formed were distilled and seemed to consist of 1,2-dibromopropane, b.p. 139–143° (743 mm.) and 2,3-dibromobutane, b.p. 153–158° along with the tetrabromide from butadiene, m.p. 118–121°.

Tetrahydrofurfuryl Benzoate.—The ester (1.4 moles) was pyrolyzed at a rate of 0.18 mole/hr. with nitrogen carrier at 0.24 mole/hr. at 563°. The contact time was 56 sec. The yield of methyl propenyl ketone was 13.3% and no unchanged ester was recovered.

Tetrahydrofurfuryl Formate.—The ester (0.54 mole) was pyrolyzed at 0.31 mole/hr. at 535° with a contact time of 79 sec. The yield was 31% of ketone.

Tetrahydrofurfuryl Oxalate.—The ester (0.22 mole) was introduced at a rate of 0.04 mole/hr. at 532° with nitrogen carrier (0.21 mole/hr.) corresponding with a contact time of 98 sec. The yield of ketone based on consumed ester was 10.5%.

Pyrolysis of 4,5-Dihydro-2-methylfuran.—The furan (6.3 g.) was passed through a semi-micro pyrolysis furnace at 540°. The product gave a dinitrophenylhydrazone, m.p. 148–154°, depressed by admixture with the derivative from cyclopropyl methyl ketone but not depressed by mixing with methyl propenyl ketone derivative.

Pyrolysis of Cyclopropyl Methyl Ketone.—The ketone (89.5 g.) was pyrolyzed at 500° with a contact time of 47 sec. The product contained methyl propenyl ketone (30.5 g.) corresponding with a 35% yield based on consumed material. A viscous residue (15 g.) remained in the flask. Like the residue obtained in the pyrolysis of tetrahydrofurfuryl esters, it was insoluble in sodium bisulfite solution and gave no dinitrophenylhydrazone.

Dehydration of Tetrahydrofurfuryl Alcohol by Boric acid.[11] —Tetrahydrofurfuryl alcohol (1 mole) and boric acid (1 mole) were placed in a 250-ml. flask fitted with a 40 × 1.3 cm. column packed with glass helices and fitted with a partial take-off head. Heat was applied and the water was removed continuously. After 1 mole of water had been removed, water and 2,3-dihydropyran distilled together. Toward the end of the distillation, tetrahydrofurfuryl alcohol also distilled. Carried along with this was a high boiling, water-insoluble, pale green liquid. Redistillation of the pyrolysate gave 14.7 g. of 2,3-dihydropyran, a 22% yield based upon alcohol consumed. The 2,4-dinitrophenylhydrazone from it had m.p. 113.5–115° and did not depress the melting point of a derivative from authentic 2,3-dihydropyran. The pale green, high boiling, water-insoluble material mentioned above was combined with the same material from other runs and vacuum distilled. A large fraction, b.p. 158–164° (2 mm.) was obtained. This substance was an ester of boric acid; it gave white crystals of boric acid when placed on a watch glass and allowed to stand overnight. A sample, b.p. 159° (2 mm.), was shown to be tetrahydrofurfuryl borate.

Anal. Calcd. for $(C_5H_9O_2)_3B$: C, 57.4; H, 8.6. Found: C, 57.5; H, 8.5.

Pyrolysis of Tristetrahydrofurfuryl Borate.—This ester (60 g.) was pyrolyzed at 500°. 2,3-Dihydropyran (6.5 g.) was obtained, along with unchanged ester (41.1 g.). This is a 43% conversion to 2,3-dihydropyran based upon the ester consumed.

NOTRE DAME, IND.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies in Purine Chemistry. II. A Facile Synthesis of 2-Substituted Adenines[1,2]

BY EDWARD C. TAYLOR, O. VOGL AND C. C. CHENG

RECEIVED AUGUST 15, 1958

The reaction of the silver salt of isonitrosomalononitrile with amidine hydrohalides yields amidine salts of isonitrosomalononitrile (I), which are quantitatively isomerized by heating in appropriate solvents to 2-substituted 4,6-diamino-5-nitrosopyrimidines (II). Heating the latter with formamide, formic acid and sodium dithionite yields 2-substituted adenines (III) in high yield. Direct conversion of I to III is realized in a mixture of formamide, formic acid and sodium dithionite, and provides what is essentially a one-step synthesis of a variety of hithertofore unavailable adenine derivatives from simple aliphatic precursors. Modifications of these procedures lead to new syntheses of adenine and isoguanine and to the preparation of a novel purine type, illustrated by α,δ-bis-(2-adenyl)-butane (VII, $n = 4$). The direct conversion of an amidine to a purine is realized in the reaction of guanidine carbonate, the potassium salt of isonitrosomalononitrile, formamide, formic acid and sodium dithionate, to give 2,6-diaminopurine in 71% yield.

The conventional synthetic route to adenines involves the condensation of guanidine or thiourea with malononitrile to give a 2-substituted 4,6-diaminopyrimidine, which is then nitrosated, reduced, acylated and subsequently ring-closed under dehydrating conditions.[3] The requisite 4,5,6-triaminopyrimidine intermediates may alternately be prepared by reduction of 5-arylazo derivatives, formed either by coupling of a 4,6-diaminopyrimidine[4] or directly by condensation of arylazomalononitriles with amidines.[4,5] Adenine itself may be prepared by desulfurization of a 2-mercapto or 2-methylmercapto substituent at an appropriate stage of the synthesis.[6–10] Alternate routes to adenines include aminolysis of 6-mercapto–,[11] 6-methylmercapto–,[12–21] 6-carboxymeth-

(1) This investigation was supported by a research grant (C-2551 PET) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Presented in part before the Division of Medicinal Chemistry at the 131st National A.C.S. Meeting in Miami, Fla., April 7–12, 1957.

