**Preparation of Compound 14.**—Compound **13** was injected into the vpc (injection port 240°; 6 ft × 0.375 in. Carbowax 20 M at 220°). This showed one peak which was collected and identified as **14**. Alternatively, compound **13** could be irradiated through Pyrex as a dilute ether soluton to give the cyclopropane in quantitative yield.

**Registry No.**—**4a**, 40447-60-7; **4b**, 40447-61-8; **4c**, 40447-62-9; **4d**, 40447-63-0; **4e**, 40447-64-1; **5**, 38312-94-6; **7**, 40447-66-3; **8**, 40447-67-4; **9**, 40447-68-5; **10**, 40447-69-6; **11**, 40447-70-9; **12**, 14309-54-7; **13**, 40447-72-1; 3,5-dinitrobenzoyl chloride, 99-33-2; dimethyl acetylenedicarboxylate.

# Models for the Pyridine Nucleotide Coenzymes. Synthesis and Properties of Bridged Dinicotinamide Derivatives[1-3]

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*Received March 30, 1973*

A number of dinicotinamide derivatives which are bridged between the 3 and the 5 positions have been prepared from dinicotinoyl chloride and $\alpha,\omega$-diamines. A special high-dilution technique involving introduction of reagents into the reaction flask by means of syringe pumps was employed which was superior to the use of constant-rate addition funnels. Models for coenzyme–substrate complexes in which a carbonyl group or alcohol group in the bridge is in close proximity to the 4 position of a dihydropyridine or of a pyridinium salt, respectively, have been prepared. Certain of the bridged derivatives show enhanced reactivity toward silver nitrate and protons which may be a function of the strain introduced into the pyridine ring. No evidence was obtained either for intramolecular hydrogen transfer from the dihydropyridine to the proximate carbonyl group, or for the transfer of hydride ion from the alcohol group to the pyridinium ring. Spectroscopic data, however, indicated addition of alkoxide ion in the bridge to the charged pyridine ring.

Proximity and orientation effects are presumed to be important factors in accounting for the catalytic power of enzymes.[4] The enzyme positions coenzyme and substrate in close proximity so that collisions between the reactants are more frequent. The enzyme also orients them so that the probability of a collision leading to a reaction is increased. Other factors such as acid–base catalysis, introduction of strain in the reactants, the formation of unstable, covalent intermediates, and the polarity of the microscopic environment also are believed to be important in enzyme catalysis.

The dehydrogenase enzymes catalyze the transfer of hydrogen to and from substrates *via* the pyridine nucleotide coenzymes. Relatively few successful model reactions for these hydrogen transfers have been accomplished in the absence of an enzyme.[5] For the model reduction of ketones or aldehydes by 1-substituted 1,4-dihydronicotinamides (models for the coenzyme), only the reduction of halo ketones,[6] the zinc ion catalyzed reduction of 1,10-phenanthroline-2-carboxaldehyde,[7a] and the reduction of pyridoxal phosphate and analogs by dihydropyridines[7b] appear to proceed in good yield in the absence of enzyme. The hydrogen transfer in the enzymic and nonenzymic reactions occurs *via* the 4 position of the pyridine ring[8] and is a direct transfer between coenzyme (or its model) and substrate,[9] although an indirect mechanism *via* tryptophane may operate in certain enzymic reactions.[10]

Introduction of a carbonyl group or an alcohol group close to the reactive 4 position of models for the pyridine nucleotide coenzymes would be a test of proximity effects. While a number of model systems for hydrogen transfer involving pyridine derivatives have been investigated,[5-7] at the time our work began no model system had been reported in which a carbonyl or alcohol moiety had been fixed in close proximity to the 4 position of the pyridine ring. Recently, the bridged dinicotinamide derivative **1** was prepared (6.6% yield in the cyclization step) and was converted to the bridged alcohol derivative **2**. A deoxy analog, **3**, and its 1-benzyl salt also were reported (6.9% yield in the cyclization step). No evidence for intramolecular hydrogen transfer in **2** was obtained,[11a] but an intramolecular hydrogen transfer to a carbonyl group in *N*-(2,6-dichlorobenzyl)-3-(*o*-formylbenzoyl)-1,4-dihydropyridine has been induced photochemically.[11b] A thermally induced intramolecular hydrogen transfer from a 1,2-dihydropyridine to the vinyl group of an acrylic ester has been proposed to account for transformations of the alkaloid, catharanthine.[11c]

We wish to describe in this paper a better procedure

(1) For complete details, see B. B. Blidner, Ph.D. Thesis, Syracuse University, 1972.

(2) This investigation was supported in part by Public Health Service Research Grant No. AM07770 from the National Institute of Arthritis and Metabolic Diseases.

(3) Reported at Northeast Regional Meeting, American Chemical Society, Buffalo, N. Y., Oct 1971, Abstract No. 80.

(4) Included in orientation effects are "freezing" or "stereopopulation control" and "orbital steering:" D. E. Koshland, Jr., and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 370 (1968); D. R. Storm and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci., U. S.*, **66**, 445 (1970); M. I. Page and W. P. Jencks, *ibid.*, **68**, 1678 (1971); S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166, 9175 (1972).

(5) Model systems have been reviewed by T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 9.

(6) D. C. Dittmer, L. J. Steffa, J. R. Potoski, and R. A. Fouty, *Tetrahedron Lett.*, 827 (1961); D. C. Dittmer and R. A. Fouty, *J. Amer. Chem. Soc.*, **86**, 91 (1964); T. P. Goldstein, Abstracts of Papers, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, C-196; A. Lombardo, Ph.D. Thesis, Syracuse University, 1967; C. S. Greene, Ph.D. Thesis, Syracuse University, 1971; J. J. Steffens and D. M. Chipman, *J. Amer. Chem. Soc.*, **93**, 6694 (1971).

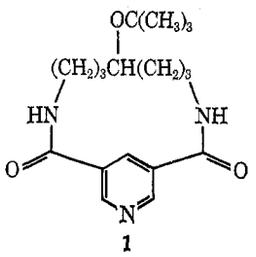
(7) (a) D. J. Creighton and D. S. Sigman, *J. Amer. Chem. Soc.*, **93**, 6314 (1971); (b) S. Shinkai and T. C. Bruice, *ibid.*, **94**, 8258 (1972).

(8) M. E. Pullman, A. San Pietro, and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954); G. W. Rafter and S. P. Colowick, *ibid.*, **208**, 773 (1954); F. A. Loewus, B. Vennesland, and D. L. Harris, *J. Amer. Chem. Soc.*, **77**, 3391 (1955); R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958); H. E. Dubb, M. Saunders, and J. H. Wang, *J. Amer. Chem. Soc.*, **80**, 1767 (1958).

(9) F. H. Westheimer, H. F. Fisher, E. E. Conn, and B. Vennesland, *J. Amer. Chem. Soc.*, **73**, 2403 (1951); H. F. Fisher, E. E. Conn, B. Vennesland, and F. H. Westheimer, *J. Biol. Chem.*, **202**, 687 (1953).

(10) K. A. Schellenberg, *ibid.*, **240**, 1165 (1965); **242**, 1815 (1967). D. Palm, *Biochem. Biophys. Res. Commun.*, **22**, 151 (1966).

(11) (a) L. E. Overman, *J. Org. Chem.*, **37**, 4214 (1972); (b) J. D. Sammes and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1023 (1972); (c) A. I. Scott and P. C. Cherry, *J. Amer. Chem. Soc.*, **91**, 5872 (1969).



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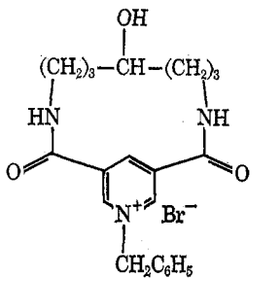

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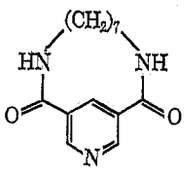
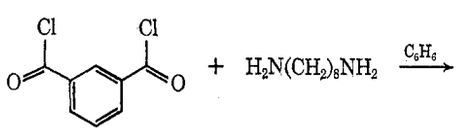
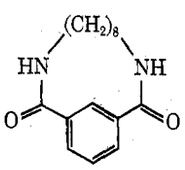


3

for the synthesis of meta bridged dinicotinamides. This new technique, which involves syringe pumps, is applied to the preparation of a number of new bridged dinicotinamides which are models for proximity effects in reactions catalyzed by the dehydrogenase enzymes. For example, we have prepared **3** and the ethylene ketal analog of **1** in 23 and 20% yields, respectively.

**Syntheses of Bridged Dinicotinamide Derivatives.**— Isophthaloyl chloride and 1,4-diaminobutane or 1,6-diaminohexane are reported to give cyclic diamides in 7 and 19% yield, respectively.[12] However, when we attempted to prepare a cyclic diamide from isophthaloyl chloride and 1,8-diaminooctane by the reported procedure, only a 1.5% yield of product **4** was

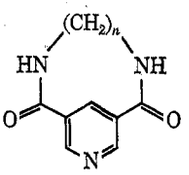




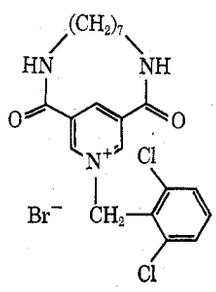
4

obtained. This procedure involved addition of reagents *via* constant-rate addition funnels to a large volume of benzene.[13]

In an attempt to improve the yield of **4**, an alternate high-dilution procedure was tried in which the acid chloride and diamine were introduced separately and very slowly into the benzene solvent *via* a syringe pump.[14] This technique resulted in an increase in the yield of **4** from 1.5 to 38%. By this method, 1,8-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, and 1,5-diaminopentane were condensed with the acid chloride of pyridine-3,5-dicarboxylic acid (dinicotinoyl chloride) to yield bridged dinicotinamides **5a–d** (**5c** and **5d** appear to form stable hydrates). A zero yield of **5d** was reported when addition funnels were used.[11a] Compound **5b** was quaternized with 2,6-dichlorobenzyl bromide to yield **6** which was reduced with sodium dithionite to the dihydropyridine derivative **7**.



