,7-naphthyridine (II).



The ultraviolet absorption of 1,7-naphthyridine is quite different from that of 1,5-naphthyridine (Fig. 1). The pentane/water partition coefficient of the 1,7-isomer is 0.02 and its pK_a is 3.7.[12] Since continuous extraction with pentane completely removed it from an aqueous solution at pH 3, any 1,7-naphthyridine present would have appeared in the N (naphthyridine) fraction. From the ultraviolet spectra and v.p.c. behavior of the compounds in this fraction as compared to that of 1,7-naphthyridine, it was established that the presence of 0.3% of 1,7-naphthyridine in this fraction would have been detected easily. Thus, we conclude that essentially none of the 1,7-isomer was formed.

Several aspects of the Skraup reaction with 3-aminopyridine deserve further comment: these are (1) the formation of 1,2,3,4-tetrahydro-1,5-naphthyridine; (2) the formation of the methyl and ethyl homologs; and (3) the fact that cyclization takes place exclusively to the 2-position.

The presence of the tetrahydro compound may result from the dihydro intermediate through the action of another molecule of dihydro compound acting as a reducing agent. By analogy with the quinoline case, the dihydro compound XI undoubtedly arises from dehydration of the carbinol (X) formed by cyclization of the arylamino aldehyde (IX), itself the product of 3-aminopyridine addition to acrolein. Since extending the reaction time leads to disappearance of the tetrahydro compound, it must be slowly oxidized to the completely aromatic system.

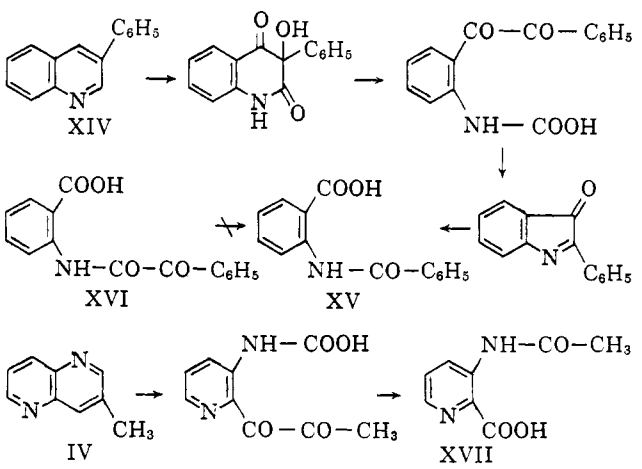


To explain the formation of the alkyl naphthyridines, we have assumed that alkylation occurs prior to aromatization. If the intermediate arylaminopropionaldehyde (IX) condenses with formaldehyde or acetaldehyde and then cyclizes, dehydration of the resulting carbinol (XII) would give the 3-methyl or 3-ethyl compound. Equimolar amounts of formaldehyde and acetaldehyde could be formed by a retro-aldol condensation of the intermediate dehydration product of glycerol, β-hydroxypropionaldehyde.

Why cyclization takes place only at the 2-position and not at all at the 4-position is puzzling. Similar orientation has been observed in other electrophilic substitutions into pyridines bearing activating substituents at the 3-position. It has been suggested[13] that a possible chelating effect involving the protonated ring-nitrogen may be responsible.

Before establishing the structure of N-3 as 3-ethyl-1,5-naphthyridine (V) by independent synthesis, an effort was made to relate it to N-2, 3-methyl-1,5-naphthyridine (IV), by oxidizing both compounds to 1,5-naphthyridine-3-carboxylic acid (XIII). Since the aromatic portion of both molecules had been oxidized in preference to the side chain under acidic conditions, alkaline permanganate was used.

From 3-ethyl-1,5-naphthyridine, a good conversion to 1,5-naphthyridine-3-carboxylic acid, m.p. 279°, was obtained. However, oxidation of 3-methyl-1,5-naphthyridine under identical conditions gave a new acid which melted with decarboxylation at 212°. This acid, $C_8H_8N_2O_3$, had two carbonyl bands in the infrared, one at 5.95 μ (aromatic acid) and the other at 6.04 μ (amide). The decarboxylated product was identical with 3-acetamidopyridine. Therefore, the oxidation product obtained from 3-methyl-1,5-naphthyridine was 3-acetamidopicolinic acid (XVII). The formation of XVII from 2-methyl-1,5-naphthyridine might be accepted; its formation from the 3-methyl isomer was surprising.



Therefore, we sought an explanation for this reaction, and a previous observation made in the quinoline series was strongly suggestive. This was the oxidation of 3-phenylquinoline (XIV) to benzoylanthranilic acid

(11) A. Albert and A. Hampton, *J. Chem. Soc.*, 4985 (1952).

(12) Reported pK_a 3.63 (ref. 4) and 3.6–3.7 [N. Ikekawa, *Chem. Pharm. Bul.* (Tokyo), **6**, 408 (1958)].