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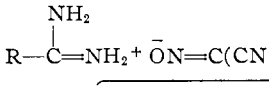
(17) C. G. Skinner, P. D. Gardner and W. Shive, *ibid.*, **79**, 2843 (1957).

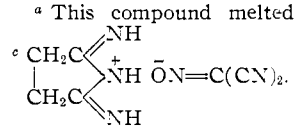
(18) C. O. Miller, F. Skoog, F. S. Okumura, M. H. von Saltza and F. M. Strong, *ibid.*, **78**, 1375 (1956).

TABLE I



R	M.p. dec., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H–	129–130	95	34.5	3.6	50.3	34.1	3.2	50.0
CH_3–	141–142	100	39.2	4.6	45.7	39.4	4.4	45.4
CH_3CH_2–	93	96	43.0	5.4	42.9	43.1	5.3	43.1
CH_3S–	125	100	32.5	3.8		32.8	4.1	
$C_6H_5CH_2$–	104[a]	93	57.6	4.9		57.8	4.9	
C_6H_5–	151–152	92	55.8	4.2	32.5	55.7	4.0	32.6
p-$CH_3OC_6H_4$–	194–195	92	54.0	4.5	28.6	54.0	4.6	28.5
p-$O_2NC_6H_4$–	176–177	83	46.1	3.1	32.3	45.5	3.0	32.6
H_2N–	157–158	100	31.2	3.9	54.5	31.3	3.9	55.0
β-Pyridyl	152–154	95	50.0	3.7	38.9	49.8	4.0	39.4
[b]	106–107	100			37.0			37.2
$-CH_2-$	144–145	88	37.4	3.5	48.2	37.2	3.7	48.3
$-CH_2CH_2$[c]	171	100	44.0	3.7	44.0	44.3	4.0	43.9
$-CH_2CH_2CH_2CH_2-$	179–180	94	43.4	4.9	42.1	43.4	5.0	41.9

[a] This compound melted without decomposition. [b] Salt of 2-aminopyridine and isonitrosomalononitrile.

[c]  .

ylmercapto–[22] or 6-chloropurines.[13,16,21–31] 4,6-Dihydroxy-5-nitropyrimidine has been used as a starting material for the synthesis of 4,5,6-triaminopyrimidines,[24,25,27,28] but this method is applicable in particular to the preparation of 6- and 9-substituted adenines and is too circuitous to be considered as a satisfactory general route to simple adenine derivatives. Existing methods are so cumbersome for the introduction of sustituents other than –H, –SR or $-NH_2$ in the 2-position that 2-methyladenine[32–34] is the only known 2-alkyl derivative, and 2-phenyladenine[35] is the only known 2-aryl derivative. Even 2-hydroxyadenine (isoguanine) must be prepared somewhat circuitously, since urea does not condense satisfactorily with malononitrile and the 2-hydroxy group must be introduced indirectly.[36–40]

It has now been found that the requisite 2-substituted 4,6-diamino-5-nitrosopyrimidine intermediates are readily available by thermal isomerization of amidine salts of isonitrosomalononitrile (I).[41] The crystalline, light yellow salts (see Table I) were prepared in almost quantitative yield by treating a solution of an amidine hydrohalide in methanol with a slight excess of the silver salt of isonitrosomalononitrile, removing silver halide by filtration and concentration of the methanol. The conclusion that these compounds are salts of the amidine and isonitrosomalononitrile rather than isomeric adducts of the type RC(=NH)NHC(=NH)CH(NO)CN is based on the following observations: (1) they are soluble in cold water, (2) addition of silver nitrate to an ethanolic solution of the compounds regenerates the silver salt of isonitrosomalononitrile and (3) their infrared spectra show two conjugated nitrile bands at 4.49 and 4.51 μ, identical in position with the nitrile bands in the spectrum of the potassium salt of isonitrosomalononitrile. Heating these salts in an appropriate solvent, such as 2-methyl-5-ethylpyridine, 2- or 3-picoline, pyridine or quinoline, resulted in isomerization to 2-substituted 4,6-diamino-5-nitrosopyrimidines (II) (see Table II). A ratio of one gram of salt to five grams of solvent was found to be optimum; too much solvent made isolation of the nitrosopyrimidine difficult because of its increased solubility, while too little solvent often led to some decomposition. Cyclization was usually complete after one hour; an exception was found in the preparation of α,δ-bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-butane (VI, $n = 4$), which required 14 hours for complete cyclization.

