Synthesis of Substituted 1,5- and 1,7-Naphthyridines and Related Lactams[1]

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Reductive cyclization of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate and of ethyl 6-methoxy-3-nitro-2-pyridinepyruvate afforded the corresponding 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one and 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one. Treatment of the latter compounds with *p*-toluenesulfonyl chloride in pyridine afforded 6-methoxy-1,7-naphthyridin-2(1*H*)-one and 6-methoxy-1,5-naphthyridin-2(1*H*)-one, which by treatment with phosphorus oxychloride were transformed into 2-chloro-6-methoxy-1,7-naphthyridine, 2-chloro-6-methoxy-1,5-naphthyridine, and 2,6-dichloro-1,5-naphthyridine. The 2-chloronaphthyridines were transformed into 2-hydrazinonaphthyridines and reduced with cupric ion to the parent naphthyridines. 2-Chloro-1,5-naphthyridine afforded 2-methoxy-1,5-naphthyridine by mild treatment with sodium methoxide. Hydrogenation of 6-methoxy-1,7-naphthyridin-2(1*H*)-one afforded 1,2,3,4-tetrahydro-6-methoxy-1,7-naphthyridin-2-one. Treatment of 6-methoxy-1,7-naphthyridin-2(1*H*)-one and its 1,5 analog with hydrogen bromide afforded the 1,2,6,7-tetrahydro-1,7-naphthyridine-2,6-dione and 1,2,6,7-tetrahydro-1,5-naphthyridine-2,6-dione, which were reduced to the *cis*-decahydro-1,7- and -1,5-naphthyridine-2,6-diones. The bicyclic lactams could not be hydrolyzed to the amino acids, which were prepared by acid hydrolysis of *meso*- and *rac*-2,2′-bi(pyrrolidine)-5,5′-dione. When the diethyl *meso*- and *rac*-4,5-diaminosuberate dihydrochlorides were equilibrated at pH 7.5, they cyclized to the six-membered bicyclic lactams, *trans*- and *cis*-decahydro-1,5-naphthyridine-2,6-dione, respectively.

In a previous paper[2] we reported that the reductive cyclization of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (1) proceeded in good yield to ethyl 5-methoxy-6-azaindole-2-carboxylate or, alternatively, yielded 1,2,3,-4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one (2). The determining factor was the catalyst used in the respective procedures, palladium on carbon or platinum oxide. Since then we have described the synthesis of a considerable number of substituted 6-azaindoles and 4-azaindoles,[3,4] obtained by reductive cyclization, using palladium on carbon, of substituted pyridinepyruvates of type **1** and **11**. We now report the synthesis of the corresponding 1,5- and 1,7-naphthyridine derivatives obtained from the same precursors by the alternative pathway, reductive cyclization using platinum oxide.

The existing synthetic methods for naphthyridines are quite limited in scope.[5] The classical Skraup-type reaction on 3-aminopyridine was improved and used for the synthesis of 1,5-naphthyridine and its alkyl derivatives.[6] 1,7-Naphthyridine and its 6-amino derivative were recently[7] obtained by an intramolecular acid cyclization of 2-cyano-3-pyridylacetonitrile. Since the ethyl *o*-nitropyridinepyruvates **1** and **11** can be easily prepared on a large scale,[3,4] they provide excellent starting materials for the synthesis of new 1,7- and 1,5-naphthyridine derivatives. The procedure described[2] for the synthesis of the ethyl pyridinepyruvate **1** was found to be useful for the synthesis of analogous ethyl *o*-nitro-4- and -2-pyridinepyruvates,[8,9] therefore, the proposed naphthyridine synthesis undoubtedly can be extended to a large number of compounds. Moreover, ethyl 2-methoxy-3-nitro-4-pyridinepyruvate (**1**) and ethyl 6-methoxy-3-nitro-2-pyridinepyruvate (**11**) can be C-alkylated and C-acylated to a number of derivatives, thus greatly increasing the number and variation of substituted 1,7- and 1,5-naphthyridines obtainable.

Discussion

The reductive cyclization of the ethyl pyridinepyruvates **1** and **11** can proceed in two directions: either a new five-membered ring can be formed giving an azaindole, or a new six-membered ring can be formed and a tetrahydronaphthyridine obtained. Formation of a five-membered ring can be expected to prevail as long as the carbonyl group is available. This is the case under mild hydrogenation conditions, in ethanol over 10% palladium on charcoal.[3,4] However, if the reaction is carried out over a relatively large amount of platinum oxide (20%), then the carbonyl group is reduced and the 3-oxynaphthyridinones **2** and **12** are obtained in good yields as the only products of the reaction. It is crucial for the course of the reaction to have the pyridinepyruvates highly purified, otherwise partial inactivation of the catalyst leads to a mixture of azaindole and naphthyridine.

The tetrahydronaphthyridines **2** and **12** are readily dehydrated by treatment with *p*-toluenesulfonyl chloride in pyridine and the corresponding 1,7- and 1,5-naphthyridinones **3** and **13** were obtained. A strong band at 1690 cm^{-1} in the ir indicated that compounds **3** and **13** exist in the lactam form, as expected, and not as 2-hydroxynaphthyridines. The amide band in the tetrahydronaphthyridines **2** and **12** was also at 1690

(1) This work was supported by the Consejo Nacional de Investigaciones and Secretaria de Salud Publica (Argentina) and the National Institutes of Health, U. S. Public Health Service.

