Conversion of Ureidomalonates and 5-Carbalkoxyhydantoins into 5-Ureido-4,6-pyrimidinediones[1]

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Both ureidomalonates and 5-carbethoxyhydantoins were readily condensed with guanidine to give the same products, 2-amino-5-(N′-substituted-ureido)-4,6-pyrimidinediones, in good yield. Acid-catalyzed cyclization of the latter compounds produced 8-hydroxyguanines. Chlorination and acylation of the ureidopyrimidinediones were studied. Thiourea condensed with the ureidomalonates, but urea did not.

In 1914, Johnson and Nicolet were unsuccessful in attempts to synthesize 5-ureido-2,4,6-pyrimidinetrione (pseudouric acid) from diethyl ureidomalonate and urea in the presence of sodium ethoxide.[2] Later, Garner showed that diethyl ureidomalonates readily cyclize in the presence of sodium ethoxide to form sodium salts of 5-carbethoxyhydantoins (**1**). Mild acidification with strong cation-exchange resin gave the free hydantoins (**2**).[3] The present work was initially directed to the possible synthesis of substituted uric acids by condensation of compounds of structure **2** with ureas, thioureas, or quanidine. In similar studies, it has been shown that 4-carbethoxy-2,3-dioxopyrrolidines condense with quanidine or urea to give 2-amino- (or hydroxy-) 4-hydroxy-5H-pyrrolo[3,4-*d*]pyrimidin-7(6H)-ones[4] and that an autoclave condensation of 3-carbethoxy-2-piperidone with guanidine yields the pyrimidopiperidone.[5]

Urea ($K_b \cong 1.5 \times 10^{-14}$)[6] and N-methylureas were not sufficiently nucleophilic to react satisfactorily with **2**. An exhaustive range of conditions and condensing agents was tested. Guanidine ($K_b \cong 3.0 \times 10^{-1}$),[6] however, reacted with **2** (R = C_6H_5, R′ = Et) in methanolic sodium methoxide to give the sodium salt of 2-amino-5-(N′-phenylureido)-4,6-pyrimidinedione (**3**, R = C_6H_5) in good yield. This salt, which showed ir absorptions and a uv spectrum consistent with the assigned structure, was acidified with cold 1 *N* hydrochloric acid to give a quantitative yield of 2-amino-5-(N′-phenylureido)-4,6-pyrimidinedione (**4**, R = C_6H_5).

Generally, facile condensation took place between quanidine and either the diethyl ureidomalonate (Table I) or the carbalkoxyhydantoin to give the corresponding 2-amino-5-ureidopyrimidinedione. The only previously known member of series **4**, 2-amino-5-ureido-4,6-pyrimidinedione, had been prepared from 2,5-diamino-4,6-pyrimidinedione and potassium cyanate.[7] The N′-substituted 2-amino-5-ureidopyrimidinediones (**4**) were isolated from the reaction of ureidomalonates or carbalkoxyhydantoins with guanidine in metal alkoxide or sodium hydride catalyzed media, or with guanidine carbonate alone. A basic medium was definitely required, and the best yields were obtained when the apparatus was arranged to remove ethanol from the reaction mixture.

The yields of **4** were generally higher when the ureidomalonate was the starting material. When the salt **1** was used rather than the parent compound **2**, condensation did not take place. Therefore, it is unlikely that the ureidomalonate first cyclized to the salt of the 5-carbalkoxyhydantoin. It is more reasonable that, under the reaction conditions, attack by the strongly nucleophilic guanidine nitrogen at the malonyl carbonyl of **5** was preferred to attack by the weakly nucleophilic outer ureido nitrogen. The examination of the uv spectra and the recovery of **2** on mild acidification of reaction mixtures from ureidomalonates (where R = H, Me, Et) and guanidine indicated that in these cases the stable quanidinium salts of the 5-carbethoxyhydantoins (**6**) were formed, which led to lower yields of **4**. Salt **6** is stabilized by resonance against nucleophilic attack at either the ester or the C-4 keto function. Guanidinium salts of this type have been observed previously.[4] Higher yields of **4** were experienced in solvents of higher polarity. Reactions where the ureidomalonate was more soluble (*e.g.*, R = C_6H_5 in methanol) were more satisfactory than those where the ureidomalonate was less soluble (*e.g.*, pyridine, N,N-dimethylformamide). Yields of **4** diminished with decreasing solvent polarity in this fashion: methanol > ethanol > N,N-dimethylformamide > 1,2-dimethoxyethane ≫ chloroform (no reaction). Increased competition for formation of **6** was observed in solvents of low polarity. The 2-amino-5-ureidopyrimidinediones are remarkably unreactive toward aqueous acids. However, basic solutions of **4** deteriorate rapidly on standing.

