Synthesis of 1,2- and 1,4-Dihydropyridines

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N-Carbomethoxy-1,2- and -1,4-dihydropyridine (1 and 2) have been prepared by the reaction of methyl chloroformate with pyridine in the presence of sodium borohydride. These compounds have been shown to be useful derivatives for the synthesis of other heterocycles and study of the dihydropyridine ring system. Reduction of 1 and 2 with $LiAlH_4$ gave the *N*-methyl derivatives. Treatment of 2 with methyllithium gave the unsubstituted dihydropyridine 7, whereas a similar treatment of 1 gave a complex mixture of products. Photolysis of 1 gave *N*-carbomethoxybicyclo[2.2.0]hex-5-ene.

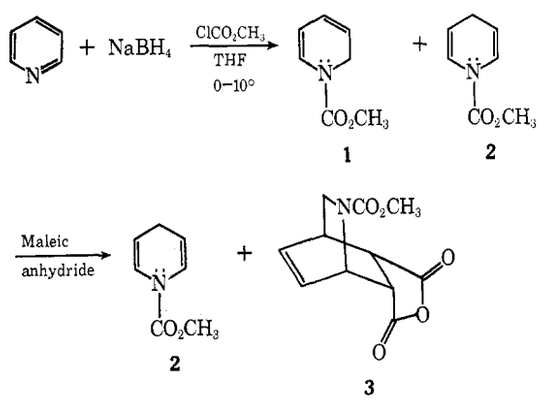
The 1,4- and 1,3-cyclohexadienes have proven to be extremely valuable intermediates in organic synthesis. The corresponding heterocycles, 1,2- and 1,4-dihydropyridine, should also prove valuable for the preparation of interesting heterocyclic compounds. In addition, the 1,4-dihydropyridine ring system is of biological importance since it occurs in the reduced forms of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH).[1] In contrast to the carbocycles, studies on the *simple* derivatives of the heterocycles have been hindered by their susceptibility to oxidation and the lack of convenient methods for their preparation.

A large number of substituted 1,2- and 1,4-dihydropyridines have been prepared by cyclization reactions (Hantzsch ring closure) and by reduction of pyridinium ions.[2] The Hantzsch ring closure works well only for the preparation of highly substituted dihydropyridines. Except in a few cases,[3] the reduction of pyridinium ions is successful only if strong electron-withdrawing groups are present on the pyridine ring.[4]

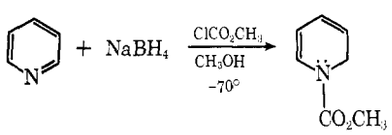
An elegant synthesis of the 1-trimethylsilyl-substituted 1,2- and 1,4-dihydropyridines has recently been accomplished by Cook and Lyons.[5] These compounds would appear very valuable derivatives for further study of the dihydropyridine structure. Unfortunately, any extensive study of these ring systems is hindered by the small quantity of 1,2 isomer produced, their instability, and by the tedious separation procedure required (vapor phase chromatography).

We report that both *N*-carbomethoxy-1,2- and -1,4-dihydropyridine can be produced by treating a mixture of pyridine and sodium borohydride with methyl chloroformate. Although this reaction can be carried out in a number of solvents (ether, glyme, tetrahydrofuran, methanol, and water), tetrahydrofuran proved to be the solvent of choice.

Carrying out the reaction in tetrahydrofuran and maintaining the temperature below 10° gave a mixture of the dihydropyridines containing about 35–40% of the 1,4 isomer. These can be separated on a small scale using either preparative layer chromatography (silica gel) or gas phase chromatography (5% SE-30 on Chrom G). This is not a convenient procedure for the preparation of large quantities of these pure dihydropyridines. However, large quantities of the pure 1,4-dihydropyridine can be obtained by simply treating the reaction mixture with maleic anhydride. The 1,2-dihydropyridine readily reacts to give a Diels–Alder adduct which can easily be removed by washing with 15% sodium hydroxide.



The amount of 1,4 isomer can be reduced substantially 2–4% by carrying out the reaction in methanol using a Dry Ice–acetone cooling bath.



The structures of these dihydropyridines are clearly evident from their spectral data[5] and their chemical conversion to known dihydropyridines (see below).

