Mesoionic Purinone Analogs. III. The Synthesis and Properties of Mesoionic Thiazolo[3,2-*a*]pyrimidine-5,7-diones

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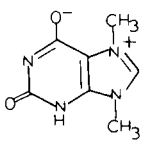
A number of mesoionic thiazolo[3,2-*a*]pyrimidine-5,7-diones, isoconjugate mesoionic analogs of xanthine, were prepared by the condensation of 2-alkylaminothiazoles with bis(2,4,6-trichlorophenyl)malonate esters. The ground state molecular properties and reactions of these compounds were found to be consistent with predictions based upon previous SCF molecular orbital treatments of the π-systems of these analogs.

Previous papers in this series have dealt with formulation of mesoionic purinone analogs, a large, new class of bicyclic heteroaromatic compounds, whose ring systems possess π-electron systems isoelectronic with those of the purinones (2,3). Over one hundred of these mesoionic ring systems may be postulated. These can be divided into two groups: the Class I analogs are those derived from known five-membered ring mesoionic systems, while the Class II analogs are derived from known six-membered ring mesoionic systems. These two classes may be further subdivided into three subclasses; the xanthine, hypoxanthine and purin-2-one analogs. The large number of these analogs, and the virtual lack of knowledge concerning the properties of these bicyclic mesoionic structures, prompted comparative quantum chemical studies of these analogs and their covalent isomers, employing methods practical for the treatment of a large series of compounds without detailed knowledge of their molecular geometries.

To date, derivatives of only two Class I mesoionic purinone structures have been reported (4); a xanthine analog **1** (5), a naturally occuring hypoxanthine analog **2** (6) and a 9-ribosyl derivative of **2** which has been isolated from the tRNA of pig liver and yeast (7,8). The syntheses of several mesoionic Class II hypoxanthine analogs and their conjugate acids have been reported (9).



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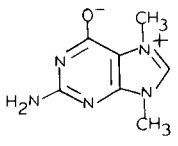

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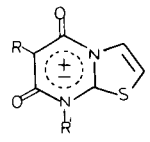
We wish to report the synthesis of the first members of the Class II xanthine analogs. *Anhydro*-5-hydroxy-8-alkylthiazolo[3,2-*a*]pyrimidinium-7-one hydroxide (**3**) may be thought of as resulting from the fusion of an electron rich thiazole ring with the electron deficient portion of the known mesoionic 1,3-dimethylpyrimidin-4,6-dione **4** ($R_1 = R_3 = H$, $R_2 = R_4 = CH_3$) (9). Various derivatives



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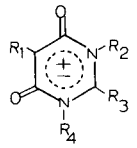

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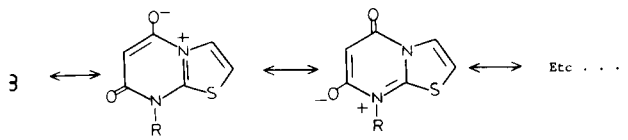
of **3** were prepared and their ground state properties and reactions compared with the results of the previous theoretical treatments (3) and, where possible, to the properties of derivatives of **4**.

These xanthine analogs, like other mesoionic compounds, can not be satisfactorily represented by any covalent or single dipolar structure. They can, however, be represented by no fewer than (in the case of the mesoionic thiazolopyrimidines) nine dipolar valence bond forms.



Initial attempts to prepare derivatives of **3**, by reaction of malonyl dichloride with the appropriately substituted alkylaminothiazoles followed by proton abstraction, were unsuccessful, resulting in decomposition at the acylation step. Kappe and Lube reported the use of bis(2,4,6-tri-

