steam bath for 4 hr. and allowed to cool. The orange precipitate was collected and washed with ethanol; yield 1.10 g. The filtrate was diluted with 100 ml. of 95% alcohol, and the resulting precipitate was collected, yield 1.75 g. The combined yield was 2.85 g. (66%). Recrystallization from acetic acid gave orange crystals, m.p. 276–278° dec., $\lambda_{max}^{C_2H_5OH}$ 461 mμ, ϵ_{max} 3700.

Anal. Calcd. for $C_{10}H_8N_6$: C, 56.6; H, 3.8. Found: C, 56.9; H, 4.00.

6-Amino-7,8-dicyano-2,3-diphenylpyrrolo-[*b*]-*as*-triazine (IVb).—A solution of 4.86 g. (0.03 mole) of 3,4-dicyano-1,2,5-triaminopyrrole, 6.10 g. (0.03 mole) of benzil and 1.0 g. of *p*-toluenesulfonic acid was heated on a steam bath for 5 hr. During this time, deep red crystals formed. The mixture was cooled, diluted with 100 ml. of water, filtered, and the crystals were washed thoroughly with ethanol; yield 9.00 g. (90%), m.p. > 300°. A sample was recrystallized from acetic acid for analysis; $\lambda_{max}^{C_2H_5OH}$ 511 mμ, ϵ_{max} 6000.

Anal. Calcd. for $C_{20}H_{12}N_6$: C, 71.4; H, 3.6; N, 25.00. Found: C, 71.2; H, 3.7; N, 25.0.

6-Amino-7,8-dicyano-3-hydroxy-2-methylpyrrolo-[*b*]-*as*-triazine (Va).—A solution of 3.22 g. (0.02 mole) of 3,4-dicyano-1,2,5-triaminopyrrole and 2.32 g. (0.02 mole) of ethyl pyruvate in a mixture of 10 ml. of dimethylformamide and 10 ml. of ethanol was heated under reflux. A solid began to separate after 1 hr., and after 2 hr. the mixture was cooled. The orange triazine was collected and washed thoroughly with ethanol; yield 2.50 g. (55%), m.p. > 300°. A sample was recrystallized from dimethylformamide–ethanol for analysis.

Anal. Calcd. for $C_9H_6ON_6$: C, 50.5; H, 2.80; N, 39.2. Found: C, 50.5; H, 3.2; N, 39.4.

Ethyl 6-Amino-7,8-dicyano-3-hydroxypyrrolo-[*b*]-*as*-triazine-2-carboxylate (Vb).—A solution of 1.62 g. of 1,2,5-triamino-3,4-dicyanopyrrole, 1.74 g. of diethyl oxomalonate, and 0.5 g. of *p*-toluenesulfonic acid in 10 ml. of dimethylformamide was heated on a steam bath for 3 hr. The deep red solution was diluted with 20 ml. of 95% alcohol and 50 ml. of water, and the precipitate was collected; yield 1.82 g., m.p. > 300°. An analytical sample of the triazine was prepared by recrystallization from acetic acid.

Anal. Calcd. for $C_{11}H_8N_6O_3$: C, 48.6; H, 3.0. Found: C, 48.4; H, 3.4.

6-Benzylideneamino-7,8-dicyano-2,3-dimethylpyrrolo-[*b*]-*as*-triazine.—A mixture of 2.12 g. (0.01 mole) of 6-amino-7,8-dicyano-2,3-dimethylpyrrolo-[*b*]-*as*-triazine, 10 ml. of benzaldehyde, and 0.3 g. of *p*-toluenesulfonic acid was heated at 160° for 1.5 hr. and allowed to cool. Fifteen milliliters of ethanol was added and the magenta solid was collected. This solid was heated with 50 ml. of benzene to remove the benzaldehyde and again collected; yield 2.75 g. (91%), m.p. 260–265°. Recrystallization from acetic acid gave the red crystalline anil, m.p. 263–265°; $\lambda_{max}^{C_2H_5OH}$ 546 mμ, ϵ_{max} 9600.

Anal. Calcd. for $C_{17}H_{12}N_6$: C, 68.0; H, 4.0; N, 28.0. Found: C, 67.6; H, 4.3; N, 27.8.

6-Benzylideneamino-7,8-dicyano-2,3-diphenylpyrrolo-[*b*]-*as*-triazine.—A mixture of 2.00 g. (0.0061 mole) of 6-amino-7,8-dicyano-2,3-diphenylpyrrolo-[*b*]-*as*-triazine, 5 ml. of benzaldehyde, and 0.3 g. of *p*-toluenesulfonic acid was heated at 150–160° for 2 hr. and then allowed to cool. Ethanol (15.0 ml.) was added and the orange crystalline anil was collected; yield 1.70 g. (67%), m.p. 276–277°. It was recrystallized from dimethylformamide–ethanol for analysis, $\lambda_{max}^{C_2H_5OH}$ 460 mμ, ϵ_{max} 5900.