When diethyl N′-phenylureidomalonate was refluxed with an excess of thiourea ($K_b \cong 10^{-15}$)[6] and sodium methoxide in methanol, a 15–19% yield of a solid was isolated after acidification. The ir and uv spectra of this paper chromatographically homogeneous material were typically those of a pseudouric acid derivative. However, it was not possible to obtain acceptable analyses. It resisted cyclization with 20% hydrochloric acid and in this way resembled 2-thio-5-ureido-4,6-pyrimidinedione (2-thiopseudouric acid).[2] It is of interest that thiourea, a poorer base than urea but a good nucleophile,[8] does condense with ureidomalonates. Ureidomalonates did not condense with O-methylisourea, S-methylisothiourea, and S-benzylisothiourea.

Reactions of 2-Amino-5-ureido-4,6-pyrimidinediones.—Yields of pseudouric acids from potassium cyanate or isocyanates have often been moderate to low because of the strongly basic aqueous medium used

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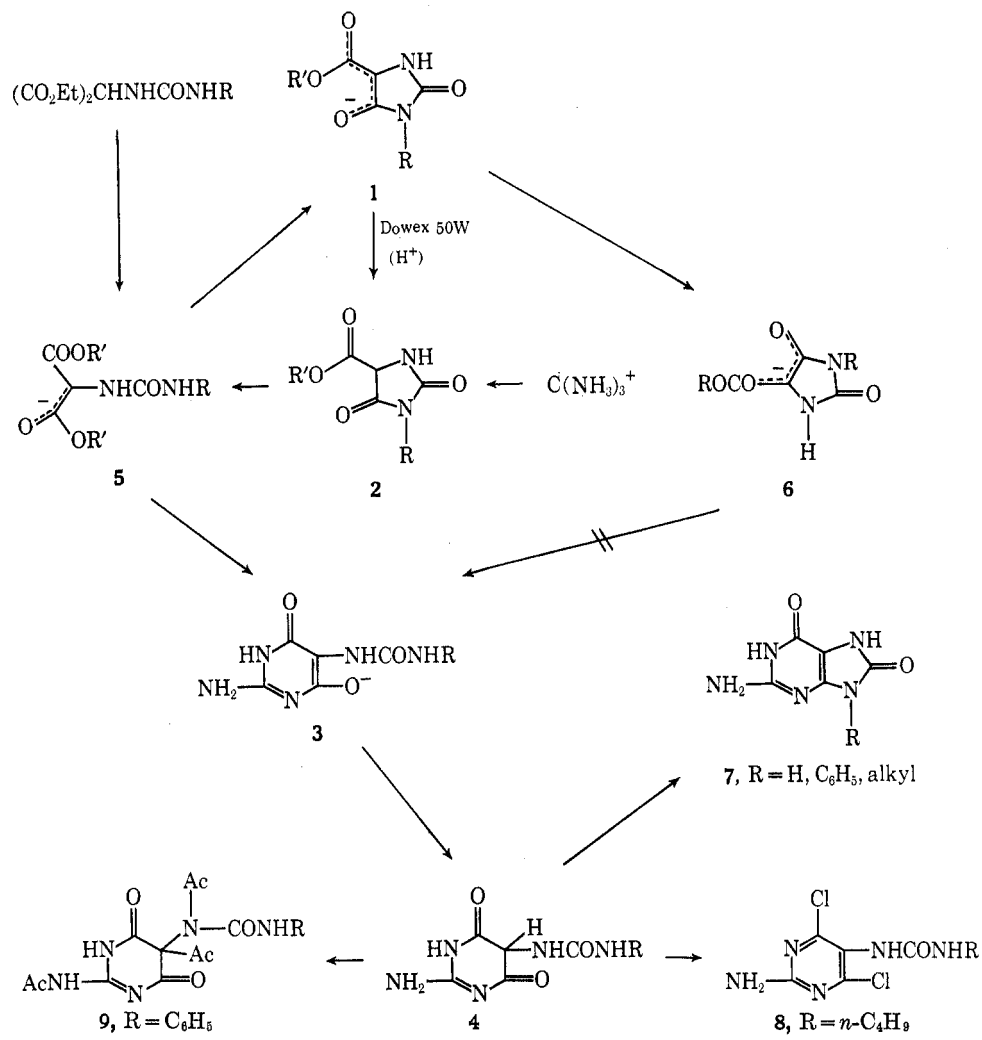
TABLE I
CONDENSATION OF DIETHYL UREIDOMALONATES WITH GUANIDINE