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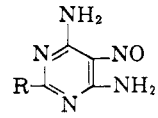
TABLE II



R II–	Cyclization method[f] Solvent[a]	(A) Temp., °C.	Time, hr.	Yield, %[b]	(B) Yield, %[c]	Color	M.p., °C.	Analyses, % Calcd. / Found C	H	N
CH_3–	5-Ethyl-2-methyl-pyridine	175–180	1/3	92	15	Green	306[d]	39.2	4.6	45.7
								39.2	4.1	46.1
C_2H_5–	5-Ethyl-2-methyl-pyridine	130–135	1/3	95		Bluish green	254	43.0	5.4	42.9
								43.2	5.6	43.0
CH_3S–	Pyridine	115–120	0.5	75		Bluish green	261–262		[e]	
$C_6H_5CH_2$–	α-Picoline	115–120	1.5	75		Olive green	247–248	57.6	4.9	
								57.2	5.0	
C_6H_5–	α-Picoline	125–130	0.5	95	28	Bluish green	243–244	55.8	4.2	32.5
								55.9	3.9	32.6
p-$CH_3OC_6H_4$–	5-Ethyl-2-methyl-pyridine	175–180	0.25	92		Green	284–286	54.0	4.5	28.6
								54.0	4.5	27.3, 29.3
p-$O_2NC_6H_4$–	α-Picoline	125–130	1/3	85		Bluish green	302–303	46.1	3.1	32.3
								46.7	3.5	32.6
H_2N–	5-Ethyl-2-methyl-pyridine	175–180	1/3	68	46	Pink	345–346	31.2	3.9	54.5
								30.7	3.5	55.0
H_2N–	Tetralin	206	1/3	89		Pink				
H_2N–	Dimethyl-formamide[f]			88		Pink				
HO–					60[g]	Violet red	>360		[e]	
β-Pyridyl	5-Ethyl-2-methyl-pyridine	135–140	0.75	54		Bluish green	304	55.0	3.7	38.9
								49.9	3.7	38.8
$-CH_2-$	5-Ethyl-2-methyl-pyridine	120–130	4	92		Green	287–289[d]			45.4[h]
										45.1
$-CH_2CH_2CH_2CH_2-$	Pyridine and α-picoline	135–145	14	80		Dark green	250[d]	41.2	5.2[h]	
								41.7	5.2	

[a] Solvents used = pyridine, α-picoline, 5-ethyl-2-methylpyridine, piperidine, ethyl acetate, nitromethane and Triton B. [b] The only product isolated after a short, vigorous reaction was a dark brown solid which was not the desired pink nitroso-pyrimidine. [c] Decomposition. [d] Decomposed without melting. [e] Known compounds. [f] Formed by heating guanidine carbonate with the potassium salt of isonitrosomalononitriile. [g] Formed by direct condensation of the potassium salt of isonitrosomalononitrile with urea. [h] Monohydrate. [i] Method A, heating in pyridine or substituted pyridines; method B, refluxing for 2 hours in ethanolic sodium ethoxide, followed by acidification with acetic acid.

Attempts to bring about these thermal isomerizations in aqueous or alcoholic solution under the influence of basic catalysts were largely unsuccessful. Aqueous solutions of Triton B at room

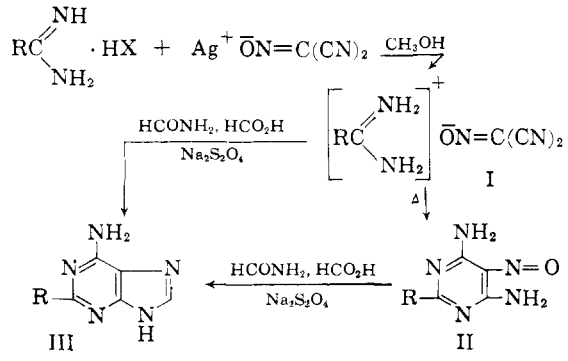


Fig. 1.

temperature or at 70°, or aqueous sodium hydroxide solutions, led only to decomposition of the amidine. Sodium ethoxide in ethanol effected cyclization in some cases, but the yields of the resulting 4,6-diamino-5-nitrosopyrimidines were lower. This latter procedure was advantageous only in the preparation of 2-hydroxy-4,6-diamino-5-nitrosopyrimidine; although urea does not condense with isonitrosomalononitrile alone because of its low basicity, a condensation of urea with the potassium salt of isonitrosomalononitrile in sodium ethoxide solution yielded the desired pyrimidine in 60% yield. 2-Aminopyridine and formamidine formed salts with isonitrosomalononitrile, but attempts to cyclize them under any of the above conditions led only to extensive decomposition. Isolation of the intermediate amidine salt was not always necessary. For example, heating the potassium salt of isonitrosomalononitrile with guanidine carbonate in dimethylformamide gave 2,4,6-triamino-5-nitrosopyrimidine (II, R = $-NH_2$) directly in 88% yield.

Heating these 2-substituted 4,6-diamino-5-nitrosopyrimidines with a mixture of formamide, formic acid and sodium hydrosulfite, according to the procedure of Bredereck and Edenhofer,[42] yielded 2-substituted adenines (III) in high yield. The purines prepared in this manner are listed in

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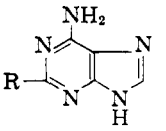
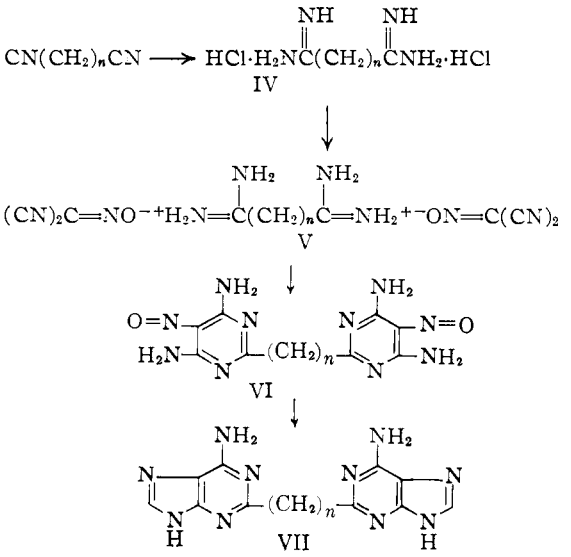
TABLE III