(2) B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965).

(3) B. Frydman, S. J. Reil, J. Boned, and H. Rapoport, *J. Org. Chem.*, **33**, 3762 (1968).

(4) B. Frydman, S. J. Reil, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 2338 (1969).

(5) For references on naphthyridine ring synthesis prior to 1960, see M. J. Weiss in R. C. Elderfield, *Heterocycl. Compounds*, **7**, 198 (1961). Recent naphthyridine syntheses are (a) Skraup-type [W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **31**, 3055 (1966); **32**, 832 (1967); W. Czuba, *Rocz. Chem.*, **41**, 289 (1967)]; (b) ethoxymethylenemalonic ester method [A. Albert and W. L. Armarego, *J. Chem. Soc.*, 4237 (1963); G. Y. Lesher, U. S. Patent 3,429,887 (1968); *Chem. Abstr.*, **70**, 344 (1969)]; (c) *via o*-disubstituted pyridines [H. E. Baumgarten, H. C. F. Su, and R. R. Barkley, *J. Heterocycl. Chem.*, **3**, 357 (1966); F. Zymalkowski and P. Messinger, *Arch. Pharm.*, **300**, 91 (1967)]; (d) *via* ammonia insertion in azachromanones [S. A. Vartanyan and Sh. L. Sagbatyan, *Khim. Geterotsikl. Soedin*, **3**, 427 (1966)].

(6) H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

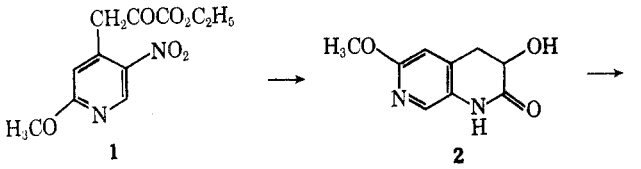
(7) R. Tam and A. Taurins, *Tetrahedron Lett.*, 1233 (1966).

(8) L. N. Yakhontov, V. A. Azimov, and E. I. Lapan, *ibid.*, 1909 (1969).

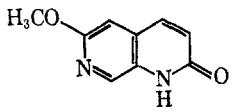
(9) M. H. Fisher and A. R. Matzuk, *J. Heterocycl. Chem.*, **6**, 775 (1969).

cm^{-1} and in the naphthyridinone **19** (prepared by an independent synthesis)[10] it was at 1700 cm^{-1}.

The transformation of the naphthyridinones, **3** and **13**, into naphthyridines was achieved by treatment with phosphorus oxychloride. In this step the properties of the 1,7-naphthyridine and 1,5-naphthyridine series diverged. While the 6-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) was easily transformed into the 2-chloro-1,7-naphthyridine (**4**), the analogous 6-methoxy-1,5-naphthyridinone (**13**) was demethylated and yielded the 2,6-dichloro-1,5-naphthyridine (**15**). However, when the reaction was carried out at room temperature for several days, demethylation was avoided, and 2-chloro-6-methoxy-1,5-naphthyridine (**14**) was obtained. Hydrogenolysis of the chloronaphthyridines was accompanied by ring reduction; the 2-hydrazino derivatives were then prepared and reduced with cupric sulfate to the corresponding naphthyridines. The 2,6-dichloro-1,5-naphthyridine (**15**) yielded only a monohydrazino derivative **16** which was reduced to 2-chloro-1,5-naphthyridine (**17**). Treatment of **17** with sodium methoxide in boiling methanol readily yielded 2-methoxy-1,5-naphthyridine (**18**).



1 → **2**



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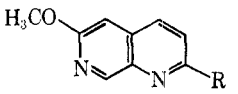
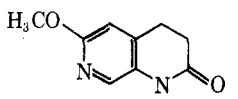


4, R = Cl
5, R = H_2NNH_2
6, R = H



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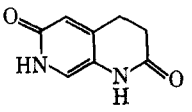

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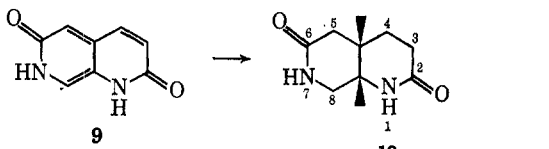
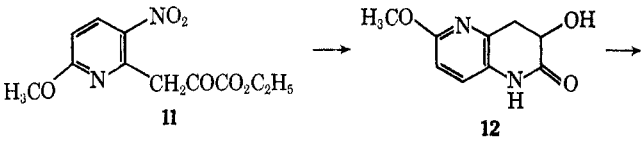
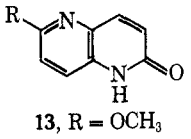