R	Condensing agent[a]	Solvent	Reaction temp, °C	Reaction time, hr	Mp of 4, °C	Yield of 4, %
H	A	MeOH	85	2.5	>400	48
H	B	Dioxane	80–100	18	...	41
H	C	(Fusion)	180	1.1	...	36
Me	A	MeOH–N,N-dimethylformamide	60–80	12	240–242 dec	35
Me	C	EtOH	110	48	...	73
Et	A	MeOH	85	5	>300 dec	33
n-Bu	A	MeOH	100	3	>350 dec	83
n-Bu	C	EtOH–pyridine	120	40	...	34
C_6H_5	A	MeOH–diglyme	105	2.5	320–322 dec	94
D-Ribosyl	A	MeOH	100	3.5	171–172	41

[a] A = guanidine hydrochloride + sodium methoxide; B = guanidine hydrochloride + sodium hydride; C = guanidine carbonate.

to dissolve the starting material, 5-amino-2,4,6-pyrimidinetrione (uramil).[9,10] Employing ureidomalonates, 2-amino-5-ureido-4,6-pyrimidinediones (pseudouric acid 2-imides) are formed under relatively mild conditions. It is thus possible to introduce even aqueous alkali sensitive groups into the N′ position and the amino and thio groups at the C-2 position of the ureidopyrimidine ring under much milder conditions than employed to date. Cyclization of **4** to 9-substituted 8-hydroxyguanines (**7**) was effected by refluxing with 20% hydrochloric acid or in somewhat better yields by heating with polyphosphoric acid (PPA) (Table II). 8-Hydroxyguanine (**7**, R = H), which occurs naturally,[11] was isolated here in 78% yield, and was first made by Fischer from **4** (R = H) in 50% yield.[12] It has also been produced in 20% yield by fusion of 2,4,5-triamino-6-pyrimidone sulfate with urea.[13]



Our route to purinones **7** is amenable to isotopic labeling studies in a more universal way than Cavalieri's classical synthesis of N-1 (and N-3) or N-9 labeled uric acid from 4,5,6-triamino-2-pyrimidone.[14]

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TABLE II

CYCLIZATION OF 2-AMINO-5-UREIDO-4,6-PYRIMIDINEDIONES TO 8-HYDROXYGUANINES

R	Cyclizing agent	Reaction temp, °C	Reaction time, hr	Mp of **7**, °C	Yield of **7**, %
H	20% HCl	110	6	>400 dec	78
H	(by fusion of urea with 2,4,5-triamino-6-pyrimidone sulfate)[a]				20
Me	20% HCl	110	3	>400 dec	52
Me	PPA	150	3.5	...	59
Et	20% HCl	110	3	359–360	52
n-Bu	20% HCl	90	2	344–346 dec	48
n-Bu	PPA	110	4	...	43
C_6H_5	20% HCl	120	2.5	>300 dec	38
C_6H_5	PPA	110	3–8	...	68

[a] Reference 13.

However, 8-hydroxyguanosine (**7**, R = D-ribosyl) could not be prepared. When **4** (R = D-ribosyl) was heated with 20% hydrochloric acid at 110° for 1 hr, only unreacted **4** and two unidentified uv-absorbing compounds were obtained. Milder methods, such as reaction of **4** (R ≠ ribosyl) with phosphorous pentoxide in N,N-dimethylformamide, with ethyl polymetaphosphate, or with dicyclohexylcarbodiimide in several solvents, all gave less than 5% yields of **7** (R ≠ ribosyl).

2-Amino-4,6-dichloro-5-(N′-*n*-butylureido)pyrimidine (**8**) was formed when **4** was heated with phosphorus oxychloride for 2 hr at 110°. However, when the reaction mixture was heated for only 2 min at 110°, an intermediate which was not characterized was isolated in good yield. It gave **8** exclusively when heated with phosphorus oxychloride for 2 hr at 110°.

In an attempt to find more manageable intermediates for cyclization to 8-purinones, two compounds of structure **4** (R = C_6H_5 and R = Me) were treated with acetic anhydride–acetic acid at 150° for 20 hr. Both substances gave the same product, which demonstrated that at least part of the ureido side chain had been cleaved.

Milder acid-catalyzed or neutral treatment gave no reaction. Acetic anhydride in cold pyridine and **4** (R = C_6H_5) afforded 2-acetamido-5-acetyl-5-(N-acetyl-N′-phenylureido)-4,6-pyrimidinedione (**9**) and a second product which was not identified but appeared to be a diacetyl derivative of **4** (R = C_6H_5).

Experimental Section[15]

Diethyl ureidomalonate was prepared by the method of Cerchez[15] in 68% yield, mp 171–173° (lit.[16] mp 169°).