Anal. Calcd. for $C_{27}H_{16}N_6$: C, 76.4; H, 3.8. Found: C, 76.2; H, 4.0.

7-Amino-8,9-dicyano-2,4-dimethylpyrrolo-[*b*]-[1,2,4]-triazepine (VI).—A solution of 6.50 g. (0.04 mole) of 3,4-dicyano-1,2,5-triaminopyrrole, 4.0 g. (0.04 mole) of acetylacetone, and 0.5 g. of *p*-toluenesulfonic acid in 10 ml. of dimethylformamide was heated on a steam bath for 2 hr. During this time a crystalline solid separated. The mixture was cooled and the tan solid was collected, washed with a small amount of dimethylformamide and then thoroughly washed with ethanol; yield 6.10 g. (60%), m.p. 273–279° dec. Recrystallization from acetic acid gave a product that melted at 278–280° dec.

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.4; H, 4.4; N, 37.2. Found: C, 58.2; H, 4.5; N, 36.9.

7-Amino-8,9-dicyano-4-hydroxy-2-methylpyrrolo-[*b*]-[1,2,4]-triazepine (VII).—A solution of 6.50 g. (0.04 mole) of 3,4-dicyano-1,2,5-triaminopyrrole, 5.20 g. (0.04 mole) of ethyl acetoacetate, and 0.5 g. of *p*-toluenesulfonic acid in 10 ml. of dimethylformamide was heated on a steam bath for 4 hr. and allowed to cool. The off-white solid was collected and washed thoroughly with ethanol; yield 3.20 g. (35%), m.p. > 300°. The compound was recrystallized from dimethylformamide–ethanol.

Anal. Calcd. for $C_{10}H_8N_6O$: C, 52.6; H, 3.5. Found: C, 52.7; H, 3.7.

Polyfunctional Aliphatic Compounds. II.[1] The Cyclization of Dinitriles by Anhydrous Halogen Acids. Pyridines

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The action of anhydrous hydrogen bromide or iodide on 3-hydroxyglutaronitriles or glutacononitriles leads to 2-amino-6-halopyridines in excellent yield. In conjunction with the facile method for the synthesis of the starting materials, this represents a mode of easy access to previously unavailable simple pyridine derivatives.

Recently, the reactions of polynitriles with anhydrous halogen acids have received considerable attention.[2–4] Tetracyanoethylene with hydrogen bromide was found to give 2-amino-5-bromo-3,4-dicyanopyrrole, while tetranitriles of structure I led to the corresponding pyridines (II) when treated

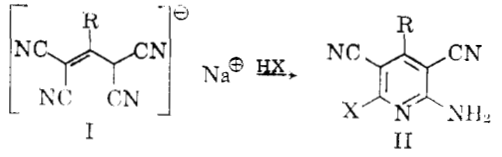
(1) Part I, Francis Johnson, J. P. Panella, and A. A. Carlson, *J. Org. Chem.*, **27**, 2241 (1962).

(2) W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

(3) E. L. Little, Jr., W. J. Middleton, D. D. Coffman, V. A. Engelhardt, and G. N. Sausen, *ibid.*, **80**, 2832 (1958).

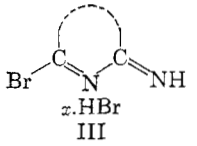
(4) R. A. Carboni, D. D. Coffman, and E. G. Howard, *ibid.*, **80**, 2838 (1958).

with the appropriate halogen acid (X = Cl, Br, or I).



I II

However, apart from these reactions, little attention appears to have been paid to simpler systems. Howard[5] and Osborn[6] have examined the reactions of succinonitriles, glutaronitriles, and phthalonitriles almost exclusively with hydrogen bromide and obtained cyclic products having the general constitution III ($x=1$ or 2):



III

A patent issued to J. R. Geigy[7] has described similar reactions with phthalonitriles, but no assignments of structure were made to any of the products. Wolf, Degener, and Petersen[8] similarly did not identify the products isolated when 1,2-dicyano-3,6-dithiacyclohexene and its derivatives were treated with hydrogen bromide.

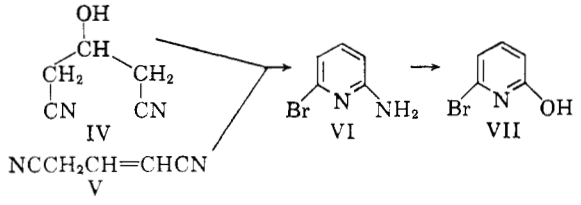
Related to the above reactions are the conversions of 1,3-dicyanoguanidines to 2-amino-6-halotriazines[9,10] and the formation of cyclic products[11] from thiocyanogen and hydrogen chloride. In a few isolated cases,[12-15] products related to III were obtained when concentrated aqueous solutions of halogen acids reacted with dinitriles.