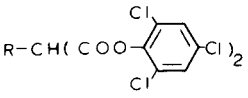
TABLE I

Mesoionic Thiazolo[3,2-*a*]pyrimidine-5,7-diones

	R	R′	Formula	M.P.	Recryst. (a) Solvent	% Yield (b)	Analysis - Found (Calcd.) C	H	N	S	Cl
3a	-H	$-C_2H_5$	$C_8H_8N_2O_2S$	206-208°	T	98.7	49.13	4.17	14.10	16.12	–
							(48.98)	(4.18)	(14.28)	(16.31)	–
3b	$-CH_3$	$-C_2H_5$	$C_9H_{10}N_2O_2S$	168-170°	T	90.6	51.62	4.80	13.41	15.20	–
							(51.43)	(4.80)	(13.33)	(15.22)	–
3c	$-CH_2C_6H_5$	$-C_2H_5$	$C_{15}H_{14}N_2O_2S$	156-158°	T	86.4	62.45	4.75	9.68	11.20	–
							(62.93)	(4.93)	(9.78)	(11.17)	–
3d	-H	$-CH_2C_6H_5$	$C_{13}H_{10}N_2O_2S$	241-242°	A	82.0	60.37	3.91	10.77	12.22	–
							(60.47)	(3.90)	(10.85)	(12.39)	–
3e	$-CH_3$	$-CH_2C_6H_5$	$C_{14}H_{12}N_2O_2S$	172-174°	B	74.1	61.57	4.31	10.12	11.57	–
							(61.76)	(4.44)	(10.29)	(11.75)	–
3f	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$C_{20}H_{16}N_2O_2S$	122-124°	E	74.0	68.74	4.82	8.01	9.15	–
							(68.94)	(4.63)	(8.04)	(9.18)	–
3g	-H	$-CH_2CH_2N(CH_3)_2$	$C_{10}H_{13}N_3O_2S$	144-145°	P	88.3	50.01	5.34	17.49	13.14	–
							(50.02)	(5.48)	(17.56)	(13.37)	–
3h	-H	3,4-$C_6H_3Cl_2CH_2$-	$C_{13}H_8Cl_2N_2O_2S$	268-269°	D	92.8	47.69	2.55	8.60	9.89	21.78
							(47.72)	(2.46)	(8.56)	(9.80)	(21.67)
3i	$-CH_3$	3,4-$C_6H_3Cl_2CH_2$-	$C_{14}H_{10}Cl_2N_2O_2S$	241-242°	E	97.8	49.38	2.89	8.38	9.56	20.68
							(49.28)	(2.94)	(8.21)	(9.40)	(20.78)

(a) Recrystallization Solvents: Toluene (T), Absolute ethanol (A), Ethanol 95% (E), Benzene (B), THF-petroleum ether (P), DMF (D). (b) Refers only to the yield of the malonate condensation step.

chlorophenyl)malonate esters **5** as a general method for preparing mesoionic pyrimidine derivatives such as **4** (11). It was found that these esters would react with 2-alkylaminothiazoles to give the desired mesoionic xanthine analogs. 2-Aminothiazole (**6**) was acylated and the resulting amides, **7a-d**, reduced with lithium aluminum hydride to yield the 2-alkylaminothiazoles **8a-d**. Heating **8** with the malonate esters **5** at 160° gives the mesoionic xanthine **3** in good yield (see Table I).



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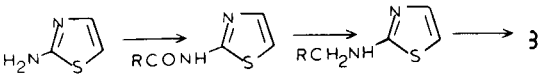
5a R = -H
b R = -CH_3
c R = -$CH_2C_6H_5$



6 **7** **8** **3**

7a R = -CH_3
b R = -C_6H_5
c R = -CH_2Cl
d R = 3,4-diClϕ

8a R = -CH_3
b R = -C_6H_5
c R = -$CH_2N(CH_3)_2$
d R = 3,4-diClϕ

Potts and Sorm (12) have reported the use of carbon suboxide for preparing mesoionic pyrimidine derivatives **4**. Kappe and Lube have also reported the use of carbon suboxide in preparing these 5-unsubstituted derivatives, since the malonate ester method appeared to be impractical in this case due to very poor yields (11). It was found, however, that with a slight modification, the malonate condensation method usually gives near quantitative yields of Class II mesoionic xanthines, either substituted or unsubstituted at the 6-position. Compound **3a** was prepared by the carbon suboxide method and was found to be identical to that obtained from the malonate condensation reaction. The inconvenience of preparing carbon suboxide may limit the practical application of this method to thermally unstable alkylaminoheterocycles.

In the nmr spectra, the signals assigned to the thiazole protons of **3a-i** have undergone a downfield shift of 50-70 Hz as compared to the thiazole proton signals of their alkylamino- or acylaminothiazole precursors. This might be expected due to acylation of the ring nitrogen and the extended conjugation resulting from cyclization. In the 6-unsubstituted mesoionic xanthine analogs (*e.g.* **3a**, **3d**, **3g**, **3h**, **21a**, **21b**) the signal assigned to the C6-H proton appears as a sharp singlet between δ 4.5 to 5.5, integrating for one proton. This high field absorption may be rationalized by the high electron density calculated for this position (3). Potts and Sorm (12) have recently reported that in the spectra of the monocyclic mesoionic pyrimidines **4** taken in trifluoroacetic acid, the C5-H proton signal undergoes a downfield solvent shift of *ca.* 1.5 ppm when compared to spectra in deuterated DMSO. This shift, and accompanying broadening of the signal, has been rationalized to have resulted from an increase in the ring current due to protonation on oxygen. In trifluoroacetic acid, the C6-H proton signal of the mesoionic xanthine analogs also undergoes a downfield solvent shift of 1.5-1.8 ppm, accompanied by broadening. Although protonation on oxygen may be expected, protonation is also possible on carbon at the 6-position. The C6 proton of **3a** and **3d** undergoes immediate exchange in perdeuteriomethanol or deuteriomethanol when catalyzed by a trace of sulfuric or trifluoroacetic acid. This exchange in perdeuteriomethanol is complete within 60 hours at room temperature in the absence of an acid catalyst. Although these experiments demonstrate the facile protonation of the 6-position, they do not distinguish between carbon versus oxygen protonation as the origin of the nmr spectral shifts in trifluoroacetic acid.