**5a**, $n = 8$ (41%) **5c**, $n = 6$ (9.8%)
**b**, $n = 7$ (23%) **d**, $n = 5$ (4.3%)



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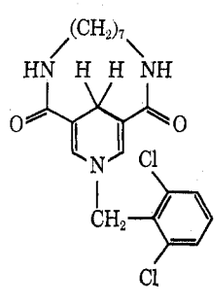


7

Scheme I shows the general synthesis of three diamino ketals and the construction of the 3,3- and 4,4-bridged dinicotinamide ketals **11a**, and **11b**. Removal of the ketal function from **11a** and **11b** yields bridged carbonyl derivatives **12a** and **12b**. Reduction of the carbonyl group with sodium borohydride gives the bridged alcohols **13a** and **13b**. Quaternization of **12a** and **12b** and **13a** and **13b** with 2,6-dichlorobenzyl bromide or with methyl iodide occurs readily to give salts **14a–c** and **15a** and **15b**. Reduction of **14a–c** with sodium dithionite yields the bridged dihydrodinicotinamides **16a–c**. CPK models indicate that the 4 position of the pyridine ring can lie in close proximity to the ketone or alcohol group of the bridge. The nmr spectra of several of the bridged dinicotinamides, most especially with **11a** which has a well-resolved spectrum, show different chemical shifts for the two amide protons ($\Delta\delta$ for **11a**, 0.74 ppm). The models show that different configurations such as an "in" or "out" for these amide protons are readily attainable within the macrocyclic ring. The different chemical shifts probably reflect either a particularly stable configuration in which the amide protons are nonequivalent chemically or two distinct but equally probable stable configurations for them.

**Properties of Bridged Dihydrodinicotinamides.**— Table I compares the uv absorption maxima, fluorescence emission, and approximate reactivity to ethanolic silver nitrate and to dilute acid of **7**, **16a**, **16b**, and **18**. Compounds **7** and **16a** which show a perturbed uv and fluorescence spectrum appear to be somewhat more

(12) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

(13) Constant-rate addition funnels from Ace Glass Co. were used. We obtained a 68% yield of cyclic product from adipyl chloride and 1,6-diaminohexane compared with Stetter's yield of 76% with specially constructed and slightly different funnels: H. Stetter and J. Marx, *Justus Liebigs Ann. Chem.*, **607**, 59 (1957).

(14) The use of syringe pumps was suggested by Dr. Owen Webster. A Sage syringe pump Model 352 was used. The plungers of two 50-ml syringes containing solutions of diamine and diacid chloride in benzene were driven at a constant rate by motor, which delivered the reagents to the reaction flask *via* thin, flexible, Teflon tubing. The rates of delivery could be varied widely, thus ensuring any dilution factor desired.

SCHEME I

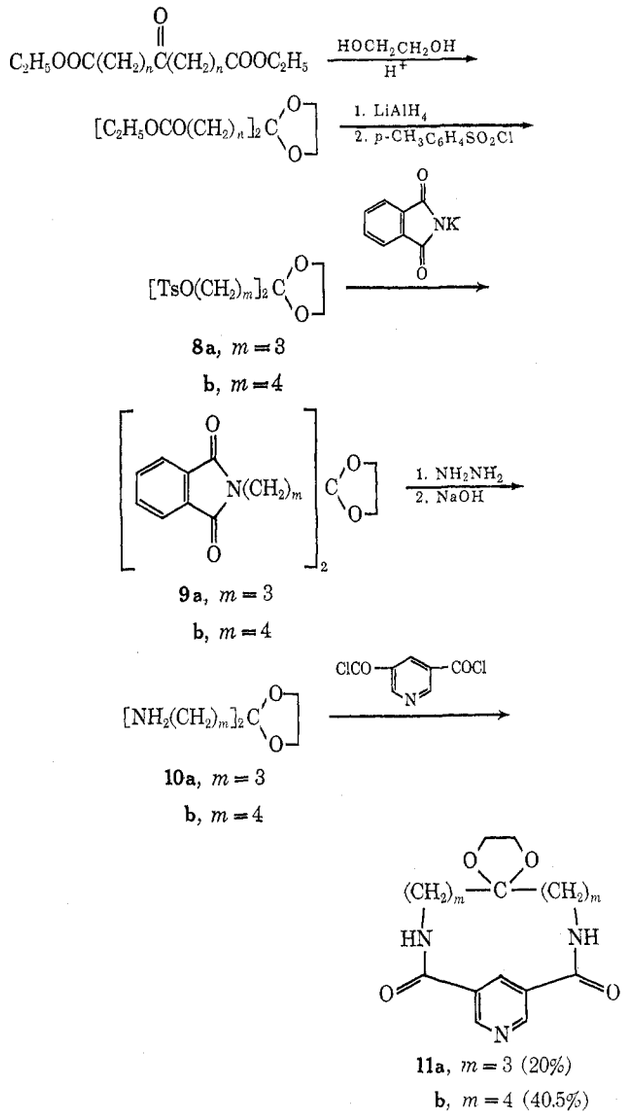


TABLE I

SOME PROPERTIES OF BRIDGED 1,4-DIHYDROPYRIDINES

| Property | 7 | 16a | 16b | 18 |
|---|---|---|---|---|
| Uv max (ethanol), nm | 338 | 338 | 381 | 391 |
| Fluorescence emission, nm | 478 (weak)[a] | 451 (weak)[a] | 447 | 445 |
| $AgNO_3$,[b] hr | 0.5 | 0.5 | 3 | 24 |
| $H_3O^+$[c] | 80 | 125 | 21 | 1 |

[a] About 10% of the emission observed for **16b** and **18**. [b] Approximate time to form silver mirror. [c] Relative rate (27°, 87% ethanol).

reactive towards silver ion[15] and protons.[16,17] Strain introduced by the smaller bridges in these compounds is a likely source of the spectroscopic and chemical differences. Distortion of the dihydropyridine ring from planarity[18] with concomitant destabilization of the conjugated system could effect the increased rate of addition of silver ion or protons to the bis enamine system. Strain in the bicyclic system also may be reduced by reaction with the Lewis acids.

The reactivity of 1,4-dihydropyridines to aqueous acid has been investigated previously.[16a] The reaction is characterized by loss of absorption at ~360 and appearance of new absorption at 290–300 nm. The products are tetrahydropyridines and dimers derived from them. Addition of dilute acid to **7**, **16a**, **16b**, and **18** causes new absorption to appear at 289 nm. The presence of two electron-withdrawing amide groups in these compounds causes them to react

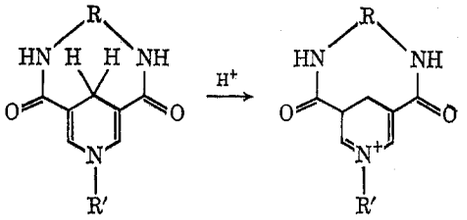
(15) The reduction of silver ions by dihydropyridines is well known: P. Karrer, G. Schwarzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(16) (a) A. G. Anderson, Jr., and G. Berkelhammer, *J. Amer. Chem. Soc.*, **80**, 992 (1958). (b) O. M. Grishin and A. A. Yasnikov, *Ukr. Khim. Zh.*, **28**, 707 (1962); *Chem. Abstr.*, **58**, 11183 (1963).

(17) The chemistry of dihydropyridines has been reviewed nicely by Bruice and Benkovic[5] and by U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

(18) X-Ray analysis indicates that two 1,4-dihydropyridines are planar in the crystalline state: I. L. Karle, *Acta Crystallogr.*, **14**, 497 (1961); H. Koyama, *Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem.*, **118**, 51 (1963).

more slowly with protons than do the monosubstituted derivatives.[16a]

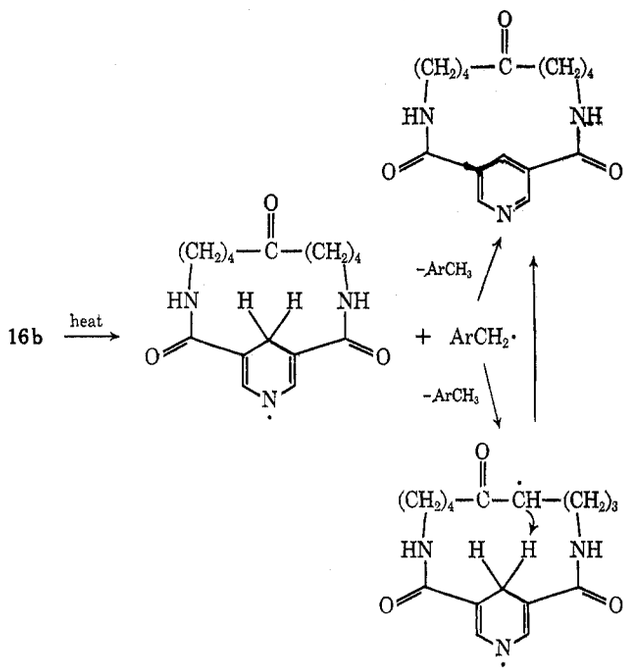


Zinc ions catalyze the reduction of 1,10-phenanthroline-2-carboxaldehyde by 1-*n*-propyl-1,4-dihydronicotinamide,[7a] but no change was observed in the uv spectrum of bridged ketone **16b** when it was treated with a solution of zinc chloride ($2 \times 10^{-2}$ *M*) in acetonitrile. The concentration of zinc ions may have been too low for catalysis to be observed, or the zinc ions may have preferentially coordinated with the acetonitrile solvent or other sites in the dihydrodinicotinamide.[19]

Photoexcitation of the carbonyl group of the bridged ketones should facilitate intramolecular hydrogen transfer. Cyclodecanone on photolysis undergoes intramolecular transfer of hydrogen to the carbonyl oxygen followed by cyclization to 9-hydroxydecalin.[20] Several remote hydrogen transfers in various systems have been reported.[11b,c,21] However, all attempts at photolysis of bridged ketones **16a** or **16b** resulted in destruction of the dihydropyridine ring, a not unexpected result.[22]

The possibility of a thermally initiated intramolecular hydrogen transfer in **16a** and **16b** was investigated. Thermolysis of **16b** was done on a Kofler hot stage melting point apparatus. The sample was heated slowly under silicone oil (to protect against oxygen); at 230° the sample melted with frothing and at 235° the melt solidified, only to melt again at 320–324°. The melting point and ir spectrum of this new substance identified it as the bridged pyridine derivative **12b**, mp 323–325°. Cleavage of the 2,6-dichlorobenzyl group to form, presumably, 2,6-dichlorotoluene (which would be soluble in the silicone oil) had occurred. A similar cleavage was observed with **16a**. The 1-methyl compound, **16c**, was stable at its melting point (231–234°). Previously, loss of toluene from 1-benzyl-1,4-dihydronicotinamide was observed at 125° *in vacuo*.[23] The themolysis very likely proceeds by cleavage of a benzyl radical which abstracts a hydrogen atom from the dihydropyridine radical. It is possible that the benzyl radical takes a hydrogen atom from the bridge instead of from the relatively less accessible 4 position of the pyridine ring (Scheme II). This could be ascertained by deuterium labeling.

