(0.0345 mole) of 70% perchloric acid in 10 ml. of acetic anhydride and 150 ml. of acetic acid. The solution was cooled to 0° and 4.5 g. (0.069 mole) of potassium cyanide in 100 ml. of acetic acid and 20 ml. of acetic anhydride was added. After the mixture had stood in an ice bath for 0.5 hr., white solid was removed by filtration. The filtrate on a steam bath was concentrated *in vacuo*. The red residue was leached with ether and the ethereal solution was washed three times with water and dried over Drierite. The solution was concentrated and the red residue was distilled (145–150° at 5 mm.) to yield after crystallization from water 0.8 g. (15%) of 2-cyanoquinoline, m.p. 91–92° (lit.[32] m.p. 94°). The infrared spectrum showed a band at 2240 cm.$^{-1}$ assignable to the cyano groups.

Acknowledgment.—The authors wish to express their gratitude for the help given them by Miss Joyce Himes, who during her tenure as a National Science Foundation Undergraduate Summer Research Participant, prepared and studied the isotopic compounds; Mr. Frank Crain, who made the radioactivity measurements; and Miss Jean Myers and Mr. Michael DeMatte for technical assistance.

(32) A. Kaufman, P. Dondliker, and H. Burkhardt, *Chem. Ber.*, **46**, 2929 (1913).

The Hantzsch Reaction. I. Oxidative Dealkylation of Certain Dihydropyridines

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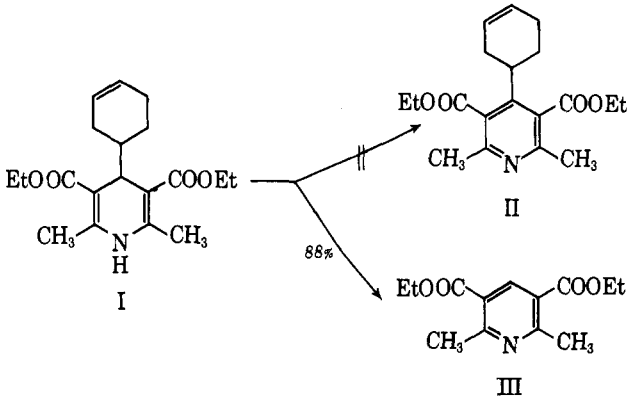
Oxidation of certain Hantzsch dihydropyridines (4-alkyl-3,5-dicarbethoxy- and 3,5-dicyano-1,4-dihydrolutidines) caused unexpected loss of the 4-substituent in addition to aromatization. A mechanism for the reaction is proposed.

One of the most widely used syntheses of pyridines is that developed by Hantzsch in 1882.[1,2] In a typical Hantzsch procedure, an aldehyde, ammonia, and a β-keto ester are condensed to give a dihydropyridine, which is subsequently oxidized to the pyridine.

In the course of attempting to synthesize a 4-cyclohexenylpyridine (II) by oxidation of the corresponding dihydropyridine (I) we found that the sole product was the *dealkylated* material III. This anomalous result led us to study the mechanism of the oxidation of the Hantzsch dihydropyridines.



The voluminous literature relating to the Hantzsch reaction reveals two pertinent references. In 1885, Engelmann[3] observed that, on oxidation of 2,6-dimethyl-3,5-dicarbethoxy-4-isopropyl-1,4-dihydropyridine (Table II, IVa, R = isopropyl) with "nitrous fumes," the isopropyl group was lost and III was obtained. In 1888, Jeanrenaud[4] noted the loss of the benzyl group when IVa (R = benzyl) was oxidized with nitrogen trioxide. Ayling[5] in 1938 reported that, when these same dihydropyridines were dehydrogenated with sulfur, the normal 4-substituted pyridines (A, Table II) were obtained.

A series of 4-substituted 3,5-dicarbethoxy- (IVa) and 3,5-dicyanodihydrolutidines (IVb) were prepared (Table I) and oxidized with nitrous acid in order to provide information necessary to postulate a mechanism for the reaction. The results of the oxidation experiments are tabulated in Table II.

Inspection of the table reveals that in the diester series (IVa), whenever R is a group having a moderate to strong electron-releasing ability (*e.g.*, secondary alkyl or benzyl[6]), it will be lost during the oxidation. In the cyano series (IVb), however, only when the R group is a strong electron releasor (*i.e.*, benzyl or *t*-butyl, but not secondary alkyl) does dealkylation occur.

These results are consistent with a mechanism involving elimination of a carbonium ion during the course of the oxidation; they also serve to emphasize the important influence of steric factors.