Perhaps the most interesting references pertaining to dinitriles are the papers by Lespieau[16] and by Kurtz, Schwarz, and Disselnkötter.[17] The former author treated both 3-hydroxyglutaronitrile and *trans*-glutacononitrile with gaseous hydrogen bromide and obtained a single product, stable to 48% hydrogen bromide at 160°, which he claimed to be a hydrobromide of 3-bromoglutaronitrile. This, with base, gave what he regarded as 3-bromoglutaronitrile, m.p. 87–88°. The latter authors did not question these structural assignments when they obtained these products from glutacononitrile and hydrogen bromide in acetic acid, despite the fact that in 1958 it already had been suggested[3] that the acid-free substance might be 2-amino-6-bromopyridine. The melting point (89–89.5°) reported[18] for this material almost coincides[3] with that of Lespieau's material.

Kurtz[17] obtained in the same way the corresponding hydrobromides and their free bases from 2-methyl- and 3-methylglutacononitriles. Prior to the appearance of the above papers,[3,17] we had undertaken an investigation of the reaction carried out by Lespieau. We now find that the products obtained by these authors are indeed pyridines, and that the reaction of dinitriles with anhydrous hydrogen bromide or iodide appears to be a general method for the preparation of cyclic nitrogen compounds. This paper reports the preparation of pyridines by such a cyclization reaction.

The 3-hydroxyglutaronitriles required by this study were prepared by a method described in a previous publication.[1] A mixture of *cis*- and *trans*-glutacononitrile was prepared by the pyrolysis of 3-acetoxyglutaronitrile. An earlier method[16,19] for the dehydration of 3-hydroxyglutaronitrile using phosphorus pentoxide, in our hands, gave fair yields of the desired product, but the reaction did not take place until a temperature of approximately 135° was reached when its violence made it unmanageable on a large scale. In addition, the product was contaminated with small amounts of a crystalline substance which, from infrared and elemental analysis, appears to be 2,6-dihydroxypyridine.

When 3-hydroxyglutaronitrile or glutacononitrile, suspended in ether, was treated with hydrogen bromide gas, there separated almost immediately a highly crystalline salt which with mild base afforded an 80% yield of a white solid. The infrared spectrum of this material showed a complete absence of nitrile absorption but had bands at 2.9–3.2 μ, characteristic of an amino group, and at 6.07, 6.27 and 6.46 μ, typical for a pyridine ring.[20] In addition, reaction of the product with nitrous acid gave the known 2-bromo-6-hydroxypyridine.[18]



IV V VI VII

(5) E. G. Howard, U. S. Patent 2,810,726.

(6) J. H. Osborn, Ph.D. thesis, University of Minnesota, 1958; Diss. Abstr., **19**, 2475 (1959).

(7) J. R. Geigy, French Patent 1,070,912 (1954).

(8) W. Wolf, D. Degener, and S. Petersen, *Angew. Chem.*, **72**, 963 (1960).

(9) D. W. Kaiser, U. S. Patent 2,630,433 (1953).

(10) J. J. Roemer and D. W. Kaiser, U. S. Patent 2,658,893 (1953).

(11) A. Söderback, *Ann.*, **419**, 217 (1919); *ibid.*, **465**, 184 (1928).

(12) H. Blitz, *Ber.*, **25**, 2543 (1892).

(13) C. Broche, *J. prakt. Chem.*, (2), **50**, 97 (1894).

(14) G. Pellizzari, *Gazz. chim. ital.*, **52**, I, 199 (1922); *ibid.*, **54**, I, 177 (1924).

(15) The product obtained by Biltz (ref. 12 above) by the action of hydrogen iodide on succinonitrile has an analysis which better agrees with the addition of three moles of hydrogen iodide, rather than the four claimed.

(16) R. Lespieau, *Bull. soc. chim.*, **33**, 725 (1923); *Compt. rend.*, **176**, 754 (1923).

(17) P. Kurtz, H. Schwarz, and H. Disselnkötter, *Ann.*, **631**, 21 (1960).

(18) H. J. den Hertog and J. P. Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).

(19) R. Legrand, *Bull. soc. chim., Belges*, **63**, 166 (1944).

(20) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, 1958, pp. 77–286.

