After the red glass had been dissolved in warm methanol (500 cc.), the first crystalline fraction (6.06 g., 0.0112 mole, 8%), m.p. 216–220°, was salmon-colored and corresponded to the higher melting crystalline fraction obtained in part (a). Four recrystallizations from methanol, with charcoal, yielded a 1:3 adduct (XIX) of indole and dimethyl acetylenedicarboxylate as small white crystals, m.p. 229–230°.

Anal. Calcd. for $C_{26}H_{25}NO_{12}$ (543.47): C, 57.46; H, 4.64; N, 2.58. Found: mol. wt. (Rast) 514, in 1,2-dibromoethane 453 ± 90 (because of low solubility)[25]; C, 57.75; H, 4.94; N, 2.64.

An Ehrlich test for an open 2- or 3-position of the indole nucleus was negative.

The second crystalline fraction (0.63 g., 0.00084 mole, 2%), m.p. 241.5–242°, was pale yellow in color. Recrystallization from methanol, with charcoal, yielded a 2:1 adduct (XX) of indole and dimethyl acetylenedicarboxylate as pale yellow crystals, m.p. 242–243°.

Anal. Calcd. for $C_{22}H_{20}N_2O_4$ (376.40): C, 70.20; H, 5.36; N, 7.44. Found: mol. wt. in 1,2-dibromoethane, 394, 386, average 390; C, 70.34; H, 5.41; N, 7.44.

An Ehrlich test for an open 2- or 3-position of an indole nucleus was positive (red color).

The third and fifth crystalline fractions (26.43 g., 0.0662 mole, 33%), m.p. 150–178°, were pale yellowish-green in color. Four or five recrystallizations from methanol, with charcoal, gave tetramethyl carbazole-1,2,3,4-tetracarboxylate, m.p. and mixed m.p. with the sample from part a, 182–182.5°.

The fourth, sixth and seventh crystalline fractions (4.79 g., 0.00881 mole, 7%), m.p. 80–172°, were bright yellowish-green in color. Three or four recrystallizations from methanol, with charcoal, yielded another 1:3 adduct (XVIII) of indole and dimethyl acetylenedicarboxylate as bright greenish-yellow crystals, m.p. 172–173°.

Anal. Calcd. for $C_{26}H_{25}NO_{12}$ (543.47): C, 57.46; H, 4.64; N, 2.58. Found: mol. wt. (Rast) 537, in 1,2-dibromoethane 582[25]; C, 57.46; H, 4.85; N, 2.72.

An Ehrlich test for an open 2- or 3-position of the indole nucleus was negative.

Dimethyl 3,4-Dicyano-9-methylcarbazole-1,2-dicarboxylate (Xb).—A mixture of 1-methyl-3-tricyanovinylindole (1.49 g., 0.00642 mole) and dimethyl acetylenedicarboxylate (10 cc., 0.081 mole) was refluxed at 230–235° for 20 minutes. After the dark tarry mixture had cooled to room temperature, benzene was added. Filtration and washing with benzene left a yellow solid (0.99 g., 0.00285 mole, 44%), m.p. 225–227°. Vacuum sublimation, followed by recrystallization from methanol yielded dimethyl 3,4-dicyano-9-methylcarbazole-1,2-dicarboxylate as glistening golden needles, m.p. 234–235°. The compound fluoresces with a bright yellow-green color.

Anal. Calcd. for $C_{19}H_{13}N_3O_4$ (347.32): C, 65.70; H, 3.77; N, 12.10. Found: C, 65.58; H, 3.94; N, 12.05.

Hydrolysis and Decarboxylation of Dimethyl 3,4-Dicyano-9-methylcarbazole-1,2-dicarboxylate (Xb).—A mixture of dimethyl 3,4-dicyano-9-methylcarbazole-1,2-dicarboxylate (2.00 g., 0.00576 mole) and a solution of methanolic 25% potassium hydroxide (10 cc.) and water (3 cc.) was refluxed for 20 hours on a steam-bath. The potassium salt of 9-methylcarbazole-1,2,3,4-tetracarboxylic acid precipitated in quantitative yield. This salt then was divided into two equal portions.

To the first portion moist soda-lime was added and the mixture was decarboxylated as previously described in the degradation of dimethyl 3,4-dicyanocarbazole-1,2-dicarboxylate, yielding colorless platelets (0.20 g., 0.00120 mole, 42%), m.p. 236–238° in a sealed capillary. The mixed m.p. with an authentic sample of carbazole was undepressed and the infrared spectra of the two samples were identical in CS_2, $CHCl_3$ and Nujol.

The second portion of the potassium salt was acidified to *p*H 1–2 with concentrated hydrochloric acid. Powdered soda-lime was added to the acid solution and the resulting pasty mixture was decarboxylated as previously described, yielding carbazole (0.15 g., 0.00090 mole, 31%), m.p. 234–236° in a sealed capillary.