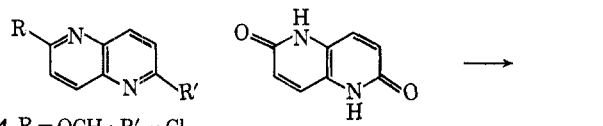
9 → **10**



11 → **12**

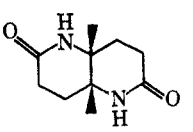


13, R = OCH_3
19, R = H



14, R = OCH_3; R′ = Cl
15, R = R′ = Cl
16, R = Cl; R′ = $NHNH_2$
17, R = Cl; R′ = H
18, R = OCH_3; R′ = H

20



21

It has already been noted that the hydrogenation of the 1,7- and 1,5-naphthyridine derivatives is difficult to control, often resulting in ring reduction. Thus, a controlled hydrogenation of **3** yielded the tetrahydro-1,7-naphthyridine **7**, but a similar hydrogenation of **13** resulted in overall ring reduction.[11] When the naphthyridine-2,6-diones **8**, **9**, and **20**, respectively, were prepared by treatment of **7**, **3**, and **13** with hydrobromic acid, they were smoothly reduced to the bicyclic lactams **10** and **21**. The naphthyridine-2,6-diones **9** and **20** existed predominantely in the α-pyridone form as shown by the strong amide band at 1690 cm^{-1} and by nmr data. The reduction of both compounds could potentially yield two pairs of diastereoisomeric lactams: the meso *cis*-decahydronaphthyridine-2,6-diones and the racemic *trans*-decahydronaphthyridine-2,6-diones. It was expected that the catalytic hydrogenation in acidic media would yield only the cis derivatives, and this was confirmed by the isolation of **10** and **21**. The bridge protons in **21** showed a sharp singlet at δ 4.4, and the bridge proton adjacent to the nitrogen in **10** was also a narrow singlet at δ 4.4, as expected from cis compounds. The bicyclic lactam **21** was reduced with lithium aluminum hydride to *cis*-decahydro-1,5-naphthyridine (**28**), identical with a sample of **28** prepared by a stereospecific reduction of 1,5-naphthyridine,[11] thus confirming the structure of **21**.

Surprisingly, the bicyclic lactams proved to be extremely resistent to hydrolysis. Mild treatments with various alkalis resulted in lactam recovery, and, when drastic conditions and a large excess of alkali were employed, no recognizable compounds could be isolated. When acidic hydrolysis conditions were invoked, lactam **21** was recovered unchanged and lactam **10** was partially hydrolyzed to **27**. The structure **27** was assigned on the basis of the nmr data. Attempted alkaline hydrolysis of **27** resulted in recovery of starting materials.[12] Since we were interested in comparing the stability of six-membered lactams *vs.* five-membered ones, we prepared the diaminosuberic esters **23** and **26**. Our starting material was the *meso*- and *rac*-2,2′-bi(pyrrolidine)-5,5′-diones (**22**) and (**25**), obtained photochemically by dimerization of 2-pyrrolidinone.[13] By an acid hydrolysis followed by esterification they were transformed into

(10) V. Petrov and B. Sturgeon, *J. Chem. Soc.*, 1157 (1949); modified according to ref 6.

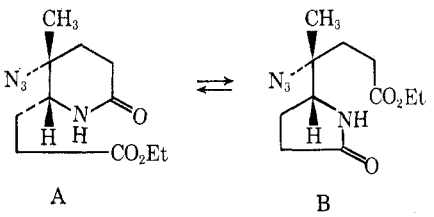
(11) Catalytic hydrogenation of 1,5-naphthyridine has been reported to yield decahydro-1,5-naphthyridine, but no decahydro-1,7-naphthyridine could be obtained by the same procedure: W. L. F. Armarego, *ibid.*, *C*, 377 (1967).

(12) It is noteworthy that the hydrolysis of five-membered bicyclic lactams was reported to proceed without difficulties: L. Birkofer and H. Feldmann, *Justus Liebigs Ann. Chem.*, **677**, 154 (1964).

(13) M. Pesaro, I. Felner-Caboga, and A. Eschenmoser, *Chimia*, **19**, 566 (1965).

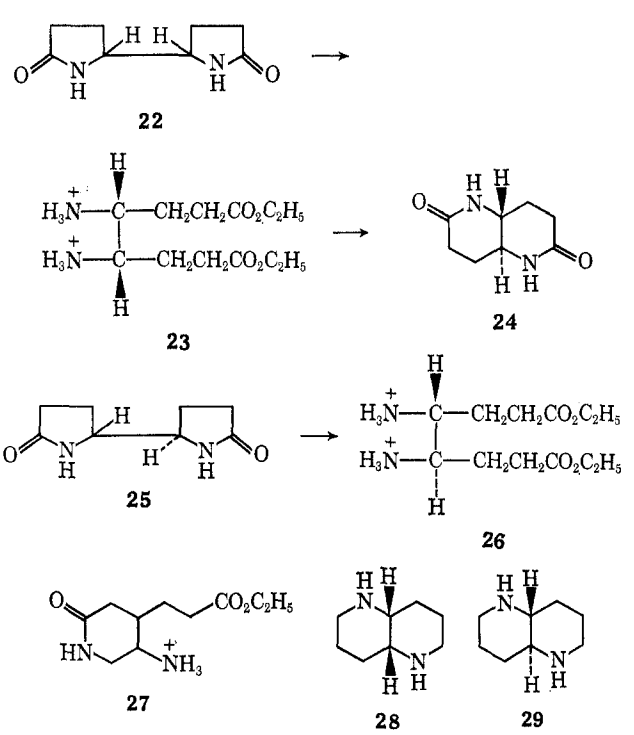
the hydrochlorides of diethyl *meso*-4,5-diaminosuberate (**23**) and diethyl *rac*-4,5-diaminosuberate (**26**). Equilibration of both hydrochlorides in neutral or slightly alkaline media could then lead to the starting five-membered lactams or to the bicyclic six-membered lactams **24** and **21**.