TABLE I

PREPARATION OF PYRIDINES BY CYCLIZATION OF DINITRILES OF THE GENERAL FORMULA $NCCH_2CR(OH)CH_2CN$

R	Pyridine	Method	Cryst. from[a]	Yield, %	M.p.	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Calcd. I	Found C	Found H	Found N	Found Br	Found I
H	2-Amino-6-bromo-	A	E/P	55	88–89°	$C_5H_5N_2Br$	34.7	2.89	16.2	46.2	...	34.8	3.0	16.1	46.1	...
		B		70												
H	2-Amino-6-iodo-	A	E/P	60	106–106.5°	$C_5H_5N_2I$	27.3	2.30	12.7	...	57.7	27.3	2.4	12.6	...	57.5
		B		90												
CH_3	2-Amino-6-bromo-4-methyl-	A	MC/P	87.5	115–116°	$C_6H_7N_2Br$	38.5	3.77	15.0	42.7	...	38.4	3.8	...	42.5	...
CH_3	2-Amino-6-iodo-4-methyl-	B	E/P	88	112–113.5°	$C_6H_7N_2I$	30.8	3.01	12.0	...	54.2	31.0	2.9	12.1	...	54.4
C_2H_5	2-Amino-6-bromo-4-ethyl-	A	E/P	65	113–113.5°	$C_7H_9N_2Br$	41.8	4.51	13.9	39.7	...	41.7	4.4	13.9	40.0	...
C_2H_5	2-Amino-6-iodo-4-ethyl-	B	MC/P	85	112–113°	$C_7H_9N_2I$	33.9	3.66	11.3	...	51.2	33.9	3.7	11.2	...	51.4
C_6H_5	2-Amino-6-bromo-4-phenyl-	A	AC/P	75	141–143°	$C_{11}H_9N_2Br$	53.0	3.64	11.3	32.1	...	52.9	3.6	11.0	31.9	...
C_6H_5	2-Amino-6-iodo-4-phenyl-	B	E/P	54	154–155.5°	$C_{11}H_9N_2I$	44.6	3.06	9.46	...	42.9	44.4	3.0	9.4	...	43.1

[a] Solvent key: E = ether; P = petroleum ether (b.p. 30–60°); MC = methylene chloride; AC = acetone.

Although our initial experiments were carried out in ether, it was found that the cyclization could be accomplished in any inert solvent. While chloroform, methylene chloride, or benzene was satisfactory, acetic acid proved most convenient, for all the reactants had excellent solubility in this medium. When nitromethane was used as the solvent, the product most easily isolated was 2-amino-5,6-dibromopyridine VIII.[21] This we consider to be due to bromination of the initially produced VI, the bromine having been formed by oxidation of the hydrogen bromide by the solvent.[22]

The structure of VIII was supported by its NMR spectrum which showed two doublets at 2.4 and 3.47 τ units, each being split by 8.3 c.p.s. These locations are more indicative of the postulated structure than of the isomeric 2-amino-3,6-dibromopyridine or 2-amino-4,6-dibromopyridine.

The previously prepared 3-substituted 3-hydroxyglutaronitriles reacted with hydrogen bromide in exactly the same way as I and afforded the corresponding 3-substituted pyridine derivatives. Hydrogen iodide[23] behaved similarly with these dinitriles and led to the expected 2-amino-6-iodopyridines. These results are summarized in Table I.

In the case of tris(cyanomethyl)carbinol (IX), the hydrobromide salt from the cyclization was refluxed briefly with methanol and the product isolated as the methyl ester X.

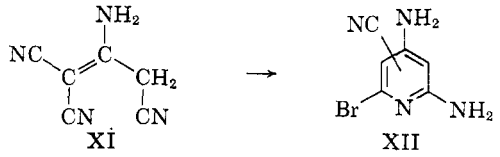
Hydrogen chloride, however, failed to effect conversion in any case examined. 3-Hydroxy-3-phenylglutaronitrile, for example, was unaffected by hydrogen chloride in acetic acid after three days at room temperature, followed by heating on the steam bath for forty minutes. 3-Acetoxyglutaronitrile with the same reagent stood at room temperature for two weeks before a colorless, highly crystalline salt was deposited. This substance did not give any 2-amino-6-chloropyridine or even a precipitate on neutralization with sodium hydrogen carbonate solution. In addition, its

(21) H. J. den Hertog and P. Bruin, *Rec. trav. chim.*, **65**, 385 (1946).

(22) The evolution of bromine from a solution of hydrogen bromide and benzyl *N*-benzoyloxycarbonate in nitromethane was observed by L. W. Jones and R. Oesper, *J. Am. Chem. Soc.*, **36**, 2208 (1914), while L. A. Carpino, C. A. Giza, and P. A. Carpino, *ibid.*, **81**, 955 (1959) noted the formation of chlorine when *t*-butyl *N*-*p*-toluenesulfonoxycarbamate in nitromethane was treated with hydrogen chloride. The latter authors ascribed the production of halogen in both instances to the oxidation of the hydrogen halide by the solute. While this may be the case, our results almost certainly indicate that the solvent itself can act as the oxidizing agent.

(23) Solutions of hydrogen iodide (15%) in acetic acid were prepared conveniently by adding acetic anhydride (280 g.) to 50% aqueous hydrogen iodide (100 g.). The presence of trace amounts of water did not adversely effect these cyclizations.