SCHEME II



The lack of transfer of hydrogen from the 4 position of the dihydrodinicotinamide to a carbonyl group in the bridge may reflect (1) the decreased reducing power of the dihydropyridine caused by the presence of two electron-withdrawing carboxamide groups and (2) the number of conformations of the bridge which are poor for intramolecular hydrogen transfer. Thus, in addition to the proximity effect, other forms of catalysis may be required to effect hydrogen transfer in the compounds discussed here.

**Properties of Bridged Pyridinium Salts.**—Although a number of reactions involving reduction of functional groups by dihydropyridine models for coenzymes are known, examples of nonenzymic oxidation of an alcohol by a pyridinium salt are rare. Oxidation of 9-fluorenol to fluorenone (8%) by 1-methyl-3,4,5-tricyanopyridinium perchlorate has been reported, the reaction apparently involving transfer of hydrogen to the pyridinium ring.[24] The oxidation of benzyl alcohol to benzaldehyde by 1-methyl-3-carbamoylpyridinium iodide also has been reported.[25] It was not clear in these two oxidations whether control reactions were run to check the possibility of autooxidation of the alcohol.

Bridged compound **2** on treatment with various bases was reported to undergo no observable intramolecular hydrogen transfer.[11a] Aqueous hydroxide apparently added to the 2 position of the charged pyridine ring and other bases in hexamethylphosphoramide caused alkoxyl exchange (aluminum isopropoxide) and destruction or modification of the pyridine ring [lithium bis(trimethylsilyl)amide, sodium hydride, potassium *tert*-butoxide].[11a]

Treatment of the nonbridged pyridinium salt **17**, bridged alcohols **15a** and **15b**, and methylene bridged salt **6** with aqueous sodium carbonate resulted in the appearance of two new absorptions in the uv spectrum

(19) Zinc ions actually decreased the rate of reduction of hexachloroacetone by 1-benzyl-1,4-dihydronicotinamide. A complex of zinc ion with the carboxamide group of the dihydronicotinamide was inferred from spectroscopic changes. The complexing of zinc ions in this way would decrease the reducing power of the dihydropyridine by increasing the electron-withdrawing character of the carboxamide group: A. Lombardo, Ph.D. Thesis, Syracuse University, 1967.

(20) M. Barnard and N. C. Yang, *Proc. Chem. Soc.* (*London*), 302 (1958).

(21) R. Breslow and M. A. Winnick, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971); R. Breslow, *et al.*, *ibid.*, **94**, 3276 (1972).

(22) G. Stein, *J. Chim. Phys. Physicochem. Biol.*, **52**, 634 (1955); G. Stein and G. Stiassy, *Nature*, **176**, 734 (1955); U. Eisner, J. R. Williams, B. W. Matthews, and H. Ziffer, *Tetrahedron*, **26**, 899 (1970); D. Abelson, E. Parthe, K. W. Lee, and A. Boyle, *Biochem. J.*, **96**, 840 (1965). *Cf.* ref 11b.

(23) E. A. Ford, Ph.D. Thesis, Syracuse University, 1967, p 89.

(24) K. Wallenfels and W. Hanstein, *Angew. Chem., Int. Ed. Engl.*, **4**, 869 (1965).

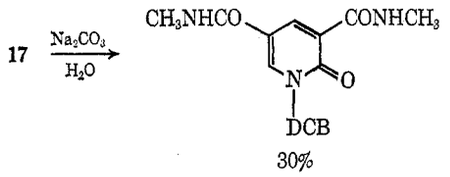
(25) B. Kadis, Abstracts of Papers, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, 24-O.

TABLE II

NEW UV ABSORPTION MAXIMA OBSERVED ON TREATMENT OF PYRIDINIUM SALTS WITH BASES[a]

| Base | Compound 6 | 15a | 15b | 17 |
|---|---|---|---|---|
| Sodium carbonate–$H_2O$ | 345 (fast) | 345 (fast) | 345 (fast) | 270, 340 (fast) |
| Potassium *tert*-butoxide–THF | 380 (5 hr) | 375 (20 min) | 378 (fast) | 348 (fast) |
| Sodium hydride–THF | No change | 375 (3 hr) | 340[b] | No change |
| Potassium 2,6-di-*tert*-butylphenoxide | No change | No change | 383 (fast) | 350 (fast) |

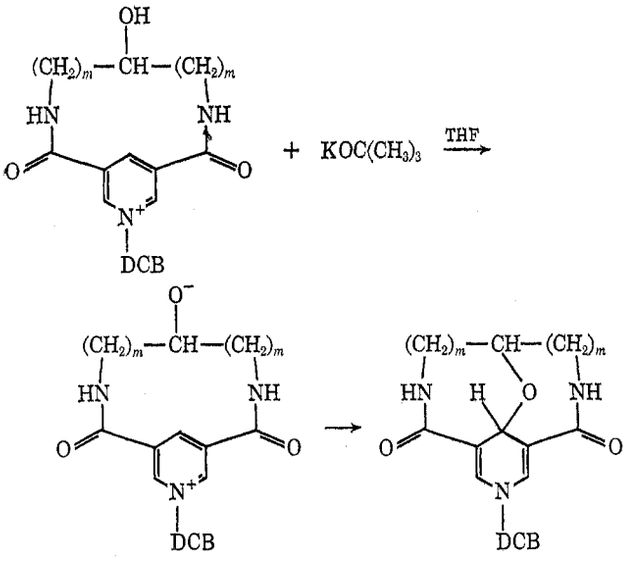
[a] Absorption maxima are reported in nanometers. Approximate times for the maximum development of the new absorption are given. [b] This weak absorption develops within 15 min and then slowly decreases in intensity.



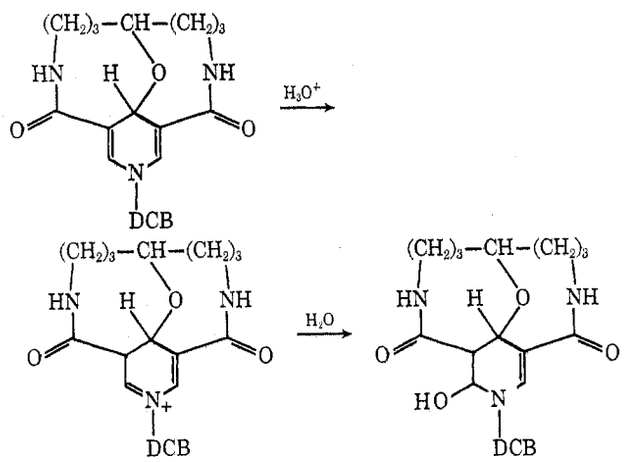

at 252–255 and at 340–345 nm. Addition of acid causes these spectra to revert to those of the pyridinium salts. These spectral data indicate addition of hydroxyl ion to the 2 position of the pyridinium salts by analogy with the spectra of similar dihydropyridine derivatives[26] and are in agreement with the data obtained on treatment of **2** with hydroxide ion.[11a] One of the products obtained from the nonbridged salt **17** was identified as the 2-pyridone (probably formed *via* oxidation of the hydroxide adduct) on the basis of its elemental analysis and its spectral data. Another, unidentified, product also was obtained.

Addition of potassium *tert*-butoxide to a saturated solution of **17** in dry THF resulted in the immediate formation of new absorption at 348 nm. Under the same conditions the methylene bridged salt **6** reacted slowly and after 5 hr only a small new absorption at 380 nm was observed. In marked contrast, bridged alcohol **15a**, which has the same number of atoms in the bridge as **6**, gave rapidly, on identical treatment with potassium *tert*-butoxide, a new absorption at 375 nm. Formation of bridged ketone **16a** was unlikely since the ketone absorbs at 330 nm in THF (it is stable to potassium *tert*-butoxide). The rapid attack of *tert*-butoxide on nonbridged **17** and the slow attack on bridged methylene salt **6** indicates that the site of attack is hindered in **6**. The 2 position in **6** does not seem to be more hindered than the 2 position of **17**; so perhaps the variation in rate reflects hindrance to attack at the 4 position. The rapid formation of new absorption from **15a** suggests alkoxyl transfer between *tert*-butoxide anion and bridged alcohol, followed by formation of a tricyclic ether resulting from attack of the proximate alkoxide on the 4 position. The aluminum salt of **2** investigated previously does not show interaction of the alkoxide with the pyridinium ring[11a] probably because of strong complexing of the oxygen anion with aluminum cation and because of stabilization of the ion by the more polar solvent, hexamethylphosphoramide. Bridged alcohol **15b** also reacts rapidly with potassium *tert*-butoxide to give new absorption at 378 nm.

Sodium hydride in THF produced no observable change with unbridged salt **17** or with bridged heptamethylene salt **6**, but, with bridged alcohol **15a**, new absorption at 375 nm was observed, again suggesting




intramolecular alkoxide addition to the ring. Addition of a few drops of concentrated hydrochloric acid to this solution destroyed the sodium hydride and led to disappearance (slow) of the absorption at 375 and to the appearance of a new band at 292 nm. This behavior is typical of that of 1,4-dihydropyridines toward aqueous acid[16] and indicates addition of a proton to the double bond of a 1,4-dihydropyridine system rather than cleavage of the tricyclic ether to yield the pyridinium salt.[27]




The feasibility of interaction of an alkoxide group in the bridge (*e.g.*, in **15a**) with the 4 position of the pyridinium ring is demonstrated by changes in the uv spectra of **6**, **15a**, and **17** in the presence of bases (Table II). The apparent failure of the bridged al-

(26) K. Wallenfels, H. Schüly, and D. Hofmann, *Justus Liebigs Ann. Chem.*, **621**, 106 (1959); K. Wallenfels and M. Gellrich *Chem. Ber.*, **92**, 1406 (1959); A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958); D. C. Dittmer and J. M. Kolyer, *ibid.*, **28**, 2288 (1963).

(27) Addition of sodium 2,6-di-*tert*-butylphenoxide in THF to **17** and to **15b** resulted in appearance of new absorption at 350 and at 382 nm, respectively. No evidence for any reaction with **6** or with **15a** was observed indicating, perhaps, that addition to these latter compounds with the smallest bridges was hindered.

koxides to transfer hydride ion to the charged pyridine ring may be ascribed to (1) the easy attack of negative oxygen itself on the electron deficient ring, (2) the number of conformations of the bridge which are poorly disposed for intramolecular hydride transfer, and (3) the decreased reducing power of the alkoxide caused by stabilization of the negative oxygen by solvent or by metal ions.

## Experimental Section[28]

Isophthaloyl chloride[12] was prepared from isophthalic acid by treatment with thionyl chloride and a catalytic amount of dimethylformamide.[29] Dinicotinoyl chloride[30] (pyridine-3,5-dicarbonyl chloride) was prepared in a similar manner (88% yield).