The *N*-carbomethoxydihydropyridines are very useful derivatives of the dihydropyridine ring system for several reasons. The carbomethoxy substituent stabilizes the dihydropyridine structure, causing these compounds to be more resistant to air oxidation than simple *N*-alkyl derivatives and therefore they can be handled relatively easily in the laboratory. However, even these dihydropyridines will decompose when exposed to atmospheric oxygen at room temperature for prolonged periods, although they can be stored indefinitely under argon at −30°. Because of the resonance interaction of the lone pair on nitrogen with the carbonyl group, the carbon–carbon double bonds of these dihydropyridines have little enamine character. For example, they are reasonably stable to aqueous solutions of mineral acids.

The carbomethoxy substituent is also a versatile

(1) S. P. Colowich, J. van Eys, and J. H. Park in "Comprehensive Biochemistry," Vol. 14, M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, 1966, Chapter 1.

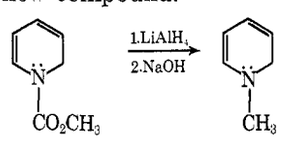
(2) A. Albert, "Heterocyclic Chemistry," 2nd ed, The Athlone Press, London, 1968, p 303 ff.

(3) The nmr spectra are similar to those previously reported for *N*-phenyl-1,2- and 1,4-dihydropyridine: M. Sanders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

(4) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).

(5) N. C. Cook and J. E. Lyons, *J. Amer. Chem. Soc.*, **88**, 3396 (1966).

functional group in organic synthesis. It can either be converted to a hydrogen-substituted derivative or reduced to a *N*-methyl group, which is a common functionality in natural products. For example, we have observed that treatment of these dihydropyridines with lithium aluminum hydride gives the relatively unstable *N*-methyl derivatives. The physical properties of **4** are consistent with those previously reported,[6] whereas **5** is a new compound.



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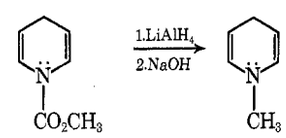

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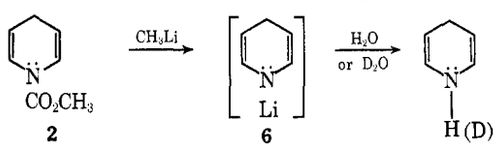
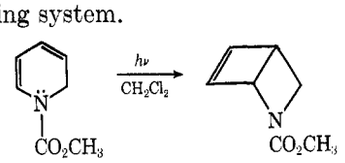
Treatment of 1,4-dihydropyridine **2** with methyllithium gave the lithio derivative **6**. This was not isolated, but treatment with either water or deuterium oxide produced the 1,4-dihydropyridine.[7] Dihydropyridine **7** is remarkably stable. It shows no tendency to decompose, isomerize, or undergo exchange of the hydrogens β to the nitrogen when treated with deuterium oxide in acetone-d_6 for several days.



2 6 7

Preliminary studies have indicated that these heterocycles are very useful for the preparation of interesting heterocyclic compounds. For example, photolysis of 1,2-dihydropyridine **1** in methylene chloride provides a very convenient synthesis to the 2-azabicyclo[2.2.0]-hex-5-ene ring system.



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Experimental Section[8]

N-**Carbomethoxy-1,4-dihydropyridine** (**2**).—Methyl chloroformate (47.3 g, 0.5 mol) was added to 10 g of $NaBH_4$ and 39.4 g (0.5 mol) of pyridine in 200 ml of THF cooled in an acetone–ice bath at a rate so that the reaction temperature did not exceed 10°. The reaction mixture was stirred for an additional 1.4 hr and enough H_2O (*ca.* 400 ml) was added to dissolve the inorganic salts. The reaction mixture was extracted with ether. The ethereal extracts were combined, washed with water, dried ($MgSO_4$), and evaporated *in vacuo* at *ca.* 40° to give *ca.* 36 g of the mixture of dihydropyridines. The pure 1,4 isomer (*ca.* 10 g) was obtained by treating this mixture with 50 g of maleic anhydride and 200 ml of CH_2Cl_2 (previously purged with N_2) and refluxed for 14 hr. The solvent was evaporated (*in vacuo*), and the residue was dissolved in ether and washed with 15% NaOH until colorless. The ethereal layer was dried ($MgSO_4$) and removed *in vacuo*. Further purification of the 1,4-dihydropyridine **2** can be effected by passing it through basic alumina with ether. This produces the dihydropyridine as a clear, mobile liquid of >97% purity: nmr ($CDCl_3$) τ 3.42 (d, broad, 2 H, J = 7.5 Hz, NCH=), 5.05–5.40 (m, 2 H, NCH=C**H**), 6.32 (s, 3 H, OCH_3), and 7.05–7.33 (m, 2 H, CH_2); ir (CCl_4) 1726 (C=O) and 1634 cm^{-1} (C=C); uv max (hexane) 224 nm (ϵ 13,700).