Tetramethyl 9-Methylcarbazole-1,2,3,4-tetracarboxylate (XIb).—A mixture of dimethyl 3,4-dicyano-9-methylcarbazole-1,2-dicarboxylate (1.68 g., 0.00484 mole) and a solution of methanolic 25% potassium hydroxide (40 cc.) and water (5 cc.) was refluxed for 20 hours on a steam-bath. The resulting homogeneous solution was acidified to *p*H 1–2 with 2.4 *N* hydrochloric acid. The resulting solution was extracted with ether (3 × 20 cc.) and the ether extracts were cooled to 0°. A solution of diazomethane[23] (~1.3–1.4 g., ~0.031–0.033 mole, from 5 g. of N-nitroso-N-methylurea) in ether was added slowly to the combined ether extracts. After the solution had stood at room temperature for 2.5 hours the ether was evaporated and the pale yellow residual oil was dissolved in hot methanol–water. Cooling the solution produced a yellow solid (0.80 g., 0.00194 mole, 40%), m.p. 100–110°. Four recrystallizations from methanol, once with charcoal, yielded tetramethyl 9-methylcarbazole-1,2,3,4-tetracarboxylate as pale yellow crystals, having a pale green fluorescence, m.p. 124–125°.

Anal. Calcd. for $C_{21}H_{19}NO_8$ (413.37): C, 61.01; H, 4.63; N, 3.39. Found: C, 60.98; H, 4.59; N, 3.44.

MINNEAPOLIS 14, MINN.

(25) Determined by Donald C. Johnson.

[CONTRIBUTION FROM THE SCIENTIFIC LABORATORY, FORD MOTOR CO.]

Condensations with 1,2-Hydrazinedicarboxamidine. 2,2′-Hydrazopyrimidines

BY ALFRED KREUTZBERGER[1]

RECEIVED MARCH 5, 1959

1,2-Hydrazinedicarboxamidine (I) reacts with β-diketones (II), giving rise to 2,2′-hydrazopyrimidines (III). These were characterized by the corresponding N,N′-diacetyl-2,2′-hydrazopyrimidines (IV). By condensation of I with either diethyl 1,3-dicarbethoxyglutaconate (V) or diethyl ethoxymethylenemalonate (VII), 4,4′-dihydroxy-5,5′-dicarbethoxy-2,2′-hydrazopyrimidine (VI) was obtained. With ethyl acetoacetate and I, an acyclic semi-condensation product (IX) resulted. Reaction of I with ethyl cyanoacetate and diethyl malonate led to the formation of 1,2-hydrazinedicarboxamidine dicyanoacetate (X) and 1,2-hydrazinedicarboxamidine malonate (XI), respectively.

One of the most important properties of amidines is their ability to undergo condensation reactions to give cyclic amidines, *e.g.*, imidazoles and pyrimidines. Application of this principle to 1,2-hydrazinedicarboxamidine (I) should lead to formation of the corresponding heterocyclic hydrazo compounds with a lesser chance for hydrazoimidazoles because of side reactions known to occur in this procedure. As a matter of fact, no hydrazoimidazole could be obtained by the reaction of I with α-halo-ketones using the method of Kunckell.[2]

In contrast to this, the cyclization of amidines with a host of bifunctional compounds is known as the commonest pyrimidine synthesis. The interaction of an amidine with a β-diketone (II), to I, has

(1) This work was presented at the 134th National Meeting of the American Chemical Society, Chicago, Ill., September, 1958.

(2) F. Kunckell, *Ber.*, **34**, 647 (1901).

TABLE I

SYNTHESIS OF 2,2′-HYDRAZOPYRIMIDINES (III) FROM 1,2-HYDRAZINEDICARBOXAMIDINE (I)

β-Diketone II applied R	R′	R″	Reacn. product III R	R′	R″	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
CH_3	CH_3	H (IIa)	CH_3	CH_3	H (IIIa)	69.6	224–225	$C_{12}H_{16}N_6$[a]	59.00	58.82	6.60	5.83	34.40	33.93
CH_3	C_2H_5	H (IIb)	CH_3	C_2H_5	H (IIIb)	71.4	129–130	$C_{14}H_{20}N_6$	61.74	61.63	7.40	7.56	30.86	30.74
C_2H_5	C_2H_5	H (IIc)	C_2H_5	C_2H_5	H (IIIc)	94.0	128–129	$C_{16}H_{24}N_6$	63.97	64.12	8.06	7.97	27.97	28.00
CH_3	CH_3	CH_3 (IId)	CH_3	CH_3	CH_3 (IIId)	68.5	264–265	$C_{14}H_{20}N_6$	61.74	61.54	7.40	7.44	30.86	30.93

[a] Molecular weight calcd. 244, found 251 (ebullioscopic in EtOH), 256 (ebullioscopic in C_6H_6).

