ride dihydrate in 10 ml of concentrated hydrochloric acid at 60° was slowly added 1.219 g (5.17 mmol) of compound **10**. The resulting solution was stirred at 60° for 1.5 hr. The solid which precipitated during this time was dissolved by the addition of 5 ml of distilled water, and the solution was made basic with 50% potassium hydroxide while maintaining the temperature of the solution at 20–25° by immersing the flask in cold water. The solid which precipitated during neutralization redissolved in the presence of the excess base. The basic solution was diluted to 50 ml with water and extracted with eight 50-ml portions of chloroform. The extract was dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator until the total volume of the solution was less than 50 ml, then concentrated further by evaporation in an air stream. The residual oil soon solidified, and was washed with *ca.* 1.0 ml of a 50:50 mixture of benzene and petroleum ether (bp 60–110°) to give 0.534 g (50%) of crude **13**, mp 107–109°. Recrystallization, performed by dropwise addition of petroleum ether (bp 60–110°) to a benzene solution afforded 0.402 g (38%) of pure **13**: mp 110.5–111.5°; ir 2.90, 3.07, and 3.20 (N–H), 5.90 μ (lactam C=O); nmr ($CDCl_3$) τ 2.69 (s, 5, C_6H_5), 3.51 (s, 1, lactam N–H), 5.92 (d, 1, J = 8.0 Hz, C-5 **H**), 6.25 (d, 1, J = 8.5 Hz, C-3 **H**), 6.36 (s, 3, OCH_3), 6.76 (quartet, 1, $J_{3,4}$ = 8.5 Hz, $J_{4,5}$ = 8.0 Hz, C-4 **H**), 8.41 (s, 2, NH_2).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.38; H, 6.93; N, 13.63.

An additional amount of product could be obtained by further extraction of the basified reaction mixture with benzene. The aqueous layer remaining after the chloroform extractions described above was diluted to *ca.* 200 ml with water and treated with 250 ml of benzene for 12 hr in an apparatus for continuous liquid–liquid extraction. The benzene extract was filtered and concentrated to a small volume under reduced pressure. Upon addition of petroleum ether (bp 60–110°) 0.21 g of white needles separated, mp 109–110°. The total yield of **13** was thereby increased to 0.75 g (71%).

Registry No.—**4**, 21690-64-2; **5a**, 21690-65-3; **6**, 21690-66-4; **7a**, 21690-67-5; **7b**, 21690-68-6; **8**, 21690-69-7; **9**, 21690-70-0; **10**, 21690-71-1; **11**, 21690-72-2; **12a**, 21690-73-3; **12b**, 21690-74-4; **12c**, 21690-75-5; **13**, 21690-76-6; **14**, 21690-77-7

A Novel Thiazole Synthesis.[1] 4,5,6,7-Tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-diones

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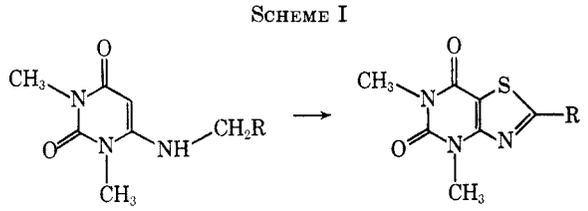
6-Amino-1,3-dimethyluracils (**1**, R = H, COOH, $COOC_2H_5$, C_6H_5, and CF_3) have been found to undergo facile conversion to the corresponding thiazolopyrimidines (**2**) upon treatment with thionyl chloride–pyridine, except for **1**, R = CF_3, where thionyl chloride is more effective in the absence of pyridine. Thiazolopyrimidines (**2**, R = H, COOH, and $COOC_2H_5$) have been reported previously by Schroeder.[2] The reaction is presumed to proceed *via* dehydration of the intermediate thiazoline S-oxides (**6**). A different reaction is observed when an inferior grade of thionyl chloride is used in the absence of pyridine, resulting in the formation of sulfides (**8**) and products derived therefrom. Speculation is offered on the mechanism of thiazole formation from suitably substituted 6-aminouracils.

Treatment of 6-carboxymethylamino-1,3-dimethyluracil (**1b**) with thionyl chloride–pyridine, in order to form the corresponding acid chloride, led to the formation of a highly fluorescent substance which was subsequently shown to be the known[2] thiazolopyrimidine **2c**. The present work is an outgrowth of this chance observation.