N-**Carbomethoxy-1,2-dihydropyridine** (**1**).—Methyl chloroformate (18.2 g, 0.2 mol) in 25 ml of ether was added to 8.0 g of sodium borohydride and 15.8 g (0.20 mol) of pyridine in 75 ml of absolute methanol cooled in Dry Ice–acetone. The rate of addition was controlled so that the temperature of the reaction mixture did not exceed −69°. The reaction mixture was stirred for an additional 1.5 hr and was then poured into ice water. Enough water was added to dissolve the inorganic salts and the mixture was extracted with ether (*ca.* 300 ml). These were combined, washed thoroughly with water, and dried ($MgSO_4$). Removal of the solvent *in vacuo* (*ca.* 50°) gave *ca.* 18 g of the 1,2-dihydropyridine **1**. Further purification can be effected by passing the product through basic alumina with ether: nmr (CCl_4) τ 3.47 (d, broad, 1 H, J = 7.5 Hz, NCH=), 4.05–5.18 (m, 3 H, olefinic), 5.85 (doublet of doublets, 2 H, J = 3.5, 2.0 Hz, CH_2), and 6.37 (s, 3 H, OCH_3); ir (CCl_4) 1718 (C=O), 1647 (C=C), and 1585 cm^{-1} (C=C); uv max (hexane) 302 nm (ϵ 3800).

N-**Methyl-1,2-dihydropyridine** (**4**).—To 2.40 g of $LiAlH_4$ in 50 ml of ether cooled in an ice bath was added 5.60 g of 1,2-dihydropyridine **1**. The reaction was allowed to warm to room temperature and stir for 3.25 hr. The reaction was worked up by decomposing the excess $LiAlH_4$ with 8.5 ml of 20% NaOH, filtering the inorganic salts, and removing the solvent *in vacuo* at room temperature (the dihydropyridine was maintained under argon at all times). This gave a quantitative yield of **4**: nmr (CCl_4) τ 4.08–4.47 (m, 2 H), 4.80–5.18 (m, 1 H), 5.37–5.67 (m, 1 H), 6.23 (d, broad, J = 3.5 Hz), and 7.43 (s, 3 H, NCH_3). The nmr spectrum of this sample proved to be the same as that of an authentic sample prepared independently.[6] The dihydropyridine was stored over KOH pellets at −30°.

N-**Methyl-1,4-dihydropyridine** (**5**).—To 2.40 g of $LiAlH_4$ in 50 ml of ether cooled in an ice bath was added over 10 min 5.60 g of *N*-carbomethoxy-1,4-dihydropyridine. The reaction mixture was allowed to warm to room temperature and was refluxed for 24 hr. The reaction mixture was cooled in an ice bath and the excess $LiAlH_4$ was decomposed with 8.5 ml of 20% NaOH. The salts were filtered and the ether was removed *in vacuo* at 25°, giving a 90% yield of **5** as a pale yellow liquid. The nmr spectrum showed the product to be >95% pure, but it could be further purified by molecular distillation (10^{-3} mm), giving **5** as a colorless liquid that was unstable to atmospheric oxygen: nmr ($CDCl_3$) τ 4.43 (doublet of triplets, J = 8.0 and 1.5 Hz, 2 H, NCH=), 5.58–5.88 (m, 2 H, NCH=C**H**), 7.00–7.23 (broad s, $W_{1/2}$ = 7.0 Hz, 2 H, CH_2) and 7.32 (s, 3 H, NCH_3); ir (CCl_4) 3065 (CH=) and 16.75 cm^{-1} (C=C); uv (hexane) 270 (ϵ 1220, shoulder) and 302 nm (ϵ 940, shoulder).