R	M.p., °C.	Yield, %[a] Meth. 1	Meth. 2	Recrystn. solvent	U.v. absorption pH 1 max, mμ	log ε	Analyses, % Calcd. C	H	N	Found C	H	N
CH_3–	>360	80		Water[i]	266[c,d]	4.11		[b]				
C_2H_5–	304–305	82		Water[i]	266	4.11	51.5	5.6		51.6	6.0	
CH_3S–	295–296	89		Water[i]	221	4.02						
					246	4.10	39.8	3.9	38.6	40.0	3.9	38.3
					284	4.02						
$C_6H_5CH_2$–	260–261	45		Water[i]	263	3.79	64.0	4.9	31.1	63.0	4.8	31.1
					355	3.11				65.4	4.9	
C_6H_5–	319–320	92	80	Water[i]	250	4.12	62.6	4.3		62.7	4.3	
					273	4.19						
p-$CH_3OC_6H_4$–	304–305	100	65	Water[i]	272	4.23	59.7	4.6	29.0	59.9	4.5	28.8
					300	4.28						
p-$H_2NC_6H_4$–	342–344	83	77	Ethanol–water[i]	238	4.17	58.4	4.5	37.1	58.1	4.6	37.4
					270	4.16						
H_2N–	302	89	71		241[d,e,f]	3.98						
					282	4.00		[b]				
HO–	>360	91			230[e,f]	3.69						
					284	4.03		[b]				
β-Pyridyl	319–321	98	87	Water[i]	239	4.26	56.6	3.8	39.6	56.2	4.1	39.9
					263	4.16						
$-CH_2-$	325[g]	66		Dil. HCl	224	4.37						
					283	4.07	36.4	3.6	38.6[h]	36.5	4.1	38.7
					305	4.03						
					380	4.00						
$-CH_2CH_2CH_2CH_2-$	268[g]	89		Methanol–water	262	4.26	46.7	5.6	38.8[i]	47.0	5.2	38.8
										46.2	5.6	

[a] Method 1, cyclized from the corresponding nitrosopyrimidine in formamide containing sodium hydrosulfite and formic acid; method 2, cyclized from the corresponding amidine salt of isonitrosomalononitrile in formamide with sodium hydrosulfite and formic acid. [b] Known compounds. [c] J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 318 (1944). [d] R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, THIS JOURNAL, **75**, 263, 6359 (1953). [e] S. F. Mason, *J. Chem. Soc.*, 2071 (1954). [f] At *p*H = 1.9–2.0. [g] Decomposed without melting. [h] Dihydrochloride-hemihydrate. [i] Dihydrate. [j] Followed by sublimation.

Table III (method 1). Thus, 2-methyladenine was prepared in 74% over-all yield from acetamidine hydrochloride, 2,6-diaminopurine in 70% over-all yield from guanidine carbonate, and 2-phenyladenine in 81% over-all yield from benzamidine hydrochloride. Several novel types of



adenine derivatives are uniquely available by this method. For example, conversion of adiponitrile to the corresponding diamidine dihydrochloride (IV, $n=4$), followed by reaction in methanol with two moles of the silver salt of isonitrosomalononitrile, gave the double salt V ($n=4$). Thermal isomerization of this salt in 2-picoline then yielded α,δ-bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-butane (VI, $n=4$), which was cyclized directly with formamide, formic acid and sodium hydrosulfite to α,δ-bis-(2-adenyl)-butane (VII, $n=4$). The corresponding bis-(2-adenyl)-methane(VII, $n=1$) was similarly prepared starting with malononitrile, but an attempt to make the corresponding derivative of ethane (VII, n = 2) was unsuccessful, since the reaction of succindiamidine dihydrochloride with the silver salt of isonitrosomalononitrile yielded the succinimidine rather than the succindiamidine salt of isonitrosomalononitrile.

Convenient new synthetic routes to adenine and isoguanine resulted from appropriate modifications of the above procedures. Methyl isothiourea hydroiodide and the silver salt of isonitrosomalononitrile condensed in methanol solution to give the methyl isothiourea salt of isonitrosomalononitrile (I, R = $-SCH_3$). Heating this salt in pyridine gave 2-methylthio-4,6-diamino-5-nitrosopyrimidine

(II, R = $-SCH_3$) which was converted directly to 2-methylmercaptoadenine (III, R = $-SCH_3$) with formamide, formic acid and sodium hydrosulfite. Desulfurization with Raney nickel then yielded adenine (III, R = –H), while treatment with hydrogen peroxide in ethanol solution gave isoguanine (III, R = –OH). This latter conversion has previously been carried out in two steps by oxidation of III (R = $-SCH_3$) to 2-methylsulfonyladenine (III, R = $-SO_2CH_3$) with chlorine, followed by alkaline hydrolysis.[40]

An important modification in the above procedure makes possible the direct synthesis of 2-substituted adenines *in one step* from the amidine salts of isonitrosomalononitrile. Since formamide serves both as solvent and as reactant in the conversion of the 4,6-diamino-5-nitrosopyrimidines to adenines, it was apparent that the use of formamide as a solvent for the thermal cyclization of the amidine salts of isonitrosomalononitrile to the pyrimidines would permit the entire reaction sequence to be carried out in a single step. This was found to be the case in many instances, and the purines prepared in this manner are listed in Table III (method 2). In a further simplification, 2,6-diaminopurine (III, R = $-NH_2$) was prepared directly in 71% yield by heating a mixture of guanidine carbonate, the potassium salt of isonitrosomalononitrile, formamide, formic acid and sodium hydrosulfite.