6-Amino-1,3-dimethyluracils (**1**, Scheme I) were prepared from 6-amino-1,3-dimethyluracil or 6-chloro-1,3-dimethyluracil and the corresponding amines, as described in Table I. Treatment of **1c** with an excess of thionyl chloride–pyridine at room temperature for 16 hr afforded the thiazolopyrimidine **2c**, a known compound,[2] in 90% yield. In a similar manner, compounds **1a**, **1b**, **1d**, and **1e** were converted to the corresponding thiazoles, as summarized in Table II. This reaction of 6-amino-1,3-dimethyluracils with thionyl chloride to form thiazolo[4,5-*d*]pyrimidines, a class of compounds previously prepared by Schroeder and Dodson from appropriately substituted pyrimido[5,4-*b*][1,4]-thiazines, represents a new synthesis of thiazoles.[3]

SCHEME I



1a, b, c, d, e → **2a, c, d, e**

a, R = H
b, R = COOH
c, R = COOEt
d, R = C_6H_5
e, R = CF_3

This reaction is envisioned as proceeding *via* dehydration of the presumed intermediate thiazoline S-oxides, as depicted in the hypothetical sequence proposed in Scheme II. Thionyl chloride is a bifunctional electrophile. Electrophilic attack at the electron-rich 5 position of **1** affords the intermediate 5-sulfinyl chloride **3**.[4] Dehydrohalogenation affords the sulfine **4**[5] which can cyclize, *via* anion **5**, to form the thiazoline S-oxide anion **6**. Dehydration of **6** *via* Pummerer reac-

(1) Paper I in the series: Reactions of 6-Amino-1,3-dimethyluracils with Thionyl Chloride.

(2) E. F. Schroeder, U. S. Patent 3,155,665 (1964); *Chem. Abstr.*, **62**, 4036 (1965). See also E. F. Schroeder and R. M. Dodson, *J. Amer. Chem. Soc.*, **84**, 1904 (1962).

(3) For examples of other thiazole syntheses, see J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, pp 484–722; "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, Part A, p 385.

(4) J. Szmuszkovicz, *J. Org. Chem.*, **29**, 178 (1964), has reported an analogous reaction of thionyl chloride with indoles to form various isolable indole-3-sulfinyl chlorides or products derived therefrom.

(5) This is analogous to the formation of sulfene intermediates in reactions of some sulfonyl halides. Sulfines, unlike sulfenes, have been isolated. See, for examples, W. A. Sheppard and J. Diekmann, *J. Amer. Chem. Soc.*, **86**, 1891 (1964); J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim.*, **86**, 641 (1967), and references cited therein; G. Optiz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).

TABLE I

6-AMINO-1,3-DIMETHYLURACILS (1)

Amino-uracil	R	Method of preparation (yield,[a] %)	Mp, °C	Analysis[a]
a	H	Chlorodimethyluracil, aqueous methylamine[b]	247–249	
b	COOH	Chlorodimethyluracil, glycine in DMF, base (80)	284–285[c]	Calcd for $C_8H_{11}O_4N_3$: C, 45.07; H, 5.20; N, 19.71. Found: C, 44.94; H, 4.95; N, 19.80.
c	COOEt	Chlorodimethyluracil, glycine ethyl ester, in DMF	184–185[d]	
d	C_6H_5	Aminodimethyluracil, benzylamine, benzylamine·HCl	147–149[e]	
e	CF_3	Chlorodimethyluracil, trifluoroethylamine, in DMSO for 7 days, 25° (15)	207–209.5	Calcd for $C_8H_{10}O_2N_3F_3$: C, 40.48; H, 4.25; N, 17.71. Found: C, 40.38; H, 4.23; N, 17.54.

[a] New compounds only. [b] Lit. mp 244–245°, W. Pfleiderer and K. H. Schundehutte, *Ann.*, **612**, 158 (1958). [c] According to procedure of footnote *d*. [d] Lit. mp 183–184°, W. Pfleiderer, *Chem. Ber.*, **90**, 2604 (1957). [e] Lit. mp 143–144°, C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960).

TABLE II

4,5,6,7-TETRAHYDROTHIAZOLO[4,5-*d*]PYRIMIDINE-5,7-DIONES (2)