1,4-Dihydropyridine (**7**).—To 6 ml of 2 *M* methyllithium in 8 ml of dry ether (previously purged with N_2) cooled in an acetone–ice bath was added 560 mg of *N*-carbomethoxy-1,2-dihydropyridine. The reaction was stirred for 20 min and enough H_2O was added to dissolve the inorganic salts. The aqueous phase was separated and the organic layer was washed several times with water. The organic phase was dried ($MgSO_4$) and the solvent was removed with a stream of nitrogen at room temperature. All of the other above operations were carried out in an argon atmosphere.

The nmr spectrum (acetone-d_6) was virtually identical with that previously reported.[7] If the above reaction mixture is worked up with D_2O, then the multiplicity of the hydrogens α to the nitrogen is simplified. They occur as a broadened doublet (J = 8.0 Hz).

N-**Carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene** (**8**).—A 5% solution of 1,2-dihydropyridine **1** was irradiated using a Rayonet photochemical reactor (RP-3000 lamps) until the nmr spectrum showed the consumption of all the starting material. Removal of the solvent gave an orange oil. The nmr spectrum showed this to be *ca.* 85% pure. Pure **8** (>95%) could be obtained by passing the crude product through basic alumina with ether: nmr ($CDCl_3$) 3.37–3.52 (m, 2 H, CH=CH), 5.17 (triplet of

(6) E. M. Fry, *J. Org. Chem.*, **29**, 1647 (1964).

(7) N. C. Cook and J. E. Lyons, *J. Amer. Chem. Soc.*, **87**, 3283 (1965).

(8) Analyses were performed by Gailbraith Laboratories, Knoxville, Tenn. The nmr spectra were recorded using a Varian A-60 spectrometer, the infrared spectra were recorded using a Perkin-Elmer 257 grating spectrometer, and the ultraviolet spectra were recorded using a Cary 14 spectrometer.

doublets, 1 H, J = 3.0, 1.5 Hz, bridgehead α to N), 5.83–6.67 (m, 3 H), and 6.32 (s, 3 H, OCH_3); ir (CCl_4) 1710 (C=O) and 1596 cm^{-1} (C=C). The analytical sample was further purified by glc (10 ft × 0.25 in. 5% SE-30 at 125°, retention time 60 min).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.24; H, 6.54.

Registry No.—**1**, 33707-36-7; **2**, 33707-37-8; **4**, 33707-38-9; **5**, 33666-44-3; **8**, 33707-39-0.

Acknowledgment.—We are indebted to the National Science Foundation (GP-20099) for financial support of this work.

2,4-Diaminopyrimidines from Dicyandiamide. IV. Condensation with Bicyclic Aromatic Ketones[1,2]

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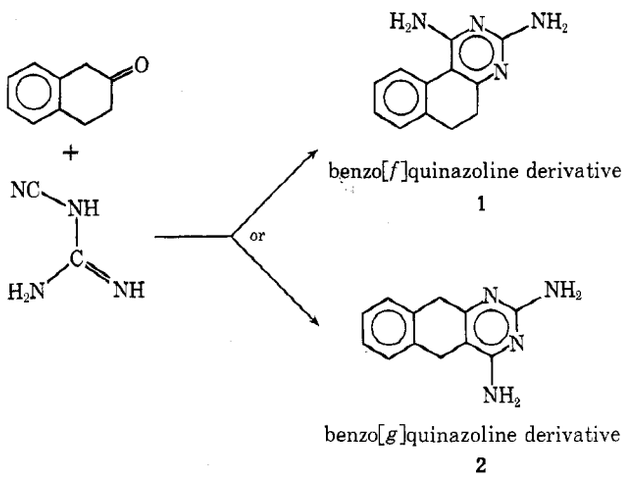
The synthesis of several tricyclic diaminopyrimidine derivatives by condensation of dicyandiamide with bicyclic aromatic ketones is reported. An interesting skeletal rearrangement was observed when 2,4-diaminobenzo[*g*]quinazoline (**5a**) was isolated as the major product of palladium–charcoal dehydrogenation (under disproportionation conditions) of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**), the 2-tetralone/dicyandiamide condensation product. Representatives of the 2,4-diaminobenzo[*h*]quinazoline, the 2,4-diaminothieno[2,3-*h*]-quinazoline, and the 2,4-diamino-5*H*-indeno[1,2-*d*]pyrimidine ring systems are described.