(13) K. Schofield, *Quart. Rev.* (London), **4**, 382 (1950).

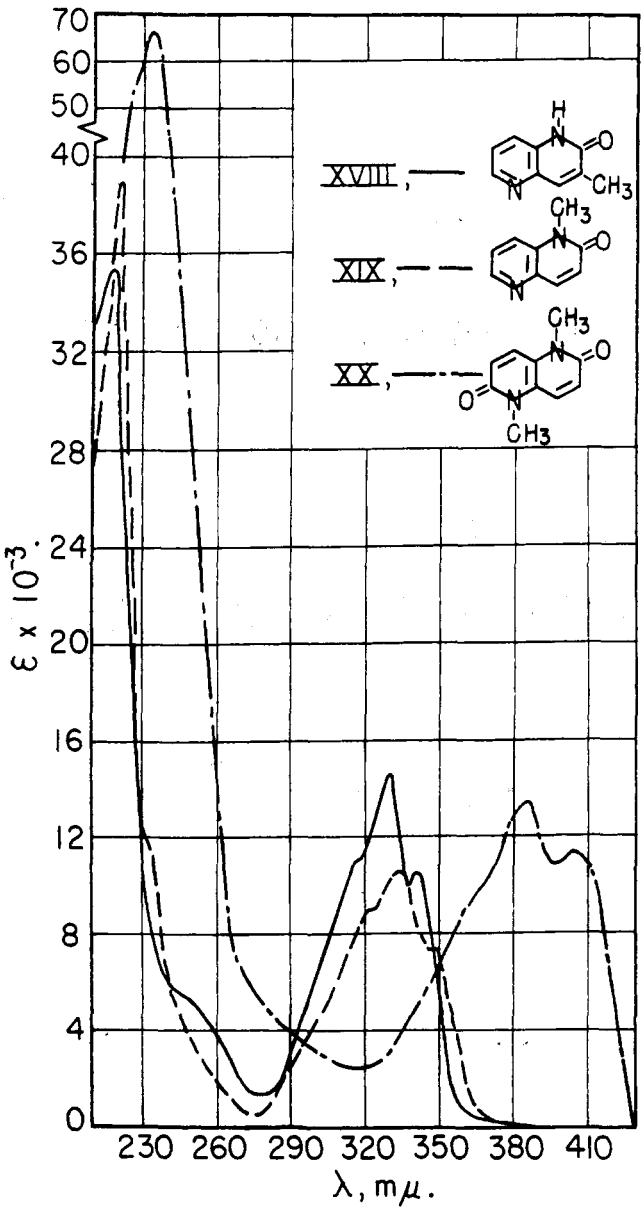
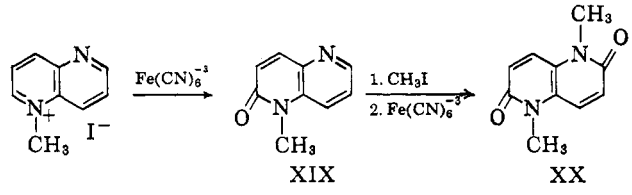


Fig. 2.—Ultraviolet absorption spectra of 3-methyl-1,5-naphthyridin-2(1*H*)-one (XVIII), 1-methyl-1,5-naphthyridin-2(1*H*)-one (XIX), and 1,5-dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XX) in methanol.

(XV)[14] which had been construed as arising from a 1,2-shift of unknown mechanism.[15] It was shown[14] that the benzoylformamide of anthranilic acid (XVI) was not an intermediate in the formation of XV. This reaction can be rationalized by assuming initial oxidation to the quinolone, followed by attack at the double bond. Oxidation now between C_2–C_3 leads to a diketone which cyclizes after decarboxylation. Oxidation of the imino ketone now gives the observed product. By an analogous mechanism, 3-methyl-1,5-naphthyridine (IV) would give 3-acetamidopicolinic acid (XVII), as it does. This mechanism provides a satisfactory explanation for the behavior of 3-methyl-1,5-naphthyridine on oxidation. And, of course, the side-chain oxidation observed with 3-ethyl-1,5-naphthyridine is quite reasonable. We have no explanation for the difference in behavior between the 3-methyl and 3-ethyl compounds.

In a continuation of oxidation experiments, 3-methyl-1,5-naphthyridine was heated with dichromate in 6 N sulfuric acid. The product was assigned the structure 3 - methyl - 1,5 - naphthyridin - 2(1*H*) - one (XVIII) on the basis of its infrared absorption and the similarity of its ultraviolet spectrum with those of naphthyridinones (Fig. 2) prepared through the methiodides. This mode of acidic oxidation of the alkyl naphthyridine is consistent with the high yield of acetic acid obtained in the Kuhn–Roth oxidation.