A prediction of the course of the reaction is difficult. In formation from an open-chain intermediate, kinetic control should give preference to a five-membered ring and thermodynamic control to a six-membered ring. However, in an equilibrium reaction between substituted six-membered lactam A and five-membered lactam B, the five-membered ring was predominant (in alkaline medium).[14]



A B

In our case we find that at pH 7.5, the *meso*-4,5-diaminosuberate **23** was quantitatively transformed into *trans*-decahydro-1,5-naphthyridine-2,6-dione (**24**) and the *rac*-diaminosuberate **26** into *cis*-decahydro-1,5-naphthyridine-2,6-dione (**21**). The transformation was unaffected by time or temperature. The identity of **24** was established by its nmr (J = 10 Hz for the bridge protons), and by its reduction with lithium aluminum hydride to **29**. *trans*-Decahydro-1,5-naphthyridine (**29**) was prepared for comparison by the stereospecific reduction of 1,5-naphthyridine in alkaline medium.[11] The ir spectra did not reveal in the equilibration products any trace of five-membered lactams **22** or **25**. These results indicate that, at least for unsubstituted bicyclic lactams, the equilibrium is displaced toward the six-membered rings.



22 23 24 25 26 27 28 29

Experimental Section[15]

1,2,3,4-Tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one (2).—Six grams of ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (**1**) was dissolved in 100 ml of ethanol and reduced during 2 hr at 40 psi with hydrogen over 1.2 g of platinum oxide. The catalyst was filtered out and washed with ethanol, the combined filtrate and washings were concentrated *in vacuo* to 10 ml, and the suspension was cooled for several hours. The resulting precipitate was crystallized from ethanol: 3.3 g (75%); mp 215°; uv max 248 nm (ε 14,700); nmr δ 3.7 (m, C-4 H_2), 4.4 (OCH_3), 5.0 (m, C-3 H), 7.6 (s, C-5 H), 8.2 (s, C-8 H).

Anal. Calcd for $C_9H_{10}O_3N_2$: C, 55.6; H, 5.2; N, 14.4. Found: C, 55.3; H, 5.1; N, 14.2.

1,2,3,4-Tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (12) was prepared following the same procedure used for the synthesis of the tetrahydro-1,7-naphthyridin-2-one **2**. Ethyl 6-methoxy-3-nitro-2-pyridinepyruvate (**11**) had to be previously purified by sublimation (115°, 5 μ) and crystallization from ethanol. From 6 g of ethyl pyridinepyruvate **11** (mp 122–123°) was obtained 3 g (69%) of **12**: mp 240°; uv max 255 nm (ε 12,300); nmr δ 3.8 (m, C-4 H_2), 4.4 (OCH_3), 5.1 (m, C-3 H), 7.5 (d, J = 10 Hz, C-7 H), 8.3 (d, J = 10 Hz, C-8 H).

Anal. Calcd for $C_9H_{10}O_3N_2$: C, 55.6; H, 5.2; N, 14.4. Found: C, 55.5; H, 5.1; N, 14.5.

6-Methoxy-1,7-naphthyridin-2(1*H*)-one (3).—Tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (**2**) (2 g) was dissolved in 10 ml of pyridine, 4 g of *p*-toluenesulfonyl chloride was added, and the mixture was heated at 150° for 4 hr. The mixture was poured over 250 g of crushed ice and filtered, and the precipitate was suspended in 10% sodium carbonate, centrifuged, washed with water, and filtered. Crystallization of the residue from ethanol gave 1.7 g (79%) of **3**: mp 250–254°; uv max 234 nm (ε 35,000); nmr δ 4.4 (OCH_3), 7.5 (d, J = 10 Hz, C-3 H), 7.9 (C-5 H), 8.5 (d, J = 10 Hz, C-4 H), 9.0 (C-8 H).

Anal. Calcd for $C_9H_8O_2N_2$: C, 61.3; H, 4.6; N, 16.1. Found C, 61.2; H, 4.6; N, 16.1.

6-Methoxy-1,5-naphthyridin-2(1*H*)-one (13) was prepared following the same procedure used for the synthesis of 5-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**). From 2 g of tetrahydro-3-oxy-6-methoxy-1,5-naphthyridin-2-one (**12**) was obtained 1.8 g (83%) of **13** after sublimation at 210° (3 μ) and crystallization from ethanol: mp 244–246°; uv max 233 nm (ε 70,000); nmr δ 4.4 (OCH_3), 7.6 (d, J = 10 Hz, C-7 H), 7.9 (d, J = 10 Hz, C-3 H), 8.5 (d, J = 10 Hz, C-8 H), 8.8 (d, J = 10 Hz, C-4 H).

Anal. Calcd for $C_9H_8O_2N_2$: C, 61.3; H, 4.6; N, 15.9. Found: C, 61.3; H, 4.6; N, 16.0.