TABLE II

PREPARATION OF N,N′-DIACETYL-2,2′-HYDRAZOPYRIMIDINES (IV) FROM 2,2′-HYDRAZOPYRIMIDINES (III) AND ACETIC ANHYDRIDE

III Applied	End product IV R	R′	R″	M.p., °C.	Empiric formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
IIIa	CH_3	CH_3	H (IVa)	167	$C_{16}H_{20}N_6O_2$	58.52	58.73	6.14	5.94	25.59	25.34
IIIb	CH_3	C_2H_5	H (IVb)	137–138	$C_{18}H_{24}N_6O_2$	60.65	60.77	6.79	7.01	23.58	23.41
IIIc	C_2H_5	C_2H_5	H (IVc)	111–112	$C_{20}H_{28}N_6O_2$	62.48	62.62	7.34	7.18	21.86	22.02
IIId	CH_3	CH_3	CH_3 (IVd)	209–210	$C_{18}H_{24}N_6O_2$	60.65	60.55	6.79	6.99	23.58	23.60

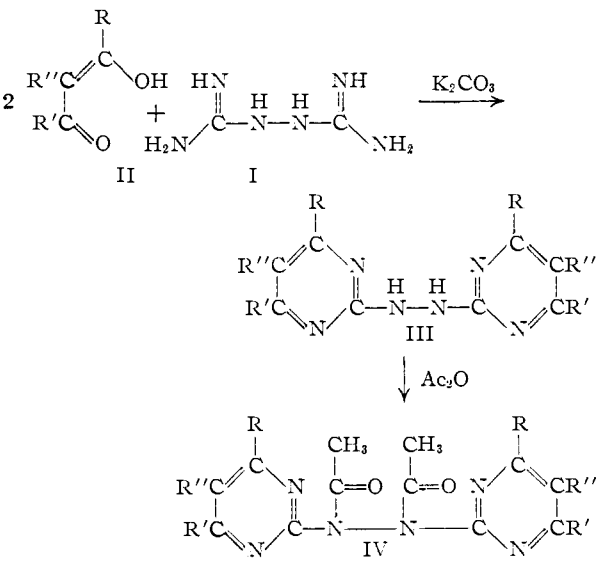
now led to the synthesis of a new class of compounds termed 2,2′-hydrazopyrimidines (III). The condensations were carried out according to Pinner's method[3] by allowing the reactants to stand for several days at room temperature in the presence of potassium carbonate. Thus with 2,4-pentanedione (IIa), 2,4-hexanedione (IIb), 3,5-heptanedione (IIc) and 3-methyl-2,4-pentanedione (IId) the corresponding 4,4′,6,6′-tetramethyl-(IIIa), 4,4′-dimethyl-6,6′-diethyl-(IIIb), 4,4′,6,6′-tetraethyl-(IIIc) and 4,4′,5,5′,6,6′-hexamethyl-2,2′-hydrazopyrimidines (IIId) were obtained. Pertinent information on these 2,2′-hydrazopyrimidines (III) is assembled in Table I. Generally, these compounds may be described as colorless stable substances which, contrary to the majority of hydrazo compounds, are not prone to autoxidation. However, they may be oxidized by various reagents to give colored solutions typical of azo compounds. All compounds III are insoluble in water and sodium hydroxide and soluble in hydrochloric acid and the common organic solvents.

The secondary amine function of the hydrazo group in III is manifested in the insolubility in alkali of the sulfonamides obtained in the Hinsberg test. The 2,2′-hydrazopyrimidines (III) prepared were characterized by the corresponding N,N′-diacetyl-2,2′-hydrazopyrimidines (IV) through the action of acetic anhydride on III. Table II lists the N,N′-diacetyl derivatives (IV) obtained.

The infrared spectra of III are consistent with the assigned structure. Thus the hydrazo group reveals itself in the NH stretching absorption between 3230 to 3270 cm.$^{-1}$ while a typical ring vibration is found in the absorption between 790–840 cm.$^{-1}$.

Under the same reaction conditions, no condensation was observed with 1,3-diphenyl-1,3-propanedione (II, R = R′ = C_6H_5, R″ = H). Also, sodioacetoacetaldehyde (II, R = CH_3, R′ = R″ = H) as prepared from acetone and ethyl formate with sodium ethoxide[4] did not undergo a condensation to the expected III derivative.[5]

In view of the fact that pyrimidine derivatives carrying functional substituents are almost invariably prepared by ring synthesis, such condensation types were also included in these investigations. As an example for the simultaneous introduction of the hydroxy and carbethoxy group into the pyrimidine ring, diethyl 1,3-dicarbethoxyglutaconate (V)[6] was found to condense with I leading to



IIa, IIIa and IVa, R = CH_3, R′ = CH_3, R″ = H
IIb, IIIb and IVb, R = CH_3, R′ = C_2H_5, R″ = H
IIc, IIIc and IVc, R = C_2H_5, R′ = C_2H_5, R″ = H
IId, IIId and IVd, R = CH_3, R′ = CH_3, R″ = CH_3

4,4′-dihydroxy-5,5′-dicarbethoxy-2,2′-hydrazopyrimidine (VI). In this synthesis, it is not necessary to start with the free ester V. Instead, one can use the sodium compound of V which is the precursor in the synthesis of V from diethyl malonate and chloroform,[7] and condense it with the equivalent of I without any additional condensing agent. The structure of VI could be proved through an independent synthesis by a more general method of making 4-hydroxy-5-carbethoxy pyrimidines.