The N-methylnaphthyridinones were prepared by alkaline ferricyanide oxidation of the corresponding methiodides. Thus, 1,5-naphthyridine was quaternized and oxidized to the mononaphthyridinone (XIX); the process was repeated to obtain the naphthyridinedione (XX). In the case of the ethylnaphthyridine, the mixture of methiodides was oxidized directly to give the 1-methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one (XXI) and 1,5-dimethyl-3-ethyl-1,5-naphthyridine-2,6-(1*H*,5*H*)-dione (XXII).



Since several substituted naphthyridines were on hand, an examination of their infrared spectra in carbon disulfide was made in an attempt to correlate the aromatic hydrogen out-of-plane vibrations in the 650–1000-cm.$^{-1}$ region with the position of substitution. Previous correlations for this region have led to the assignments for substituted benzenes[16] of 750–810 cm.$^{-1}$ for three adjacent ring hydrogens, 800–860 cm.$^{-1}$ for two adjacent ring hydrogens, and 860–900 cm.$^{-1}$ for an isolated ring hydrogen. These assignments seem to be valid for pyridines and quinolines as well[17]; however, in the naphthyridines examined here, the values are shifted to higher frequencies (Table I). The spectrum of 1,2,3,4-tetrahydro-1,5-naphthyridine (III) shows the expected peak for three adjacent ring hydrogens at 790 cm.$^{-1}$; however, although 1,5-naphthyridine (I) and 2-methyl-1,5-naphthyridine (IVa) have this peak at 816 cm.$^{-1}$ and 818 cm.$^{-1}$, respectively, 4-methyl-1,5-naphthyridine (IVb) absorbs at 786 cm.$^{-1}$. The latter two compounds show peaks at 837 cm.$^{-1}$ and 845 cm.$^{-1}$, respectively, for two adjacent ring hydrogens. For 1,7-naphthyridine (II) and 8-chloro-1,7-naphthyridine (VII), the peaks for three adjacent hydrogens appear at 818 cm.$^{-1}$ and 801 cm.$^{-1}$, respectively.[18] There may be some doubt as to whether the slightly weaker peak at 764 cm.$^{-1}$ might not be due to three adjacent hydrogens, but since this band disappears along with the band at 943 cm.$^{-1}$

(14) K. Ueda, *J. Pharm. Soc. Japan*, **57**, 827 (1937).

(15) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 256.

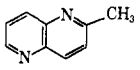
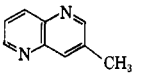
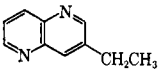
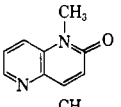
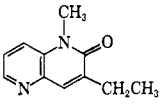
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co., London, 1958, p. 75.

(17) H. Shindo and S. Tamura, *Pharm. Bull.* (Tokyo), **4**, 292 (1956); H. Shindo, *ibid.*, **5**, 472 (1957); C. Karr, P. A. Estep, and A. J. Papa, *J. Am. Chem. Soc.*, **81**, 152 (1959).

(18) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 404 (1958), has reported the infrared spectrum of 1,7-naphthyridine in Nujol and it appears to be quite different from ours except for the strong band at 818 cm.$^{-1}$. Consequently, his assignments differ from ours.

TABLE I

INFARED[a] ASSIGNMENTS FOR AROMATIC HYDROGEN OUT-OF-PLANE VIBRATIONS IN 1,5- AND 1,7-NAPHTHYRIDINES

	Compound	Assignments, ν in cm.$^{-1}$ 3 adjacent H's	2 adjacent H's	Isolated H
III		790	...	...
I		816	...	...
IVa		818	837	...
IVb		786	845	...
IV		823	...	890, 773
V		821	...	904, 772
II		818	838	943, 764
VII		801	841	...
XIX		796	841	...
XXI		797	...	912, 754

[a] In carbon disulfide.

when the isolated hydrogen at position 8 is replaced with chlorine, these latter two peaks have been assigned to the isolated ring hydrogen. The spectrum of 1-methyl-1,5-naphthyridin-2(1*H*)-one (XIX) has bands at 796 cm.$^{-1}$ and 841 cm.$^{-1}$ for three and two adjacent ring hydrogens, respectively. The peak at 841 cm.$^{-1}$ disappears when there is an ethyl group at the 3-position (XXI) and two new bands of medium intensity appear for the isolated hydrogen at 912 cm.$^{-1}$ and 754 cm.$^{-1}$. The spectra of 3-methyl- (IV) and 3-ethyl-1,5-naphthyridine (V), which seemed complex at first, now can be interpreted on the basis of previous correlations. The strong peak near 900 cm.$^{-1}$ accompanied by another strong peak near 770 cm.$^{-1}$ is due to the two isolated hydrogens and the band near 820 cm.$^{-1}$ is due to three adjacent ring hydrogens.