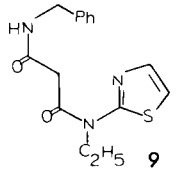
While 2-acylaminothiazoles usually fail to give a parent molecular ion in the mass spectrum, the molecular ion is quite prominant (*ca.* 25% rel. intensity) in the spectra of the mesoionic analogs of this series, indicating an enhanced degree of aromatic stability. The fragmentation pattern observed is consistant throughout the series: bond rupture is possible at either the N4-C5 or C7-N8 bond followed by a loss of an m/e 28 unit fragment. To identify this m/e 28 fragment, **7a** was reduced with lithium aluminum deuteride and then reacted with **5b** to give the methylene-deuterated derivative of **3b**. The mass spectrum of this compound indicates the fragment lost is carbon monoxide, and not ethylene. When unsubstituted in the 6-position (*e.g.* **3a**) an additional fragmentation pathway is observed, that due to loss of carbon suboxide.

True integrated infrared carbonyl absorption intensities were determined for the pseudocarbonyl groups of **3c** and **3g** employing the method of direct integration by Ramsay (13). The absorption intensities of carbonyl bands can be used as a measure of polarity of the carbonyl group. Two bands are generally observed in the carbonyl stretching region for these analogs, at 1690-1680 cm^{-1} and 1655-1630 cm^{-1}. In determining the integrated absorption intensities, the intensities of the two bands were averaged, discounting the overlap intensity. The average integrated intensities determined for the carbonyl bands of **3c** and **3g** (11.7 x 10^4 and 9.9 x 10^4 $M^{-1}lcm^{-2}$/C=O, respectively) are in the same range as those determined for sydnones (7-12 x 10^4 $M^{-1}lcm^{-2}$) (14) and isosydnones (12-12.5 x $10^4 lcm^{-2}$) (15), and are much higher than those observed for covalent carbonyl groups (*e.g.* ketones, 1.5-2.4 x 10^4, or amides, 3.7-5.7 x 10^4 $M^{-1}lcm^{-2}$), indicating a highly

polar nature for these pseudocarbonyl groups. On the other hand, the carbonyl stretching frequencies of these analogs suggest bond orders similar to covalent models. These findings support the charge distribution and bond order calculations previously reported (3).

Potts and Sorm (12) have found the monocyclic mesoionic compound **4** (R_1 = R_3 = H, R_2 = R_4 = phenyl) to undergo hydrolytic ring-opening upon dissolution in wet acetonitrile. The mesoionic xanthine analogs, *e.g.* **3a** and **3c**, display a greater degree of stability and can be recrystallized from 5% hydrochloric acid. Refluxing **3a** or **3c** in 5% HCl for five hours followed by neutralization does, however, lead to ring opening, 2-ethylaminothiazole being isolated.

Nucleophilic attack was predicted by the localization energy method to occur at either the 5- or 7-position (purine 2- or 6-position) of **3a** while the nucleophilic superdelocalizability and frontier electron density indicies favor attack at the 8a-position (purine 4-position) (3). Although at room temperature, **3a** does not react with benzylamine in ethanol over a period of one hundred hours, refluxing **3a** with benzylamine in tetrahydrofuran for 26 hours gives rise to a thiazole derivative possessing two amide groups. This product could presumably arise from attack at the 5-position to give **9** or at the 7-position



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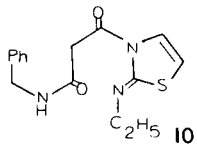

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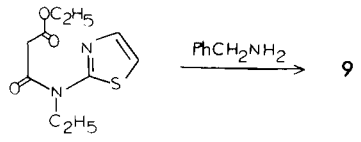
to give **10**. In order to determine the structure of the ring-opened product, ethyl malonyl chloride **11** was reacted with 2-ethylaminothiazole (**7a**) to afford **12**. Compound **12** was reacted with benzylamine to yield **9**, which was identical to that product obtained from the ring-opening reaction. Although it is possible that acylation of **7a** could



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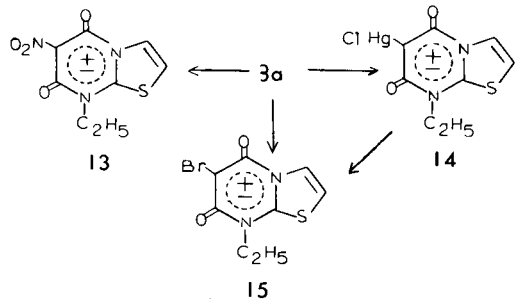
have occurred at the ring nitrogen, amino group acylation occurs consistantly under the conditions employed (16-18). The spectral properties, infrared and ultraviolet spectra, support structure **12** rather than its imino isomer.