**General Procedure for the Synthesis of Macrobicyclic Diamides.**—The freshly distilled diamine (0.02000 mol) was diluted to 24 ml with dry, reagent grade benzene (Baker and Adamson) (stored over sodium) in a 25-ml volumetric flask which had been dried for 24 hr at 120° and stored in a desiccator over sodium hydroxide. Recrystallized and freshly sublimed diacid chloride (0.01000 mol) was diluted to 24 ml with dry, reagent grade benzene in another dry 25-ml volumetric flask. These two solutions were allowed to stand for 2 hr at room temperature to equilibrate thermally and were then diluted to the 25-ml mark.

These solutions were introduced into two "delivery" 50-ml hypodermic syringes (Becton, Dickinson and Co., Yale, Luer-Lok), the ground glass plungers of which had been lubricated with silicone oil (Dow-Corning 550 fluid). A 2-ft Teflon "needle" (18 gauge) with Kel-F hub (Hamilton) was locked onto the "delivery" syringe and the air was pushed out of the barrel. The two syringes were then placed in a Sage syringe pump (Model 352) and the driving motor was started. When the air was forced out of both Teflon needles, the motor was stopped and the ends of the needles were dried and passed through airtight (tightly fitting and greased) holes in individual neoprene rubber stoppers into 1600 ml of dry, reagent grade benzene in a 2000-ml, five-necked, round-bottomed flask equipped with a nitrogen inlet, a calcium sulfate and sodium hydroxide drying tube which served as the nitrogen outlet, a cone-drive stirrer, and two neoprene rubber stoppers. A stream of nitrogen was passed through the flask during all operations. When the Teflon needles were placed below the surface of the benzene in the flask, the nitrogen flow was stopped, stirring was begun, and the syringe pump was set to deliver the solutions at a rate of 0.2 ml/hr (total time of delivery ~5 days) or at any convenient rate.

**3,12-Diazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (4).**—Benzene solutions (49 ml) of 1,8-diaminooctane (0.4591 *M*) and isophthaloyl chloride (0.2296 *M*) were introduced *via* syringe pump into 1200 ml of dry benzene at a rate of ~1 ml/hr. After 45 hr, when addition was complete, the Teflon needles were removed, and the mixture was stirred for an additional hour. The benzene solution was filtered to remove amine hydrochloride mixed with product, and the benzene was removed on a rotary evaporator. A small amount of product (0.035 g), mp 297°, was obtained by treatment of the material from evaporation of the benzene with hot ethanol, concentration of the ethanol solution to 7 ml, and chilling. All of the remaining solid obtained, including the amine hydrochloride mixture, was wetted with THF, placed in Soxhlet thimble, and continuously extracted with dry THF for ~2 days. The THF was removed on a rotary evaporator at room temperature. The yellow solid obtained was dissolved in hot ethanol (70 ml) and treated with activated charcoal. The charcoal was removed by filtration, and the filtrate was concentrated by heating until slightly turbid. It was allowed to stand for 1 hr at room temperature and 4 hr in a freezer. The white solid which had formed was collected by filtration, washed with ether, and dried for 0.5 hr in a vacuum oven. This product was combined with the small amount obtained earlier (total yield: 1.165 g, 0.00425 mol, 38%): mp 293–296°; ir (KBr) 3275 (NH), 1660 (sh), 1640 (amide C=O) $cm^{-1}$; pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.00, 7.66 (m, 6, NH, $C_6H_4$), 3.28 (m, 4, $CH_2N$), 1.50 (m, 12, $CH_2$).

*Anal.* Calcd for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22; mol wt, 274. Found: C, 70.17; H, 8.25; N, 10.06; mol wt, 295.

**Octamethylene-Bridged Dinicotinamide: 3,12,16-Triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (5a).**—A solution (25 ml) of freshly sublimed 1,8-diaminooctane (3.48795 g, 0.023485 mol) in dry, reagent grade benzene was placed in a 50-ml delivery syringe. Likewise, a solution (25 ml) of 3,5-pyridinedicarbonyl chloride (2.38323 g, 0.011743 mol) in benzene was placed in the other 50-ml syringe of the syringe pump. These solutions were added to dry benzene (1600 ml) at a rate of 0.2 ml/hr. After completion of addition of the reagents to the reaction flask, the white solid which had formed was removed by filtration and dried in a vacuum oven for 3 hr at 50°. The benzene was removed by a rotary evaporator to yield a white solid. The two solids were combined and extracted with THF in a Soxhlet extractor for 48 hr. The tetrahydrofuran was removed by a rotary evaporator to yield a white solid which was recrystallized from 95% ethanol to give the 3,5-octamethylene-bridged pyridine (**5a**) (1.335 g, 0.00476 mol, 41%): mp 341–343° dec; ir (KBr) 3300 (m, NH), 3100 (w, aromatic), 2925 (m), 2850 (m), 1670 (m, amide C=O), 1640 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.00, 8.85, 8.65, 8.25 (5, NH, pyridine H), 3.30 (m, 4, $NCH_2$), 1.45 (m, 12).

*Anal.* Calcd for $C_{15}H_{21}N_3O_2$: C, 65.45; H, 7.64; N, 15.27. Found: C, 65.72; H, 7.79; N, 15.32.

**Heptamethylene-Bridged Dinicotinamide: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dione (5b).**—Freshly sublimed 1,7-diaminoheptane (3.05869 g, 0.023485 mol) and 3,5-pyridinedicarbonyl chloride (2.38323 g, 0.011743 mol) were allowed to react as described for **5a** to yield the 3,5-heptamethylene-bridged pyridine (**5b**) (0.706 g, 0.00271 mol, 23%): mp 342–343° dec; ir (KBr) 3250 (m, NH), 3050 (w aromatic), 2900 (m), 2850 (sh), 1640 $cm^{-1}$ (s, amide C=O); pmr (DMSO-$d_6$) $\delta$ 8.92, 8.20 (br complex m, 5, NH, pyridine H), 3.16 (br m, 4, $CH_2N$), 1.38 (br m, 10).

*Anal.* Calcd for $C_{14}H_{19}N_3O_2$: C, 64.38; H, 7.28; N, 16.09. Found: C, 64.59; H, 7.41; N, 16.03.

**Hexamethylene-Bridged Dinicotinamide: 3,10,14-Triazabicyclo[10.3.1]hexadeca-1(16),12,14-triene-2,12-dione (5c).**—Freshly sublimed 1,6-diaminohexane (2.36309 g, 0.0203347 mol) and 3,5-pyridinedicarbonyl chloride (2.28764 g, 0.0101674 mol) were allowed to react as described above. Extraction with THF failed to separate the product from the benzene-insoluble material. The material insoluble in THF was removed from the Soxhlet extractor, dried for 1 hr in a vacuum oven at 50°, and treated with 50 ml of hot 95% ethanol. The insoluble material was removed by filtration. The treatment with ethanol was repeated on the ethanol-insoluble material. The insoluble solid was collected by filtration to yield 3,5-hexamethylene-bridged pyridine (**5c**) (0.246 g, 0.001 mol, 9.8%): mp 298–300°; ir (KBr) 3400 (sh), 3260 (m, NH), 3050 (w, aromatic), 2900 (m), 2940 (sh), 1635 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.23, 8.98, 8.78 (5, NH, pyridine H), 3.40 (br s, 4, $CH_2N$), 1.50 (br m, 8).

*Anal.* Calcd for $C_{13}H_{17}N_3O_2 \cdot {}^1/_3H_2O$: C, 61.67; H, 6.98, N, 16.60. Found (after 24 hr at 120° under vacuum): C, 61.73; H, 7.10; N, 16.71.

**Pentamethylene-Bridged Dinicotinamide: 3,9,13-Triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-2,10-dione (5d).**—Freshly distilled 1,5-diaminopentane (2.40427 g, 0.0235298 mol) and 3,5-pyridinedicarbonyl chloride (2.40031 g, 0.011765 mol) were allowed to react as described above. Again, extraction with THF failed to separate the product from the benzene-insoluble material. The material insoluble in THF was removed from the Soxhlet extractor, dried for 1 hr in a vacuum oven at 50°, and treated with 50 ml of hot 95% ethanol. The insoluble

(28) Melting points were taken on either a Fisher-Johns or Mel-Temp melting point apparatus and are uncorrected. Ir spectra were obtained on either a Perkin-Elmer Model 521 spectrophotometer or a Perkin-Elmer Model 137 spectrophotometer: w, weak; m, medium; s, strong; sh, shoulder; d, doublet. Uv spectra were taken on a Perkin-Elmer uv–visible spectrophometer, Model 202. Proton nuclear magnetic resonance (pmr) spectra were recorded on a Varian Model A-60 or on a 100-MHz Japan Electronic Optics Laboratory Model JNM-4H-100 nmr spectrophotometer: s, singlet; d, doublet; m, multiplet; br, broad. Mass spectra were obtained on a Hitachi Perkin-Elmer mass spectrometer, Model RMU-6D. Fluorescence spectra were obtained on an Aminco-Bowman spectrophotofluorimeter. Nitrogen refers to Burco high purity nitrogen, oxygen content between 4 and 15 ppm. A drying tower containing Drierite and sodium hydroxide was used to remove the last traces of water from the nitrogen.

(29) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y. 1967, p 286.

(30) H. Meyer and H. Tropsch, *Monatsh. Chem.*, **35**, 782 (1914).

material was collected by filtration, and the treatment with ethanol was repeated. The insoluble 3,5-pentamethylene-bridged pyridine (**5d**) was again collected (0.123 g, 0.00053 mol, 4.3%): mp 236–238°; ir (KBr) 3400 (sh), 3230 (m, amide NH), 3030 (w, aromatic), 2900 (m, 2830 (sh), 1635 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.12, 8.84, 8.64 (5, NH, pyridine H), 3.35 (m, 4, $NCH_2$), 1.60 (br m, 6).

*Anal.* Calcd for $C_{12}H_{15}N_3O_2 \cdot 0.7H_2O$: C, 58.77; H, 6.78; N, 17.17. Found (after 24 hr at 100° under vacuum): C, 58.94; H, 7.09; N, 17.27.