The unlikely possibility that the reaction involves a carbanionic displacement was eliminated since IVa (R = isopropyl) was recovered unchanged after stirring with sodium hydride in benzene while oxygen was bubbled through the solution. The most likely mechanism involves attack at the 1-position, as shown in eq. 1.[7]

(1) A. Hantzsch, *Ann.*, **215**, 1 (1882).

(2) R. A. Barnes, F. Brody, and P. R. Ruby, "Pyridine and Its Derivatives. Part I," in "The Chemistry of Heterocyclic Compounds," E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 80 and 500.

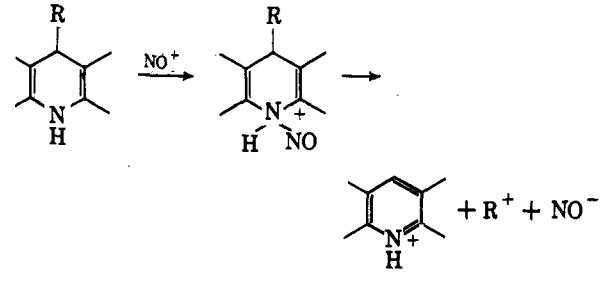
(3) F. Engelmann, *Ann.*, **231**, 37 (1885).

(4) A. Jeaurenaud, *Ber.*, **21**, 1783 (1888).

(5) E. E. Ayling, *J. Chem. Soc.*, 1014 (1938).

(6) The 4-*t*-butyl compound (IVa) could not be prepared, presumably because of steric hindrance.

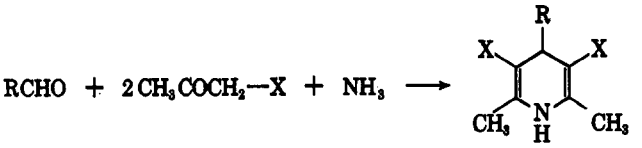
(7) In this and subsequent discussions of mechanism, the result would be the same whether one postulates the first step to be hydride extraction, as in eq. 1, or nitrosation, as follows.



(1a)

TABLE I

DIHYDROPYRIDINES



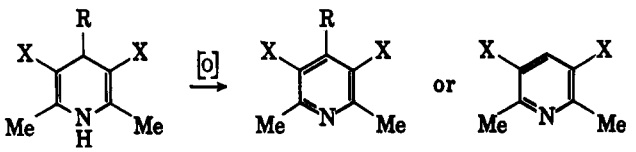
IVa

R	X	M.p., °C.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Me	COOEt	130–131[a]	80						
Et	COOEt	110–111[b]	72						
i-Pr	COOEt	95–97[c]	61						
	COOEt	139–140	73	68.44	8.16	4.20	68.54	8.01	4.36
	COOEt	128–130	48	68.03	8.71	4.18	67.71	8.55	4.50
C_6H_5	COOEt	157–159[d]	75						
$C_6H_5CH_2$	COOEt	115–117[e]	63						
C_6H_5CH=CH	COOEt	148–150[f]	52						
i-Pr	CN	148–149	62	71.61	7.51	20.88	71.64	7.41	20.81
t-Bu	CN	208–210	38	72.52	7.96	19.52	72.43	7.96	19.44
	CN	220–223 dec.	72	75.28	7.16		75.22	7.25	
$C_6H_5CH_2$	CN	167–170	26	77.08	6.06	16.86	77.38	6.16	16.81
Me, Me	CN	237–238[g]	35						
Me, $C_6H_5CH_2$	CN	157–160[h]	26						

[a] Lit [1] m.p. 131°. [b] Lit.[3] m.p. 110°. [c] Lit.[3] m.p. 97°. [d] M.p. 157–159°: L. Kirchner, *Ber.*, **25**, 2786 (1892). [e] Lit.[4] m.p. 117–118°. [f] M.p. 148–149°; W. Epstein, *Ann.*, **231**, 1 (1885). [g] M.p. 235–239°: D. Hofmann, E. M. Kosower, and K. Wallenfals, *J. Am. Chem. Soc.*, **83**, 3314 (1961). [h] M.p. 158–160°: E. V. Meyer, *J. prakt. Chem.*, **92**, 174 (1915).