Refluxing **3a** in 5% aqueous sodium hydroxide for thirty minutes, followed by neutralization, gives a mixture of products with a strong sulfur-like odor, whose nmr spectrum is devoid of thiazole ring proton signals. It appears that attack by hydroxide may have occurred at the 8a-position or possibly at one of the pseudo-carbonyl positions followed by attack at the 8a-position to give a thiazole ring-open product. Difficulties encountered in separation precluded product identification. Evidence for thiazole ring-opening is also supported by two other factors. Base hydrolysis of thiazolium compounds has been reported to give rise to vinyl mercaptans by hydroxide attack at the thiazole 2-position, the products not being isolated presumably due to possible di- and trimerization (19-21). Secondly, 2-(*N*-acetyl-*N*-ethylamino)thiazole was found to be stable to these reaction conditions.

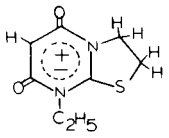
Molecular orbital calculation of frontier electron densities, electrophilic superdelocalizability and localization energy terms, predict the 6-position (purine 1-position) of **3a** to be favored for electrophilic attack (3) and this has been found to be true. Nitration of **3a**, employing anhydrous nitric acid, proceeds rapidly at 0° to give a quantitative yield of the expected product **13**. Chloromercuration, employing mild reaction conditions, also proceeds quantitatively to give **14**, although amino thiazoles usually chloromercurate readily at the thiazole 4- and 5-position (21). Bromination of **3a** with bromine and



13 14 15

an intermediate-base ion exchange resin in tetrahydrofuran yields **15** which can also be obtained by bromination of the chloromercuri derivative **14** with a bromine-ammonium bromide mixture.

Several attempts were made to catalytically reduce the C2-C3 double bond of **3a** to **16**. Reductions employing palladium or platinum (chloroplatinic acid) at both atmospheric and 50 psi of hydrogen were unsuccessful, starting material being recovered. Compound **16** was prepared from 2-amino-2-thiazoline by acetylation, reduction to **17**, followed by reaction with **5a**. Compound **16** was found to be higher melting than its unsaturated counterpart and a hypsochromic shift was observed in the ultraviolet spectrum of **16** indicating decreased conjugation. An attempt to dehydrogenate **16** to **3a** by stirring (up to 100 hours) and heating with 5% palladium on charcoal was unsuccessful.



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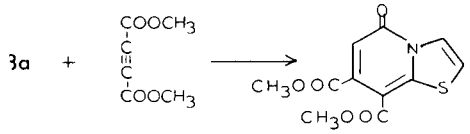
It has been reported that the monocyclic mesoionic pyrimidines **4**, as well as pyridine ring-fused derivatives of **4** undergo 1,4-dipolar cycloaddition reactions (11,22,23). Theoretical considerations involving the values of the eigenvectors of the frontier orbitals of the Class II xanthine analogs indicate the possibility that **3a** should also react with dipolarophiles (3). Compound **3a** was reacted with dimethylacetylene dicarboxylate (**18**) to give **19** in good



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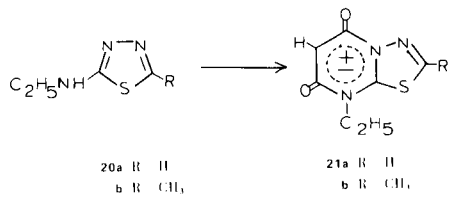
yield. This synthetic sequence may provide a novel method for the preparation of heterocyclic ring-fused 2-pyridones which might otherwise be difficult to obtain. This scheme is especially attractive for the preparation of thiazolo[3,2-*a*]pyridin-5-ones, due to the ready accessability of mesoionic thiazolo[3,2-*a*]pyrimidinediones from commercially available starting material.

To test the generality of the malonate condensation method, **5a** was condensed with the 1,3,4-thiadiazole derivatives **20a** and **20b**, where the N3-position of **20** is less basic than the corresponding N3-position of the thiazoles. The products **21a** and **21b** were obtained in good yield.



20a R = H
b R = CH_3

21a R = H
b R = CH_3

Conclusion.

Convenient synthetic routes have been found which may be used in the preparation of a large number of Class II mesoionic xanthine analogs.

Many of the physical properties (melting point, solubility in organic solvents, carbonyl band frequencies, etc.) of the mesoionic thiazolo[3,2-*a*]pyrimidinediones **3** appear to be not unusual for what one might expect of analogous covalent structures. Reference to these structures as betaines or inner salts, therefore, would seem to be inappropriate. Since this subclass of mesoionic purinone analogs has been predicted to contain the most polar analogs, structures within the remaining subclasses may be expected to display many molecular properties very similar to those of their covalent isomers.