**1-Dichlorobenzylheptamethylene-Bridged Pyridinium Bromide: 15-(2,6-Dichlorobenzyl)-2,12-dioxo-3,11-diaza-15-azoniabicyclo-[11.3.1]heptadeca-1(17),13,15-triene Bromide (6).**—Heptamethylene-bridged pyridine (**5b**, 0.260 g, 0.001 mol) was dissolved in a solution of $\alpha$-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dimethyl sulfoxide (10 ml) (dried over 3A molecular sieves) and the reaction mixture was stirred and heated in an oil bath at 70° for 2 hr. A white precipitate was obtained by the addition of ether (100 ml). The solid was collected by filtration and recrystallized from ethanol to yield **6** (0.403 g, 0.00076 mol, 76%): mp 288–290°; ir (KBr) 1670 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.48, 9.29, 8.88, 8.62 (m, 5, NH, pyridine H), 7.73 (s, 3, Ar H), 6.33 (s, 2, Ar $CH_2$), 3.00 (m, $NCH_2$), 1.55 (m, 12).

*Anal.* Calcd for $C_{21}H_{24}BrCl_2N_3O_2$: C, 50.32; H, 4.83. Found: C, 50.39; H, 5.17.

**1-Dichlorobenzylheptamethylene-Bridged 1,4-Dihydrodinicotinamide: 15-(2,6-Dichlorobenzyl)-3,11,15-triazabicyclo[11.3.1]heptadeca-13,16-diene-2,12-dione (7).**—Pyridinium bromide **6** (0.258 g, 0.0005 mol) was added to a solution of sodium hydrosulfite (0.350 g, 0.002 mol) and sodium carbonate (0.224 g, 0.002 mol) in distilled water (25 ml) at 70°. A stream of nitrogen was passed over the solution during all operations. The rapidly stirred reaction mixture immediately turned orange and within 10 min a yellow solution had formed. A yellow solid precipitated 15 min later. Heating and stirring continued for 1 hr, the mixture was allowed to cool to room temperature, and the yellow solid was collected by filtration and recrystallized from ethanol-water to yield **7** (0.130 g, 0.000296 mol, 60%): mp 230–231° dec; uv max (95% ethanol) 344 nm ($\epsilon$ 5100); fluorescence (max) (95% ethanol) excitation, 343 nm, and emission, 478 nm; ir (KBr) 3300 (br m, amide NH), 3020 (w), 2900 (m), 2830 (sh), 1640 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 7.90 (s, 2, vinyl H), 7.5–7.1 (5, NH, Ar H), 5.00 (s, 2, Ar $CH_2$), 3.35 (m, unintegrated, water contamination, $CH_2N$), 3.00 (s, unintegrated, 4-$CH_2$), 1.35 (m, 10).

*Anal.* Calcd for $C_{21}H_{25}Cl_2N_3O_2 \cdot {}^1/_3H_2O$: C, 58.89; H, 6.05. Found: C, 58.88; H, 5.93.

**Ethylene Ketal of 1,7-Heptanediol-4-one Bis-*p*-toluenesulfonate (8a).**—*p*-Toluenesulfonyl chloride (152 g, 0.80 mol) was added to a cold (−10°) solution of the ethylene ketal of 1,7-heptanediol-4-one[31] (38 g, 0.20 mol) in pyridine (400 ml, dried over potassium hydroxide). A precipitate appeared and after 1 hr the reaction mixture was poured into ice–water (3000 ml) which was rapidly stirred. A pink oil formed which solidified after 1 hr. This solid was collected by filtration, washed thoroughly with cold water, and dried overnight in a vacuum oven at room temperature to yield **8a** (94.5 g, 0.19 mol, 96%): mp 78–80°; pmr ($CDCl_3$) $\delta$ 7.56 (q, 8 H, $C_6H_4$), 4.00 (m, 4 H, $SO_3CH_2$), 3.82 (s, 4 H, $OCH_2CH_2O$), 2.43 (s, 6 H, $CH_3$), 1.56 (m, 8 H).

This compound could be stored at −20° without noticeable decomposition for periods of 1 week.

**Ethylene Ketal of 1,9-Nonanediol-5-one Bis-*p*-toluenesulfonate (8b).**—The ethylene ketal of 1,9-nonanediol-5-one[31] (43.6 g, 0.20 mol) was treated with *p*-toluenesulfonyl chloride (152 g, 0.80 mol) as described for the preparation of **8a**. The oily, impure product was dissolved in ether which was extracted with water. The ether was dried over 3A molecular sieves and removed on a rotary evaporator to yield **8b** (97 g, 0.185 mol, 92%): mp 79–80°; pmr ($CDCl_3$) $\delta$ 7.50 (q, 8, $C_6H_4$), 3.93 (m, 4, $SO_3CH_2$), 3.78 (s, 4, $OCH_2CH_2O$), 2.73 (s, 6, $CH_3$), 1.43 (m, 12).

*Anal.* Calcd for $C_{25}H_{34}O_8S_2$: C, 57.03; H, 6.46. Found: C, 56.96; H, 6.49.

**Ethylene Ketal of 1,7-Bisphthalimidoheptan-4-one (9a).**—Bis-*p*-toluenesulfonate **8a** (90 g, 0.18 mol) was dissolved in dimethylformamide (400 ml) and potassium phthalimide (140.7 g, 0.76 mol) was added to the rapidly stirred reaction mixture which was heated at 100° for 1 hr and then cooled to room temperature. The reaction mixture was transferred to an extraction funnel, treated with water (500 ml), and extracted with chloroform. The chloroform was washed with water, dried over 3A molecular sieves, and removed on a rotary evaporator to yield an oily, brown residue. The residue was treated with 95% ethanol (200 ml) and chilled to −20°. Recrystallization from 95% ethanol afforded white, crystalline **9a** (53.9 g, 0.12 mol, 66%): mp 135–136.5°; ir (KBr) 1725 $cm^{-1}$ (vs, C=O); pmr (DMSO-$d_6$) $\delta$ 7.81 (s, 8, $C_6H_4$), 3.83 (s, 4, $OCH_2CH_2O$), 3.50 (br, 4, $NCH_2$), 1.57 (br, 8).

*Anal.* Calcd for $C_{25}H_{24}N_2O_6$: C, 66.96; H, 5.36; N, 6.25. Found: C, 66.82; H, 5.45; N, 5.96.

**Ethylene Ketal of 1,9-Bisphthalimidononan-5-one (9b).**—Bis-*p*-toluenesulfonate **8b** (94.7 g, 0.18 mol) was treated with potassium phthalimide (140.7 g, 0.76 mol) as described for the preparation of **9a**. Recrystallization from 95% ethanol gave **9b** (32 g, 0.067 mol, 37%): mp 149–150°; ir (KBr) 1700 $cm^{-1}$ (vs, C=O); pmr ($CDCl_3$) $\delta$ 7.83 (s, 8, $C_6H_4$), 3.90 (s, 4, $OCH_2CH_2O$), 3.56 (t, 4, $J$ = 6.5 Hz, $NCH_2$).

*Anal.* Calcd for $C_{27}H_{28}N_2O_6$: C, 68.07; H, 5.88. Found: C, 68.20; H, 5.89.

**Ethylene Ketal of 1,7-Diaminoheptan-4-one (10a).**—Hydrazine (95%, 6.84 g, 0.206 mol) was added to a suspension of **9a** (44.8 g, 0.10 mol) in 95% ethanol (600 ml). After the reaction mixture had been refluxed for 5 min, a solution was formed; after an additional 10 min, a white precipitate appeared. The reaction mixture was heated for 6 hr. Addition of water (100 ml) to the hot mixture caused the precipitate to dissolve and the hot solution was treated with sodium hydroxide (8.1 g, 0.202 mol) and cooled to room temperature. Long white needles of sodium phthaloyl hydrazide slowly formed. The mixture was chilled to −20° for 2 hr and the phenyl hydrazide salt was removed by filtration and discarded. The filtrate was concentrated to 500 ml on a rotary evaporator and THF (300 ml) was added to precipitate the remainder of the salt, which was removed by filtration. The solvent was removed on a rotary evaporator and the residue distilled to yield **10a** (16.35 g, 0.087 mol, 87%): bp 105–108° (0.03–0.05 mm); ir (neat) 3325 (m, $NH_2$), 3250 (sh, $NH_2$), 1600 $cm^{-1}$ ($NH_2$, m); pmr (neat) $\delta$ 3.90 (s, 4, $OCH_2CH_2O$), (2.56, t, 4, $J$ = 5.5 Hz, $CH_2NH_2$), 1.51 (br, 8, $H_2NCH_2CH_2$), 1.32 (s, 4, $NH_2$).

*Anal.* Calcd for $C_9H_{20}N_2O_2$: C, 57.44; H, 10.64. Found: C, 57.23; H, 10.83.

**Ethylene Ketal of 1,9-Diaminononan-5-one (10b).**—Bis phthalimido derivative **9b** (32 g, 0.067 mol) was treated with hydrazine (4.6 g, 0.135 mol) as described for the preparation of **10a**. Distillation gave **10b** (12.7 g, 0.06 mol, 90%): bp 128–134° (0.02–0.04 mm); ir (neat) 3300 (m, $NH_2$), 3200 (m, $NH_2$), 1600 $cm^{-1}$ (m, $NH_2$); pmr (neat) $\delta$ 3.87 (s, 4, $OCH_2CH_2O$), 2.58 (t, 4, $J$ = 6 Hz, $CH_2NH_2$), 1.40 (m, 12), 1.22 (s, 4, $NH_2$).

*Anal.* Calcd for $C_{11}H_{24}N_2O_2$: C, 61.11; H, 11.11. Found: C, 61.40; H, 11.30.

**3,3-Bridged Dinicotinamide Ketal: Spiro[3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dione-2′,7(1′,3′)-dioxolane] (11a).**—Diamine **10a** (3.86322 g, 0.020519 mol) and 3,5-pyridinedicarbonyl chloride (2.09318 g, 0.010259 mol) were allowed to react as described in the preparation of **5a**. Isolation of the product was attempted by a Soxhlet extraction with THF; however, the solid material became gummy upon exposure to the atmosphere. It was dissolved in boiling 95% ethanol (50 ml) and the product was allowed to crystallize without removal of impurities. After several days, transparent, cubic crystals separated. This solid was collected by filtration and recrystallized from 95% ethanol (35 ml) to yield **11a** (0.642 g, 0.00202 mol, 20%): mp 266–267°; ir (KBr) 3450 (m, d, NH), 3225 (m, d, NH), 1640 $cm^{-1}$ (vs, d, C=O); pmr (100 MHz, DMSO-$d_6$–$D_2O$) $\delta$ 8.92 (d of d, $J$ = 2.5, 12 Hz, 2, pyridine $\alpha$ H), 8.30 (br s, 1, pyridine $\gamma$ H), 3.77 (s, 4, $OCH_2CH_2O$), 3.20 (m, 4, $CH_2N$), 1.90 (m, 4, $CH_2CO$), 1.45 (m, 4, $CH_2$). In the absence of water, the amide protons appear as broadened multiplets at $\delta$ 8.16 and at 8.80, near and under the absorptions of the pyridine ring protons.