Diethyl N′-Methylureidomalonate.—The following procedure is typical for the preparation of the N′-substituted ureidomalonates. Freshly distilled diethyl aminomalonate (44.9 g, 0.256 mol), prepared from diethyl isonitrosomalonate, was dissolved in 1.2 l. of absolute ether under nitrogen. With cooling to 0°, a solution of distilled methyl isocyanate (17.12 g, 0.300 mol) in 200 ml of ether was added dropwise with stirring. A white precipitate appeared in 10 min. The mixture was stirred at 25° for 20 hr. Ether and unreacted isocyanate were removed at 20–35° under reduced pressure. The quite pure product (57.6 g, 97%) was desiccated over phosphorus pentoxide, washed well with water, and recrystallized from chloroform to give the analytical sample, mp 140–141°.

Anal. Calcd for $C_9H_{16}N_2O_5$: C, 46.54; H, 6.94; N, 12.07. Found: C, 46.76; H, 7.03; N, 12.32.

Diethyl N′-Ethylureidomalonate.—Colorless needles (mp 114–115°) were obtained from ethanol, in 75% yield.

Anal. Calcd for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.38. Found: C, 49.03; H, 7.49; N, 11.51.

Diethyl N′-*n*-Butylureidomalonate.—The crude solid which was formed in 97% yield was recrystallized from ethanol–ether, mp 88–89°.

Anal. Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.09; N, 10.21. Found: C, 52.34; H, 7.88; N, 10.30.

Diethyl N′-Phenylureidomalonate.—Fine needles from ethanol–ligroin (*d* 0.64, 1:1) were obtained in 80% yield, mp 118–119° (lit.[16] mp 117°).

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Isocyanate (10).[17]—An ethereal solution of dry 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (10.08 g, 0.02 mol), prepared by the method of Recondo,[18] was used to make 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride, according to the method of Kissman.[19] The resulting yellowish syrup was dissolved in 60 ml of dry toluene. Freshly prepared, dried, and pulverized silver cyanate (12.00 g, 0.08 mol) was added in two portions of 8 and 4 g, respectively, at 0.5-hr intervals. Both portions were slurried in with 50-ml quantities of toluene and the suspension was stirred at 105° for 3 hr in the dark. The yellowish solution was filtered from the silver salts and 50 ml of ligroin (*d* 0.64) was added to the filtrate. This solution was used at once in the next reaction. According to the yield of the ureidomalonate formed directly from **10**, the yield of **10** was at least 75%.

In order to isolate **10**, the toluene filtrate was poured successively three times into 50-ml volumes of ligroin (*d* 0.64). On standing, gums settled out, from which the isocyanate solutions were decanted and combined. After evaporation of solvents, crystallization of the remaining powder from chloroform–ligroin (*d* 0.67–0.69) gave **10** (5.32 g, 55%), mp 58–60°, which was contaminated with some N,N′-di(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea. The ir spectrum had bands at 4.43 (N=C=O) and 5.75 and 7.89 μ (benzoate C=O).

Diethyl N′-2,3,5-Tri-O-benzoyl-β-D-ribofuranosylureidomalonate.—Freshly distilled diethyl aminomalonate (3.50 g, 0.02 mol) was dissolved in 200 ml of absolute ether at 0° under nitrogen. A solution of freshly prepared **10** (9.3 g, *ca.* 0.019 mol) in 150 ml of toluene and 50 ml of ligroin (*d* 0.64) was added dropwise. The mixture was stirred at 40° for 18 hr, an additional 1.77 g (0.01 mol) of diethyl aminomalonate was added, and the yellow-green solution was stirred at 70° for 2 hr. The mixture was filtered and the golden yellow filtrate was evaporated to yield an opaque syrup. The crude material was crystallized from ether to give colorless, lustrous needles of pure product: yield 8.95 g (71%); mp 119–119.5°; $[\alpha]^{27}D$ −43.8 (*c* 0.4, $CHCl_3$); uv max (EtOH) 230 mμ (ε 37,600), 275 (ε 4000), and 283 (ε 3800); nmr ($CDCl_3$) δ 5.20 (d, 1, *J* = 7.5 Hz, methine), 6.15 (br d, 1, *J* = 7.5 Hz, N proton), 6.63 (br, d, 1, *J* = 9.0 Hz, H_1' methine), and 6.90 (br d, 1, *J* = 9.0 Hz, N′ proton).

Anal. Calcd for $C_{34}H_{34}N_2O_{12}$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.11; H, 5.05; N, 4.16.

5-Carbethoxyhydantoin (2, R = H; R′ = Et) was prepared by Garner's method[3] except that a batch process was used for the acidification step with Dowex 50 W-X12 (H^+). Trituration of the product with ether gave a white, crystalline solid: yield 72%; mp 85.5–86.5° (lit.[3] mp 87.5–88.5°).

5-Carbethoxy-3-methylhydantoin (2, R = Me; R′ = Et) was prepared in 72% yield by the procedure of Garner[3] with batch resin modification: mp 87–88.5°; nmr ($CDCl_3$) δ 4.80 (s, 1, methine), 7.07 (s, 1, NH), and 3.02 (s, 3, N-methyl).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.40; H, 5.34; N, 14.66.