Table IV records R_f values, determined in various solvents by the descending method and at

TABLE IV

R_f VALUES OF 2-SUBSTITUTED ADENINES

R	1-Butanol–5 *N* acetic acid, 2:1	3% NH_4Cl	4% sodium citrate	1-Propanol–1% NH_4OH, 2:1	Spot[a]
H			0.35	0.67	A
CH_3–			.36	.74	A
C_2H_5–			.42	.82	A
CH_3S–				.75	A
$C_6H_5CH_2$–	0.85	0.35	.22	.94	F
C_6H_5–	.55			.84	F
p-$CH_3OC_6H_4$–				.75	F
p-$H_2NC_6H_4$–	.25			.54	FF
H_2N–			.19	.49	A
HO–			.40	.43	A
β-Pyridyl				.77	F
$-CH_2-$	.21	.13	.16		F
$-CH_2CH_2CH_2CH_2-$	.26	.25	.22		A

[a] A = absorbent under ultraviolet light, F = fluorescent under ultraviolet light, FF = very strongly fluorescent under ultraviolet light.

20°, for the 2-substituted adenines prepared in this study. It will be noted that all derivatives carrying a 2-aryl or benzyl grouping, including bis-(2-adenyl)-methane (VII, n = 1) are *fluorescent* under ultraviolet light. In order to exclude the possibility that the observed fluorescence might have been an artifact due to a small amount of impurity arising from the use of formamide in the cyclization step (formamide alone fluoresces when heated), a sample of 2-phenyladenine was prepared independently by the reaction of ethyl orthoformate and acetic anhydride on 2-phenyl-4,5,6-triaminopyrimidine. The product of this reaction was identical in every respect, including fluorescence, with the product prepared by the formamide-sodium hydrosulfite route.

This observation may be of significance in natural product work, for the only previously recorded fluorescent purines are 2-monosubstituted derivatives.[43] It should be re-emphasized that high-nitrogen content, naturally-occurring heterocycles which are fluorescent need not be pteridines.

Experimental[44]

Silver Salt of Isonitrosomalononitrile was prepared by the method of Longo[45]; the yield was quantitative. The product was dried in a vacuum desiccator over phosphorus pentoxide and was stored in the dark.

Potassium Salt of Isonitrosomalononitrile.—A solution of 16 g. of potassium iodide in 150 ml. of methanol was added to a suspension of 20 g. of the silver salt of isonitrosomalononitrile in 100 ml. of methanol. The reaction mixture was stirred for one hour, filtered to remove silver iodide and the filtrate evaporated to dryness under reduced pressure. Recrystallization of the resulting solid from ethanol yielded the potassium salt of isonitrosomalononitrile as light yellow platelets, m.p. 211–212° dec. The yield was quantitative.

Anal. Calcd. for C_3H_3NO: N, 31.6. Found: N, 31.6.

Preparation of Amidine Salts of Isonitrosomalononitrile. General Procedure.—To a stirred solution of 0.1 mole of the amidine hydrohalide in 100 ml. of methanol was added, in small portions, 0.11 mole of finely divided silver salt of isonitrosomalononitrile. Cooling was usually not necessary. Stirring was continued for one hour after addition was complete. By this time, the yellow silver salt had disappeared and a heavy precipitate of white silver halide had separated. The reaction mixture was filtered, and the yellow filtrate was evaporated at room temperature under reduced pressure to dryness. The yield of crude product was almost quantitative. Recrystallization from ethyl acetate yielded the pure amidine salts of isonitrosomalononitrile usually in the form of light yellow needles. These salts are readily soluble in ethanol, methanol, acetone and water.

Cyclization of Amidine Salts of Isonitrosomalononitrile to 2-Substituted 4,6-Diamino-5-nitrosopyrimidines. General Procedure. Method A.—A mixture of 2 g. of the amidine salt of isonitrosomalononitrile in 10 ml. of solvent was heated under the conditions specified in Table II. The salt rapidly dissolved and the color of the mixture gradually turned green. The reaction mixture was then cooled and diluted with ethanol (when 5-ethyl-2-methylpyridine was used as a solvent) or water (when other solvents were employed). Filtration after standing yielded the 2-substituted 4,6-diamino-5-nitrosopyrimidines. With the exception of 2,4,6-triamino-5-nitrosopyrimidine, which is pink, and 2-hydroxy-4,6-diamino-5-nitrosopyrimidine, which is violet-red, all other 5-nitrosopyrimidines listed in Table II are green. Most of them were highly crystalline solids with a bright metallic luster.

Method B.—A mixture of 0.01 mole of the amidine salt of isonitrosomalononitrile in 20 ml. of ethanol containing 0.012 mole of sodium was heated under reflux for 2 hours. The reaction mixture was then cooled and acidified with the calculated amount of dilute acetic acid. The crude nitrosopyrimidine which immediately precipitated was collected by filtration and washed well with water.