TABLE II

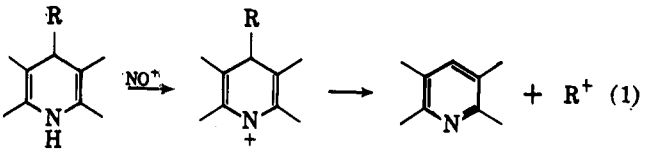
OXIDATION RESULTS



IV A B (III)

Starting material: IVa (X = COOEt), R	Starting material: IVb (X = CN), R	Product[a]	M.p. of A, °C.	Yield of A, %
Me		A	Liquid	87
	Me	A	110–111[b]	46
Et		A[c]		
	Et	A		
i-Pr		B[c]		
	i-Pr	A	Liquid[d]	90
	t-Bu	B (48%)		
		B (70%) A B (91%)	160–162	70[e]
				
C_6H_5		A	63–64.5[f]	53[f]
$C_6H_5CH_2$		B (90%)		
	$C_6H_5CH_2$	B (48%)		
C_6H_5CH=CH		A	162–165	60[g]

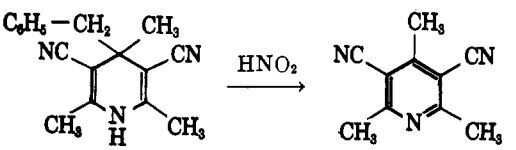
[a] The yield of B is given in parentheses. Mixtures of products A and B from the same reaction were never observed. [b] M.p. 111°: E. V. Meyer, *J. prakt. Chem.*, [2] **98**, 497 (1908). [c] Reference 3; yield not given. [d] B.p. 82–83° (0.1 mm.); *Anal.* Calcd.: C, 72.3; H, 6.57; N, 21.1. Found: C, 71.9; H, 6.47; N, 21.2. [e] *Anal.* Calcd.: C, 75.9; H, 6.37; N, 17.7. Found: C, 75.5; H, 6.42; N, 17.6. [f] M.p. 66°: S. Skraup, *Ann.*, **419**, 58 (1919). [g] *Anal.* Calcd.: C, 63.8; H, 6.18; N, 3.55. Found: C, 63.5; H, 6.21; N, 3.56.



(1)

In two reactions, oxidation of IVa and IVb, R = benzyl, using sodium nitrite in acetic acid, the fate of the leaving group was determined. The products in both instances were those expected of a benzyl carbonium ion, *i.e.*, benzyl alcohol, benzyl acetate, and benzaldehyde. These were obtained in a ratio of 1:1.6:2.4 from IVa, and 1:1:0.52 from IVb.

To prove that the initial attack was at the 1-position rather than at the 4-position, a 4,4-disubstituted dihydropyridine,[8] having one group capable of forming a good carbonium ion, was oxidized. In accordance



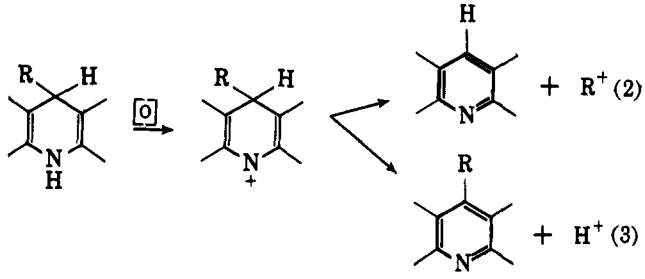
with the proposed mechanism, oxidation occurred with loss of this latter group. The 4,4-dimethyl analog *was recovered unchanged* from a similar oxidation attempt.

By proper combinations of groups in the 4,4-position, it should be possible to assess the relative electronegativities of two groups. Unfortunately, because of steric factors, the availability of 4,4-disubstituted derivatives is limited. Thus, attempts to synthesize

(8) 4,4-Disubstituted compounds could only be prepared in the cyano series (IVb).

the 4-benzyl-4-isopropyl compound in the cyano series failed.

It is clear from the results described above that in the oxidation reaction the course of the reaction, *i.e.*, whether dealkylation (eq. 2) or proton loss (eq. 3) will occur, is governed both by the stability of the potential leaving carbonium ion and by steric factors, such as the size of the groups in the 3- and 5-positions (CO_2Et *vs.* CN) and the bulk of the leaving group R in the 4-position.



Experimental[9]

Synthesis of Dihydropyridines.—All of the dihydropyridines were prepared in the same manner, using the appropriate aldehyde, ammonia, and ethyl acetoacetate or aminocrotononitrile. A typical synthesis of an ester and of a nitrile is given.

4-Cyclohexenyl-3,5-dicarbethoxy-1,4-dihydrolutidine.—A solution of 22.0 g. (0.2 mole) of 3-cyclohexenecarboxaldehyde, 52.0 g. (0.4 mole) of ethyl acetoacetate, 40 ml. of ethanol, and 20 ml. (0.3 mole) of concentrated ammonium hydroxide was heated at reflux for 2 hr. The solution was cooled and poured into 500 ml. of ice–water. The oil which separated soon crystallized and was filtered to give 60.6 g. of crude product. One recrystallization from cyclohexane–hexane gave 48.8 g. (73.4% yield) of pure material, m.p. 139–140°. Attempted catalytic reduction of the cyclohexenyl ring using 0.5% palladium-on-carbon catalyst, in ethanol as the solvent, failed.