5-Carbethoxy-3-phenylhydantoin (2, R = C_6H_5; R′ = Et) was prepared in 91% yield by the above method, mp 110–111° (lit.[3] mp 110°).

(15) Melting points are uncorrected. Microanalyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. Ir spectra were taken on a Beckman IR-5A spectrophotometer and uv spectra were taken on a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nmr spectra were obtained on a Varian A-60 spectrometer. All chemical shifts are reported in δ (parts per million) from internal tetramethylsilane reference.

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(18) E. F. Recondo and H. Rinderknecht, *Helv. Chim Acta*, **52**, 1171 (1959).

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2-Amino-5-ureido-4,6-pyrimidinedione (4, R = H).—The following procedure is illustrative of the preparation of the 2-amino-5-ureidopyrimidinediones. Dry diethyl ureidomalonate (8.74 g, 0.04 mol) was dissolved in 60 ml of methanol, previously distilled from magnesium methoxide. To this solution was added sodium methoxide (4.43 g, 0.082 mol), followed by dry guanidine hydrochloride (7.80 g, 0.082 mol). Another 40 ml of methanol was added with stirring at 85°. The yellowish mixture was stirred for 2.5 hr in a nitrogen atmosphere under reflux. Most of the solvent was removed under a nitrogen flow at 80° and the last traces were removed under reduced pressure. The resulting solid cake was washed with 100 ml of cold water, and colorless **3** (R = H) was dried over phosphorus pentoxide (3.94 g, 48%). All of the salt was then suspended in 15 ml of water at 5° and stirred with 15 ml of 6 *N* hydrochloric acid for 1 hr, and the milky-white suspension was filtered. The product (3.54 g, 100%) was washed with water and ethanol. This compound could only be purified by dissolving in dilute base, filtering through Norit, and precipitating with dilute acid. The solid was dried over phosphorus pentoxide at 140° (0.1 mm): mp >400°; uv max (10% aqueous EtOH) 260 mμ (ε 6300) at pH 9.5.

Anal.[20] Calcd for $C_5H_7N_5O_3$: C, 32.43; H, 3.81; N, 37.83. Found: C, 33.07; H, 3.89; N, 35.81.

2-Amino-5-(N′-methylureido)-4,6-pyrimidinedione (4, R = Me). Method A.—The product, obtained by the procedure for **4** (R = H), was dissolved in dilute sodium hydroxide and precipitated twice with dilute acetic acid: mp 240–242° dec; yield 35%.

Method B.—The same product was obtained in 73% yield by refluxing an equimolar mixture of diethyl N′-methylureidomalonate and guanidine carbonate in a minimum volume of absolute ethanol at 110° for 2 days: uv max (10% aqueous EtOH) 259 mμ (ε 12,700) at pH 7.

Anal. Calcd for $C_6H_9N_5O_3 \cdot 1.25H_2O$: C, 32.50; H, 5.23; N, 31.59. Found: C, 32.33; H, 5.33; N, 31.80.

2-Amino-5-(N′-ethylureido)-4,6-pyrimidinedione (4, R = Et).—The crude solid, obtained by method A, was recrystallized from boiling water: yield 33%; mp >300° dec; uv max (H_2O) 259 mμ (ε 12,500) at pH 6.

Anal. Calcd for $C_7H_{11}N_5O_3 \cdot 0.75H_2O$: C, 37.08; H, 5.56; N, 30.89. Found: C, 37.08; H, 5.43; N, 30.35.

2-Amino-5-(N′-*n*-butylureido)-4,6-pyrimidinedione (4, R = *n*-Bu).—The light tan product was prepared by method A, dissolved in dilute potassium hydroxide, and reprecipitated with glacial acetic acid: yield 83%; mp 350° dec; uv max (50% aqueous EtOH) 259 mμ (ε 16,100) at pH 7.

Anal. Calcd for $C_9H_{15}N_5O_3 \cdot 0.5H_2O$: C, 43.19; H, 6.44; N, 27.99. Found: C, 43.29; H, 7.24; N, 27.83.

2-Amino-5-(N′-phenylureido)-4,6-pyrimidinedione (4, R = C_6H_5).—This compound was prepared by method A, except that a methanol–diglyme mixture was used with reflux at 105° for 2.5 hr. The product was taken up in dilute potassium hydroxide, precipitated with dilute acetic acid, filtered, and desiccated over phosphorus pentoxide at 140° (0.1 mm): yield 94%; mp 320–322° dec; uv max (10% aqueous EtOH) 244 (ε 17,500) and 260 mμ (shoulder, ε 15,100) at pH 7.