Cyclization of 2-Substituted 4,6-diamino-5-nitrosopyrimidines to 2-Substituted Adenines. General Procedure.—To a suspension of 0.05 mole of the 2-substituted 4,6-diamino-5-nitrosopyrimidine in a mixture of 50 ml. of formamide and 8 ml. of 98% formic acid was added, with shaking and in very small portions, 0.0006–0.02 mole of sodium dithionite dihydrate at 100–110°. Addition was complete within 10–15 minutes and a brown solution was obtained. The temperature was maintained at 110° for another 10 minutes

(43) A. Albert, in "Fortschritte der Chemie Organischer Naturstoffe," Vol. 11, ed. by L. Zechmeister, Springer Verlag, Vienna, 1954, p. 350.

(44) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J., and to Drs. G. Weiler and F. B. Strauss, Oxford, England. All melting points are corrected.

(45) G. Longo, *Gazz. chim. ital.*, **61**, 575 (1931).

and then raised to 190–200°. The reaction mixture was maintained at this temperature for 30 minutes and was then cooled and poured into 300 ml. of water. The light yellow solid which separated was collected by filtration and washed well with water. In the case of 2-methyl- and 2-ethyladenine, the crude reaction mixture was poured into 300 ml. of hot water, which was then heated to boiling, treated with charcoal, filtered, and the yellow filtrate evaporated to a small volume under reduced pressure and diluted with ethanol. The light yellow crystalline product which formed after cooling was then collected by filtration.

One-step Conversion of Amidine Salts of Isonitrosomalononitrile to 2-Substituted Adenines. 2-β-Pyridyladenine.—A solution of 4 g. of the nicotinamidine salt of isonitrosomalononitrile in 25 ml. of formamide was heated to 110° for 30 minutes. During the heating the color of the solution changed from yellow through light green to deep green. During the final stages of the heating, a green solid separated from the hot solution. To this mixture was added 5 ml. of 98% formic acid followed by portionwise addition, with shaking, of 1.2 g. of sodium dithionite dihydrate. The brown solution was kept at 110° for 20 minutes and then heated at 190–200° for 30 minutes. The light brown reaction mixture was cooled and diluted with 200 ml. of water. The crude product was collected by filtration and recrystallized from water; yield 3.4 g. (86.6%), m.p. 319–321° dec.

One-step Conversion of Potassium Salt of Isonitrosomalononitrile to 2-Substituted Adenines. 2,6-Diaminopurine.—A mixture of 0.5 g. of the potassium salt of isonitrosomalononitrile and 0.6 g. of guanidine carbonate in 5 ml. of formamide was heated at 130° for 30 minutes to give a deep red solution. To this solution, cooled to 100–110°, was added 0.16 g. of sodium dithionite dihydrate and 1 ml. of 98% formic acid. The temperature was then raised to 200° for 30 minutes. The reaction mixture was cooled, diluted with 100 ml. of water and filtered to yield 0.4 g. (71%) of a light tan solid. This material was identical with the product obtained by the above-described procedure from 2,4,6-triamino-5-nitrosopyriminidine, and with an authentic sample of 2,6-diaminopurine, as judged by a comparison of ultraviolet absorption spectra and by paper chromatography.

Malondiamidine Salt of Isonitrosomalononitrile (V, n = 1).—To a stirred solution of 18 g. of malondiamidine dihydrochloride in 450 ml. of methanol and 50 ml. of water was added in small portions 50 g. of finely powdered silver salt of isonitrosomalononitrile. The mixture was stirred for 3 hours and then filtered from the precipitated silver chloride. The yellow filtrate was concentrated to dryness under reduced pressure at room temperature and the yellow residue washed with ether to give 25.6 g. (88.4%) m.p. 130–133° dec. The crude product was purified by recrystallization from methanol–ether (m.p. 144–145° dec.) and finally from ethyl acetate–methanol to yield light yellow needles, m.p. 150–151° dec.

Bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-methane (VI, n = 1).—A solution of 2 g. of the malondiamidine salt of isonitrosomalononitrile in 10 ml. of 5-ethyl-2-methylpyridine was heated at 135° for 15 minutes, whereupon a dark green solid separated from the hot solution. The mixture was then held at 120–130° for 4 hours, cooled, and diluted with 100 ml. of petroleum ether. After standing overnight, it was filtered and the collected green solid washed with aqueous ethanol to give 1.85 g. (92.5%). Recrystallization from water yielded a crystalline green solid which decomposed without melting at 287–289°.

Bis-(2-adenyl)-methane Dihydrochloride (VII, n = 1).—To a mixture of 3.1 g. of bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-methane, 5 ml. of formic acid and 25 ml. of formamide at 100–110° was added slowly, and with stirring, 1.5 g. of sodium dithionite dihydrate. After addition was complete, the reaction mixture was held at 110° for 30 minutes and then heated at 190–200° for 30 minutes. It was then cooled and poured into 200 ml. of water. The precipitated brown solid was collected by filtration, washed with water and dissolved in aqueous methanol. Decolorization of this solution, followed by evaporation of the yellow filtrate to dryness, yielded a residue which was redissolved in 20 ml. of ethanol. Addition of dilute hydrochloric acid then precipitated the dihydrochloride of bis-(2-adenyl)-methane as a yellow microcrystalline solid which decomposed at 325° without melting; yield 2.6 g. (66%).