Experimental[19]

Skraup Reaction with 3-Aminopyridine.—To a 12-l. flask were added the following ingredients in sequence: 280 g. (1.2 moles) of arsenic pentoxide, 80 g. (0.53 mole) of ferrous sulfate, 220 g. (2.34 moles) of pure 3-aminopyridine, a solution prepared by heating on the steam bath 140 g. (2.3 moles) of boric acid, 830 g. (10 moles) of anhydrous glycerine, and 2 ml. of concentrated sulfuric acid, 240 ml. of concentrated sulfuric acid, and 30 ml. of fuming (15%) sulfuric acid. The reaction mixture was stirred and heated to 100°, and after the initial reaction had subsided, it was heated during 2 hr. to a final internal temperature of 135°. This temperature was maintained for 3 additional hr. The black reaction mixture was made basic and steam distilled until the optical density of the distillate at 304 mμ was less than 10. The distillate (20 l.) was adjusted to pH 3.1 with phosphoric acid and extracted continuously with pentane. Evaporation of the pentane gave 95 g. of semicrystalline product. This material showed three peaks by vapor phase chromatography (v.p.c.).

The residual pH 3 aqueous phase was made alkaline with sodium hydroxide and continuously extracted with ether to yield 34 g. of oil after evaporation of the ether. Fractionation through a 1-m. Podbielniak column gave the following two fractions.

Fraction A-1, 18.3 g. (8% recovery), b.p. 118–120° (44 mm.), was crystallized from benzene–hexane, m.p. 59–61°. It was identical with 3-aminopyridine by melting point, mixture melting point, and infrared and ultraviolet absorption; λ_{max} 303 mμ (ϵ 3200), 242 (11,000).

Fraction A-2 amounted to 15.5 g. (5% yield), b.p. 117–120° (18 mm.). Crystallization from benzene–hexane followed by sublimation at 80° (50 μ) gave 1,2,3,4-tetrahydro-1,5-naphthyridine (III), m.p. 109–111° (reported[8] m.p. 105°); λ_{max} 321 mμ (ϵ 3960), 258 (8830), 209 (9390).

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.6; H, 7.5; N, 20.9. Found: C, 71.7; H, 7.3; N, 20.9.

When the Skraup reaction was repeated, using an increased reaction time of 20 hr. at 135°, a total of 34 l. of steam distillate was collected. Using the same isolation procedure, the pH 3 pentane extract amounted to 118 g., while the alkaline ether extract amounted to only 2 g. The pH 3 extract showed the same three peaks by v.p.c. as previously, and fractionation through a 1-m. Podbielniak column separated this extract into three fractions, N-1, N-2, and N-3.

The fraction N-1, 87.4 g. (31% yield), b.p. 150–152° (54 mm.), was crystallized from pentane to give 1,5-naphthyridine (I), m.p. 74–75° (reported[1,4] m.p. 75°); λ_{max} 250 mμ (ϵ 4430), 259 (4300), 268 (3210), 297 (5620), 304 (6130), 309 (5970); in acid, 235 (5160), 275 (4900), 307 (11,200), 312 (11,400), 363 (1890).

Anal. Calcd. for $C_8H_6N_2$: C, 73.8; H, 4.6; N, 21.5. Found: C, 73.6; H, 4.5; N, 21.4.

Fraction N-2, 14.7 g. (4.4% yield), b.p. 173–175° (56 mm.), was crystallized from pentane and sublimed at 60° (0.2 mm.) to give 3-methyl-1,5-naphthyridine (IV), m.p. 73–75°; λ_{max} 252 mμ (ϵ 4130), 259 (3720), 268 (2390), 302 (6300), 308 (6800), 314 (6700); in acid, 321 (11,000), 313 (10,400 sh), 276 (3090 sh).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4; equiv. wt., 144; C–CH_3, 10.4. Found: C, 75.1; H, 5.7; N, 19.5; equiv. wt., 140; C–CH_3, 8.2.

Fraction N-3 amounted to 15.5 g. (4.4%) of 3-ethyl-1,5-naphthyridine (V), b.p. 181–182° (56 mm.), λ_{max} 251 mμ (ϵ 4700), 259 (3900), 268 (2760), 303 (6800), 315 (6700).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7; equiv. wt., 158; C–CH_3, 9.5. Found: C, 76.1; H, 6.5; N, 17.7; equiv. wt., 153; C–CH_3, 7.0.

3-Methyl-1,5-naphthyridine (IV).—A stirred suspension of 2 g. of ferrous sulfate, 14 g. (0.06 mole) of arsenic pentoxide, 9.4 g. (0.10 mole) of 3-aminopyridine, and 30 ml. of concentrated sulfuric acid was heated to 120° (bath temp.) and 15 ml. of methylacrolein was added dropwise over 2 hr. After 4 hr., an additional 17 ml. (total, 0.4 mole) of methylacrolein was added over 1 hr. The resultant mixture was heated for 15 hr. at 170°. Isolation in the usual manner gave 4.3 g. (30% yield) of 3-methyl-1,5-naphthyridine which was crystallized from pentane, and sublimed at 50° (0.2 mm.); m.p. 73–75°. This material was identical with fraction N-2.