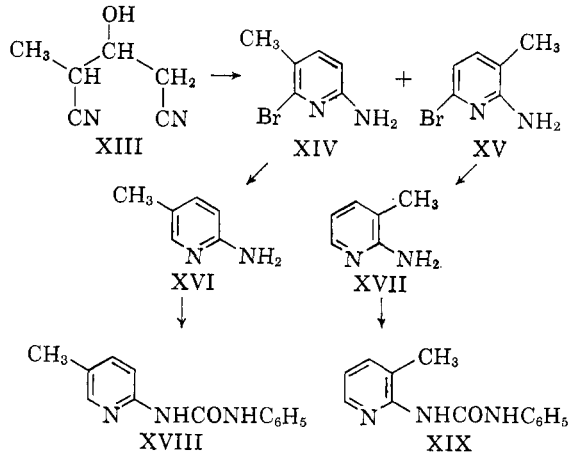
infrared spectrum was dissimilar to that of a 2-aminopyridine hydrochloride. On long standing in the atmosphere, it decomposed to a tarry substance and, to date, has not been investigated further. No precipitate was formed when glutacononitrile was allowed to stand in acetic acid in the presence of hydrogen chloride. 3-Hydroxyglutaronitrile in ethanolic ether reacted with hydrogen chloride and led to a highly crystalline salt. This, however, on decomposition in water gave only diethyl 3-hydroxyglutarate in 65% yield. It should be noted that while dry hydrogen chloride is without significant action on the dinitriles under discussion, it does cause cyclization of I (R = NH_2). Reduction of the number of nitrile groups appears to have an adverse effect, for XI, prepared by the action of hydrogen chloride on malononitrile, does not undergo further cyclization in the presence of this reagent.[4] This comparison is only valid, however, if the free acid of I is formed before cyclization occurs.



XI XII

Hydrogen bromide, however, converts XI to the pyridine derivative XII.

The action of hydrogen bromide on an unsymmetrical 3-hydroxyglutaronitrile was also examined to determine whether the dissymmetry had any effect on the direction of cyclization. For this purpose 2-methyl-3-hydroxyglutaronitrile[24] (XIII) was prepared, albeit in poor yield by the action of a magnesium sulfate–buffered potassium cyanide solution on 3-chloro-1,2-epoxybutane. A considerable quantity of a low-boiling material also was isolated from this reaction and appears to be 4-hydroxy-2-pentenecarbonitrile having arisen by a mechanism discussed in a previous paper.[1] Treatment of XIII with hydrogen bromide in methylene chloride followed by decomposition of the resulting salt[25] with base afforded an almost quantitative yield of a solid, m.p. 65°. By crystallization and careful chromatography, this material was separated into two aminobromopicolines XIV and XV. The structures of these were proved by hydrogenation over a palladium catalyst and characterization of the resulting aminopicolines XVI and XVII as their phenylurethane derivatives, XVIII and XIX, respectively. Comparison of the latter with samples prepared from authentic XVI and XVII permitted the assignments XIV and XV to be made. The infrared spectra of synthetic mixtures of the latter compounds revealed that the crude cyclization product was, as expected, a 1:1 mixture of these two components, thus demonstrating no specificity in the direction of cyclization of XIII. This



XIII XIV XV XVI XVII XVIII XIX

reasoning assumes that each racemic form of XIII cyclizes in both directions and does not invalidate the argument that the above results would be observed if each racemate, (a) cyclizes in one specific direction, opposite to that of the other and, (b) is present in equimolar amount in the starting material.

It seems likely that the loss of water is the last step in the formation of the pyridines from the hydroxydinitriles for, as mentioned above, 3-hydroxy-3-phenylglutaronitrile is unaffected by hydrogen chloride as is glutacononitrile, while the removal of water from 3-hydroxyglutaronitrile requires phosphorus pentoxide around 135°. Some aspects of the mechanism of this cyclization will be discussed in a later paper.

The methods used here for the preparation of these simple 2-amino-6-halopyridines offer a new route to compounds that were difficultly accessible or unavailable before. 2-Amino-6-bromopyridine had been prepared previously either by the bromination[21,26] or 2-aminopyridine which gave complex mixtures, or by the amination[18] of 2,6-dibromopyridine itself, available only by the high temperature bromination of pyridine. 2-Amino-6-iodopyridines have not been reported previously. Further studies on other cyclizations of these dinitriles and the synthesis of isoquinolines, thiazoles, and imidazoles using similar procedures will be reported in subsequent papers.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model No. 4–55 as films or as Nujol mulls. Hydrogen bromide (30–33%) in acetic acid was used as supplied by Eastman-Kodak.

3-Acetoxyglutaronitrile.—To acetic anhydride (214 g., 2.1 moles) containing pyridine (6 ml.) there was added over 3

(24) No attempt was made to determine the racemic composition of this material.