Adipodiamidine Dihydrochloride (IV, n = 4).—A solution of 55 g. (0.5 mole) of adiponitrile in 50 g. (1.08 mole) of absolute ethanol and 200 ml. of dioxane cooled to 0° was saturated with dry hydrogen chloride. A white precipitate formed after 1.5 hours. The mixture was allowed to stand at 0° for 8 hours and then at room temperature for 7 days, and the white crystalline diethyl iminoadipate dihydrochloride was collected by filtration and washed with ether. It was resuspended in a large volume of ether, stirred and filtered; yield 131 g. (95.5%).

Fifty grams of diethyl iminoadipate dihydrochloride was added with shaking to 800 ml. of 20% ethanolic ammonia. The mixture, which became cloudy after 1 hour, was allowed to stand at room temperature with occasional shaking for 48 hours, and was then filtered to give a white solid, m.p. 293° dec., yield 33 g. (83.5%).

Adipodiamidine Salt of Isonitrosomalononitrile (V, n = 4).—To a partial solution of 22 g. of adipodiamidine dihydrochloride in 1 l. of methanol and 50 ml. of water was added, with stirring, 42 g. of finely divided silver salt of isonitrosomalononitrile. Stirring was continued for 1.5 hours, and the silver chloride was then removed by filtration. Concentration of the filtrate followed by addition of ether to the concentrate caused the separation of 31 g. (94%) of yellow needles, m.p. 179–180° dec. (with prior darkening at 144°). Recrystallization from ethyl acetate and methanol (2:1) did not change the melting point.

α,δ-Bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-butane (VI, n = 4).—A partial solution of 5 g. of the adipodiamidine salt of isonitrosomalononitrile in 25 ml. of 2-picoline and 5 ml. of pyridine was heated at 145° (oil-bath temperature) for 2 hours, and then at 135° for 12 hours. The deep green reaction solution was poured into 400 ml. of water with stirring, and the solid which separated was collected by filtration and washed with water to give 4.0 g. (80%). Recrystallization of this material from aqueous ethanol gave a dark green solid which decomposed at 250° without melting.

α,δ-Bis-(2-adenyl)-butane (VII ,n = 4).—To a mixture of 20 ml. of formamide and 4 ml. of 98% formic acid was added 1.3 g. of finely powdered α,δ-bis-(4,6-diamino-5-nitroso-2-pyrimidyl)-butane. The mixture was heated to 100–110° and 0.5 g. of sodium dithionite dihydrate was added in small portions with stirring. After the addition was complete, the brown solution was maintained at 100–110° for 15 minutes and then at 190–200° for 1 hour. The reaction mixture was then diluted with 200 ml. of water and cooled overnight. Filtration yielded a dark solid which was recrystallized from ethanol and finally water to give 1.25 g. (88.7%) of a yellow powder which decomposed at 268° without melting.

Succinimidine Salt of Isonitrosomalononitrile.—To a stirred solution of 19 g. of succindiamidine dihydrochloride[46] in 800 ml. of methanol was added 50 g. of finely powdered silver salt of isonitrosomalononitrile. The product was isolated as described previously, and was recrystallized from ethyl acetate and methanol (2:1) to give 19 g. of a light yellow crystalline solid, m.p. 171° dec. Microanalysis indicated that the product was the succinimidine salt of isonitrosomalononitrile and not the expected succindiamidine salt of isonitrosomalononitrile.

S-Methylisothiouronium Salt of Isonitrosomalononitrile (I, R = $-SCH_3$).—To a finely divided suspension of 26 g. of the silver salt of isonitrosomalononitrile in 100 ml. of methanol was added in small portions and with mechanical stirring, 25 g. of S-methylisothiourea hydroiodide.[47] A heavy precipitate of silver iodide formed immediately. The mixture was stirred for one hour, filtered and the light yellow filtrate evaporated under reduced pressure at room temperature to give 21 g. (quantitative yield) of light yellow crystals. The product was recrystallized from ethyl acetate; m.p. 125° dec.

2-Methylthio-4,6-diamino-5-nitrosopyrimidine (II, R = $-SCH_3$).—A solution of 2 g. of the S-methylisothiouronium salt of isonitrosomalononitrile in 10 ml. of dry pyridine was heated under reflux for 30 minutes. The light yellow solution rapidly turned dark green. The reaction mixture was poured with stirring into 200 ml. of water. On standing, a green crystalline solid separated which was collected by

(46) A. Pinner, *Ber.*, **16**, 352 (1883).

(47) H. L. Wheeler and H. F. Marriam, *Am. Chem. J.*, **29**, 478 (1903).

filtration, washed with water and dried at 70° *in vacuo* to give 1.5 g. (75%) of green platelets exhibiting a bright metallic luster. The infrared absorption spectrum of this material was identical with that of an authentic sample of 2-methylthio-4,6-diamino-5-nitrosopyrimidine prepared by nitrosation of 2-methylthio-4,6-diaminopyrimidine.

2-Methylthioadenine (III, R = $-SCH_3$).—To a suspension of 6.0 g. of 2-methylthio-4,6-diamino-5-nitrosopyrimidine in a mixture of 8 ml. of 98% formic acid and 60 ml. of formamide warmed to 100–110°, was added slowly, in small portions and with stirring, 2.5 g. of sodium dithionite dihydrate. The addition required 15 minutes, during which time the green suspension had changed to a brown solution. The reaction mixture was then heated for 30 minutes at 190–200°, and the clear solution poured with stirring into 500 ml. of water. A yellow precipitate formed gradually on standing. It was filtered, washed with cold water and dried to give a yellow solid which was recrystallized from absolute ethanol and then from water to give 5.2 g. (88.5%) of a light yellow powder, m.p. 295–296° dec. This compound has been reported[32] to melt at 290°.