(3) A. Pinner, *Ber.*, **26**, 2122 (1893).

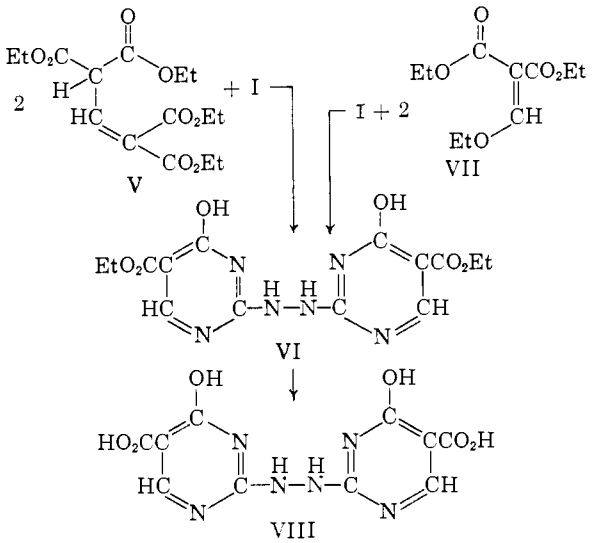
(4) L. Claisen and N. Stylos, *ibid.*, **21**, 1144 (1888).

(5) A. Pinner, *ibid.*, **26**, 2124 (1893), also found that sodioacetoacetaldehyde cannot be caused to react with benzamidine under pyrimidine formation. The opposite statement that these two agents do react to form a disubstituted pyrimidine [R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 397 (1944)] is most probably due to an error in the translation.

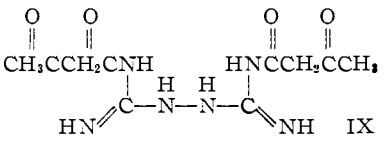
(6) S. Ruhemann, *Ber.*, **30**, 821 (1897).

(7) M. Conrad and M. Guthzeit, *ibid.*, **15**, 2842 (1882); C. K. Ingold and E. A. Perren, *J. Chem. Soc.*, **119**, 1591 (1921).

This method has been studied by Mitter, *et al.*,[8] and involves the condensation of amidines with ethoxymethylene derivatives of β-ketonic esters. Thus VI could also be obtained by the condensation of I with diethyl ethoxymethylenemalonate (VII). In this reaction, VI was found along with 4,4′-dihydroxy-5,5′-dicarboxy-2,2′-hydrazopyrimidine (VIII) whose formation apparently is due to the concurrent hydrolyzing action of sodium hydroxide which is commonly used as condensing agent in this reaction type.



Introduction of OH groups in the 2,2′-hydrazopyrimidine system was to be expected from the reaction of I with β-keto esters. By application of Pinner's reaction conditions[9] it seemed conceivable to synthesize 4,4′-dihydroxy-6,6′-dimethyl-2,2′-hydrazopyrimidine from I and ethyl acetoacetate. However, an acyclic semi-condensation product was obtained. Inasmuch as in the reaction of amidines with bifunctional carboxylic esters the ester group reacts usually first,[10] the reaction product of I and ethyl acetoacetate has been assigned the structure of 1,2-bis-(acetoacetguanyl)-hydrazine (IX).



Still another course of reaction was observed in the attempted condensation of I with ethyl cyanoacetate. Amidines are known to react with a variety of both active methylene groups and cyano esters forming either a new C=C double bond or a pyrimidine ring. Since formation of the latter is usually favored by alkali, sodium hydroxide was expected to bring about the condensation of I and ethyl cyanoacetate to 4,4′-diamino-6,6′-dihydroxy-2,2′-hydrazopyrimidine. However, the resulting crystalline product $C_8H_{14}N_8O_4$ did not contain a pyrimidine nucleus. Thus the infrared spectrum shows a typical C≡N absorption band at 2250 cm.$^{-1}$ indicating that the nitrile group of the ester is still intact. Furthermore, strong absorption bands at 1360, 1620 and 3120 cm.$^{-1}$ indicate salt formation between a carboxylic and an amino group. It may thus be concluded that the reaction product of I and ethyl cyanoacetate is simply the dicyanoacetate salt of 1,2-hydrazinedicarboxamidine $[C_2H_{10}N_6]^{++}\cdot 2N{\equiv}C{-}CH_2{-}COO^-$ (X). The correctness of this assignment is supported by a successful direct synthesis from I and cyanoacetic acid.