Anal. Calcd for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.71; H, 4.41; N, 26.68.

2-Amino-5-(N′-β-D-ribofuranosylureido)-4,6-pyrimidinedione (4, R = D-Ribosyl).—This compound was prepared by method A. A Barrett trap was used and the suspension was stirred at 100° for 3.5 hr. As the methanol was depleted from the mixture, toluene was added for homogeneity. The odor of methyl benzoate was detectable within seconds of starting the reaction. After removal of solvents at 65° (25 mm), the buff-colored salt mixture was dissolved in a minimum of 10% aqueous ethanol (pH 11), the solution was filtered from a pink solid, and the filtrate was stirred at 4° with Dowex W-X8 (H^+) resin for 5 min to pH 1. The resulting golden yellow filtrate was brought to pH 6 by stirring with Bio-Rad Analytical Grade mixed bed resin 501-X8 (D, 20–50 mesh), and this colorless filtrate was extracted with ether. The aqueous layer was evaporated at 30° (1 mm), leaving a white powder which, on trituration with ether, gave colorless crystals of the product: yield 41%; mp 171–172°; uv max (H_2O) 204 (ε 7100), 226 (ε 4000), and 259 mμ (ε 7200). The analytical sample was the paper chromatographically homogeneous solid obtained by elution from a cellulose column with 7:3 ethanol–water, mp 170–172°. Upon spraying a spot of this material on filter paper with sodium metaperiodate–Schiff's reagent,[21] the spot became lilac-colored at once.

Anal. Calcd for $C_{10}H_{15}N_5O_7 \cdot 2H_2O \cdot 0.5C_2H_5OH$: C, 35.11; H, 5.89; N, 18.61. Found: C, 35.72; H, 5.75; N, 18.79.

8-Hydroxyguanine (7, R = H).—The following procedure is typical for the preparation of the 8-hydroxyguanines. Crystalline **4** (R = H, 0.45 g, 2.43 mmol) was refluxed in 150 ml of 20% hydrochloric acid at 110° for 6 hr. The solution was evaporated almost to dryness at 60° (25 mm). The residue was covered with 30 ml of cold water, filtered, and dried over phosphorus pentoxide at 140° (0.5 mm): yield 0.32 g (78%); mp >400° dec; uv max (10% aqueous EtOH) 243 (ε 7200) and 290 mμ (ε 8200). This solid was taken up in warm, dilute sodium hydroxide, filtered through Norit, and precipitated with dilute hydrochloric acid to give a compound identical (paper chromatography, ir, and uv spectra) with that prepared by Cavalieri's method.[13]

Anal. Calcd for $C_5H_5N_5O_2 \cdot 0.95H_2O$: C, 32.59; H, 3.78; N, 38.01. Found: C, 33.04; H, 3.39; N, 37.50.

8-Hydroxy-9-methylguanine (7, R = Me). Method A.—The colorless powder obtained by the procedure used for **7** (R = H) was crystallized from boiling water: yield 52%; mp >400°; uv max (H_2O) 248 (ε 10,100) and 293 mμ (ε 10,100) at pH 2, 250 (ε 8400) and 282 mμ (ε 10,200) at pH 12.

Anal. Calcd for $C_6H_7N_5O_2 \cdot 0.5H_2O$: C, 37.89; H, 4.24; N, 36.83. Found: C, 37.53; H, 4.44; N, 36.62.

Method B.—Into a mixture of **4** (R = Me, 0.997 g, 5.00 mmol) and phosphorus pentoxide (9.4 g, 33.5 mmol) cooled in an ice bath was slowly pipetted 7 ml of 85% phosphoric acid. The brown mixture was stirred at 25° and then at 150° for 3.5 hr. The resulting red-brown syrup was allowed to cool to 25° and poured cautiously into 100 ml of cracked ice. At first the mixture remained gummy, but after several minutes a tan solid formed which was filtered and crystallized from hot water to give a product (0.53 g, 59%) identical with **7** (R = Me) prepared by method A.

9-Ethyl-8-hydroxyguanine (7, R = Et).—The solid obtained by method A was crystallized from dilute potassium hydroxide–glacial acetic acid: yield 52%; mp 359–360°; uv max (H_2O) 247 and 294 mμ at pH 7.

Anal.[20] Calcd for $C_7H_9N_5O_2$: C, 43.10; H, 4.65; N, 35.90. Found: C, 42.97; H, 4.45; N, 31.80 (normal digestion time); N, 34.38 (longer digestion time).

9-*n*-Butyl-8-hydroxyguanine (7, R = *n*-Bu).—The solid obtained by method A was precipitated from a dilute base solution with dilute acetic acid: yield 48%; mp 344–346° dec; uv max (50% aqueous EtOH) 249 (ε 10,100) and 296 mμ (ε 9700) at pH 7.