In a program of synthesis of pyrimidine derivatives as potential folic acid antagonists and antitumor agents,[3] a number of 2,4-diaminopyrimidine ring systems have been synthesized in our laboratory by the direct, one-step condensation of dicyandiamide with ketones having an available α-methylene group.[2–5] We reported the isolation of a single product from the condensation of 2-tetralone with dicyandiamide.[2,4] Although cyclization can theoretically involve the methylene group on either side of the carbonyl group of 2-tetralone, leading to **1** or **2**, we have established the structure of the reaction product as 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**).[6,7] A number of substituted 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines were subsequently prepared by this route.[8,9] Application of this versatile pyrimidine ring-forming reaction to bicyclic aromatic ketones is now described; in connection with the present work, an interesting thermal rearrangement was observed and confirmed by alternative synthesis.

A disproportionation reaction of compound **1** was conducted in the presence of tetralin and 10% palladium–charcoal catalyst in 2-(2-ethoxyethoxy)ethanol at 198–202° for 38 hr. The major product was 2,4-diaminobenzo[*g*]quinazoline (**5a**), the structure of which was proved by comparison with an authentic



sample prepared by an unambiguous synthesis.[10–14] Isolation of **5a** suggested that the product of condensation of 2-tetralone and dicyandiamide might have been 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline. It is now obvious that **5a** resulted by rearrangement under disproportionation conditions. This, to our knowledge, is the only example of a thermal rearrangement of a benzo[*f*]quinazoline to a benzo[*g*]quinazoline. The minor product from this reaction (**10**) retained the benzo[*f*]quinazoline ring structure of the parent compound.[15]

An authentic sample of 2,4-diaminobenzo[*g*]quinazoline was prepared according to the procedures of Curd, Landquist, and Rose[10] and Legrand[11–14] with certain modifications. 2,4-Dihydroxybenzo[*g*]quinazoline (**3a**) was obtained by reaction of 2-amino-3-

(1) This investigation was supported in part by research grant C6516 and research career development award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) S. K. Sengupta, S. Chatterjee, H. Kangur, and E. J. Modest, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 3, 1963, p 37-L.

(3) E. J. Modest, G. E. Foley, and S. Farber, *Acta, Unio Int. Contra Cancrum*, **16**, 702 (1960).

(4) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(5) E. J. Modest, S. Chatterjee, and H. K. Protopapa, *J. Org. Chem.*, **30**, 1837 (1965). This is part III of the series.

(6) A. Rosowsky, E. P. Burrows, S. K. Sengupta, and E. J. Modest, Abstracts of Papers, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 15, 1967, Abstract No. 104.

(7) E. P. Burrows, A. Rosowsky, and E. J. Modest, *J. Org. Chem.*, **32**, 4090 (1967).

(8) A. Rosowsky and E. J. Modest, *Ann. N. Y. Acad. Sci.*, **186**, 258 (1971).

(9) A. Rosowsky, K. K. N. Chen, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, in press.

(10) F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 1759 (1948).

(11) A. Etienne and M. Legrand, *C. R. Acad. Sci.*, **229**, 220 (1949).

(12) A. Etienne and M. Legrand, *ibid.*, **231**, 232 (1950).

(13) M. Legrand, *ibid.*, **231**, 1318 (1950).

(14) M. Legrand, private communication.

(15) Compound **10** was identified as 3-amino-1-[2-(2-ethoxyethoxy)-ethoxy]benzo[*f*]quinazoline (see Experimental Section). Mass spectrometric analysis of **10**, together with the fragmentation pattern of the ether side chain, is described separately: S. K. Sengupta, H. K. Protopapa, E. J. Modest, and B. C. Das, *Org. Mass Spectrom.*, (submitted for publication).