The mesoionic thiazolo[3,2-*a*]pyrimidinediones are thermally stable and are more resistant to hydrolytic ring opening than the mesoionic pyrimidones **4**; thus electrophilic substitution reactions proceed readily in these bicyclic compounds. The moderate reactivity of these compounds toward amines may suggest the possibility of their utility as selective acylating agents. The pharmacological properties of these compounds are currently being evaluated.

EXPERIMENTAL

Pmr spectra were obtained on a Varian T-60 spectrometer and chemical shifts are reported relative to TMS. Ultraviolet spectra were recorded on a Carey-15 spectrophotometer. Infrared spectra were obtained on a Beckman IR-18 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. All melting points were determined by a Mel-Temp melting point apparatus and are uncorrected. Mass spectra were obtained by a Hitachi-Perkin-Elmer RMC-6 single focusing mass spectrometer, using the solid sample direct inlet.

Anhydro-6-ethyl-5-hydroxythiazolo[3,2-*a*]pyrimidinium-7-one Hydroxide (**3a**).

Method A.

Bis(2,4,6-trichlorophenyl)malonate (**5a**) (3.69 g., 7.8 mmoles) and 2-ethylaminothiazole (**8a**) (1.0 g., 7.8 mmoles) were heated on an oil bath at 160° until a clear melt resulted (3 minutes). A slow stream of nitrogen was passed through the flask, during the heating period to remove 2,4,6-trichlorophenol. When cool, the resultant gum was triturated with anhydrous ether (30 ml.) until crystallization occurred. Recrystallization from toluene yielded 1.5 g. (98.7%) of **3a** as white crystals, m.p. 206-208°; ir (chloroform): 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.6 (t, 3H, $-CH_3$), 4.2 (q, 2H, $-CH_2-$), 5.2 (s, 1H, C_6-H), 7.2 (d, 2H) and 8.25 (d, 1H, thiazole protons); (DMSO-d_6) δ 1.05 (t, 3H), 3.85 (q, 2H), 4.55 (s, 1H), 7.42 (d, 1H), 7.95 (d, 1H); (trifluoroacetic acid) δ 1.6 (t, 3H), 4.4 (q, 2H), 6.35 (broad s, 1H), 7.75 (d, 1H), 8.40 (d, 1H); uv max (water): 180 nm (ε 3800), 248 (27,500), 242 (29,000); mass spectrum (70 eV) m/e (relative intensity) 196 (27.8), 168 (10.3), 128 (29.7), 113 (100), 100 (32.1), 69 (37.1). See Table I for analytical data.

Method B.

Liquid carbon suboxide (24) (1 ml.) was added to a solution of 2-ethylaminothiazole (**8a**) (0.06 g., 5 mmoles) in anhydrous ether (10 ml.) at 0° with the immediate formation of a white precipitate. The precipitate was collected and recrystallized from toluene to give 0.08 g. (87.2%) of **3a**, identical with an authentic sample prepared by Method A.

The mesoionic thiazolopyrimidines in Table I were obtained in a manner similar to Method A used for the preparation of **3a**, by heating the 2-alkylaminothiazole with an equimolar amount of **5** at 160° until a clear melt resulted (*ca.* 1-5 minutes). The product was crystallized by trituration with anhydrous ether.

2-(3,4-Dichlorobenzamido)thiazole (**7d**).

3,4-Dichlorobenzoyl chloride (2.1 g., 10 mmoles) was added dropwise with stirring to a solution of 2-aminothiazole (1.0 g., 10 mmoles) and triethylamine (1.1 g., 11 mmoles) in THF (20 ml.) at 0°. The reaction was allowed to stir at room temperature for 2.5 hours, was filtered and the filtrate evaporated to dryness *in vacuo*. Recrystallization from absolute ethanol afforded 2.2 g. (80.8%) of **7d** as off-white crystals, m.p. 189-191°; ir (chloroform): 1670 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 6.7 (d, 1H) and 7.2 (d, 1H, thiazole protons), 7.6 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{10}H_6Cl_2N_2OS$: C, 43.97; H, 2.21; N, 10.26; S, 11.74. Found: C, 44.02; H, 2.31; N, 10.24; S, 11.92.

The amides **7a-c** were prepared in a manner similar to that employed for **7d**: 2-Acetamidothiazole **7a**, 98.6%, m.p. 203-204° [lit. (25) 205°. 2-Benzamidothiazole **7b**, 80.0%, m.p. 150-151° [lit. (25) 152°]. 2-Chloroacetamidothiazole **7c**, 68.5%, m.p. 159-160° [lit. (26) 159-160°].

2-Dimethylaminoacetamidothiazole (**7e**).