(25) This is no doubt identical with the material obtained by Kurtz[17] from 2-methylglutacononitrile and hydrogen bromide.

(26) H. J. den Hertog, *Rec. trav. chim.*, **65**, 129 (1946).

hr., 3-hydroxyglutaronitrile (220 g., 2.0 moles) with cooling and stirring. After 1 hr. the mixture was poured into water (300 ml.) containing sodium acetate (200 g.) and the mixture extracted with methylene chloride (2 × 200 ml.). The methylene chloride solution was washed with water (50 ml.) and dried over sodium sulfate. Removal of the ether gave the crude product (298 g.) which, on vacuum distillation, afforded 3-acetoxyglutaronitrile (261 g., 86%) b.p. 120–124° (0.25 mm.) which solidified in the receiver m.p. 45–46°. A sample was redistilled for analysis, b.p. 126.5° (1.0 mm.), m.p. 45°.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.5; H, 5.4; N, 18.40.

cis- and *trans*-**Glutacononitrile.**—A. 3-Acetoxyglutaronitrile (96 g. 0.676 mole) was dissolved in glacial acetic acid (75 g.) and the solution dripped through a vertical glass tube furnace packed with glass helices at 450° at the rate of 1 ml./min. Concomitant with the addition, a slow flow of nitrogen was maintained through the furnace. After the addition was complete, the column was flushed with acetic acid (20 ml.). The total effluent was combined and the acetic acid removed under reduced pressure to give a dark brown oil (79.5 g.). Fractional distillation of this material led to a mixture of *cis*- and *trans*-glutacononitrile (20.8 g.), b.p. 85–94° (0.6 mm.), and recovered 3-acetoxyglutaronitrile (54 g.). The latter fraction was dissolved in glacial acetic acid (30 ml.) and repyrolyzed at 460°. Processing the effluent as above led to a mixture of *cis*- and *trans*-glutacononitrile (17.5 g.), b.p. 94–100° (1.2 mm.), and recovered starting material (19.3 g.). The crude glutacononitrile fractions from these pyrolyses were combined and refractionated to give a mixture of the two geometrical isomers (35.5 g.), b.p. 84–86° (0.35 mm.), $n^{25}D$ 1.4646 (yield = 58%, based on unrecovered starting material). (Reported[27] for *trans* isomer, b.p. 127–128 (10 mm.), $n^{30}D$ 1.4646.)

Anal. Calcd. for $C_5H_4N_2$: C, 65.2; H, 4.38; N, 30.42. Found: C, 65.1; H, 4.4; N, 30.3.

B. 3-Hydroxyglutaronitrile (20 g; 0.18 mole) was mixed with phosphorus pentoxide (14.2 g.) and the mixture slowly heated under reduced pressure to 120–130° when a rather violet reaction took place and distillation commenced. The distillate (8 g.) contained small amounts of crystalline material and toward the end of the reaction this substance clogged the condenser. The distillate, filtered then redistilled under reduced pressure, afforded pure glutacononitrile (6.0 g.), b.p. 85–86.5° (0.5 mm.).

The solid material from this reaction was recrystallized from methanol (0.35 g.), m.p. 195–196°. Two further crystallizations raised this to 196–197°. Reported[28] for 2,6-dihydroxypyridine, m.p. 202–203°.

Anal. Calcd. for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.1; H, 4.5; N, 12.4.

Its infrared spectrum showed bands at 3.24 (broad) and 6.09 μ.

The Cyclization of 3-Hydroxyglutaronitriles. Method A.—The dinitrile was suspended or dissolved in 10 to 20 times its weight of dry ether, and cooled in an ice bath. Dry hydrogen bromide or hydrogen iodide was then bubbled through the mixture for 30 min. to 1 hr. until precipitation of the hydrogen halide salt appeared complete. The total reaction mixture was poured into an excess of sodium hydrogen carbonate solution. After the addition of more ether, the organic phase was separated, washed with a small amount of water, and dried over anhydrous sodium sulfate. Evaporation of the ether gave the crude 2-amino-6-halopyridine which was recrystallized from the appropriate solvent.

Method B.—The dinitrile was dissolved in a minimum of acetic acid (or if liquid used neat) and added dropwise with stirring and cooling to a solution of hydrogen halide in acetic acid (~3 equivalents). Stirring was continued until separation of the hydrohalide salt was judged complete. This was then separated by filtration and added to an excess of sodium hydrogen carbonate solution. Isolation of the pyridine derivative was then accomplished as in method A.

2-Amino-6-bromopyridine from Glutacononitrile.—Glutacononitrile (2.5 g.) was added dropwise to a solution of hydrogen bromide in acetic acid (30 g., 30% hydrogen bromide) during 5 min., with cooling and stirring. After a further 5 min., the copious yellow precipitate was removed by filtration and treated with sodium hydrogen carbonate solution. Isolation by means of ether extraction and crystallization from ether–petroleum ether (b.p. 30–60°) afforded pure 2-amino-6-bromopyridine (2.7 g.), m.p. 88–89°.