*Anal.* Calcd for $C_{16}H_{21}N_3O_4 \cdot {}^1/_3H_2O$: C, 59.07; H, 6.67; N, 12.92; O, 21.33. Found (after 24 hr at 120° under vacuum): C, 59.05, H, 6.54; N, 13.6; O, 21.25.

**4,4-Bridged Dinicotinamide Ketal: Spiro[3,12,16-triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,14-dione-2′,8(1′,3′-dioxolane] (11b).**—Diamine **10b** (4.43398 g, 0.0204965 mol)

(31) H. Stetter and H. Rauhut, *Chem. Ber.*, **91**, 2543 (1958).

and 3,5-pyridinedicarbonyl chloride (2.09087 g, (0.0102482 mol) were allowed to react as described for the preparation of **5a**. The same isolation and purification techniques used for **11a** were applied to yield **11b** (1.434 g, 0.00415 mol, 40.5%): mp 347–351° dec; ir (KBr) 3400 (sh, NH), 3275 (m, NH), 1660 (sh), 1640 $cm^{-1}$ (s, C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 2, pyridine $\alpha$ H), 8.17 (s, 1, pyridine $\gamma$ H), 7.97 (br m, 2, NH), 3.86 (s, 4, $OCH_2CH_2O$), 3.35 (br m, $CH_2N$), 1.60 (m, 12).

*Anal.* Calcd for $C_{18}H_{23}N_3O_4$: C, 62.25; H, 7.20; N, 12.10. Found: C, 62.42; H, 7.01; N, 12.01.

**3,3-Bridged Ketone Dinicotinamide: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,7,12-trione (12a).**—Ketal **11a** (0.720 g, 0.0023 mol) was added to a solution of 48% hydrogen bromide (1 ml) in water (9 ml) and 95% ethanol (10 ml), warmed to 50°. The solid dissolved and the reaction mixture was stirred and heated for 1 hr. The ethanol was removed on a rotary evaporator and the aqueous solution was treated with a saturated solution of sodium carbonate. A white solid was collected by filtration, washed thoroughly with water, and dried to yield **12a** (0.578 g, 0.0021 mol, 91%): mp 313–316°; ir (KBr) 3400 (m, NH), 3150 (m, NH), 1700 (m, C=O), 1640 $cm^{-1}$ (s, d, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.95–8.40, 7.95–7.6 (m, 5, NH, pyridine H), 3.20 (br m, $NCH_2$), 2.60 (m, unintegrated, DMSO interference, $CH_2CO$), 1.70 (br m, 4).

*Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.18; N, 15.27. Found: C, 61.07; H, 6.13; N, 15.18.

**4,4-Bridged Dinicotinamide Ketone: 3,13,17-Triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,8,14-trione (12b).**—Ketal **11b** (1.110 g, 0.0032 mol) was hydrolyzed according to the procedure given for **11a** to yield **12b** (recrystallized from ethanol) (0.708 g, 0.00234 mol, 73%): mp 323–325°; ir (KBr) 3250 (m, NH), 1700 (m, C=O), 1635 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.88 (s, 2, pyridine $\alpha$ H), 8.57–8.25 (m, 3, NH, pyridine $\gamma$ H), 3.36 (m, not integrated, interference with $H_2O$, $CH_2N$), 1.65 (br m, 12).

*Anal.* Calcd for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.56, H, 7.12; N, 13.56.

**3,3-Bridged Dinicotinamide Alcohol: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dion-7-ol (13a).**—Sodium borohydride (0.054 g, 0.00137 mol) was added to a suspension of **12a** (0.375 g, 0.00136 mol) in absolute ethanol (30 ml) and the mixture was stirred and heated at 60° for 2 hr after which water (5 drops) was added to the suspension. The mixture was allowed to come to room temperature and stirred overnight. The white insoluble material was collected by filtration and recrystallized from ethanol to yield **13a** (0.290 g, 0.00105 mol, 77%): mp 313–316°; ir (KBr) 3310 (s, OH), 3200 (m, NH), 3025 (m), 1660 (s, C=O), 1640 $cm^{-1}$ (s, C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.85 (d, 3, pyridine $\alpha$ H, NH), 8.10 (s, 2, pyridine $\gamma$ H, NH), 4.42 (d, 1, COH), 3.50 and 2.95 (m, CHOH, $CH_2N$, water interference), 1.50 (br m, 8).

*Anal.* Calcd for $C_{14}H_{19}N_3O_3 \cdot {}^1/_3H_2O$: C, 59.36; H, 6.95. Found (after 24 hr at 120° under vacuum): C, 59.16; H, 7.02.

**4,4-Bridged Dinicotinamide Alcohol: 3,13,17-Triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,14-dion-8-ol (13b).**—Reduction of **12b** (1.100 g, 0.00345 mol) by sodium borohydride (0.76 g, 0.002 mol) as described for **12a** gave **13b** (0.950 g, 0.0031 mol, 90%): mp 352–354°; ir (KBr) 3250 (s, NH, OH), 1650 (sh), 1630 $cm^{-1}$ (vs, C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 8.83 (s, 2, pyridine $\alpha$ H), 8.40 (br s, 2, NH), 8.14 (s, 1, pyridine $\gamma$ H), 4.37 (br s, 1, COH), 3.52 and 3.25 (m, water interference, CHOH, $CH_2N$), 1.57 (m, 12).

*Anal.* Calcd for $C_{16}H_{23}N_3O_3$: C, 62.95; H, 7.54; N, 13.77. Found: C, 63.18; H, 7.54; N, 13.62.

**1-(2,6-Dichlorobenzyl)-3,3-Bridged Dinicotinamide Ketone Bromide: 15-(2,6-Dichlorobenzyl)-2,7,12-trioxo-3,11-diaza-15-azoniabicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (14a).**—Bridged dinicotinamide ketone **12a** (0.275 g, 0.001 mol) was dissolved in dimethyl sulfoxide (10 ml) (dried over 3A molecular sieves) containing $\alpha$-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol). The reaction mixture was stirred and heated in an oil bath at 60° for 90 min. A white precipitate, obtained by the addition of diethyl ether (100 ml), was collected by filtration and recrystallized from 20% aqueous ethanol to yield **14a** (0.452 g, 0.00087 mol, 87%): mp 257–259°; ir (KBr) 3150 (m, NH), 1700 (m, C=O), 1660 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.23, 9.11, and 8.39 (m, 5, NH, pyridine H), 7.67 (s, 3, Ar H), 6.29 (s, 2, Ar $CH_2$), 3.20 (m, 4, $CH_2N$), 2.73 (m, 4, $CH_2CO$), 1.77 (m, 4).

*Anal.* Calcd for $C_{21}H_{22}BrCl_2N_3O_3$: C, 48.93; H, 4.27; N, 8.16. Found: C, 48.93; H, 4.55; N, 8.16.

**1-Dichlorobenzyl-4,4-Bridged Dinicotinamide Ketone Bromide: 17-(2,6-Dichlorobenzyl)-2,8,14-trioxo-3,13-diaza-17-azoniabicyclo[13.3.1]nonadeca-1(19),15,17-triene Bromide (14b).** Bridged dinicotinamide ketone **12b** (0.303 g, 0.001 mol) was quaternized with $\alpha$-bromo-2,6-dichlorotoluene (0.048 g, 0.002 mol) as described for **12a** to give salt **14b** (0.410 g, 0.00076 mol, 76%): mp 221–224°; ir (KBr) 3180 (m, NH), 1670 $cm^{-1}$ (br, C=O and amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.25, 9.10, and 9.00 (5, NH, pyridine H), 7.80 (s, 3, Ar H), 6.35 (s, 2, Ar $CH_2$), 3.40 (m, interference with $H_2O$, $CH_2N$), 1.70 (br m, 12).

*Anal.* Calcd for $C_{23}H_{26}BrCl_2N_3O_3$: C, 50.83; H, 4.79; N, 7.73. Found: C, 50.53; H, 4.84; N, 7.67.

**1-Methyl-4,4-Bridged Dinicotinamide Ketone Iodide: 17-Methyl-2,8,14-trioxo-3,13-diaza-17-azoniabicyclo[13.3.1]nonadeca-1(19),15,17-triene Iodide (14c).**—Bridged dinicotinamide **12b** (0.830 g, 0.00275 mol) was dissolved in dry dimethyl sulfoxide (10 ml) containing methyl iodide (2.8 g, 0.05 mol). The solution was refluxed gently for 5 hr and the solvent was removed on a rotary evaporator. The yellow solid was recrystallized from ethanol to yield **14c** (1.160 g, 0.0026 mol, 95%): mp 262–266°; ir (KBr) 3200 (m, NH), 1670 $cm^{-1}$ (s, amide C=O and C=O); pmr (DMSO-$d_6$) $\delta$ 9.60 (s, 2, pyridine $\alpha$ H), 8.94 (d, 3, NH and pyridine $\gamma$ H), 4.51 (s, 3, $CH_3$), 3.43 (m, 4, $CH_2N$), 1.70 (m, 12).

*Anal.* Calcd for $C_{17}H_{24}N_3O_3I$: C, 45.84; H, 5.39; N, 9.44. Found: C, 45.96; H, 5.48; N, 9.40.

**1-Dichlorobenzyl-3,3-Bridged Dinicotinamide Alcohol Bromide: 15-(2,6-Dichlorobenzyl)-2,12-dioxo-7-ol-3,11-diaza-15-azoniabicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (15a).**—Bridged alcohol **13a** (0.320 g, 0.00115 mol) was treated with $\alpha$-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dry dimethyl sulfoxide (10 ml) as described for the preparation of **14a** to yield **15a** (0.541 g, 0.000965 mol, 84%): mp 254–255°; ir (KBr) 3400 (m, OH), 3150 (m, NH), 1655 $cm^{-1}$ (s, C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.50 (m, 1, NH), 9.25 (d, 2, pyridine $\alpha$ H), 8.88 (m, 1, pyridine $\gamma$ H), 8.55 (s, 1, NH), 7.67 (s, 3, Ar H), 6.30 (s, 2, Ar $CH_2$), 4.46 (s, 1, COH), 3.15 (m, 5, CHOH, $CH_2N$), 1.60 (m, 8).

*Anal.* Calcd for $C_{21}H_{24}BrCl_2N_3O_3 \cdot {}^1/_3H_2O$: C, 48.18; H, 4.72; N, 8.02. Found (after 24 hr at 100° in vacuum); C, 48.11; H, 4.88; N, 7.72.