Essentially the same result was obtained when the condensation of I with diethyl malonate to give 4,4′,6,6′-tetrahydroxy-2,2′-hydrazopyrimidine was attempted. The crystalline product $C_5H_{12}N_6O_4$ behaves chemically and spectroscopically like a typical salt. The assigned structure of 1,2-hydrazinedicarboxamidine malonate $[C_2H_{10}N_6)^{++}\cdot H_2C(COO)_2^{--}$ (XI) was proved by a direct synthesis from I and malonic acid.

Acknowledgment.—The author gratefully acknowledges the technical assistance of Mr. Paul A. Kalter with the infrared measurements.

Experimental[11]

1,2-Hydrazinedicarboxamidine Dinitrate Monohydrate (I).—For the preparation of this compound, the procedure of Thiele[12] was employed with some modifications, *e.g.*, to start with aminoguanidine bicarbonate which is commercially available.

A 15-l. jar was charged with 1400 ml. of 70% HNO_3, 300 g. of aminoguanidine bicarbonate was introduced portionwise, and 1000 g. of crushed ice was added. While the contents were stirred and continuously kept between 0 to 10° by adding more ice from time to time, $KMnO_4$ solution saturated at room temperature was added in portions until the violet color became prevailing for several minutes. The total amount of saturated $KMnO_4$ solution was between 7 to 10 liters. The contents were allowed to stand overnight at 0° to complete the separation of azodicarboxamidine dinitrate and to dissolve any traces of precipitated MnO_2. The yellow solid was vacuum-filtered and washed with two ice-cold 25-ml. dilute HNO_3 portions, two ice-cold 20-ml. portions of 50% EtOH and two ice-cold 20-ml. portions of absolute EtOH to give 70–80 g., corresponding to 23–27% yield based on aminoguanidine bicarbonate. The crude material was pure enough to be converted directly into III.

For this purpose, H_2S was passed into a suspension of the azodicarboxamidine dinitrate in 350–400 ml. of water with occasional shaking. Thereby the intensively yellow colored solid disappeared gradually because I is water-soluble, and faintly yellow colored sulfur was deposited. When all of the azodicarboxamidine dinitrate had disappeared, the mixture was filtered, allowed to stand overnight and deposited sulfur filtered again. The clear filtrate was concentrated in vacuum to dryness. The remaining white crystalline material weighed between 65–75 g. (85–95% yield based on azodicarboxamidine dinitrate), m.p 125–127° dec. Compound I may be recrystallized from water and shows then a decomposition point of 137–139°, but non-recrystallized I also proved to be sufficiently pure for the synthesis of 2,2′-hydrazopyrimidines.

β-Diketones (II).—2,4-Pentanedione (IIa) was pure grade purchased from Eastman Kodak Co. and used as received. 3-Methyl-2,4-pentanedione (IId) was prepared by

(8) P. C. Mitter and J. C. Bardhan, *J. Chem. Soc.*, 2179 (1923); P. C. Mitter and N. Palit, *Quart. J. Indian Chem. Soc.*, **2**, 61 (1925).

(9) A. Pinner, *Ber.*, **22**, 1615 (1889).

(10) W. Traube, *ibid.*, **33**, 1371, 3035 (1900); W. Bergmann and T. B. Johnson, THIS JOURNAL, **55**, 1733 (1933); R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 395 (1944).

(11) All melting points were determined using a Fisher–Johns melting point apparatus. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn., and the Clark Microanalytical Laboratory, Urbana, Ill.

(12) J. Thiele, *Ann.*, **270**, 42 (1892).

methylation of IIa with CH_3I.[13] 2,4-Hexanedione (IIb)[14] and 3,5-heptanedione (IIc)[15] were prepared by Claisen condensations from 2-butanone and ethyl acetate or ethyl propionate, respectively. The standard procedure for isolating II from the reaction mixture consists of precipitating II as the copper compound followed by the decomposition of this by H_2SO_4. It has now been found that these Claisen condensations can be simplified by skipping the precipitation of the copper compound of II. Instead, the ethereal extracts of II may be distilled directly provided that through the entire condensation the reaction contents are well cooled by an ice-salt mixture.

2,4-Hexanedione (IIb) may be given as a typical example. To an agitated suspension of 23 g. of sodium powder (1mole) in 352 g. of ethyl acetate (4 moles) cooled in an ice-salt-bath was added 72 g. of 2-butanone (1 mole) at such a rate that the reaction contents were held continuously at 0°. After standing overnight, the mixture was heated on the steam-bath for 1.5 hours and then allowed to stand for 3 days at room temperature. By adding glacial acetic acid (approx. 30 ml.), it was acidified to reach *p*H 6 and then poured onto 500 g. of crushed ice. The upper oily layer thus formed was separated and the lower aqueous layer was several times extracted with ether. The combined ethereal extracts and the upper oily layer were dried with $CaCl_2$, stripped of ether and fractionated *in vacuo*. The main fraction boiled at b.p. 73–75° (30 mm.) and amounted to 57.6 g. (50.5%). An analytical sample of IIb was refractionated and exhibited then b.p. 54–55° (12 mm.).