2-Chloro-6-methoxy-1,7-naphthyridine (4).—6-Methoxy-1,7-naphthyridin-2(1*H*)-one (**2**) (4.2 g) and 40 ml of phosphorus oxychloride were heated at reflux overnight. Excess phosphorus oxychloride was distilled *in vacuo*, the residue was treated with 100 g of ice water, the pH was adjusted to 6 with sodium hydroxide, and the aqueous phase was extracted continuously with chloroform for 48 hr. Evaporation of the chloroform and sublimation of the residue at 120° (3 μ) gave 3 g (63%) of **4**: mp 185–190° (from benzene–methylcyclohexane); uv max 242 nm (ε 17,000), 350 (1500).

Anal. Calcd for $C_9H_7N_2OCl$: C, 55.7; H, 3.6; N, 14.4. Found: C, 55.9; H, 3.5; N, 14.4.

2-Chloro-6-methoxy-1,5-naphthyridine (14).—6-Methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) (2 g), purified by sublimation, and 50 ml of phosphorus oxychloride were stirred at 70° until total dissolution of the solid, and then left at room temperature for 72 hr. The same procedure used in the synthesis of **4** was then followed and 1.6 g (70%) of **14** was obtained after sublimation at 70° (2 μ): mp 130–134° (from cyclohexane); uv max 221 nm (ε 60,200), 314 (8000), 326 (9500); nmr δ 4.6 (s, OCH_3), 8.0 (d, J = 10 Hz, C-7 H), 8.5 (d, J = 10 Hz, C-3 H), 8.8 (d, J = 10 Hz, C-8 H), 9.2 (d, J = 10 Hz, C-4 H).

(14) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, **3**, 490 (1964).

(15) All melting points were taken on the Kofler block; uv absorptions were measured in ethanol; ir spectra were obtained on potassium bromide wafers; and nmr spectra were taken in trifluoroacetic acid, unless otherwise noted. Microanalyses were performed by the Analytical Laboratory, University of California, Berkeley.

Anal. Calcd for $C_9H_7N_2OCl$: C, 55.7; H, 3.6; N, 14.4. Found: C, 55.4; H, 3.5; N, 14.3.

2-Hydrazino-6-methoxy-1,7-naphthyridine (**5**).—A solution of 6 g (0.03 mol) of 2-chloro-6-methoxy-1,7-naphthyridine (**4**) in 40 ml of ethanol and 33 ml (0.57 mol) of 85% hydrazine hydrate was heated at 100° for 1 hr. Evaporation of the solvent *in vacuo* left a crystalline residue which was crystallized from benzene giving 4.9 (84%) of **5**, mp 170–172°.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.8; H, 5.3; N, 29.4. Found: C, 57.0; H, 5.2; N, 29.6.

2,6-Dichloro-1,5-naphthyridine (**15**).—6-Methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) (2 g) and 40 ml of phosphorus oxychloride were heated at reflux for 15 hr. The same procedure used for the preparation of **4** was then followed. The product obtained was sublimed at 134° (2 μ) and crystallized from benzene–cyclohexane, giving 5.1 g (57%) of **15**: mp 190–194; uv max 214 nm (ϵ 61,300), 256 (4250), 266 (2500), 310 (8300), 324 (9600); nmr δ 8.3 (d, J = 10 Hz, C-3 H, C-7 H), 9.1 (d, J = 10 Hz, C-4 H and C-8 H).

Anal. Calcd for $C_8H_4N_2Cl_2$: C, 48.6; H, 2.0; N, 14.1; Cl, 35.3. Found: C, 48.4; H, 2.2; N, 14.2; Cl, 35.2.

2-Hydrazino-6-chloro-1,5-naphthyridine (**16**) was prepared following the same procedure used for the preparation of **5**. From 3 g of 2,6-dichloro-1,5-naphthyridine (**15**) was obtained 2 g (70%) of **16**: mp 178–180° (sublimed at 130°, 2 μ); uv max 230 nm (ϵ 26,400), 284 (29,400), 364 (12,700).

Anal. Calcd for $C_9H_7N_4C$: C, 49.5; H, 3.6; N, 28.8; Cl, 18.0. Found: C, 49.7; H, 3.8; N, 29.0; Cl, 18.2.

6-Methoxy-1,7-naphthyridine (**6**).—2-Hydrazino-6-methoxy-1,7-naphthyridine (**5**) (2.1 g) was dissolved in a mixture of 20 ml of water and 5 ml of acetic acid, and 45 ml of a 10% aqueous solution of cupric sulphate was added dropwise. The resulting mixture was heated on the steam bath until gas evolution ceased (1 hr) and then adjusted to pH 8 with 4 *M* ammonium hydroxide. Continuous extraction with chloroform and evaporation of the solvent left a residue which was sublimed at 40° (2 μ) to give 0.8 g (45%) of **6**: mp 45–46° (from methylcyclohexane); uv max 224 nm (ϵ 29,100), 259 (3500), 339 (3200); nmr ($CDCl_3$) δ 4.0 (s, OCH_3), 7.1 (s, C-5 H), 9.3 (s, C-8 H), 7.5 (m, $J_{3,4}$ = 9 Hz, $J_{2,3}$ = 4 Hz, C-3 H), 8.1 (m, $J_{4,3}$ = 9 Hz, $J_{4,2}$ = 9 Hz, C-4 H), 9.0 (m, $J_{2,3}$ = 4 Hz, $J_{2,4}$ = 9 Hz, C-2 H).