2-Methyl-1,5-naphthyridine (IVa).—A solution of 70 ml. of "sulfo mix,"[20] 25 ml. of water, and 23.5 g. (0.25 mole) of 3-aminopyridine was heated to 125–130° and freshly distilled crotonaldehyde (25 ml., 0.3 mole) was added dropwise over an hour. The bath was raised to 150° and the reaction mixture was heated overnight. The usual isolation procedure gave 3 g. of material which was chromatographed on alumina and sublimed at 40° (0.1

(19) All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley. Ultraviolet spectra were determined in methanol, and those in acid (1 *N* hydrochloric acid) and in alkali (0.1 *N* sodium hydroxide) were taken in 90% aqueous methanol. Infrared spectra were taken in carbon disulfide unless otherwise noted. Vapor phase chromatograms were obtained at 140° using a 1.5-m. column packed with silicone grease on firebrick.

(20) W. P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

mm.) to give 2-methyl-1,5-naphthyridine, m.p., 60–61° (reported[8] m.p. 62°); λ_{max} 242 mμ (ε 3790 sh), 249 (4000), 257 (3740), 265 (2700), 300 (5450), 307 (5930), 313 (5600); in acid, 317 (10,200), 308 (9700), 264 (4680).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4; C–CH_3, 10.4. Found: C, 74.7; H, 5.7; N, 19.1; C–CH_3, 5.1.

2-Styryl-1,5-naphthyridine.—A solution of 0.5 ml. of glacial acetic acid, 1.0 ml. of acetic anhydride, 1.0 ml. of benzaldehyde, and 1.04 g. (7.2 mmoles) of 2-methyl-1,5-naphthyridine was heated at reflux for 2 days under a nitrogen atmosphere. Hydrochloric acid (100 ml. of 3 *N*) was added; the solution was extracted with methylene chloride (five 25-ml. portions), back-washing each time with acid. The aqueous phase and washings were combined, made alkaline, and extracted with chloroform to give a total of 1.2 g. of material. A sample was sublimed at 100° (10 μ), and crystallized from hexane–benzene to give 2-styryl-1,5-naphthyridine, m.p. 120–121°; λ_{max} 218 mμ (ε 46,500), 262 (16,500), 270 (16,000), 300 (16,000), 339 (21,200); in acid, 292 (16,700), 306 (11,000), 385 (33,000).

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.7; H, 5.2; N, 12.1. Found: C, 82.9; H, 5.1; N, 12.1.

4-Methyl-1,5-naphthyridine (IVb).—The same procedure was used as for the preparation of the 2-methyl compound, except that 18 g. (0.26 mole) of methyl vinyl ketone was substituted for the crotonaldehyde. The yield was 4.0 g. (11%) of 4-methyl-1,5-naphthyridine, m.p. 30–32°; λ_{max} 257 mμ (ε 5370), 265 (5880), 273 (4660), 296 (5030), 303 (5410), 308 (5430); in acid, 281 (7500), 304 (10,500), 309 (10,000).

Anal. Calcd. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4. Found: C, 74.6; H, 5.7; N, 19.0.

3-Ethyl-1,5-naphthyridine (V).—To a 3-l. flask were added 3 g. of ferrous sulfate, 35 g. (0.15 mole) of arsenic pentoxide, 23.5 g. (0.25 mole) of 3-aminopyridine, 90 g. (0.75 mole) of 2-hydroxymethyl-2-methyl-1,3-propanediol, 15.5 g. (0.25 mole) of boric acid, and 140 ml. of concentrated sulfuric acid. This mixture was stirred and heated until the internal temperature reached 150° at which point the reaction became violent and the heat source was removed. Heating was resumed when the reaction had subsided, and the temperature was maintained at 130° for 4 hr. The usual naphthyridine isolation procedure gave 5.5 g. of liquid which was fractionated and gave 5.0 g. of 3-ethyl-1,5-naphthyridine, b.p. 162–170° (40 mm). This material was identical with fraction N-3.

1,2,3,4-Tetrahydro-1,5-naphthyridine (III).—A suspension of 13 mg. of platinum oxide in a solution of 1.31 g. (10 mmoles) of 1,5-naphthyridine in 10 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure. After 26 hr., absorption ceased with an uptake of 200 mole % of hydrogen. The mixture was filtered, the filtrate was evaporated, and the residue was sublimed at 80° (50 μ) to give a quantitative yield of 1,2,3,4-tetrahydro-1,5-naphthyridine, m.p. 111–113°. This material was identical with fraction A-2.

1,7-Naphthyridin-8(7*H*)-one (VI).—This material was prepared as described[11] except that "sulfo mix"[20] was used. The crude product was purified by crystallization from methanol and sublimation at 180° (10 μ); yield, 90%; m.p. 236–239° (reported[11] yield, 20%, m.p. 233.5°).