Run no.	Uracil	Thiazole	Conditions	Yield, %	Mp, °C	Analysis
1	1a	2a	109 mg 1a, 10 ml $SOCl_2$, 1 ml pyridine, reflux 45 min	65	223.5–224.5[a]	Calcd for $C_7H_7O_2N_3S$: C, 42.60; H, 3.58; N, 21.30; S, 16.3. Found: C, 42.61; H, 3.55; N, 20.89; S, 16.2.
2	1a	2a	200 mg 1a, 40 ml $SOCl_2$, reflux 30 min	14[b]		
3	1b	2c	5.0 g 1b, 200 ml $SOCl_2$, 10 ml pyridine at 25° for 16 hr; ethanol added after removal of $SOCl_2$ to form ester 2c	53	110–111[c]	Calcd for $C_{10}H_{11}O_4N_3S$: C, 44.65; H, 4.12; N, 15.61; S, 11.9. Found: C, 44.60; H, 4.13; N, 15.31; S, 11.9.
4	1b	2c	100 mg 1b, 10 ml $SOCl_2$, reflux 20 min	25[d]		
5	1c	2c	3.0 g 1c, 100 ml $SOCl_2$, 10 ml pyridine at 25° for 16 hr	90	110–111[c]	
6	1c	2c	51 mg 1c, 10 ml $SOCl_2$, reflux 20 min	65[d]		
7	1d	2d	132 mg 1d, 10 ml $SOCl_2$, 0.5 ml pyridine, reflux 15 min	75[d]		
8	1d	2d	13 g 1d, 400 ml $SOCl_2$, reflux 15 min	34	245–248	Calcd for $C_{13}H_{11}O_2N_3S$: C, 57.13; H, 4.06; N, 15.38. Found: C, 56.90; H, 4.20; N, 15.19.
9	1e	2e	800 mg 1e, 200 ml $SOCl_2$, reflux 6 hr	55	77.5–78.5	Calcd for $C_8H_6O_2N_3SF_3$: C, 36.23; H, 2.28; N, 15.84. Found: C, 36.46; H, 2.22; N, 15.40.
10	1e	2e	121 mg 1e, 10 ml $SOCl_2$, 1 ml pyridine, reflux 45 min	Trace[e]		

[a] Lit.[2] mp 223–224°. [b] Tlc analysis showed the presence of **8a**, **9a**, and **10**, as described in the Experimental Section. [c] Lit.[2] mp 115–116°. [d] Crude yield, combined fractions from column chromatography showing one spot by tlc. [e] Tlc analysis.

tion[6] intermediate **7** leads to formation of product thiazole **2**. The intermediates **3**–**7** have not been isolated[7] and are assumed from mechanism considerations.

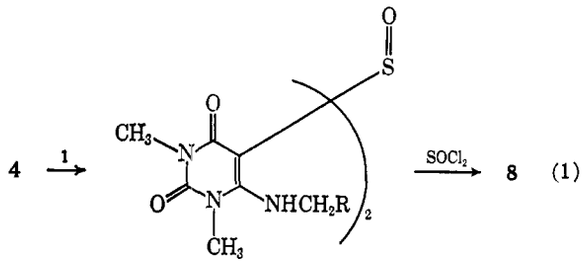
As noted in Table II, thiazole formation from **1a**, **1b**, **1c**, and **1d** is facilitated in the presence of pyridine, presumably by increasing the rate of formation of anion **5** (Scheme II). A greater effect of the presumed base catalysis is seen with the unactivated methylene in **1a** than with the activated methylene in **1c**. The trifluoromethyl compound, **1e**, was an exception in that pyridine had a deleterious effect on thiazole formation, possibly owing to conjugate addition of pyridine and elimination of trifluoroethylamine.

When the reaction was tried in the absence of pyridine, in order to intercept the assumed sulfinyl chloride intermediate **3**, in analogy to the work of Szmuszkovicz,[4] a different course was followed for **1a** as depicted in Scheme III. Reflux of **1a** in thionyl chloride for a few minutes affords sulfide **8a** in good yield, along with a lesser amount of **9a** and small amounts of **10**; only trace amounts of the thiazole **2a** were detected by tlc. Further reaction of **8a** with thionyl chloride afforded **9a** and **10**, and further reaction of **9a** afforded **10**. A similar formation of **8e** was observed when **1e** was treated with practical thionyl chloride under mild conditions. The appearance of sulfides **8a** and **8e** was originally interpreted as evidence that intermediates **4** are more reactive toward **1** than is thionyl chloride in the absence of pyridine, leading to sulfoxides **11** which are converted to sulfides **8** *via* oxygen exchange with thionyl chloride (eq 1).

Alternately, it was considered that sulfides **8** are formed by disproportionation[4] of the sulfinyl chlorides

(6) For recent mechanism discussions and examples of Pummerer reactions, the conversion of sulfoxides to α-substituted sulfides, see W. E. Parham and L. D. Edwards, *J. Org. Chem.*, **33**, 4150 (1968); C. R. Johnson, J. C. Sharp and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967); S. Oae and M. Kise, *ibid.*, 2261 (1968); C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969).

(7) Reaction mixtures from treatment of **1a** with thionyl chloride or thionyl chloride–pyridine were checked carefully *via* tlc for the presence of the assumed sulfinyl chloride intermediate **3a**. This substance either was not present or was too unstable to survive the deliberately mild work-up conditions employed. Szmuszkovicz[4] noted that various indole-3-sulfinyl chlorides and -3-sulfinamides were unstable under a variety of conditions, giving sulfides or products derived therefrom. Sulfides were, in fact, isolated in the present work, but these were only observed when practical grade thionyl chloride was employed, as described in the text.