**1-Dichlorobenzyl-4,4-Bridged Dinicotinamide Alcohol Bromide: 17-(2,6-Dichlorobenzyl)-2,14-dioxo-8-ol-3,13-diaza-15-azoniabicyclo[13.3.1]nondeca-1(19),15,17-triene Bromide (15b).**—The bridged dinicotinamide **13b** (0.350 g, 0.00115 mol) was treated with $\alpha$-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dimethyl sulfoxide (10 ml) as described for the preparation of **14a** to give **15b** (0.480 g, 0.00088 mol, 77%): mp 224–226°; ir (KBr) 3300 (m, OH), 3160 (m, NH), 1660 $cm^{-1}$ (vs, C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 9.20 (m, 5, NH and pyridine H), 7.70 (s, 3, Ar H), 6.35 (s, 2, Ar $CH_2$), 4.05 (s, 1, OH), 3.35 (m, interference with $H_2O$, CHOH, $CH_2N$), 1.57 (m, 12).

*Anal.* Calcd for $C_{23}H_{28}Cl_2BrN_3O_3$: C, 50.64; H, 5.14; N, 7.71. Found: C, 50.65; H, 5.39; N, 7.75.

**1-Dichlorobenzyl-3,3-Bridged 1,4-Dihydrodinicotinamide Ketone: 15-(2,6-Dichlorobenzyl)-3,11,15-triazabicyclo[11.3.1]heptadeca-13,16-diene-2,7,12-trione (16a).**—Pyridinium bromide **14a** (0.743 g, 0.00144 mol) was added to a solution of sodium hydrosulfite (1.30 g, 0.0063 mol) (Mallinckrodt, 90%) and sodium carbonate (0.742 g, 0.007 mol) in distilled water (25 ml). The reaction mixture was heated and stirred at 90° under nitrogen. It immediately became orange and after 5 min the pyridinium salt had dissolved. A yellow solid precipitated 10 min later. Heating and stirring was continued for 4 hr after which the reaction mixture was cooled to room temperature and the yellow solid collected by filtration and recrystallized from ethanol–water to yield **16a** (0.389 g, 0.0009 mol, 62%): mp 265–268°; uv max (95% ethanol) 338 nm ($\epsilon$ 6700); fluorescence excitation (max), 340 nm, and emission (max), 451 nm; ir (KBr) 1700 (sh, C=O), 1650 $cm^{-1}$ (s, amide C=O); pmr (100 MHz, DMSO-$d_6$) $\delta$ 7.52 (m, 4, Ar H, NH), 7.00 (m, 3, pyridine $\alpha$ H, NH), 4.95 (s, 2, Ar $CH_2$), 3.05 (m, 6, pyridine $\gamma$ $CH_2$, $CH_2N$), 1.65 (m, 8).

*Anal.* Calcd for $C_{21}H_{23}Cl_2N_3O_3 \cdot {}^2/_3H_2O$: C, 56.26; H, 5.47; N, 9.38. Found (after 24 hr at 80° under vacuum): C, 56.01; H, 5.74; N, 9.54.

**1-Dichlorobenzyl-4,4-Bridged 1,4-Dihydrodinicotinamide Ketone: 17-(2,6-Dichlorobenzyl)-3,13,17-triazabicyclo[13.3.1]-nonadeca-15,18-diene-2,8,14-trione (16b).**—Bridged pyridinium salt **14b** (0.250 g, 0.00046 mol) was reduced by sodium hydrosulfite (0.300 g, 0.0015 mol) in aqueous sodium carbonate (0.160 g, 0.0015 mol, 25 ml) as described for **16a** except that the temperature was 70°. After 1 hr, the yellow solid was collected by filtration and recrystallized from ethanol–water to yield **16b** (0.160 g, 0.00035 mol, 75%): mp 215–217°; uv max (95% ethanol) 381 nm (ε 6450); fluorescence excitation (max) (ethanol), 375 nm, and emission (max), 447 nm; ir (KBr) 1690 (s, C=O) 1650 cm$^{-1}$ (w, amide C=O); pmr (100 MHz, DMSO-$d_6$) δ 7.52 and 6.86 (7, Ar H, pyridine α H, NH), 4.85 (s, 2, Ar $CH_2$), 3.33 and 3.25 (interference with $H_2O$, pyridine γ $CH_2$, $CH_2N$), 1.55 (m, 12).

*Anal.* Calcd for $C_{23}H_{27}Cl_2N_3O_3 \cdot {}^1/_3H_2O$: C, 58.71; H, 5.94; N, 8.94; O, 11.33. Found (after 24 hr at 80° under vacuum): C, 58.86; H, 5.85; N, 8.98; O, 10.66.

**1-Methyl-4,4-Bridged 1,4-Dihydrodinicotinamide Ketone: 17-Methyl-3,13,17-triazabicyclo[13.3.1]nonadeca-15,18-diene-2,-8,14-trione (16c).**—The methyl-substituted salt **14c** (0.444 g, 0.0001 mol) was reduced by sodium hydrosulfite (0.6 g, 0.003 mol) in aqueous sodium carbonate (0.318 g, 0.003 mol, 25 ml) as described for **16a** except that the temperature was 60°. After 90 min, the yellow solid was collected by filtration and recrystallized from ethanol–water to yield **16c** (0.233 g, 0.0007 mol, 70%): mp 231–234°; uv max (95% ethanol) 388 nm (ε 7700); fluorescence excitation (max) (ethanol), 389 nm, and emission (max), 445 nm; ir (KBr) 1695 (s, C=O), 1650 cm$^{-1}$ (m, amide C=O); pmr (100 MHz, DMSO-$d_6$) δ 7.24 (m, 2, NH), 7.01 (s, 2, pyridine α H), 3.45, (s, unintegrated, interference with pyridine α H, $CH_3$), 3.36 (s, unintegrated, interference with $CH_3$, pyridine α H), 3.20 (m, 4, $CH_2N$), 1.61 (m, 12).

*Anal.* Calcd for $C_{17}H_{25}N_3O_3$: C, 63.95; H, 7.84; N, 13.17. Found: C, 63.83; H, 7.91; N, 12.88.

**1-(2,6-Dichlorobenzyl)-3,5-(*N*,*N*′-dimethyldicarbamoyl)-1,4-dihydropyridine (18).**—Quaternization of 3,5-(*N*,*N*′-dimethyldicarbamoyl)pyridine[32] (5.4 g, 0.032 mol) with α-bromo-2,6-dichlorotoluene following the procedure described for the bridged dinicotinamide salts gave 1-(2-6-dichlorobenzyl)-3,5-(*N*,*N*′-dimethyldicarbamoyl)pyridinium bromide (**17**, 8.5 g, 0.020 mol, 62%): mp 248–250° dec; uv max (95% ethanol) 220 nm (ε 78,300); uv max (water) 200 nm (ε 78,000); ir (KBr) 1670 (vs, C=O), 1650 (vs, C=O), 1550 cm$^{-1}$ (s, amide); pmr (DMSO-$d_6$) δ 9.66 (m, 1, pyridine γ H), 9.48 (m, 2, pyridine α H), 9.36 (m, 2, NH), 7.72 (s, 3, Ar H), 6.36 (s, 2, Ar $CH_2$), 2.90 (t, 6, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{16}BrCl_2N_3O_2$: C, 44.34; H, 3.70. Found: C, 44.35; H, 3.88.

The pyridinium bromide **17** (7.5 g, 0.0173 mol) was reduced by sodium hydrosulfite as described for the bridged dihydronicotinamides and the crude product was recrystallized by dissolving the solid in hot 95% ethanol (100 ml) and adding hot distilled water (100 ml). This solution was cooled 3 hr at 0° and the precipitate collected by filtration to yield long yellow needles of **18** (4.1 g, 0.0114 mol, 61%): mp 205–207° (loses water of hydration at 105–108°); uv max (95% ethanol) 391 nm (ε 6070); fluorescence excitation (max) (ethanol), 378 nm, and emission (max), 445 nm; ir (KBr) 3380 (m), 1690 (s, C=O), 1580 (s), 1540 cm$^{-1}$ (s, amide); pmr (DMSO-$d_6$) δ 7.58, 7.20, and 6.94 (m, 7, pyridine α H, NH, Ar H), 4.73 (s, 2, Ar $CH_2$), 3.13 (s, 2, pyridine γ $CH_2$), 2.68 (d, interference with DMSO, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{17}Cl_2N_3O_2 \cdot {}^1/_4H_2O$: C, 53.56; H, 4.88; N, 11.71. Found (50° under vacuum, 24 hr): C, 53.67; H, 4.72; N, 11.82.

**Chemical Properties of Bridged 1,4-Dihydrodinicotinamides. 1. Silver Nitrate.**—Treatment of the dihydropyridines in ethanol (0.005 *M*) with an equal volume of aqueous silver nitrate (0.002 *M*) resulted in formation of a silver mirror.[33] The times for formation of the mirror are recorded in Table I.

**2. Malachite Green.**—Dihydropyridine derivatives **7**, **16a**, **16b**, and **18** (1.15 × 10$^{-5}$ *M*) caused decoloration of Malachite Green (1.15 × 10$^{-7}$ *M*) in ethanol solutions at 27°.[34] The kinetic behavior was complex but half-lives of 597, 666, 1044, and 918 sec, respectively, were noted.

**3. Aqueous Hydrochloric Acid.**—Ethanolic solutions (2 × 10$^{-4}$ *M*, 25 ml) of **7**, **16a**, **16b**, and **18** were treated with aqueous hydrochloric acid (2.4 *N*, 1 ml). The absorption of aliquots were monitored at 27° at the uv maximum for each dihydropyridine and the relative pseudo-first-order rate constant given in Table I were obtained. The respective rate constants for **7**, **16a**, **16b**, and **18** are 1.25 × 10$^{-4}$, 1.96 × 10$^{-4}$, 3.22 × 10$^{-5}$, and 1.57 × 10$^{-6}$ sec$^{-1}$.

**4. Attempted Photoreduction.**—Irradiation of **18** or bridged ketone **16b** (2 × 10$^{-4}$ *M*) in 95% ethanol by a low pressure mercury immersion lamp (Hanovia, maximum output at 253.7 nm) for 30 min destroyed the 1,4-dihydropyridine chromophore. External irradiation of an ethanol solution of **18** in a Pyrex test tube in a Rayonet photochemical reactor of maximum output at 300 or 350 nm for 30 min gave the same result. Irradiation of **16b** (2 × 10$^{-4}$ *M*) in ethanol for 30 min resulted in complete destruction of dihydropyridine chromophore at 381 nm, but **16a** was stable and only slowly underwent loss of its chromophore at 338 nm when irradiated at 300 nm. A large scale photolysis of **16a** (0.0441 g) in ethanol at 300 nm resulted in loss of the chromophore at 338 nm in 7 hr. Examination of the yellow solid obtained after removal of solvent revealed no evidence for formation of a pyridinium salt (nmr) and indicated loss of the vinyl protons at the 2 and the 6 positions of the starting material.