8-Chloro-1,7-naphthyridine (VII).—1,7-Naphthyridin-8(7*H*)-one (VI) (17.5 g., 0.12 mole) and 125 g. of phosphorus oxychloride were heated at reflux overnight. Excess phosphorus oxychloride was distilled *in vacuo*, the residue was treated with 200 g. of ice–water, the pH was adjusted to 5 with sodium hydroxide, and the aqueous phase was extracted continuously with methylene chloride. Evaporation of the methylene chloride and sublimation of the residue at 80° (0.5 mm.) gave 11.5 g. (58% yield) of 8-chloro-1,7-naphthyridine which, on crystallization from benzene–hexane, melted at 87–88°; λ_{max} 228 mμ (ε 25,000), 268 (4100), 308 (3600), 319 (3200).

Anal. Calcd. for $C_8H_5N_2Cl$: C, 58.4; H, 3.1; Cl, 21.5. Found: C, 58.3; H, 3.3; Cl, 21.6.

8-Hydrazino-1,7-naphthyridine (VIII).—A solution of 8.02 g. (0.049 mole) of 8-chloro-1,7-naphthyridine (VII) in 55 ml. of ethanol and 23 ml. (0.40 mole) of 85% hydrazine hydrate was heated to a boil on the steam bath for 10 min. Evaporation of the ethanol *in vacuo* left an oil which solidified and was sublimed at 100° (0.1 mm.), giving 7.73 g. (99% yield) of 8-hydrazino-1,7-naphthyridine, m.p. 98–99°; λ_{max} 229 mμ (ε 12,200), 247 (12,700), 316 (4140), 346 (4460).

Anal. Calcd. for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0. Found: C, 59.9; H, 5.2; N, 34.8.

1,7-Naphthyridine (II).—To a solution of 2.68 g. (0.017 mole) of 8-hydrazino-1,7-naphthyridine (VIII) in 25 ml. of water and 6 ml. of acetic acid was added dropwise 60 ml. of a 10% aqueous solution of cupric sulfate. The resulting mixture was heated on the steam bath until gas evolution ceased (45 min.) and cautiously made alkaline with concentrated sodium hydroxide. Continuous extraction with methylene chloride and evaporation of the solvent left a residue which was dissolved in benzene and chromatographed on alumina. The crystalline eluate was sublimed at 60° (0.1 mm.) to give 500 mg. of 1,7-naphthyridine, m.p. 60–62° (reported m.p., 57–60°,[10] 64°[4]); λ_{max} 219 mμ (ε 26,600 sh.), 262 (3820), 302 (2130), 313 (1930).

Anal. Calcd. for $C_8H_6N_2$: C, 73.8; H, 4.7; N, 21.5. Found: C, 73.9; H, 4.7; N, 21.6.

1,5-Naphthyridine-3-carboxylic Acid (XIII).—To a stirred solution of 8.9 g. (0.057 mole) of 3-ethyl-1,5-naphthyridine (V) in 100 ml. of water heated to 70° was added 36 g. (0.23 mole) of potassium permanganate in six equal portions over 1 hr. The suspension was heated for an additional 30 min. and filtered. Manganese dioxide residue was digested with hot water (three 20-ml. portions); these digests were added to the filtrate. Filtrate (pH 9) was extracted continuously with methylene chloride to recover 3.6 g. (40%) of 3-ethyl-1,5-naphthyridine. Adjusting the aqueous phase to pH 3.0 with phosphoric acid and extracting continuously with chloroform gave 2.4 g. of 1,5-naphthyridine-3-carboxylic acid, m.p. 279° after sublimation at 150° (5 μ); λ_{max} 213 mμ (ε 55,000), 254 (8560), 303 (7400), 310 (7200), 316 (7170); in alkali, 246 (8210), 304 (7240), 309 (7470), 317 (7430); in acid, 258 (6800), 312 (10,400), 318 (10,700).

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.1; H, 3.5; N, 16.1; equiv. wt., 174. Found: C, 62.2; H, 3.4; N, 16.2; equiv. wt., 175.

1,5-Naphthyridine-3-carboxamide was prepared by treating the acid with thionyl chloride, evaporating the excess thionyl chloride, and adding concentrated aqueous ammonia to the residue. Extraction with chloroform, evaporation of the chloroform, crystallization of the residue from methanol–acetone and sublimation at 150° (10 μ) gave the **amide**, m.p. 257°.

Anal. Calcd. for $C_9H_7N_3O$: C, 62.4; H, 4.0. Found: C, 62.6; H, 4.2.