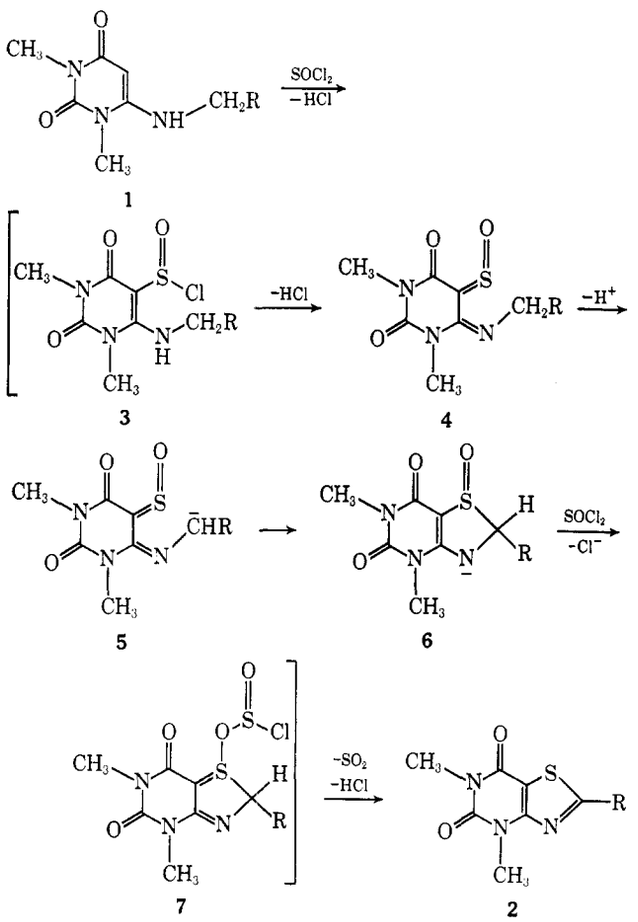


11

3 during work-up. Both possibilities were eliminated when it was observed that the yields of sulfides **8** were, in fact, dependent on the purity of the thionyl chloride employed, the highest rates and yields being realized with old samples of practical grade thionyl chloride, presumably owing to the presence of sulfur chlorides.[8] Thiazole formation from **1a**, therefore, is facilitated in the presence of pyridine at the expense of the reaction path leading to sulfide formation; and, conversely, sulfide formation occurs at the expense of thiazole formation in practical grade thionyl chloride. Sulfide **8a** is not converted to thiazole in appreciable yield upon treatment with thionyl chloride–pyridine.

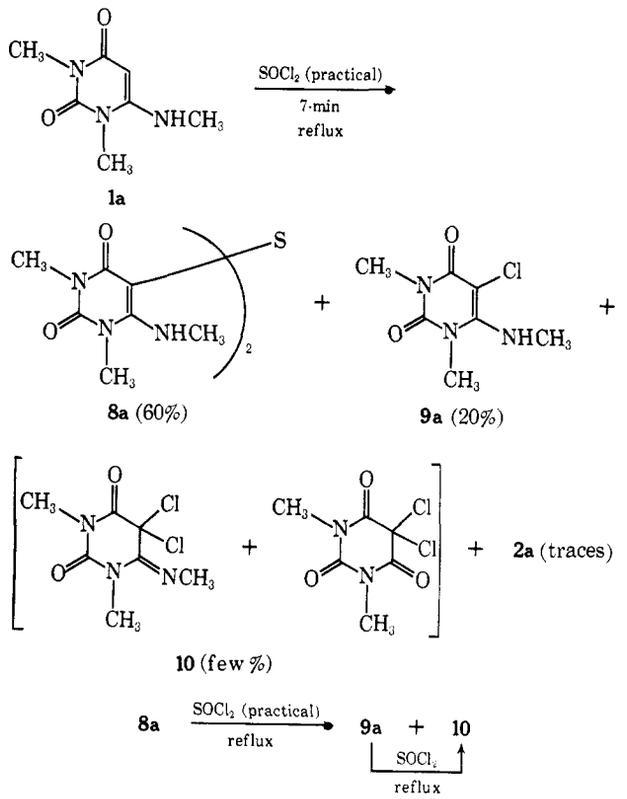
The structural parameters for thiazole formation from other enamines have not been defined as yet. The enamine, in order to function in this synthesis, must contain an NH group and yet react with carbon as the nucleophile. 6-Amino-1,3-dimethyluracils are ideal substrates in this regard, since they exist in the

SCHEME II



(8) *Cf.* ref 4, in which analogous sulfides are formed through use of sulfur monochloride.