3,5-Heptanedione (IIc) was obtained analogously from ethyl propionate and 2-butanone; yield 48.6%, b.p. 35–36°, $n^{18}D$ 1.4470.

Condensation of 1,2-Hydrazinedicarboxamidine Dinitrate Monohydrate (I) with β-Diketones (II).—In a typical experiment, 20 g. (0.2 mole) of IIa and 92 g. of an aqueous 30 wt. % solution of K_2CO_3 (0.2 mole) was added to a solution of 26.0 g. (0.1 mole) of I in 90 ml. of lukewarm water. Within 1 hr. a white solid started to crystallize. After one week the crystallization was completed and the solid was isolated by vacuum filtration. This 4,4′,6,6′-tetramethyl-2,2′-hydrazopyrimidine (IIIc) weighed 16.8 g. (69.6%) and could be obtained in the form of white stout prisms by recrystallization from ethanol; m.p. 224–225°.

Acetylation of 2,2′-Hydrazopyrimidines (III).—The following example describes a typical acetylation experiment: A suspension of 0.7 g. of IIIa in 10 ml. of acetic anhydride was heated on the steam-bath when, within 10 minutes, a clear solution was formed. Heating was continued for a total of 1.5 hr. After cooling, the solution was evaporated in vacuum to dryness leaving thereby a beige crystalline material (1.0 g.). Recrystallization of this material was possible only if a minimum amount of glacial acetic acid was employed since otherwise even a larger amount of water would not cause precipitation. Thus 1 g. of the crude material was dissolved in 2 ml. of glacial acetic acid, activated charcoal added, heated up to short boiling, filtered and rinsed with 0.5 ml. of glacial acetic acid. When 15 ml. of water was added to the clear acetic acid filtrate, upon cooling white leaflets of N,N′-diacetyl-4,4′,6,6′-tetramethyl-2,2′-hydrazopyrimidine (IVa) crystallized which were isolated by vacuum filtration; m.p. 167°.

4,4′-Dihydroxy-5,5′-dicarbethoxy-2,2′-hydrazopyrimidine (VI). (A) From Sodium Diethyl 1,3-Dicarbethoxyglutaconate (V).—A solution prepared by dissolving 35.2 g. (0.1 mole) of V[7] in 600 ml. of hot water, filtering and cooling to room temperature, was gradually added to a solution of 13 g. (0.05 mole) of I in 50 ml. of water. The mixture was filtered after 2.5 hr. and the clear filtrate was allowed to stand when a slightly yellowish substance started to precipitate. This was vacuum filtered and dried and could best be purified by dissolving in hot N,N-dimethylformamide. Upon cooling, VI crystallized as a slightly yellowish substance, m. p. 227–228°, yield 3.1 g. (17%). A mixed melting point with a specimen of VI as obtained by route B given below was not depressed.

Anal. Calcd. for $C_{14}H_{16}N_6O_6$: C, 46.15; H, 4.43; N, 23.07. Found: C, 45.89; H, 4.62; N, 23.28.

(B) **From Diethyl Ethoxymethylenemalonate (VII).**—To a solution of 6.5 g. (0.025 mole) of I in 20 ml. of lukewarm water was added 20 g. of an aqueous 10 wt. % NaOH solution (0.05 mole of NaOH) and 10.8 g. (0.05 mole) of VII. The yellow substance which started to crystallize within a few days was vacuum filtered and proved to be a substance mixture. Extraction of this mixture with hot water rendered 1.9 g. (20.8%) of VI which, after recrystallization from N,N-dimethylformamide, melted at 227–228°.

Anal. Calcd. for $C_{14}H_{16}N_6O_6$: C, 46.15; H, 4.43; N, 23.07. Found: C, 45.92; H, 4.28; N, 23.32.

From the aqueous extracts, upon cooling, **4,4′-dihydroxy-5,5′-dicarboxy-2,2′-hydrazopyrimidine (VIII)** crystallized as a slightly yellowish substance. Collected on a Hirsch funnel, it amounted to 2.4 g. (31.2%) and melted at 216–217°.

Anal. Calcd. for $C_{10}H_8N_6O_6$: C, 38.97; H, 2.62; N, 27.27. Found: C, 39.24; H, 2.83; N, 27.21.

1,2-Bis-(acetoacetguanyl)-hydrazine (IX).—Upon the addition of 40 g. of an aqueous 10 wt. % NaOH solution (0.1 mole) to a solution of 13 g. of I (0.05 mole), the transparent solution turned brown instantaneously, but gradually became colorless again when 13 g. (0.1 mole) of ethyl acetoacetate was added. Within one hour, a faintly yellowish substance started crystallizing which was vacuum filtered after standing for 3 weeks. The substance was readily soluble in glacial acetic acid, dil. NaOH and dil. HCl, less soluble in ethanol and pyridine and insoluble in all other common organic solvents. Further purification could be achieved by trituration with ether; yield 3.3 g. (23.2%), m.p. 228–230°.