Anal. Calcd for $C_9H_8ON_2$: C, 67.5; H, 4.9; N, 17.5. Found: C, 67.4; H, 4.9; N, 17.7.

2-Chloro-1,5-naphthyridine (**17**) was prepared following the same procedure used for the synthesis of 6-methoxy-1,7-naphthyridine (**6**). From 4 g of 2-hydrazino-6-chloro-1,5-naphthyridine (**16**) was obtained, after sublimation at 45° (2 μ) and crystallization from cyclohexane, 1.6 g (50%) of **17**: mp 110–112°; uv max 215 nm (ϵ 29,600), 242 (4000), 248 (4100), 258 (3700), 267 (2600), 302 (6400), 308 (6700), 316 (6600); nmr δ 8.3 (d, $J_{7,8}$ = 10 Hz, C-7 H), 9.6 (d, $J_{7,8}$ = 10 Hz, C-8 H), 8.6 (m, $J_{3,4}$ = 9 Hz, $J_{2,3}$ = 6 Hz, C-3 H), 8.9 (m, $J_{4,3}$ = 9 Hz, $J_{2,4}$ = 1.5 Hz, C-4 H), 9.4 (m, $J_{2,3}$ = 6 Hz, $J_{2,4}$ = 1.5 Hz, C-2 H).

Anal. Calcd for $C_8H_5N_2Cl$: C, 58.5; H, 3.0; N, 17.1; Cl, 21.3. Found: C, 58.8; H, 3.3; N, 17.1; Cl, 21.1.

The 2-chloro-1,5-naphthyridine was identical (melting point and ir) with a sample prepared by the action of phosphorus oxychloride on 2-hydroxy-1,5-naphthyridine (**19**).[16]

2-Methoxy-1,5-naphthyridine (**18**).—2-Chloro-1,5 naphthyridine (**17**) (1.3 g, 7.9 mmol) was added to a solution of 230 mg (10 g-atoms) of sodium in 20 ml of anhydrous methanol, and the mixture was heated under reflux for 4 hr. The solvent was evaporated *in vacuo*, the residue dissolved in 20 ml of chloroform, the solution washed with 5 ml of water, the chloroform evaporated, and the residue sublimed at 30° (2 μ) giving 450 mg (38%) of **18**: mp 38°; uv max 221 nm (ϵ 15,100), 311 (7500), 321 (7100).

Anal. Calcd for $C_9H_8ON_2$: C, 67.5; H, 4.9; N, 17.5. Found: C, 67.4; H, 4.8; N, 17.4.

1,2,3,4-Tetrahydro-6-methoxy-1,7-naphthyridin-2-one (**7**).—6-Methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) (1.2 g) was dissolved in 100 ml of ethanol and reduced during 2 hr at 40 psi with hydrogen over 1 g of 10% palladium on charcoal. The catalyst was filtered off and thoroughly washed with ethanol and the combined filtrate and washings were concentrated *in vacuo* to 5 ml. Cooling gave a precipitate which was sublimed at 200° (1 μ) to give 0.9 g (75%) of **7**: mp 205–209; uv max 250 nm (ϵ 13,500), 300 (7500); nmr δ 3.05 (m, C-3 H_2), 3.45 (m, C-4 H_2), 7.5 (s, C-5 H), 8.15 (s, C-8 H), 4.3 (s, OCH_3).

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Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.7; H, 5.7; N, 15.7. Found: C, 60.8; H, 5.7; N, 15.6.

1,2,3,4,6,7-Hexahydro-1,7-naphthyridine-2,6-dione (**8**).—The tetrahydro-1,7-naphthyridin-2-one (**7**) (0.6 g) was dissolved in 12 ml of 48% hydrobromic acid and heated at reflux for 2 hr. Excess acid was distilled *in vacuo*, the residue dissolved in 5 ml of water, and the solution adjusted to pH 7 with 10% sodium carbonate, concentrated to 1 ml, and cooled for several hours. The solid obtained was sublimed at 250° (2 μ) and crystallized from water, giving 0.21 g (38%) of **8**: mp 350° dec; uv max 254 nm (ϵ 6000), 320 (2000); nmr δ 3.1 (m, C-3 H_2), 3.4 (m, C-4 H_2), 7.55 (s, C-5 H), 8.15 (s, C-8 H).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.7; H, 5.2; N, 17.0.

1,2,6,7-Tetrahydro-1,7-naphthyridine-2,6-dione (**9**) was prepared following the same procedure used for the synthesis of the hexahydro derivative **8**. From 3 g of 6-methoxy-1,7-naphthyridin-2(1*H*)-one (**3**) was obtained 2.2 g (80%) of **9**, sublimed at 240° (1 μ) and crystallized from glacial acetic acid: mp 350°; uv max 236 nm (ϵ 27,600), 246 (26,700); nmr δ 7.5 (d, J = 10 Hz, C-3 H), 8.3 (d, J = 10 Hz, C-4 H), 7.8 (s, C-5 H), 9.0 (s, C-9 H).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.4; H, 3.8; N, 17.0.

1,2,5,6-Tetrahydro-1,5-naphthyridine-2,6-dione (**20**) was prepared following the same procedure used for the synthesis of the hexahydro derivative **8**. From 3 g of 6-methoxy-1,5-naphthyridin-2(1*H*)-one (**13**) was obtained 2.3 g (83%) of **20**, sublimed at 240° (1 μ) and crystallized from trifluoroacetic acid–water: mp dec above 350°; nmr δ 7.6 (d, J = 10 Hz, C-3 H and C-7 H), 8.4 (d, J = 10 Hz, C-4 H and C-8 H).