The product was dried *in vacuo* over phosphorus pentoxide for 8 hours at 130° to give a hemi-hydrate.

Anal. Calcd. for $C_6H_7N_5S \cdot {}^1/_2H_2O$: C, 37.9; H, 4.2; N, 36.9. Found: C, 38.1; H, 4.2; N, 37.3.

Anhydrous material was readily prepared by sublimation at 230° (0.05 mm.). Paper chromatography of the compound before and after sublimation showed only one spot.

Direct conversion of the S-methylisothiouronium salt of isonitrosomalononitrile in formamide, formic acid and sodium dithionite, gave a very low yield of product and the simultaneous formation of isoguanine and unidentified products. This latter procedure is thus unsatisfactory in this instance.

Adenine (III, R = -H).—To a suspension of 2.05 g. of 2-methylthioadenine in 400 ml. of water was added freshly prepared Raney nickel saturated with hydrogen (14 g. in 200 ml. of water). The mixture was heated under reflux with vigorous stirring for 16 hours, the hot suspension filtered and the residue extracted with hot water. The combined filtrates were evaporated to 200 ml. and cooled. The white solid which separated was collected by filtration and recrystallized from water to give 0.8 g. (51%) of adenine, identified by comparison of its ultraviolet absorption spectrum and paper chromatographic behavior with an authentic sample.

Isoguanine (III, R = -OH).—To a solution of 2 g. of 2-methylthioadenine in 50 ml. of absolute ethanol was added 25 ml. of 30% hydrogen peroxide. A white precipitate gradually separated. The mixture was warmed on a water-bath, whereupon vigorous boiling ensued and the precipitated solid slowly redissolved. The clear solution was allowed to reflux overnight until the evolution of gas had ceased. The reaction solution was allowed to stand for two days, and was then filtered to give a light yellow solid. This product was purified by dissolution in dilute potassium hydroxide, decolorization with charcoal and reprecipitation with acetic acid; yield 1.4 g. (94%) of colorless isoguanine, identified by comparison of its ultraviolet absorption spectrum and paper chromatographic behavior with an authentic sample.

2-Phenyladenine (III, R = $-C_6H_5$).—To a suspension of 28 g. of 2-phenyl-4,6-diamino-5-nitrosopyrimidine in 1200 ml. of boiling water was added, in small portions, 100 g. of sodium dithionite dihydrate. After addition was complete, the mixture was boiled for 2 minutes and filtered. The light yellow filtrate was treated cautiously with 200 ml. of 18 *N* sulfuric acid (in the hood!), charcoal added and the mixture filtered. The filtrate upon cooling deposited the sulfate salt of 2-phenyl-4,5,6-triaminopyrimidine in the form of white needles; yield 19 g.

A mixture of 6 g. of the above sulfate salt and 90 ml. of a 1:1 molar mixture of ethyl orthoformate and acetic anhydride (which had been allowed to stand for one week prior to use) was heated under reflux for 4 hours. Cooling caused the separation of a light yellow solid which was collected by filtration and dissolved in dilute potassium hydroxide. Acidification with dilute acetic acid yielded a colorless solid which was recrystallized from water to give 2.4 g. of 2-phenyladenine, m.p. 320–321°, identical in every respect with the samples of 2-phenyladenine prepared directly from 2-phenyl-4,6-diamino-5-nitrosopyrimidine or from the benzamidine salt of isonitrosomalononitrile (see Table III).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Synthesis of 2-Aminonicotinamides by Raney Nickel Cleavage of Pyrazolo[3 4-b]-pyridines[1]

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A new synthesis of 2-aminonicotinamides is described which involves the reductive ring cleavage with Raney nickel of 3-hydroxy- and 3-ketopyrazolo[3,4-b]pyridines. The reaction is used as a means of establishing the structure of pyrazolopyridines formed by the condensation of 3-amino-5-pyrazolones with unsymmetrical 1,3-dicarbonyl compounds.

A recent publication from this Laboratory described the reductive ring cleavage of a number of 3-hydroxy-1-pyrazolo[b]pyrazines to yield 2-aminopyrazine-3-carboxamides.[2] The present paper is concerned with an extension of this work in which a new synthetic route to 2-aminonicotinamides by reductive ring cleavage of pyrazolo[3,4-b]-pyridines is described.

Several synthetic routes to derivatives of 2-aminonicotinic acid are known. The parent amino acid may be prepared by the Hofmann reaction on quinolinic acid imide,[3] ethyl 2-carboxamidonicotinate,[4] 2-carboxamidonicotinic acid[5–8] or quinolinamide,[9] by alkaline cleavage of 2,4-dihydroxypyrimido[4,5-b]pyridine,[9] strong acid hydrolysis of 2-aminonicotinonitrile[10] or by the action of ammonium hydroxide on 2-chloronicotinonitrile or 2-chloronicotinamide.[10] 2-Aminonicotinamide has been prepared by the action of alkaline hydrogen peroxide on 2-aminonicotinonitrile,[10] by the action of sodium amide on nicotinamide[11] and by the

(1) This investigation was supported by a grant from the American Cancer Society.

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