Dimethylamine was passed through a stirred solution of 2-chloroacetamidothiazole (**7c**) (3.0 g., 1.7 mmoles) in tetrahydrofuran (100 ml.) at room temperature, until no further precipitate formation was observed. The reaction mixture was filtered and the filtrate evaporated *in vacuo* to an oil which crystallized upon standing. Recrystallization from benzene-petroleum ether gave 3.1 g. (98.5%) of **7e** as white needles, m.p. 70-71°; ir (chloroform): 3270 (NH), 1680 (C=O), 1525 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 2.65 (s, 6H, $-N(CH_3)_2$), 3.45 (s, 2H, $-CH_2-$), 7.2 (d, 1H) and 7.7 (d, 1H, thiazole protons).

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.40; H, 5.99; N, 22.69; S, 17.28. Found: C, 45.38; H, 6.03; N, 22.53; S, 17.07.

2-(3,4-Dichlorobenzylamino)thiazole (**8d**).

Under a nitrogen atmosphere, **7d** (5.44 g., 20 mmoles) was added in small portions to a stirred suspension of lithium aluminum hydride (0.84 g., 33 mmoles) in THF (30 ml.) at 0°. The reaction mixture was refluxed for 2 hours and then cooled to 0°. Water was added dropwise until there was no further evolution of hydrogen. Filtration and evaporation of the filtrate *in vacuo* resulted in a colorless oil which crystallized upon standing. Recrystallization from 2-propanol gave 4.8 g. (93%) of **8d** as colorless needles, m.p. 133-134°; ir (deuteriochloroform): 3380 (NH) cm^{-1}; nmr (deuteriochloroform): δ 4.7 (s, 2H, benzyl-CH_2-), 6.6 (d, 1H) and 7.3 (d, 1H, thiazole protons), 7.7 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{10}H_8N_2SCl_2$: C, 46.34; H, 3.11; N, 10.81; S, 12.37. Found: C, 46.55; H, 3.03; N, 10.94; S, 12.10.

The amines **8a-c** were prepared in a manner similar to that employed for **8d**: 2-Ethylaminothiazole **8a**, 95% m.p. 48-49° [lit. (27) 49-50°]. 2-Benzylaminothiazole **8b**, 63.2%, m.p. 126-127° [lit. (27) 126-127°]. 2-(2-Dimethylaminoethylamino)thiazole **8c**, 80%, b.p. 83-84°/0.45 mm., [lit. (28) 83-84°/0.45 mm.].

N-Benzyl-*N'*-(2-thiazolyl)-*N'*-ethylmalonamide (**9**).

Method A.

A solution of **3a** (0.2 g., 1 mmole) and benzylamine (0.1 g., 1 mmole) in tetrahydrofuran (50 ml.) was refluxed until tlc analysis indicated the disappearance of starting material (26 hours). The solvent was evaporated *in vacuo* and the product recrystallized from tetrahydrofuran/petroleum ether to yield 0.3 g. (99.1%) of **9** as white crystals, m.p. 139-140°; ir (chloroform): 3300 (N-H), 1670 (C=O), 1650 (C=O), 1530 (C=N) cm^{-1}; nmr (deuteriochloroform) δ 1.5 (t, 3H, $-CH_3$), 3.8 (s, 2H, $-COCH_2CO-$), 4.3-4.65 (m, 4H, benzyl and ethyl $-CH_2-$), 7.2 (d, 1H, thiazole proton), 7.5 (s, 5H, benzyl protons), 7.7 (d, 1H, thiazole proton), 8.0 (broad signal, 1H, -NH); mass spectrum (70 eV) m/e (relative intensity) 260 (0.7), 205 (0.7), 148 (12.5), 128 (55), 113 (100), 106 (20), 91 (51), the parent molecular ion was not observed.

Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.40; H, 5.65; N, 13.85; S, 10.55. Found: C, 59.19; H, 5.47; N, 13.64; S, 10.68.

Method B.

Ethyl malonyl chloride (0.82 g., 5.5 mmoles) in THF (5 ml.) was added dropwise with stirring to a solution of **7a** (2.56 g., 5.4 mmoles) and triethylamine (0.54 g., 5.4 mmoles) in THF (30 ml.). The reaction was allowed to stir overnight (18 hours), was filtered and the filtrate was evaporated *in vacuo* to a pale orange oil. The oil was taken up in chloroform (15 ml.) and passed through a column of Rexyn 101 (H+) (3 g.) to remove any residual 2-ethylaminothiazole to yield 0.7 g. (53.8%) of **12** as colorless liquid; ir (neat) 1745 (C=O), 1670 (C=O), 1510 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 1.5 (t, 6H, $-CH_3$), 3.9 (s, 2H, $-COCH_2-CO-$), 4.4 (q, 4H, ethyl and ethoxy CH_2), 7.25 (d, 1H) and 7.75 (d, 1H, thiazole protons).

Ethyl *N*-ethyl-*N*-(2-thiazolyl)malonamate (**12**) (0.1 g., 4.4 mmoles) was refluxed with benzylamine (0.1 g., 9 mmoles) in THF (5 ml.) for 2 hours. After standing overnight, the solution was filtered and white crystals collected. Recrystallization from THF-petroleum ether gave 0.4 g. (30%) of **9** as white crystals, m.p. 138-139°. Spectral data (ir and nmr) was identical to that product obtained from Method A. No depression was observed for mixed melting point.