Anal.[20] Calcd for $C_9H_{13}N_5O_2 \cdot 0.5H_2O$: C, 46.54; H, 6.08; N, 30.16. Found: C, 46.91; H, 6.07; N, 28.30.

8-Hydroxy-9-phenylguanine (7, R = C_6H_5).—The product obtained by heating **4** (R = C_6H_5) in PPA at 110° for 8 hr according to method B was purified by dilute acid precipitation from a basic solution: yield 68%; mp 300° dec; uv max (10% aqueous EtOH) 244 (ε 6700) and 294 mμ (ε 7000) at pH 7.

Anal. Calcd for $C_{11}H_9N_5O_2 \cdot H_2O$: C, 50.57; H, 4.25; N, 26.81. Found: C, 50.84; H, 4.04; N, 26.57.

2-Amino-4,6-dichloro-5(N′-*n*-butyl)ureidopyrimidine (8).—Dry **4** (R = *n*-Bu, 0.50 g, 2.08 mmol) was refluxed in 15 ml of phosphorus oxychloride at 110° for 2 hr. Upon evaporation to dryness at 50° (25 mm), the orange residue was dried over phosphorus pentoxide (0.05 mm). This material was covered with 10 ml of cold water, filtered, dried, and recrystallized from hot acetone. The crystalline product was dried over phosphorus pentoxide at 110° (0.05 mm): yield 0.42 g (72%); mp 228–229°; uv max (EtOH) 240 (ε 20,000) and 311 mμ (ε 5000) at pH 7; nmr (DMSO-d_6) δ 0.92 (m, 3) 1.36 (m, 4) 3.09 (m, 2, N-*n*-butyl), and 7.47 and 7.63 (m, 2, $N_{(2)}$).

Anal. Calcd for $C_9H_{13}Cl_2N_5O$: C, 38.86; H, 4.71; Cl, 25.50; N, 25.18. Found: C, 38.81; H, 4.79; Cl, 25.25; N, 25.22.

2-Acetamido-5-acetyl-5(N-acetyl-N′-phenylureido)-4,6-pyrimidinedione (9).—Dry **4** (R = C_6H_5, 1.57 g, 0.0060 mol) was suspended in 36 ml of dried, distilled pyridine at 25°. At 0° with stirring, 3 ml (0.080 mol) of acetic anhydride was added drop-

(20) It was later found for other members of this series that a longer digestion time was required for the N determination.

(21) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1960).

wise. The mixture was stirred under nitrogen to 25° for 20 hr. A yellowish solution was obtained, which on cooling to 0° afforded a colorless precipitate. Ether was added to complete the precipitation. The finely divided, colorless needles (1.71 g, 74%) were filtered, washed well with ether, and dried over phosphorus pentoxide (0.03 mm). Recrystallization from chloroform–ether gave the analytical sample: mp 174–175° (resolidification occurred at 185° followed by mp >300°); uv max (H_2O) 218, 254, and 277 mμ (shoulder) at pH 6; nmr (DMSO-d_6) δ 1.93 (s, 3, $C_{(6)}$-acetyl), 2.18 (s, 3), 2.23 (s, 3, $N_{(2)}$- and $N_{(7)}$-acetyls), 7.23 (m, 8, N-phenyl), and 7.55 (m, 8, N protons).

Anal. Calcd for $C_{17}H_{17}N_5O_6$: C, 52.71; H, 4.43; N, 18.08. Found: C, 53.06; H, 4.70; N, 18.55.

When the above reaction was conducted at −15° for 5 hr and followed by the addition of ether to the mixture, 1.14 g of a slightly yellowish solid was collected, mp >300°. This product was not identified, but its nmr spectrum indicated that it was a product of diacetylation of **4**.

Registry No.—**2** (R = Me, R′ = Et), 21823-24-5; **4** (R = H), 21823-25-6; **4** (R = Me), 21823-26-7; **4** (R = Et), 21823-79-0; **4** (R = Bu), 21823-80-3; **4** (R = Ph), 21823-81-4; **4** (R = D-ribosyl), 21823-82-5; **7** (R = H), 21823-83-6; **7** (R = Me), 21823-84-7; **7** (R = Et), 21823-85-8; **7** (R = Bu), 21823-86-9; **7** (R = Ph), 21850-65-7; **8**, 21823-87-0; **9**, 21823-88-1; **10**, 21823-89-2; diethyl N′-methylureidomalonate, 21823-90-5; diethyl N′-ethylureidomalonate, 21823-91-6; diethyl N′-butylureidomalonate, 21823-92-7; diethyl N′-2,3,5-tri-O-benzoyl-β-D-ribofuranosylureidomalonate, 21823-93-8.