SCHEME III



enamine form in solution and react with electrophiles at the 5 position. Ensuing papers in this series will deal with reactions of 6-anilino-1,3-dimethyluracils and 6-α-azaheteroarylamino-1,3-dimethyluracils to form the corresponding thiazines[9] and imidazoles[10] (*via* loss of SO from the intermediate sulfinamides), respectively.

Experimental Section[11-13]

Preparation of 1a, 1b, 1c, 1d, and 1e.—Aminouracils **1a**, **1c**, and **1d** were prepared according to the published procedures as designated in Table I. 6-Carboxymethylamino-1,3-dimethyluracil (**1b**) was prepared by treating a solution of glycine (30 g, 0.40 mol) and sodium hydroxide (16 g, 0.40 mol) in 50 ml of water and 200 ml of DMF with 6-chloro-1,3-dimethyluracil (16.8 g, 0.095 mol) on the steam bath for 5 min. The solvent was removed *in vacuo* and the residue was taken up in 300 ml of water, acidified with dilute HCl, and cooled to crystallize the product. Recrystallization from aqueous ethanol afforded 16.5 g (80%) of the pure **1b**, mp 284–285°. 6-Trifluoroethylamino-1,3-dimethyluracil (**1e**) was prepared by treating 6-chloro-1,3-

(9) I. M. Goldman, Abstracts, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967, papers 51 and 52.

(10) I. M. Goldman, Abstracts, First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968, paper 220.

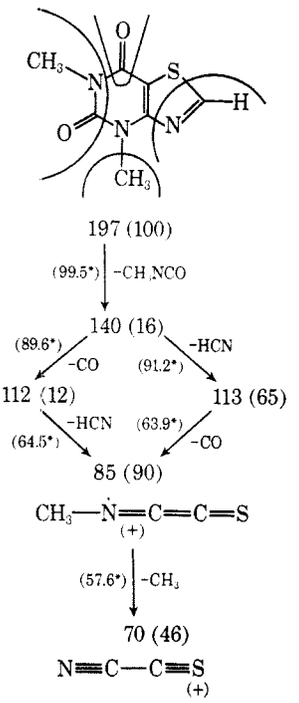
(11) Ultraviolet spectra were recorded on a Cary Model 14. Infrared spectra were recorded on a Perkin-Elmer, Model 21. Mass spectra were recorded by direct inlet at 70 eV on an AEI MS9 or an Hitachi Perkin-Elmer RMU-6D. Nmr spectra were recorded on a Varian A-60 with internal TMS. Matheson Coleman and Bell thionyl chloride (reagent) or thionyl chloride (practical) were employed, as designated. Work-up procedures included removal of thionyl chloride *in vacuo* followed by an addition of ethanol to destroy residual reagent. This was shown not to have any effect on product composition except in runs 3 and 4, where the intermediate acid chloride is not isolated.

(12) The technical assistance of Mr. Edmund G. Andrews and Mr. Richard C. Adams is gratefully acknowledged. The author is indebted to Drs. Gerald O. Dudek and Jerry M. Rice of Harvard University for preliminary mass spectra, and to Mr. Thomas Toolan and associates for microanalytical and spectral data.

(13) See Tables I and II for data not included in the Experimental Section.

dimethyluracil (10 g, 0.062 mol) with 50 ml of 2,2,2-trifluoroethylamine in 100 ml of DMSO at room temperature for 14 days. The excess amine and DMSO were removed *in vacuo* and the residue was recrystallized from chloroform–hexane to yield 2.20 g of colorless crystals, mp 187–195°. A second crop of 1.30 g, mp 182–194°, was obtained by addition of hexane. Recrystallization from chloroform afforded 2.84 g (15%) of pure **1e**, mp 207–209.5°.

4,6-Dimethyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine (2a). Run 1.—Thionyl chloride (reagent, 10 ml) and pyridine (1 ml) were added to **1a** (109 mg) and the mixture was refluxed for 45 min. Excess thionyl chloride and pyridine were removed *in vacuo*. Ethanol was added, to destroy residual thionyl chloride, and then removed *in vacuo*. The yellow residue was triturated with a mixture of chloroform–benzene and the solution was passed through a short column of alumina (Woelm I) to give 146 mg of **2a**. Recrystallization from ethanol gave 84 mg (65%) of the thiazole **2a**, mp 219–220°. A second recrystallization afforded analytically pure **2a**: mp 223.5–224.5°; ir (KBr) 5.90, 6.00, 6.35, and 6.75 μ; uv max (CH_3OH) 299 mμ (ϵ 5900); nmr (saturated in $CDCl_3$) δ 3.40 (s, 3, CH_3N), 3.70 (s, 3, CH_3N), and 8.92 ppm (s, 1); mass spectrum[14] (70 eV) *m/e* (rel intensities and metastable peaks*).