Anhydro-6-nitro-8-ethyl-5-hydroxythiazolo[3,2-*a*]pyrimidinium-7-one Hydroxide (**13**).

Compound **3a** (0.1 g., 0.5 mmole) was triturated with nitric acid (29) (100%, 1 ml.) at 0° for 2 minutes. The mixture was poured onto 1 g. of ice and stirred for 2 minutes. The crude pink product was filtered, washed twice with water (10 ml.) and air dried. Recrystallization from acetonitrile yielded 0.115 g. (97%) of **13** as yellow crystals, m.p. 240-241°; ir (potassium bromide): 1715 (C=O), 1695 (C=O) cm^{-1}; nmr ($DMSOd_6$): δ 1.35 (t, 3H, $-CH_3$), 4.1 (q, 2H, $-CH_2-$), 7.7 (d, 1H) and 8.3 (d, 1H, thiazole protons).

Anal. Calcd. for $C_7H_7N_3O_4S$: C, 39.80; H, 2.93; N, 17.42; S, 13.29. Found: C, 39.96; H, 3.06; N, 17.33; S, 13.09.

Anhydro-6-chloromercuri-8-ethyl-5-hydroxythiazolo[3,2-*a*]pyridinium-7-one Hydroxide (**14**).

A solution of mercuric chloride (0.16 g.) and sodium acetate (0.32 g.) in water (6 ml.) was added to a solution of **3a** (0.1 g., 0.5 mmole) in water (3 ml.) at 90°. A precipitate formed immediately. The white precipitate was collected and washed successively with 30 ml. portions of water, chloroform and ether. Drying *in vacuo* gave 195 mg. (90.6%) of **14** which slowly decomposed over 250°.

Anal. Calcd. for $C_8H_7N_2O_2SHgCl$: C, 22.27; H, 1.63; N, 6.49; S, 7.43; Hg, 46.51. Found: C, 22.30; H, 1.71; N, 6.52; S, 7.32; Hg, 46.76.

Anhydro-6-bromo-8-ethyl-5-hydroxythiazolo[3,2-*a*]pyridinium-7-one Hydroxide (**15**).

Method A.

Bromine (1.6 g., 10 mmoles) was added dropwise with stirring, at room temperature, to a suspension of **3a** (1.0 g., 5 mmoles) and an intermediate base ion-exchange resin (Baker A-302, 2 g.) in

tetrahydrofuran (10 ml.). A clear solution resulted after the addition of bromine was completed. After 15 minutes of stirring, the precipitate which formed was collected and recrystallized from THF to yield 0.4 g. of **15**. The reaction mother liquor was chilled to 0° and petroleum ether (20 ml.) added to yield, after recrystallization from tetrahydrofuran, an additional 0.2 g. of product, yield 43%. An analytical sample was prepared by recrystallization from THF, m.p. 174-175°; ir (potassium bromide): 1690 (C=O) cm^{-1}; nmr ($DMSOd_6$) δ 1.4 (t, 3H, $-CH_3$), 4.2 (q, 2H, $-CH_2-$), 7.7 (d, 1H), and 8.25 (d, 1H, thiazole protons).

Anal. Calcd. for $C_8H_7BrN_2O_2S$: C, 34.92; H, 2.56; N, 10.18; S, 11.65; Br, 29.04. Found: C, 34.96; H, 3.06; N, 9.80; S, 11.45; Br, 29.10.

Method B.

Ammonium bromide (0.23 g., 2.3 mmoles) was dissolved in methanol (10 ml.) to which water was added to cause complete solution. This solution was added to a suspension of **14** (1.0 g., 2.3 mmoles) in methanol (5 ml.). Bromine (0.4 g., 2.5 mmoles) in methanol (5 ml.) was added dropwise with stirring at room temperature. The solvent was evaporated *in vacuo* to yield an orange oil which was taken up in chloroform (15 ml.), filtered and the solvent removed *in vacuo*. The oil was dissolved in hot THF (5 ml.) and petroleum ether added to yield 0.4 g. of pale yellow crystals. Recrystallization from tetrahydrofuran yielded 0.36 g. (56.3%) of **15**, m.p. 174-176°. Spectral data (ir, nmr) was identical to the spectra of that product obtained from Method A and no depression was observed for a mixed melting point determination.

Anhydro-8-ethyl-5-hydroxythiazolino[3,2-*a*]pyrimidinium-7-one Hydroxide (**16**).