Dithia Aromatic Systems. I. The Isomeric Thianaphthenothiapyrylium Perchlorates[1]

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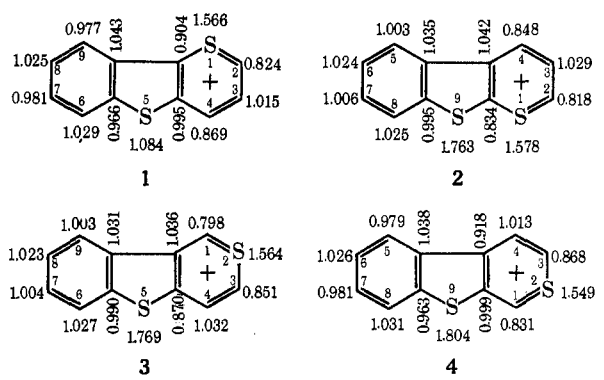
Syntheses of thianaphtheno[3,2-*b*]-, -[2,3-*b*]-, -[3,2-*c*]-, and -[2,3-*c*]thiapyrylium perchlorates (**1–4**, respectively), the prototypes of a class of 14-π-electron dithia aromatic systems, are described. These stable salts exhibit nmr spectra in which protons α and γ to the thionium center of the thiapyrylium rings experience the usually strong deshielding (δ 10.57–9.00 ppm) typical of positions of markedly low electron density. Hückel molecular orbital calculations, based on the assumption that both the thiapyrylium sulfur and the thiophenelike sulfur can be represented by the same set of parameters (h_S = 0.9 and k_{CS} = 0.6), yield predicted first electronic transition frequencies significantly at variance with the observed spectral frequencies.

In a recent article[3] we reported an excellent correlation of the longest wavelength electronic absorption frequencies ($\tilde{\nu}$) of thiapyrylium ion and 11 of its polynuclear benzologs with the first transition energies (Δm) calculated by Hückel molecular orbital (HMO) theory. These calculations were based on a simple p-orbital model in which the coulomb integral for sulfur and the carbon–sulfur bond integral were expressed as $\alpha_S = \alpha + h_S\beta$ and $\beta_{CS} = k_{CS}\beta$, respectively.[4] Systematic variation of the parameters yielded an optimum set, h_S = 0.9 and k_{CS} = 0.6, which maximized the correlation coefficient to 0.992 and gave a corresponding regression line, $\tilde{\nu} = 26.053\ \Delta m - 0.677$ (kcm^{-1}), having a standard deviation of 0.609 kcm^{-1}. Since such an empirically optimized set of parameters, as well as the spectral correlation, should have broader validity, we sought to extend their use to encompass new classes of dithia heterocycles in which each sulfur is essentially σ-bivalent and formally contributes two electrons to a potentially aromatic π system. The isomeric thienothiapyrylium cations and their various benzo derivatives (*e.g.*, **1–4**), which fulfill the foregoing structural requirements, were selected for initial attention, and we report here the syntheses of several perchlorate salts representative of this novel group, along with some properties appropriate for possible correlations with HMO indices (Chart I).

When this work was begun, no examples of the desired thienothiapyrylium salts were known; however,

CHART I

STRUCTURES AND ELECTRON DENSITIES OF THE THIANAPHTHENOTHIAPYRYLIUM CATIONS[a]



1 **2** **3** **4**

[a] All isolated as the perchlorates.

during recent months both thieno[2,3-*b*]- and thieno[3,2-*b*]thiapyrylium perchlorates have been described in detail,[5] and 2,4-dimethylthianaphtheno[2,3-*b*]- and 2,4-dimethylthianaphtheno[3,2-*b*]thiapyrylium perchlorates have been disclosed in a preliminary note.[6] In this laboratory we have also prepared thieno[2,3-*c*]- and thieno[3,2-*c*]thiapyrylium perchlorates, which will be described in a separate communication.[7]

Synthetic sequences leading to the parent thianaphthenothiapyrylium perchlorates having [3,2-*b*], [2,3-*b*], [3,2-*c*], and [2,3-*c*] modes of ring fusion (**1–4**, respectively) are illustrated in Schemes I–IV. In

(1) Based on the Ph.D. dissertation of C. R. Hamel, Lehigh University, 1969. Supported in part by National Science Foundation Grant GP-8597.
(2) National Science Foundation Trainee, 1967–1969.
(3) T. E. Young and C. J. Ohnmacht, *J. Org. Chem.*, **32**, 444 (1967).
(4) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 5.
(5) I. Degani, R. Fochi, and G. Spunta, *Ann. Chim.* (Rome), **58**, 263 (1968).
(6) J. Fabian and H. Hartmann, *Tetrahedron Lett.*, 239 (1969).
(7) T. E. Young and C. R. Hamel, *J. Org. Chem.*, **35**, 821 (1970).