Run 2.—Thionyl chloride (reagent, 40 ml) was added to **1a** (200 mg) and the mixture was refluxed for 0.5 hr. Tlc analysis showed the presence of **2a**, **8a**, **9a**, and **10**. Thionyl chloride was removed *in vacuo* and the residue was treated with ethanol to destroy residual thionyl chloride. The residue, after removal of ethanol *in vacuo*, was dissolved in benzene and passed through a column of alumina (Woelm I) to give 32 mg (14%) of **2a**, mp 222.5–224.5°. Also isolated from this reaction was 64 mg of **8a**. The yields of **8a**, **9a**, and **10** were increased at the expense of **2a** when thionyl chloride (practical) was employed, as described below.

Run 2. Isolation of 8a, 9a, and 10.—Thionyl chloride (practical, 40 ml) was added to **1a** (500 mg) and the mixture was refluxed for 7 min. Tlc analysis showed the presence of **8a** (major), **9a** (minor), **10** (trace), and **2a** (trace). Thionyl chloride was removed *in vacuo* and the residue was treated with ethanol as above. The residue was then triturated with several portions of chloroform. The chloroform was removed *in vacuo* and the residue was passed through a column of alumina (Woelm I) with benzene to give 328 mg (60%) of pure sulfide **8a** from ethyl acetate–chloroform: mp 251–252°; ir (KBr) 3.10, 5.92, 6.10, and 6.35 μ; uv max (CH_3OH) 286 mμ (ϵ 26,800); nmr ($CDCl_3$) δ 3.05 (d, 6, J = 5.5 Hz, $NHCH_3$), 3.33 (s, 6, NCH_3), 3.47 (s, 6, NCH_3), and 8.08 ppm (broad m, 2, $NHCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 368 (44), 201 (44), 200 (51), 170 (78), 169 (89), 156 (13), 141 (31), 112 (13), 82 (41), and 71 (100).

Anal. Calcd for $C_{14}H_{20}O_4N_6S$: C, 45.64; H, 5.47; N, 22.81; S, 8.7. Found: C, 45.70; H, 5.22; N, 23.02; S, 8.7.

The first benzene eluates contained a small amount (40 mg, 6%) of 5,5-dichloro-1,3-dimethyl barbituric acid (**10**) recrystallized from ethanol: mp 158.5–161.5° (pure and mixed with an authentic sample[15]); ir (KBr) 5.80 (sh), 5.87, 5.95, 6.95, and 7.30 μ; nmr ($CDCl_3$) δ 3.41 ppm (s).

Elution with benzene–5% chloroform yielded 133 mg (22%) of 5-chloro-6-methylamino-1,3-dimethylbarbituric acid (**9a**): mp 190–192° (pure and mixed with an authentic sample[16]); ir (KBr) 2.95, 5.85, 6.15, 6.25, and 6.45 μ; uv max (CH_3OH) 243 and 278 mμ (ϵ 7100 and 14,800); nmr ($CDCl_3$) δ 3.03 (d, 3, J = 5.5 Hz, $NHCH_3$), 3.37 (s, 3, NCH_3), 3.50 (s, 3, NCH_3), and 4.67 ppm (broad m, 1, $NHCH_3$).

Anal. Calcd for $C_7H_{10}O_2N_3Cl$: C, 41.29; H, 4.95; N, 20.64; Cl, 17.4. Found: C, 41.26; H, 4.89; N, 20.64; Cl, 17.5.

Treatment of sulfide **8a** (200 mg) with thionyl chloride (practical) at reflux for 30 min, followed by removal of thionyl chloride *in vacuo* and chromatography through alumina as above, afforded 33 mg of 5,5-dichloro-1,3-dimethylbarbituric acid (**10**) and 24 mg of **9a** along with some unchanged **8a**. Treatment of **9a** with thionyl chloride at reflux for 45 min afforded tlc evidence for partial conversion of **9a** to **10**. The rate of conversion of **1a** to **8a**, **9a**, and then **10** was markedly enhanced, as judged by tlc analysis, when **1a** was treated under mild conditions with thionyl chloride (practical) which had been stored for long periods of time. Treatment of **1a** with an especially poor specimen of practical thionyl chloride for 1 min at room temperature afforded **10** in essentially quantitative yield (by tlc). Removal of the thionyl chloride *in vacuo* and precipitation of the residue from methylene chloride–hexane afforded the mixture **10**:[17] mass spectrum (70 eV) *m/e* (rel intensity) 239 (6), 237 (10), 226 (8), 224 (11), 210 (34), 208 (48), 204 (9), 203 (9), 202 (27), 201 (12), 169 (21), 167 (33), 147 (19), 145 (55), 125 (26), 123 (40), 118 (11), 116 (31), 112 (61), 110 (100), 88 (23), 76 (78), and 70 (96).