3-Acetamidopicolinic Acid (XVII).—The oxidation procedure was the same as that used for the ethyl compound. From 10.9 g. (76 mmoles) of 3-methyl-1,5-naphthyridine (IV) and 53 g. (33 moles) of potassium permanganate there was obtained a 37% (4.0 g.) recovery of starting material, and a 30% yield (4.5 g.) of 3-acetamidopicolinic acid, m.p. 212° dec. after sublimation at 150° (10 μ); λ_{max} 254 mμ (ε 16,500), 307 (6700); in alkali, 251 (18,700), 293 (6200); in acid, 229 (18,100), 262 (13,400), 318 (5800); λ_{max}^{KBr} 5.95, 6.04 μ.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.3; H, 4.6; N, 15.6; equiv. wt., 180; C–CH_3, 8.3. Found: C, 53.8; H, 4.4; N, 15.8; equiv. wt., 177; C–CH_3, 7.6.

This material was decarboxylated in boiling *p-tert*-butyltoluene to give **3-acetamidopyridine**, m.p. 129–131°, identical with an authentic sample prepared by acetylation of 3-aminopyridine.

3-Methyl-1,5-naphthyridin-2(1*H*)-one (XVIII).—To a solution of 4.0 g. (28 mmoles) of 3-methyl-1,5-naphthyridine (IV) in 100 ml. of 6 *N* sulfuric acid heated at 100° was added dropwise a solution of 8.4 g. (28 mmole) of sodium dichromate dihydrate over 2 hr. Heating was continued overnight, and the solution then was cooled and the pH adjusted to 3.1 with sodium hydroxide. This suspension was filtered and continuously extracted with chloroform. The residue obtained on evaporation of the solvent was dissolved in aqueous sodium carbonate and again extracted with chlofororm. Evaporation of the chloroform gave 2.7 g. of material which was chromatographed on alumina. Methylene chloride eluted 2.3 g. (57%) of starting material. Water removed the remaining material which was extracted at pH 7 with chloroform. The chloroform was evaporated and the residue was sublimed at 100° (10 μ) to give 400 mg. of 3-methyl-1,5-naphthyridin-2(1*H*)-one, m.p. 261–262°; λ_{max} 219 mμ (ε 36,000), 329 (14,700), 342 (10,700); in acid, 224 (24,000), 261 (4600), 340 (17,000), 353 (16,000).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.2; H, 4.9; N, 17.6.

1,5-Naphthyridine Methiodide.—To a solution of 1.00 g. (7.7 mmoles) of 1,5-naphthyridine (I) in 10 ml. of methanol was added 5 ml. (70 mmoles) of methyl iodide and the solution was heated at reflux for 12 hr. on the steam bath. The excess methyl iodide was allowed to boil off and the methanol solution was cooled to

yield 1.6 g. of 1,5-naphthyridine methiodide, m.p. 254–255° dec.; λ_{max} 288 mμ (5500), 319 (10,100), 326 (10,100); in acid, 268 (6250), 311 (11,900), 318 (12,100), 362 (2500).

Anal. Calcd. for $C_9H_9N_2I$: C, 39.7; H, 3.3; N, 10.3; I, 46.6. Found: C, 39.4; H, 3.3; N, 10.0; I, 46.4.

1-Methyl-1,5-naphthyridin-2(1*H*)-one (XIX).—To a stirred solution of 2.0 g. (7.7 mmoles) of 1,5-naphthyridine methiodide in 20 ml. of water, cooled in an ice–methanol bath, was added dropwise a solution of 1.3 g. (32 mmoles) of sodium hydroxide in 2.5 ml. of water during 5 min. and 5.3 g. (16 mmoles) of potassium ferricyanide in 10 ml. of water during 30 min., both additions starting at the same time. After 1.5 hr., the ice bath was removed and stirring was continued for an additional 5 hr. at room temperature. Continuous extraction of the reaction mixture with chloroform and evaporation of the chloroform led to 0.8 g. of residue which was dissolved in 5 ml. of chloroform and applied to 30 g. of alumina packed in benzene. The fractions eluted with chloroform–benzene (2:1) were combined and sublimed at 95° (5 μ) to give 685 mg. (56% yield) of 1-methyl-1,5-naphthyridin-2(1*H*)-one, m.p. 104–105°; λ_{max} 220 mμ (ε 39,900), 335 (11,000), 350 (7500); in acid, 223 (28,000), 261 (6200), 345 (11,700).

Anal. Calcd. for $C_9H_8ON_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.4; H, 5.0; N, 17.0.

1-Methyl-1,5-naphthyridin-2(1H)-one methiodide was prepared by heating under reflux for 2 days a solution of the naphthyridinone XIX and methyl iodide in benzene. Cooling and filtering gave a precipitate of methiodide which was crystallized from methanol–ether as orange needles, m.p. 216° dec.

Anal. Calcd. for $C_{10}H_{11}N_2OI$: C, 39.8; H, 3.7; N, 9.3; I, 42.0. Found: C, 39.9; H, 3.8; N, 9.0; I, 42.3.