Anal. Calcd. for $C_{10}H_{16}N_6O_4$: C, 42.25; H, 5.67; N, 29.57. Found: C, 42.48; H, 5.49; N, 29.33.

1,2-Hydrazinedicarboxamidine Dicyanoacetate (X). (A) From Ethyl Cyanoacetate.—A 10 wt. % solution of NaOH in water (40 g. = 4 g. of dry NaOH = 0.1 mole) and ethyl cyanoacetate (22.6 g., 0.1 mole) were added to a solution of I (13 g., 0.05 mole) in 40 ml. of water and allowed to stand for 4 weeks. Upon grinding with a glass rod, yellowish scales crystallized which, after vacuum filtration and drying, amounted to 9.6 g. (67.2%) of X. This substance was soluble in water, dil. NaOH, dil. HCl, glacial acetic acid and nitrobenzene but insoluble in all other common organic solvents. After recrystallization from a hot concentrated solution of water, X was obtained in the form of white sturdy needles melting at 203–204° with effervescence. When mixed with a specimen of X as prepared by method B, no depression in melting point was observed.

Anal. Calcd. for $C_8H_{14}N_8O_4$: C, 33.56; H, 4.93; N, 39.15. Found: C, 33.34; H, 5.04; N, 39.23.

(B) **From Cyanoacetic Acid.**—When a solution of 3.4 g. (0.04 mole) of cyanoacetic acid in 5 ml. of water and 16 g. of an aqueous 10 wt. % NaOH solution (0.04 mole of NaOH) were added to a solution of 5.2 g. (0.02 mole) of I in 17 ml. of warm water, long needles started to crystallize within 2 days. They were vacuum filtered and the filtrate concentrated *in vacuo* to give another crop of the same material; total wt. 4.1 g. (71.6%). Recrystallization from water could be accomplished only by working in concentrated solution. Thus white stout needles of X were obtained, m.p. 203–204° with effervescence.

Anal. Calcd. for $C_8H_{14}N_8O_4$: C, 33.56; H, 4.93; N, 39.15. Found: C, 33.45; H, 5.02; N, 38.99.

1,2-Hydrazinedicarboxamidine Malonate (XI). (A) From Diethyl Malonate.—An amount of 9.6 (0.06 mole) of diethyl malonate and 33 g. of an aqueous 10 wt. % KOH solution (0.06 mole of KOH) were added to a solution of 7.8 g. (0.03 mole) of I in 20 ml. of water. Within a few days, crystallization set in, and after a total of 2 weeks the crystals were collected; 3.9 g. (59%). The substance was soluble in water, dil. HCl, dil. NaOH and glacial acetic acid and insoluble in other common organic solvents. Recrystallization of a 2-g. sample of the crude material from 115 ml. of boiling water furnished 1.5 g. of XI in the form of white glistening prisms. The melting point of 216–217° (with bubbling) was not lowered when mixed with a sample obtained by method B.

Anal. Calcd. for $C_5H_{12}N_6O_4$: C, 27.27; H, 5.49; N, 38.17. Found: C, 27.35; H, 5.35; N, 38.06.

(B) **From Malonic Acid.**—After adding a solution of 2.1 g. (0.02 mole) of malonic acid in 3 ml. of water and 22 g. of an aqueous 10 wt. % KOH solution (0.04 mole of KOH) to a solution of 5.2 g. (0.02 mole) of I in 15 ml. of warm wa-

(13) W. H. Perkin and L. Claisen, *J. Chem. Soc.*, **61**, 848 (1892); L. Claisen, *Ber.*, **27**, 3184 (1894).

(14) L. Claisen and E. F. Ehrhardt, *ibid.*, **22**, 1014 (1889); G. T. Morgan and H. G. Reeves, *ibid.*, **123**, 447 (1923).

(15) H. Fisher and E. Bartholomäus, *Ber.*, **45**, 1983 (1912).

ter, sturdy needles started to crystallize within a few minutes. The crystals were filtered after 3 days and amounted to 2.8 g. (63.6%). By recrystallization from water, XI was obtained in the form of white prisms melting at 216–217° (with bubbling). The infrared spectrum shows salt formation between carboxylic and amino groups at 1350, 1620 and 3120 cm.$^{-1}$.

Anal. Calcd. for $C_5H_{12}N_6O_4$: C, 27.27; H, 5.49; N, 38.17. Found: C, 27.03; H, 5.35; N, 38.39.