2-Amino-6-iodopyridine from Glutacononitrile.—This was prepared as above using glutacononitrile (1.5 g.) and hydrogen iodide in acetic acid (35 g, 15.0% hydrogen iodide). The product (0.6 g.) had m.p. 104–105°. It is possible that the low yield here is due to reductive dehalogenation of the product by hydrogen iodide. This type of reaction has been observed by others.[9,13]

Methyl 2-Amino-6-bromo-4-pyridylacetate.—Tris(cyanomethyl)carbinol (0.74 g.) dissolved in acetic acid (12 ml.) was added dropwise with stirring to 30% hydrogen bromide in acetic acid (4.8 cc.). After stirring for 1.5 hr., the heavy precipitate was removed by filtration, washed with methylene chloride, and added to methanol (12 ml.). This solution was stirred at room temperature for 1.5 hr. and then refluxed for 1 hr. The volatile solvents were removed under reduced pressure and the residue treated with sodium hydrogen carbonate solution. The insoluble white solid, (0.6 g.) was separated by filtration and dried, m.p. 115°. Recrystallization from aqueous methanol afforded the pure material m.p. 120–122°.

Anal. Calcd. for $C_8H_9BrN_2O_2$: C, 39.2; H, 3.70; N, 11.4; Br, 32.6. Found: C, 39.0; H, 3.8; N, 11.3; Br, 32.6.

The Action of Hydrogen Bromide on 3-Hydroxyglutaronitrile in Nitromethane.—Hydrogen bromide was bubbled through nitromethane (35 ml.) for 30 min. with cooling. To this solution there was then added 3-hydroxyglutaronitrile (5 g.) in nitromethane (10 ml.) dropwise during 15 min. Hydrogen bromide was then bubbled through for 30 min. and the mixture allowed to stand 20 hr. The liquid was then poured into sodium hydrogen carbonate solution and extracted with ethyl acetate. Evaporation of this extract led to a dark solid (8.55 g.). This was redissolved in ethyl acetate and percolated through a column (3 × 33 cm.) of alumina (150 g.) to remove color. The material (6.8 g.) recovered from the eluate was fractionally crystallized from ethanol–petroleum ether (b.p. 60–80°) and afforded 2-amino-5,6-dibromopyridine (1.1 g.) m.p. 151–152.5°.

Anal. Calcd. for $C_5H_4Br_2N_2$: C, 23.8; H, 1.6; Br, 63.4; N, 11.1. Found: C, 24.0; H, 1.5; Br, 63.2; N, 11.1%.

This material did not depress the melting point of a sample, m.p. 151–152°, prepared according to den Hertog.[21]

3-Hydroxy-2-methylglutaronitrile.—With good stirring 3-bromo-1,2-epoxybutane (25 g., 0.166 mole) was added dropwise at room temperature during 15 min. to a solution of magnesium sulfate heptahydrate (74 g., 0.3 mole) and potassium cyanide (23.6 g., 0.33 mole) in water (110 ml.). The temperature of the mixture rose spontaneously to 35° but fell to room temperature again within 1 hr. After stirring overnight, the inorganic salts in suspension were removed by filtration and washed with ethyl acetate. The dark brown aqueous filtrate was then extracted continuously with ethyl acetate (500 ml.) for 48 hr. The organic extract was dried over anhydrous sodium sulfate and decolorized with a little charcoal. Removal of the ethyl acetate left a dark brown oil (11.2 g.) which was fractionally distilled under reduced pressure. The fraction (4.8 g.) distilling between 150–155° (0.6 mm.) was collected and redistilled

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b.p. 150° (1.5 mm.) $n^{25}D$ 1.4580. The infrared spectrum of this material showed bands at 2.89 and 4.41 μ.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.0; H, 6.5; N, 22.2.

From the reaction mixture a lower boiling fraction (4.3 g.), b.p. 79–82° (0.6 mm.), was obtained. Redistillation gave the pure material (2.9 g.), b.p. 68–70° (0.3 mm.), $n^{25}D$ 1.4620. This substance exhibits bands in the infrared at 2.91, 4.46, and 6.10 μ and appears to be 4-hydroxy-2-pentenecarbonitrile.

Anal. Calcd. for C_5H_7NO: C, 61.9; H, 7.2; N, 14.4. Found: C, 61.8; H, 7.4; N, 14.4.