Conversion of 1b to Ethyl 4,6-Dimethyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine-2-carboxylate (2c). Run 3.—Thionyl chloride (reagent, 200 ml) and pyridine (10 ml) were added to **1b** (5.0 g), and the mixture was kept at 25° for 16 hr. Excess thionyl chloride and pyridine were removed *in vacuo*. Ethanol was added to destroy residual thionyl chloride and to convert the acid chloride to the ester. The ethanol was removed *in vacuo* and the residue was taken up in benzene and passed through a column of alumina (Woelm II) to give 3.33 g (53%) of ester **2c**: one spot by tlc; mp 104–108°. One recrystallization from ethanol afforded pure **2c**: mp 110–111°; ir (KBr) 5.71, 5.78, 6.00, 6.36, 6.67, and 7.96 μ; uv max (CH_3OH) 226 (ϵ 20,000), 252 (ϵ 5100), and 342 mμ (ϵ 6500); nmr ($CDCl_3$) δ 1.47 (t, 3, J = 7.0 Hz, OCH_2CH_3), 3.43 (s, 3, NCH_3), 3.75 (s, 3, NCH_3), and 4.51 ppm (q, 2, J = 7.0 Hz, OCH_2CH_3).

Run 4.—Thionyl chloride (reagent, 10 ml) and **1b** (100 mg, finely powdered to facilitate solution) were heated under reflux for 20 min. Work-up according to run 3 afforded 33 mg (25%) of **2c**: one spot by tlc; mp 99–104°.

Conversion of 1c to 2c. Run 5.—Thionyl chloride (reagent, 100 ml) and pyridine (10 ml) were added to **1c** (3.0 g), and the mixture was kept at 25° for 16 hr. The reaction was worked up as in run 3 to give 2.98 g (90%) of ester **2c**, mp 104–107° (from 2-propanol). A single recrystallization from ethanol afforded pure **2c**, mp 110–111°.

Run 6.—Thionyl chloride (10 ml) and **1c** (51 mg) were heated under reflux for 20 min. Work-up according to the procedure used in run 3 afforded 37 mg (65%) of **2c**, mp 104–108°.

Conversion of 1d to 4,6-Dimethyl-2-phenyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine (2d). Run 7.—Thionyl chloride (reagent, 10 ml) and pyridine (0.5 ml) were added to **1d** (132 mg) and the mixture was heated under reflux for 15 min. Work-up according to the procedure in run 1 afforded 114 mg (75%) of **2d**, mp (crude) 238–241°.

(14) *Cf.* J. M. Rice, G. O. Dudek, and M. Barber, *J. Amer. Chem. Soc.*, **87**, 4569 (1965), for mass spectra of closely related systems.

(15) Lit. mp 157°: H. Biltz and T. Hamburger, *Chem. Ber.*, **49**, 635 (1916).

(16) Lit. mp 181°: H. Bredereck, G. Kupsch, and H. Wieland, *ibid.*, **92**, 583 (1959).

(17) Recrystallization two times from ethanol afforded 5,5-dichloro-1,3-dimethylbarbituric acid. Assignment of the dichloromethylimino structure to the other component of the mixture is based on mechanism considerations and the mass spectrum.

Run 8.—Thionyl chloride (reagent, 400 ml) and **1d** (13 g) were heated under reflux for 15 min. Work-up according to run 3, except that column chromatography was not employed, afforded 5.93 g of crude **2d**, mp 222–232°. Recrystallization from chloroform–ethanol afforded 4.8 g (34%) of pure **2d**: mp 245–248°; ir (KBr) 5.85, 6.04, and 6.37 μ; uv max (CH_3OH) 248 (ε 18,200), 270 (ε 13,900), and 342 mμ (ε 15,200); nmr ($CDCl_3$) δ 3.48 (s, 3), 3.80 (s, 3), 7.55 (m, 3), and 8.05 ppm (m, 2).

Conversion of 1e to 4,6-Dimethyl-2-trifluoromethyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine (2e). Run 9.—Thionyl chloride (reagent, 200 ml) and **1e** (800 mg) were heated under reflux for 6 hr. Work-up according to run 3 afforded 490 mg (55%) of **2e**, mp 74–76°. Recrystallization from chloroform–hexane afforded pure **2e**: mp 77.5–78.5°; ir (KBr) 5.80, 6.02, and 6.33 μ; uv max (CH_3OH) 317 mμ (ε 4800); nmr ($CDCl_3$) δ 3.48 (s, 3) and 3.77 ppm (s, 3); mass spectrum (70 eV) *m/e* (rel intensity and pertinent metastables) 265 (93), 246 (8), 208 (12), 180 (37), 153 (3), 113 (42), 85 (100), 70 (50); 163.2 (265 → 208), 155.7 (208 → 180), 130.0 (180 → 153), 122.1 (265 → 180), 63.9 (113 → 85), and 57.6 (85 → 70).