**Chemical Properties of Bridged Dinicotinamide Salts. 1. Sodium Carbonate.**—Solutions 2 × 10$^{-4}$ *M* in salts **6**, **15a**, **15b**, and **17** were separately prepared and the uv spectrum of each was recorded. Sodium carbonate (0.106 g, 0.001 mol) was then added and the uv spectrum was recorded again. The solution was acidified by the addition of concentrated hydrochloric acid and the spectrum recorded. In all cases, addition of sodium carbonate caused new absorption to appear at 340–345 and at 252–255 nm. Addition of acid caused these absorptions to disappear and the spectrum reverted to that observed originally for the salts.

Compound **17** (1.300 g, 0.003 mol) was dissolved in distilled water (40 ml) heated at 65° and sodium carbonate (1.06 g, 0.01 mol) was added to this solution. The solution immediately turned yellow and became turbid. A yellow oil separated within 5 min. This oil was solidified by allowing the reaction mixture to stir for 1 hr in an oil bath and was collected by filtration and dried overnight at 50° in a vacuum oven.

Thin layer chromotography (Eastman prepared aluminum oxide sheet, elution by chloroform) indicated the presence of at least two components, one at $R_f$ 0.9–0.7 which showed a purple fluorescence and the other at $R_f$ 0.6–0.3 which showed a blue-white fluorescence.

The entire sample was dissolved in chloroform (10 ml) and chromatographed on a column of aluminum oxide (Woelm activity grade I, 200 ml, wet-packed with chloroform). The sample was eluted with chloroform and the separation of components was monitored by following the fluorescent bands which appeared when the column was irradiated with long-wavelength uv light. After the first band was collected, the second band was rapidly eluted with 10% ethanol in chloroform.

The first fraction yielded a white solid (0.287 g): mp 256–257°; uv max (95% ethanol) 333 nm (ε 8080), 253 ( 14,200);[35] ir (KBr) 3300 (m, NH), 3050 (w, Ar H), 1675 (vs, C=O), 1620 (m), 1530 cm$^{-1}$ (s, amide); nmr (DMSO-$d_6$) δ 9.28 (m, 1, NH), 8.84 (d, 1, $J$ = 2.5 Hz, 4-pyridine H), 8.55 (m, 1, NH), 8.03 (d, 1, $J$ = 2.5 Hz, 6-pyridine H), 7.53 (s, 3, Ar H), 5.49 (s, 2, Ar $CH_2$), 2.85 (d, 3, $J$ = 6.5 Hz, $CH_3$), 2.74 (d, 3, $J$ = 6.5 Hz, $CH_3$).

*Anal.* Calcd for $C_{16}H_{15}Cl_2N_3O_3$: C, 52.17; H, 4.08; N, 11.41; O, 13.04. Found: C, 51.92; H, 4.21; N, 11.27; O, 13.10.

The second fraction yielded a yellow oil which was triturated with diethyl ether to yield a yellow solid (0.634 g) (this compound sintered when heated and could not be purified by recrystallization: uv max (95% ethanol) 375 nm; nmr (DMSO-$d_6$) δ 7.51, 7.22, 6.92, 4.67, 3.33, 3.11, 2.66.

A structure consistent with the elemental analysis could not be determined.

*Anal.* Found: C, 52.72; H, 5.07; N, 11.92; O, 12.81.

(32) M. Samejima, *Yakugaku Zasshi*, **80**, 1713 (1960); *Chem. Abstr.*, **55**, 10439 (1961).

(33) The reactions were done in sealed tubes at room temperature.

(34) D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2261 (1955).

(35) The uv max for the 2-pyridone of 1-methylnicotinamide is at 330 nm: M. E. Pullman and S. P. Colowick, *J. Biol. Chem.*, **206**, 121 (1954).

2. **Potassium *tert*-Butoxide, Sodium Hydride, Sodium 2,6-Di-*tert*-Butylphenoxide in THF.**—Saturated solutions of the pyridinium salts **6**, **15a**, **15b**, and **17** were prepared by stirring 50 mg of each of the salts in THF (100 ml, freshly distilled from lithium aluminum hydride) for 24 hr. The uv spectra of the three solutions were recorded. The bases (50 mg) were added to 25-ml aliquots of the solutions of the pyridinium salts and the ultraviolet spectra recorded. Table II summarizes the observations.

**Acknowledgment.**—We wish to thank Professor Jack Vriesenga for assistance in obtaining the 100-MHz nmr spectra. Also, we wish to acknowledge the National Science Foundation for aid in the purchase of the 100-MHz nmr spectrometer and Bristol Laboratories for a gift of 60-MHz nmr spectrometer.

**Registry No.**—**4**, 40430-00-0; **5a**, 40430-01-1; **5b**, 36612-08-5; **5c**, 40513-85-7; **5d**, 40430-03-3; **6**, 40513-86-8; **7**, 40513-87-9; **8a**, 40430-04-4; **8b**, 40430-05-5; **9a**, 36844-27-6; **9b**, 40430-06-6; **10a**, 36844-26-5; **10b**, 40430-08-8; **11a**, 40513-89-1; **11b**, 40429-16-1; **12a**, 40429-17-2; **12b**, 40429-18-3; **13a**, 36612-07-4; **13b**, 40429-20-7; **14a**, 40429-21-8; **14b**, 40429-22-9; **14c**, 40429-23-0; **15a**, 40429-24-1; **15b**, 40429-25-2; **16a**, 40429-26-3; **16b**, 40429-27-4; **16c**, 40429-28-5; **17**, 40429-29-6; **18**, 40429-30-9; 1,8-diaminooctane, 373-44-4; isophthaloyl chloride, 99-63-8; 3,5-pyridinedicarbonyl chloride, 15074-61-0; 1,7-diaminoheptane, 646-19-5; 1,6-diaminohexane, 124-09-4; 1,5-diaminopentane, 462-94-2; α-bromo-2,6-dichlorotoluene, 20443-98-5; *p*-toluenesulfonyl chloride, 98-59-9; 1,7-heptanediol-4-one ethylene ketal, 5694-96-2; 1,9-nonanediol-5-one ethylene ketal, 5694-92-8; potassium phthalimide, 1074-82-4; 1-(2,6-dichlorobenzyl)-3,5-(*N*,*N*′-dimethyldicarbamoyl)-2(1*H*)-pyridone, 40429-36-5; 3,5-(*N*,*N*′-dimethyldicarbamoyl)pyridine, 40429-35-4.

# Model Studies of the Synthesis of Echitamine and Related Indole Alkaloids.[1] II

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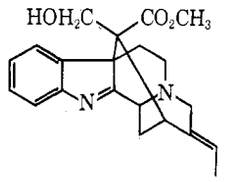
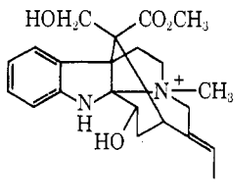
*Received February 16, 1973*

Attempts to synthesize the pentacyclic skeleton of akuammiline are described. The key step in this synthetic approach is the formation of the C-6 to C-7 bond by a nucleophilic substitution reaction. This transformation would complete the akuammiline skeleton from the tetrahydrocarbazole intermediate **16** which bears four of the required five rings. However, all attempts to generate the crucial C-6 to C-7 bond met with failure. The synthesis of several novel tetracyclic tetrahydrocarbazole derivatives is presented along with a sequence leading unexpectedly to indolo[2,3-*c*]norcar-3-en-2-one (**12**) and indolo[2,3-*b*]cyclohepta-2,4-dienone (**13**).

Echitamine and its probable biogenetic precursor deacetylakuammiline are examples of a group of indole alkaloids bearing a C-16–C-7 bond. A number of these alkaloids are now known[2,3] but no representative of this group has been obtained by chemical synthesis.



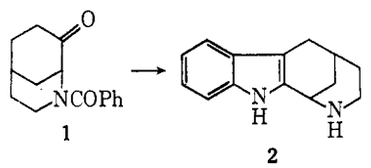
deacetylakuammiline



echitamine

In investigating routes to the pentacyclic framework of these molecules we sought to take advantage of the nucleophilic character of the indole nucleus in forming the final ring from a tetracyclic intermediate possessing the C-7–C-16 bond. Thus, elimination of *p*-toluenesulfonic acid from the tosylate shown in Scheme I would lead to the skeleton of deacetylakuammiline. A similar approach has been successfully employed in the synthesis of minovine,[4] and a previous report from these laboratories[5] describes results of a model system which proved encouraging.

The tetracyclic intermediate required for this scheme was obtained by two independent routes. In one route 2-azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (**2**) arose from a Fischer indole synthesis with 2-

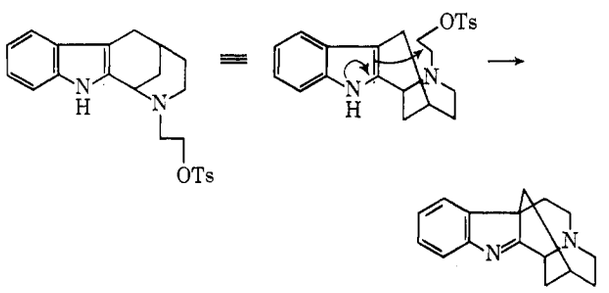


**1** **2**

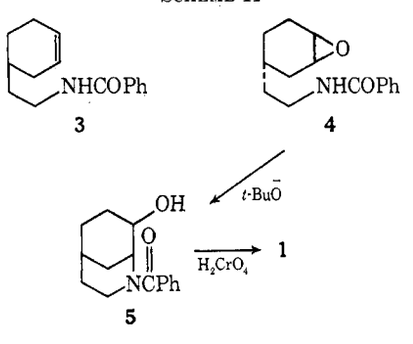
benzoyl-2-azabicyclo[3.3.1]nonan-8-one (**1**) followed by alkaline hydrolysis of the benzoyl moiety.

The ketone utilized in the Fischer indole synthesis was prepared following the route outlined in Scheme II.

SCHEME I



SCHEME II



**3** **4** **5**

(1) The authors gratefully acknowledge financial support from the National Institutes of Health (Grant GM18196) and a Public Health Service Career Program Award (1-K3-NB-28,105) from the National Institute of Neurological Disease and Blindness.

(2) J. E. Saxton, "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 501.

(3) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(4) F. E. Ziegler and F. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3493 (1970).

(5) L. J. Dolby and Z. Esfandiary, *J. Org. Chem.*, **37**, 43 (1972).