2-Amino-6-bromo-3-methylpyridine and 2-Amino-6-bromo - 5 - methylpyridine.—3 - Hydroxy - 2 - methylglutaronitrile (2.9 g.) was dissolved in methylene chloride (25 ml.) and hydrogen bromide bubbled through the solution for 1 hr. The methylene chloride was removed under reduced pressure and the oily residue treated with saturated sodium hydrogen carbonate solution (100 ml.) The tan colored crystals which deposited were removed by filtration and air-dried (3.2 g.) m.p. 63–65°. Further crystallization of this material from ether–petroleum ether (b.p. 30–35°), while serving to give a colorless product, scarcely affected the melting point. A sample of this material (1.2 g., m.p. 67–68.5°) was dissolved in ether and chromatographed over neutral alumina (20 g.). The first two fractions eluted by ether (100 ml.) contained 0.63 g. of material which, after three crystallizations from ether–petroleum ether, afforded pure 2-amino-6-bromo-3-methylpyridine (0.25 g. as long white needles, m.p. 114–114.5°).

Anal. Calcd. for $C_6H_7N_2Br$: C, 38.5; H, 3.74; N, 14.97; Br, 42.78. Found: C, 38.4; H, 3.8; N, 14.7; Br, 42.5.

Subsequent elution of the column with ether (7 × 50 ml.) also gave crystalline material which was recrystallized from ether–petroleum ether to give white feathery crystals (0.25 g.) m.p. 90–95°. The infrared spectrum of this material indicated the presence of approximately 5% of the higher melting isomer. However, three further crystallizations from the same solvent mixture led to pure 2-amino-6-bromo-5-methylpyridine (0.1 g.), m.p. 97.5–98°. Found: C, 38.7; H, 3.6; N, 14.8; Br, 42.7.

The Phenylurethane of 2-Amino-3-methylpyridine.—2-Amino-6-bromo-3-methylpyridine (0.1 g.) was dissolved in dry ethanol (20 ml.) containing potassium hydroxide (0.05 g.). This solution was then stirred with hydrogen and a palladium catalyst (50 mg., 10% palladium-on-charcoal) until the calculated amount of hydrogen had been adsorbed (10 min.). Removal of the catalyst and the alcohol by the usual methods, followed by dilution with water and isolation of the product by ether extraction, led to a small quantity of a brown oil. This was dissolved in ether (2 ml.) and 2 drops of phenyl isocyanate added. Almost immediately, white crystals began to separate and after 30 min. these were removed by filtration and recrystallized from acetone–ether, m.p. 176–177°. A mixed melting point of this material with a sample of the phenylurethane (m.p. 178°) prepared from an authentic specimen of 2-amino-3-methylpyridine showed no depression.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.7; H, 5.8; N, 18.3.

The Phenylurethane of 2-Amino-5-methylpyridine.—2-Amino-6-bromo-3-methylpyridine (42 mg.) was hydrogenated and the product isolated as in the above experiment. The white crystalline solid obtained had m.p. 73–75° and did not depress the melting point of authentic 2-amino-5-methylpyridine (m.p. 73–76°). The infrared spectra of the two materials were also identical. The phenylurethan prepared as in the above experiment crystallized from methanol in white needles, m.p. 197.5–198.5°, and did not depress the melting point of authentic 2-amino-5-methylpyridine phenylurethan, m.p. 196.5–197.5°. Found: C, 69.0; H, 5.8; N, 18.6.

Diethyl 3-Hydroxyglutarate.—3-Hydroxyglutaronitrile 11 g., 0.1 mole) was dissolved in dry ethanol (13.8 g., 0.3 mole) and dry ether (50 ml.). The mixture was cooled to −15° and dry hydrogen chloride gas passed through slowly for 6 hr. The excess hydrogen chloride, ether, and alcohol were removed under reduced pressure, and the remaining solid dissolved in water (40 ml.) and warmed at 40–50° for 30 min. The oil which separated out of solution was isolated by ether extraction and distilled under reduced pressure. Diethyl 3-hydroxyglutarate (13.3 g., yield 65%) was collected at 91–93° at 0.25 mm. [reported[29] b.p. 105–107° (2 mm.)].

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Condensed Pyrimidine Systems. XXII. *N*-Methylpurines

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A group of 1- and 3-monomethylpurines has been prepared by complete synthesis. Among the new derivatives are 3-methyladenine, 3-methylguanine, and the 1- and 3-methyl derivatives of 6-mercaptopurine. A number of 7- and 9-methyl derivatives have been obtained by direct methylation of 6-chloropurine, conversion to the mercapto derivatives, and subsequent separation of the 7- and 9-methylpurine-6-thiols. Several ring openings and rearrangements have been observed in the course of attempts to prepare 1-methyladenine.

Studies on *N*-methylpurines were undertaken in this laboratory a number of years ago in connection with investigations of the effect of such substitution upon biological activity, e.g. the specificity of the purine requirement of microorganisms,[1,2] the specificity of enzymes such as guanase[3] and xanthine oxidase,[4] and the effects of structural modifications upon the activity of purine antagonists such as 6-mercaptopurine (purine-6-thiol)

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