The malonate condensation method was employed, heating **17** (0.3 g., 2.3 mmoles) with **5a** (1.07 g., 2.3 mmoles). Recrystallization from THF gave 0.42 g. (92.5%) of **16** as yellow crystals, m.p. 228-230°; ir (chloroform): 1670 (C=O), 1570 (C=N) cm^{-1}; uv max (water): 222 nm (ε 19,200), 265 (7,500), 284 (sh) (2890); nmr (deuteriochloroform): δ 1.5 (t, 3H, $-CH_3$), 4.0 (m, 4H, thiazoline protons), 4.7 (q, 2H, $-CH_2-$), 5.1 (s, 1H, C_6-H).

Anal. Calcd. for $C_8H_{10}N_2SO_2$: C, 48.47; H, 5.08; N, 14.13; S, 16.17. Found: C, 48.20; H, 5.04; N, 13.91; S, 15.86.

2-Acetamido-2-thiazoline.

Acetyl chloride (0.4 g., 5 mmoles) was added dropwise with stirring to a solution of 2-amino-2-thiazoline (0.5 g., 5 mmoles) and triethylamine (0.5 g., 5 mmoles) in THF (25 ml.) at 0°. After stirring for 2 hours, the solution was filtered and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the reisude from 95% ethanol gave 0.5 g. (69.5%) of product as white crystals, m.p. 198-200° [lit. (30) 196-197°].

2-Ethylamino-2-thiazoline (**17**).

2-Acetamido-2-thiazoline (1.44 g., 10 mmoles) was added in small portions to a suspension of lithium aluminum hydride (0.46 g., 12 mmoles) in THF (25 ml.) at 0°. After addition was complete, the mixture was refluxed for 5 hours; water was added dropwise at 0° to destroy excess reagent. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. Recrystallization from THF-petroluem ether gave 0.52 g. (26.4%) of **17** as white needles, m.p. 82-83°; ir (chloroform): 3440 (NH) cm^{-1}; nmr (deuteriochloroform) δ 1.3 (t, 3H, $-CH_3$), 3.4-4.6 (m, 6H).

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.11; H, 7.74; N, 21.52; S, 24.63. Found: C, 46.05; H, 7.69; N, 21.67; S, 24.82.

7,8-Dicarbomethoxythiazolo[3,2-*a*]pyridin-5-one (**19**).

A solution of **3a** (0.5 g., 2.5 mmoles) and dimethylacetylene dicarboxylate (**18**) (0.7 g., 5 mmoles) in chloroform (25 ml.) was refluxed for 20 hours. The solvent was removed *in vacuo* and the resultant oil triturated with petroleum ether (30 ml.) and allowed to stand overnight (16 hours). The crystals which had formed were collected and recrystallized from isopropanol to yield 0.4 g. (64.8%) of **19** as yellow needles, m.p. 157-158°; ir (chloroform): 1745 (ester C=O), 1710 (ester C=O), 1660 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 4.1 (s, 6H, $-CH_2$), 6.5 (s, 1H, C_6-H), 7.45 (d, 1H) and 8.5 (d, 1H, thiazole protons); mass spectrum (70 ev) m/e (relative intensity) 267 (100), 235 (34.2), 208 (66.8), 181 (16.8).

Anal. Calcd. for $C_{11}H_9NO_5S$: C, 49.43; H, 3.39; N, 5.24; S, 11.98. Found: C, 49.60; H, 3.35; N, 5.12; S, 11.90.

Anhydro-8-ethyl-5-hydroxythiadiazolo[3,2-*a*]pyrimidium-7-one Hydroxide (**21a**).

The malonate condensation method was employed using a mixture of **20a** (10 g., 7.8 mmoles) and **5a** (3.6 g., 7.8 mmoles). Recrystallization from acetonitrile gave 1.1 g. (72.8%) of **21a** as yellow crystals, m.p. 208° dec.; ir (potassium bromide): 1630 (C=O) cm^{-1}; nmr ($DMSOd_6$) δ 1.3 (t, 3H, $-CH_3$), 4.1 (q, 2H, $-CH_2-$), 4.7 (s, 1H, C_6-H), 9.4 (s, 1H, C_2-H).

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.65; H, 3.58; N, 21.31; S, 16.23. Found: C, 42.90; H, 3.70; N, 21.51; S, 16.08.

Anhydro-8-ethyl-5-hydroxy-2-methylthiadiazole[3,2-*a*]pyrimidinium-7-one Hydroxide (**21b**).

The malonate condensation method was employed using **20b** (31) (0.9 g., 6.3 mmoles) and **5a** (2.86 g., 6.3 mmoles). Recrystallization from isopropanol afforded 0.48 g. (36.2%) of **21b** as pale yellow crystals, m.p. 209° dec.; ir (potassium bromide): 1680 (C=O), 1630 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.6 (t, 3H, ethyl CH_3), 3.0 (s, 3H, C_6-CH_3), 4.3 (q, 2H, $-CH_2-$), 5.2 (s, 1H, C_2-H).

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.49; H, 4.30; N, 19.39; S, 15.18. Found: C, 45.52; H, 4.42; N, 19.72; S, 14.94.

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