1,5-Dimethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XX).—To a stirred solution of 3.0 g. (10 mmoles) of 1-methyl-1,5-naphthyridin-2(1*H*)-one methiodide in 25 ml. of water, cooled in an ice bath, were added a 5-ml. portion of a solution of 2.8 g. (70 mmoles) of sodium hydroxide in 25 ml. of water and a solution of 10 g. (30 mmoles) of potassium ferricyanide in 50 ml. of water. The remaining 20 ml. of alkali solution was added portionwise over a 5 min. period and the suspension was stirred for 15 min. Continuous extraction with chloroform and evaporation of the chloroform afforded 1.8 g. of crystalline material which was sublimed [190° (10 μ)] and recrystallized from methanol–acetone as yellow needles, m.p. 220–222° dec.; λ_{max} 233 mμ (ε 66,000), 387 (13,000), 405 (11,400).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.2; H, 5.1; N, 14.7.

1-Methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one (XXI) and 1,5-Dimethyl-3-ethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione (XXII).—A solution of 2.0 g. (13 mmoles) of 3-ethyl-1,5-naphthyridine (V) in 25 ml. of dry benzene and 10 ml. of methyl iodide was heated on the steam bath for 2 days. The benzene and excess methyl iodide were removed *in vacuo*, and to the residue was added 6 g. (50 mmoles) of potassium ferricyanide in 25 ml. of water. This solution was cooled to 5° in an ice bath, and 13 g. (0.33 mole) of sodium hydroxide in 20 ml. of water was added slowly with stirring. After an hour, the solution was extracted with chloroform, the chloroform was evaporated, and the residue taken up in 3 *N* hydrochloric acid. Extraction with chloroform and evaporation of the chloroform led to the isolation of a yellow solid which was sublimed at 150° (10 μ) to give 479 mg. (17% yield) of 1,5-dimethyl-3-ethyl-1,5-naphthyridine-2,6(1*H*,5*H*)-dione, m.p. 261–262°; λ_{max} 234 mμ (ε 47,000), 383 (15,000), 402 (12,000).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8. Found: C, 66.1; H, 6.5; N, 12.8.

The acid solution was made alkaline and extracted with methylene chloride which was filtered through alumina. Evaporation of the filtrate gave a white solid which was sublimed at 80° (50 μ) to give 335 mg. (14% yield) of 1-methyl-3-ethyl-1,5-naphthyridin-2(1*H*)-one, m.p. 107–108°; λ_{max} 221 mμ (ε 37,000), 248 (5000), 330 (13,000), 343 (9400); in acid, 219 (25,000), 262 (5900), 343 (16,500), 355 (15,900).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.3; H, 6.4; N, 14.8.

Determination of pK_a values was carried out by partitioning the base between an organic solvent (hexane or ether) and aqueous phosphate buffer at various pH values. Concentrations were determined spectrophotometrically, and the pK_a values were calculated from the equation

$$\frac{P}{P'} = 1 + \frac{(H^+)}{K_a}$$

where P is the true partition coefficient and P' is the apparent partition coefficient at the specific pH.

New Heteroaromatic Compounds. XVII.[1] Fluoro Derivatives of 10-Methyl-10,9-borazarophenanthrene[2]

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Four monofluoro derivatives of 10-methyl-10,9-borazarophenanthrene have been synthesized in the hope that their fluorine n.m.r. chemical shifts may provide information concerning the π-electron distribution. In the course of this work a number of new derivatives of biphenyl have been prepared.

The chemical shifts shown by the fluorine nuclear magnetic resonance in derivatives of fluorobenzene seem to reflect the π-electron density of the ring atom adjacent to fluorine.[3] It occurred to us that the corresponding chemical shifts in monofluoro derivatives of heteroaromatic systems might be used to prepare π-electron density maps of the rings and so used to check the predictions of current MO treatments.

One particularly interesting system from this point of view is 10,9-borazarophenanthrene,[4] and, therefore, we decided to synthesize as many as possible of its eight monofluoro derivatives. For convenience we included a methyl substituent in the 10-position since the parent compounds, being in effect boron hydrides, tend to oxidize rather easily in air. Unfortunately these compounds proved unexpectedly recalcitrant and we were able to obtain only four of the isomers, with fluorine in the 2-, 3-, 6-, and 7-positions.

The fluorine n.m.r. spectra of these compounds, together with those of a number of other fluoro derivatives of various aromatic systems, will be reported elsewhere and discussed. Here we describe the synthesis of the four fluoroborazarophenanthrenes, and of various new derivatives of biphenyl which we obtained as intermediates.

In order to obtain the various fluoroborazarophenanthrenes, we needed[4] the corresponding fluoro derivatives of 2-aminobiphenyl, and the most obvious route

(1) Part XVI, M. J. S. Dewar, C. Kaneko, and M. K. Bhattacharjee, *J. Am. Chem. Soc.*, **84**, 4884 (1962).

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(3) *Cf.* R. W. Taft, S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).

(4) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).