***cis*-Decahydro-1,7-naphthyridine-2,6-dione** (**10**).—1,2,6,7-Tetrahydro-1,7-naphthyridine-2,6-dione (**9**) (2 g) was dissolved in 50 ml of glacial acetic acid and reduced during 72 hr at 50 psi with hydrogen over a mixture of 0.5 g of platinum oxide and 0.5 g of 10% palladium on charcoal. The catalyst was filtered and washed with glacial acetic acid, and the filtrates were evaporated to dryness *in vacuo* at 50°. The crystalline residue was sublimed (250°, 1 μ) and crystallized from ethanol–water giving 2.1 g (80%) of **10**: mp 285°; ir 3230 (NH), 1690 (CO), 1660 cm^{-1} (CO); nmr δ 2.2 (b, 2, C-4 H_2), 3.0 (b, 5, C-3 H_2, C-5 H_2 and C-4a H), 4.2 (b, C-8 H_2), 4.4 (s, 1, C-8a H).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.1; N, 16.6. Found: C, 56.9; H, 7.2; N, 16.6.

***cis*-Decahydro-1,5-naphthyridine-2,6-dione** (**21**) was prepared following the same technique used for the synthesis of *cis*-decahydro-1,7-naphthyridine-2,6-dione (**10**). From 2 g of 1,2,5,6-tetrahydro-1,5-naphthyridine-2,6-dione (**20**) was obtained, after sublimation (280°, 1 μ) and crystallization from ethanol–water, 2.2 g (81%) of **21**: mp dec above 350; ir 3220 (NH), 1640–1660 cm^{-1} (CO); nmr δ 2.5 (b, 4, C-3 H_2 and C-7 H_2), 2.9 (b, 4, C-4 H_2 and C-8 H_2), 4.4 (s, 2, >CH).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.1; N, 16.6. Found: C, 57.0; H, 7.3; N, 16.6.

Diethyl *meso*-4,5-Diaminosuberate Dihydrochloride (**23**).—*meso*-2,2′-Bi(pyrrolidine)-5,5′-dione (**22**) (300 mg, sublimed at 250°, 2 μ) was suspended in 5 ml of 6 *N* hydrochloric acid and the solution heated under reflux for 12 hr. Evaporation *in vacuo* left a residue which was dissolved in 5 ml of absolute ethanol saturated with hydrogen chloride and left at 5° for 48 hr. Evaporation *in vacuo* at 30° left a residue which was crstallized from ethanol–ether giving 236 mg (40%) of **23**: mp 160–162°; ir 1720 cm^{-1} (CO ester); nmr δ 1.4 (t, 6, CH_2CH_3), 2.5 (b, H>CCH_2), 3.0 (b, $-CH_2CO_2C_2H_5$), 4.45 (q, 4, CH_2CH_3).

Anal. Calcd for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.4; H, 7.8; N, 8.4. Found: C, 43.5; H, 7.8; N, 8.4.

***trans*-Decahydro-1,5-naphthyridine-2,6-dione** (**24**).—**23** (150 mg) was dissolved in 5 ml of absolute ethanol, the pH was adjusted to 7.5 with potassium ethoxide, and the suspension stirred at 5° for 12 hr. The solution was filtered, the filtrate was concentrated to dryness, and the residue was sublimed at 300° and 2 μ, giving 40 mg (93%) of **24**: mp dec above 350°; ir 1655 cm^{-1} (CO); nmr δ 2.3 (m, 4, C-3 H_2 and C-7 H_2), 3.0 (m, 4, C-4 H_2 and C-8 H_2), 3.8 (m, 2, J = 10 Hz, –CH).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 57.1; H, 7.2; N, 16.6. Found: C, 57.1; H, 7.2; N, 16.9.

Diethyl *rac*-4,5-diaminosuberate dihydrochloride (**26**) was prepared following the technique described for the meso isomer **23**. From 500 mg of *rac*-2,2′-bi(pyrrolidine)-5,5′-dione (**25**) was obtained 95 mg (20%) of **26**, mp 137–140°.

Anal. Calcd for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.4; H, 7.8; N, 8.4. Found: C, 43.4; H, 7.8; N, 8.3.

When equilibrated at pH 7.5 as described for **24**, **26** afforded *cis*-decahydronaphthyridinedione **21** in 95% yield.

Ethyl 3-Amino-6-oxohexahydropyridine-4-propionate Hydrochloride (27).—Bislactam **10** (300 mg) was dissolved in 5 ml of 6 *N* hydrochloric acid and the solution heated under reflux for 24 hr. The same technique described previously for the synthesis of **23** was then followed and 225 mg (50%) of **27** was obtained: mp 134–136°; ir 1690 (CO), 1740 cm^{-1} (CO ester); nmr δ 1.4 (t, CH_2CH_3), 2.2 (b, C-5 H_2), 2.7 (m, $CH_2CH_2CO_2Et$), 3.7 (b, C-2 H_2), 4.4 (q, CH_2CH_3).