4-*t*-Butyl-3,5-dicyano-1,4-dihydrolutidine.—A mixture of 32.8 g. (0.4 mole) of *β*-aminocrotonitrile, 17.2 g. (0.2 mole) of pivaldehyde, and 100 ml. of glacial acetic acid was heated at boiling under reflux for 18 hr. The solution was chilled and the crude product was crystallized and filtered. One recrystallization from methanol gave 16.4 g. (38.2% yield) of pure product, m.p. 208–210°.

Dilution of the filtrate from the original reaction mixture with water or ether gave 4,6-dimethyl-5-cyano-2-pyridone, m.p. 300–302° dec. (from the self-condensation of *β*-aminocrotonitrile, lit.[10] m.p. 305°).

Oxidation of the Dihydropyridines.—All of the oxidations were carried out in the same manner. A typical oxidation is given.

Oxidation of 4-Benzyl-3,5-dicarbethoxy-1,4-dihydrolutidine.—To a solution of 5.0 g. (0.0146 mole) of 4-benzyl-3,5-dicarbethoxy-1,4-dihydrolutidine in 5.0 ml. of glacial acetic acid at 15–20° was added, with stirring, 5.0 g. (0.9725 mole) of sodium nitrite in small portions. When addition was complete, stirring was continued until all the brown fumes were gone. The mixture was poured into 200 ml. of ice–water. The mixture was then extracted with three 200-ml. portions of ether. The combined ether extracts were then extracted with dilute (1:3) hydrochloric acid. The combined acid extracts were neutralized with sodium bicarbonate to give a precipitate which was filtered to give 3.3 g. (90.4% yield) of pure 3,5-dicarbethoxy-2,6-dimethylpyridine, m.p. 69–71°.

The ethereal layer was washed with 5% sodium bicarbonate until neutral, then dried over magnesium sulfate, and evaporated at 100° to give a brown oil. Injection of the oil into an F and M Model 500 gas chromatograph using 3% Ucon Polar on Gas CromZ, programmed for 75 to 225°, showed the material to contain 47.3% benzaldehyde, 32.3% benzyl acetate, and 20% benzyl alcohol.

Acknowledgment.—The authors wish to thank Dr. James W. Wilson for helpful discussions.

(9) All melting points are corrected.

(10) J. Moir, *J. Chem. Soc.*, **81**, 100 (1902).

Dehydrocyclization of 4-Amino-5-arylamidopyrimidines to Purines with Polyphosphoric Acid[1a,b]

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Polyphosphoric acid was found to be an effective reagent for the dehydrocyclization of 4-amino-5-arylamidopyrimidines to purines. A number of 8-arylpurines were synthesized by this new procedure in high purity and yield. Cyclization to purines occurred with all pyrimidines, except in the case of 4-amino-6-mercapto-5-benzamidopyrimidine which resulted in a substituted thiazolo[5,4-*d*]pyrimidine. The ultraviolet absorption spectra of the arylamidopyrimidines and arylpurines synthesized were measured.

Several 8-arylpurines have been synthesized by cyclization of 4-amino-5-arylamidopyrimidines with phosphorus oxychloride[2,3] or phosphorus oxybromide,[2] by dry heating of the pyrimidines[2-4] and by other approaches.[2,5] However, no single method was found effective and applicable to the synthesis of all 8-arylpurines.

In conjunction with our investigation on antifolic acid agents, we found that polyphosphoric acid, which has been used previously for cyclization of other ring systems,[6] is an outstanding dehydrocyclization reagent for the formation of purines from 4-amino-5-arylamidopyrimidines. Substitutions on the C-2 and C-6 positions of the pyrimidine ring, and on the *para* position of the phenyl ring had little or no influence on cyclization. Accordingly, a number of previously

(1) (a) Presented in part before the Organic Chemistry Division, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, Abstracts of Papers, 108, p. 55N. (b) Supported in part by research grants from the National Institutes of Health, USPHS No. CY-3335 and C-6516.

(2) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 5235 (1951).

(3) E. A. Falco, G. B. Elion, E. Burgi, and G. H. Hitchings, *ibid.*, **74**, 4897 (1952).

(4) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(5) (a) G. M. Timmis, I. Cooke, and R. G. W. Spickett, "The Chemistry and Biology of Purines," G. E. Wolstenholme and C. M. O'Connor, Ed., Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1957, p. 134; (b) F. Bergmann and M. Tamari, *J. Chem. Soc.*, 4468 (1961); (c) H. Bredereck, H. G. v. Schuch, and A. Martini, *Ber.*, **83**, 201 (1950); (d) A. H. Cook and G. H. Thomas, *J. Chem. Soc.*, 1884 (1950).

(6) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958).