Run 9. Isolation of 8e.—Thionyl chloride (practical, 10 ml) was added to **1e** (500 mg). A clear yellow solution resulted immediately, and the thionyl chloride was removed *in vacuo*. The residue was recrystallized from methylene chloride–hexane to give 300 mg of crude **8e**, mp 250–253°. Sublimation afforded pure **8e** as colorless crystals: mp 251–253.5°; ir (KBr) 3.1, 5.86, 6.09, and 8.67 μ; uv max (CH_3OH) 280 mμ (ε 20,800); nmr ($CDCl_3$) δ 3.37 (s, 3), 3.49 (s, 3), 3.80 (m, 2, J = 8 Hz), and 8.33 ppm (t, 1, J = 8 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 504 (34), 269 (29), 268 (41), 238 (64), 237 (100), 224 (14), 209 (23), 198 (19), 180 (14), 152 (17), 150 (14), 139 (100), and 119 (25).

Anal. Calcd for $C_{16}H_{18}N_6O_4F_6S$: C, 38.10; H, 3.60; N, 16.66. Found: C, 38.16; H, 3.45; N, 16.57.

Run 10.—Thionyl chloride (reagent, 10 ml) and pyridine (1 ml) were added to **1e** (121 mg) and the mixture was heated under reflux for 45 min. Tlc analysis showed only trace amounts of **2e** along with a large amount of polar material. Work-up in the usual way followed by column chromatography did not lead to the isolation of any **2e**.

Registry No.—**1b**, 21544-64-9; **1e**, 21544-65-0; **2a**, 1781-18-6; **2c**, 3764-04-3; **2d**, 21544-68-3; **2e**, 21544-69-4; **8a**, 21544-70-7; **8e**, 21544-71-8; **9a**, 21544-72-9; **10**, 21544-73-0.

Observation of a Large Isotope Effect in the Manganese Dioxide Oxidation of Benzyl Alcohol

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An intramolecular isotope effect for the manganese dioxide oxidation of α-deuteriobenzyl alcohol in benzene solution is determined to be 14.2 ± 0.9, indicating that the rate-determining step for this heterogeneous reaction involves C–H bond cleavage. When equal amounts of benzyl alcohol and α,α-dideuteriobenzyl alcohol are allowed to compete for a limited amount of activated manganese dioxide, an isotope effect of 18.2 is observed, presumably resulting from the combined primary and secondary kinetic isotope effects, and indicating that the assumed adsorption step is reversible. A primary adsorptive isotope effect is postulated as a possible explanation for the magnitude of the isotope effect observed in this work. These findings are considered in terms of current concepts about the mechanism of oxidations with activated manganese dioxide.

Attempts to elucidate the mechanism of manganese dioxide oxidations underscore the difficulties encountered in the study of heterogeneous reactions.[1] The undetermined nature of the adsorptive process and the chemistry of the surface add to the challenges posed by the usual steric and electronic effects in organic reactions. Previous studies suggest the presence of an adsorptive process[2] and formation of a complex,[3] assert the intermediacy of free radicals,[4] and document the significance of solvent, type and quantity of manganese dioxide, temperature, and time[5] in a variety of oxidations with manganese dioxide.[6] We have attempted to provide further insight into the mechanism by an examination of the oxidation of α-deuteriobenzyl and α,α-dideuteriobenzyl alcohols. Isotope effect data is presented which suggests that the rate-determining step in the manganese dioxide oxidation of benzyl alcohols involves C–H bond cleavage, and that the assumed adsorption step is reversible.

In a previous publication, we reported[7] that activation of precipitated manganese dioxide can be achieved by simple dehydrative techniques, including azeotropic removal of water with benzene. It was also observed that some degree of activation can be achieved simply by extractive removal of water from the wet filter cake, using solvents having an avidity for water. Acetonitrile was found to be especially effective for this purpose. These observations lend credulence to the assumption of Ball, Goodwin, and Morton[2a] that there is an adsorption step in manganese dioxide oxidations of allylic alcohols, in that the thermal, azeotropic, and solvent extraction activation procedures probably serve to liberate active sites on the reagent surface by desorption of adsorbed water. The oxidative process on such a surface would reasonably involve a prior adsorption step which is facilitated by polar functionalities.

Accepting the presence of an adsorptive process, two sets of experiments were planned with a typical substrate, benzyl alcohol, to see if α-C–H bond cleav-

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