Infrared spectra were determined on a Perkin–Elmer double beam spectrophotometer, model 137, using solid samples dispersed in potassium bromide.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, TULANE UNIVERSITY, SCHOOL OF MEDICINE]

A Convenient Preparation of 5-Amino-4-imidazolecarboxamide Riboside. Ring Opening of N^1-*p*-Toluenesulfonyl-inosine

BY ELLIOTT SHAW

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The nucleic acid precursor, 5-amino-4-imidazolecarboxamide riboside is now made readily available from inosine (hypoxanthine riboside) by a new degradative reaction in which a purine riboside is converted to an imidazole riboside. The N^1-tosyl derivative of inosine is easily prepared and hydrolyzes in alkali to 5-amino-4-imidazole-N-(tosyl)-carboxamide riboside (II). Hydrazinolysis removes *p*-toluenesulfonamide from this imide and provides the imidazole carboxhydrazide III which undergoes smooth hydrogenolysis to the amide IV.

Recently it was shown that, although inosine is very stable to alkali, 1-benzylinosine undergoes an alkaline hydrolysis of the purine ring to an imidazole nucleoside.[1] This observation was made use of in the preparation of aminoimidazolecarboxamide riboside from inosine. Difficulty in removing the benzyl group limited the value of this method and a different labilizing group was sought. Since the ring-opening reaction apparently depended merely on the replacement of the ionizable hydrogen at N-1 of the purine ring, the chemical nature of the group used for the purpose did not appear to be important, providing that it had alkaline stability greater than the ring. The sulfonyl group suggested itself since the sulfonamide bond, if it formed in this case, would probably have its characteristic high stability. An eventual removal of the sulfonyl group together with the ring nitrogen was visualized as more promising than the earlier difficult debenzylation.

Sulfonamide derivatives of purines of the type shown in I do not appear to have been prepared before. 1-*p*-(Toluenesulfonyl)-inosine was obtained as the triacetate in good yield when inosine triacetate, converted to its sodium salt by means of sodium hydride in dimethylformamide, was treated with *p*-toluenesulfonyl chloride. The structure of the product is indicated by the following reactions. When the nucleoside was heated with alkali, formation of a primary aromatic amine was soon detectable by diazotization and coupling.[2] This test permitted determination of the optimal time for complete reaction. The product, 4-amino-5-imidazole-N-(*p*-toluenesulfonyl)-carboxamide ribofuranoside (II) was readily crystallized from the reaction mixture and, in addition to the aromatic amino group, had the expected acidic properties, *viz.*, a pK_a of 6.3 (in 35% aqueous dimethylformamide).[3] Attempts were then made to split the imide structure of II in order to remove the *p*-toluenesulfonamide group. The substance was not altered by prolonged treatment with hot alkali. This stability toward alkali is in contrast to the cleavage of saccharin to *o*-carboxybenzenesulfonamide.[4] However, although saccharin is the most familiar example of an imide such as II, it contains this grouping in a five-membered ring where it may be somewhat strained and therefore more labile than an acyclic example. Ammonolysis with concentrated ammonium hydroxide in sealed tubes could be achieved only at elevated temperatures (*ca.* 160°) and was not considered promising as a means of proceeding directly to the amide due to accompanying decomposition. The cleanest cleavage of the N-sulfonylcarboxamide (II) was accomplished by hydrazinolysis to *p*-toluene-sulfonamide and the hydrazide of 5-amino-4-imidazolecarboxylic acid riboside (III). The hydrazide was reduced to the amide by means of Raney nickel in ethanol[5] which provided the desired riboside IV in satisfactory yield.

The method described here is very convenient for the laboratory preparation of 5-amino-4-imidazolecarboxamide riboside in gram quantities.[6] The extension to related ribosides and ribotides of biosynthetic importance is under study.

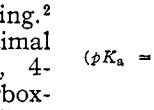
Experimental[7]

1-(*p*-Toluenesulfonyl)-inosine Triacetate.—Sodium hydride (1.5 g. of the 50% dispersion in mineral oil, Metal Hydrides Corp.) was added to dimethylformamide (100 ml.) in

(1) E. Shaw, THIS JOURNAL, **80**, 3899 (1958).

(2) A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

(3) Measurements of the acid strength of strictly comparable models have not been reported. However, derivatives of sulfanilamide (pK_a = 10.43) which contain the



grouping such as N^1-acetylsulfanilamide (pK_a = 5.38) suggest that the observed value for II is a reasonable one for the structure. The data are from P. H. Bell and R. O. Roblin, THIS JOURNAL, **64**, 2905 (1942).

(4) C. Fahlberg and R. List, *Ber.*, **21**, 242 (1888).

(5) S. Akabori and K. Narita, *Proc. Japan Acad.*, **29**, 264 (1953); *cf. C. A.*, **49**, 864 (1955); C. Ainsworth, THIS JOURNAL, **76**, 5774 (1954).

(6) Preliminary account of a synthesis of this nucleoside starting with methyl 5-nitro-4-imidazolecarboxylate and ribofuranose tribenzoate has appeared: J. Baddiley, J. G. Buchanan and J. Stewart, *Proc. Chem. Soc.*, 149 (1957).

(7) Melting points were taken on a Fisher block and are uncorrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Copenhagen.