Anal. Calcd for $C_{10}H_{19}N_2O_3Cl$: C, 47.9; H, 7.6; N, 11.2. Found: C, 47.7; H, 7.6; N, 11.4.

***cis*-Decahydro-1,5-naphthyridine (28).**—*cis*-Decahydro-1,5-naphthyridine-2,6-dione (**21**) (1.7 g) was slowly added with constant stirring to a suspension of 3 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The resulting mixture was heated at reflux for 10 hr, and then 200 ml of water was added. The solution was adjusted to pH 12 with a concentrated sodium hydroxide solution and extracted with five 50-ml portions of chloroform. The extract was dried (Na_2SO_4), concentrated, and distilled giving 500 mg (50%) of **28**: bp 66° (0.25 mm) [lit.[11] bp 55° (0.1 mm)]; identical (ir, nmr, tlc) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Anal. Calcd for $C_8H_{16}N_2$: C, 68.5; H, 11.5; N, 20.0. Found: C, 68.6; H, 11.5; N, 20.1.

***trans*-Decahydro-1,5-naphthyridine (29)** was obtained following the procedure described for the synthesis of **28**. From 560 mg of **24** was obtained 210 mg (45%) of **29**: mp 176–177° (lit.[11] mp 177–178°); identical (ir, tlc, melting points, nmr) with a sample prepared by reduction of 1,5-naphthyridine.[11]

Registry No.—**2**, 3469-64-5; **3**, 27017-56-7; **4**, 27017-57-8; **5**, 27017-58-9; **6**, 27017-59-0; **7**, 27017-60-3; **8**, 27017-61-4; **9**, 27017-62-5; **10**, 27022-27-1; **12**, 27017-63-6; **13**, 27017-64-7; **14**, 27017-65-8; **15**, 27017-66-9; **16**, 27017-67-0; **17**, 7689-62-5; **18**, 27017-69-2; **20**, 27017-70-5; **21**, 27022-28-2; **23**, 27022-29-3; **24**, 27022-30-6; **26**, 27022-31-7; **27**, 27017-71-6.

Further Evidence as to the Nature of the Transition State Leading to Decarboxylation of 2-Pyridinecarboxylic Acids. Electrical Effects in the Transition State

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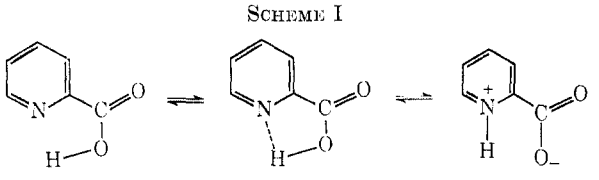
The rates of decarboxylation of 6-nitro-2-pyridinecarboxylic, 6-chloro-2-pyridinecarboxylic, 6-bromo-2-pyridinecarboxylic, 2-pyridinecarboxylic, 6-acetamido-2-pyridinecarboxylic, 6-methyl-2-pyridinecarboxylic, 6-methoxy-2-pyridinecarboxylic, and 6-amino-2-pyridinecarboxylic acids in 3-nitrotoluene were determined. The $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were then calculated. An examination of a linear free-energy plot of relative rates *vs.* the σ' constants suggested that the electron density on the ring nitrogen affects the $\Delta G^{\ddagger}$ of the reaction. The observation that 6-methoxy and 6-acetamido groups decrease the rate of decarboxylation by a factor of 4 and 10, respectively, as compared to 6-amino and 6-methyl groups was indicative of a steric effect by the larger substituents. A mechanism is suggested which is consistent with the available data.

Preliminary work has been done on the decarboxylation of 2-pyridinecarboxylic acid in various solvents.[1-4] All of these investigators have looked at the transition state and tried to deduce the structure of the intermediate leading to the transition state. Different methods must be used to study the distribution of reactant other than those used to deduce the structure of the transition state. Thus, we have not tried to postulate that either I or II is the principal reactant but assumed that both are present and that a rapid equilibrium exists between the two reactants (Scheme I).

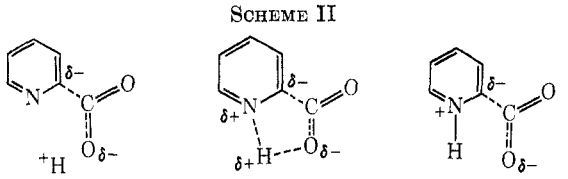
SCHEME I



I II

Irrespective of which reactant leads to which transition state, there are a total of three possible transition states, III, IV, or V (Scheme II). The electrical effects

SCHEME II



III IV V

in the three possible transition states are quite different. If transition states III or V lead predominantly to decarboxylation, one would predict that electron-withdrawing effects would stablize the transition state and lead to larger rate constants.

If transition state IV were the one leading to products, one would argue that there are opposing effects. In one case electron withdrawal should increase the rate constants and in the other case decrease the rate constants. On close examination of IV, it can be seen that two events are occurring: (1) NH bond formation, and (2) CC bond cleavage. With these two events three possibilities exist: (a) CC bond cleavage is leading NH bond formation resulting in a developing negative charge on C-2 in the transition state, (b) CC bond cleavage is lagging behind NH bond formation resulting in a developing positive charge on the ring nitrogen in the transition state, or (c) CC bond cleavage has progressed at an even rate with NH bond formation, resulting in no overall charge being developed on the ring in the

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