Thiazolo-*N*-hydroxyuracils(1)

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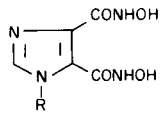
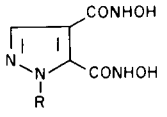
The partial Lossen degradation of the hydroxamic acid group at C-4 or C-5 of sodium 4,5-thiazoledicarbohydroxamate (IIIb) and its 2-methyl analog (IIIe) initiated a multicoursed reaction which furnished a mixture of thiazolo[4,5-*d*]- and thiazolo[5,4-*d*]-*N*-hydroxyuracils. The isomer distribution was sensitive to the solvent systems in which these reactions were carried out. The structure of the isomers so obtained was established by chemical and spectral methods.

The ready transformation of 1-substituted 4,5-imidazole- and 4,5-pyrazoledicarbohydroxamic acids (I and II) to 1-hydroxyxanthines and pyrazolo-*N*-hydroxyuracils, respectively (2,3), prompted us to explore analogous conversions of 4,5-thiazoledicarbohydroxamic acids. Besides wishing to establish if *vicinal* hydroxamic acids in the thiazole series were amenable to a similar reaction sequence, such syntheses would provide a number of thiazolo-*N*-hydroxyuracils for anticancer screening (4). Before commencing this project, there was envisioned the problem of isomer separation and identification which was experienced when the unsymmetrical 4,5-imidazole- and 4,5-pyrazoledicarbohydroxamic acids (I and II) served as starting materials. In these systems, it was found that the initial degradation could take place at either the C-4 or C-5 hydroxamic acid group by benzenesulfonyl chloride. Such a Lossen rearrangement at one of these ring positions in I or II would give rise to the isocyanate which cyclized with the neighboring hydroxamic acid to furnish the bicyclic product. It was not possible to predict rationally the preference shown in such multistaged reactions from I or II to the condensed *N*-hydroxyuracil. It was not surprising to find the isomer distribution quite sensitive to change in solvents and also to the sulfonyl chloride utilized (3). Since in such transformations so many different types of reaction take place and since in a solvent like tetrahydrofuran (THF), the reaction mixture appears heterogeneous, (the sodium hydroxamate being insoluble), no attempt has been made to rationalize the overall course of events. It is reasonable to assume that the facile Lossen reaction (5) initiates this multicourse cyclization, but insufficient data do not permit speculation whether such preferential acylation by sulfonyl halides takes place at the hydroxamate at C-4 or C-5 in I and II. At the onset of this program



I



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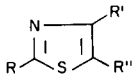
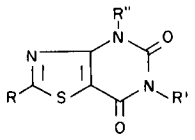
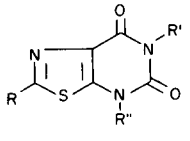


III

where a R = H; R′ = R″ = $CO_2C_2H_5$
b R = H; R′ = R″ = $CONHO^-Na^+$
c R = H; R′ = $CO_2C_2H_5$; R″ = NH_2
d R = CH_3; R′ = R″ = $CO_2C_2H_5$
e R = CH_3; R′ = R″ = $CONHO^-Na^+$



IV



V

where a R = R″ = H; R′ = OH
b R = R″ = H; R′ = $OSO_2C_6H_5$
c R = R′ = R″ = H
d R = CH_3; R′ = OH; R″ = H
e R = CH_3; R′ = $OSO_2C_6H_5$; R″ = H
f R = CH_3; R′ = R″ = H
g R = R′ = R″ = CH_3

a number of years ago, it was hoped that the Lossen degradation of these bis-hydroxamic acids paralleled the behavior of the Hofmann degradation of similarly constituted bis-carboxamides, but no correlation could be established

to date (6). As a matter of fact, the Hofmann degradation of 4,5-thiazoledicarboxamides involved only the 4-amide as witnessed by the isolation of thiazolo[4,5-*d*]uracils (7) while the present study of the corresponding hydroxamates revealed that either of the rearrangeable groups could participate in the construction of the thiazolo[4,5-*d*]- or thiazolo[5,4-*d*]pyrimidine systems.

Starting from ethyl 4,5-thiazoledicarboxylate (IIIa) the hydroxamate (IIIb) was prepared and then treated with benzenesulfonyl chloride in either water or tetrahydrofuran. The conversion of IIIb gave rise to a mixture of IVa and Va (in water) and to the sulfonates (IVb and Vb) (in THF). In a cognate series of reactions, ethyl 2-methyl-4,5-thiazoledicarboxylate (IIId) was transformed in quite the same manner to a mixture of 2-methylthiazolo[4,5-*d*] and thiazolo[5,4-*d*]pyrimidinediones (IVd and Vd) in water and the sulfonates (IVe and Ve) in THF. The task of establishing the structure of these sets of isomers by chemical means proved arduous. The method used so successfully in reducing a number of pyrazolo-*N*-hydroxyuracils by zinc and acid to their corresponding *N*-deoxy derivatives proved generally unreliable in the thiazole series. In a number of these attempted reductions, the evolution of hydrogen sulfide was observed and frequently unidentifiable products were isolated; and only in one instance could reproducible results by obtained (see above). Ultraviolet spectroscopy (UV) was resorted to primarily as a means to assign structures to these isomers although some chemical evidence is also offered. The approach taken is based on the observation that 1-hydroxyxanthines (2) and pyrazolo-*N*-hydroxyuracils (3) possessed identical UV spectra (95% ethanol) to the corresponding *N*-deoxy derivatives.

The UV spectrum of each of the two pairs of thiazolo-*N*-hydroxyuracils was examined. One isomer each in both series exhibited absorption maxima (in water or 95% ethanol) at 255 ± 2 mμ which compared well with the maxima in the UV spectra of thiazolo[5,4-*d*]pyrimidine-5,7-(4*H*, 6*H*)-dione (7-9) and its 2-methyl analog (7, 9, 10). On this basis, Va and Vd were assigned to the thiazolo-[5,4-*d*]pyrimidine system.

The other two isomers, IVa, IVd, exhibited characteristic λ max at 292.5 ± 1 mμ, and were classified as members of the thiazolo[4,5-*d*]pyrimidine series. This assignment is corroborated by the observation that the similarly constituted 2-methylthiazolo[4,5-*d*]-pyrimidine-4,6-(5*H*, 7*H*)-dione (IVf) possessed λ max 293 mμ (H_2O) (7). That IVd was the correct structure and a member of the thiazolo[4,5-*d*]pyrimidine series was reinforced by the following experiments: Reduction of IVd by zinc and acetic acid produced IVf whose UV was identical to the one in the literature (7). Furthermore IVf, on methylation, yielded the trimethyl derivative (IVg) whose physical properties (m.p. 124-126°, λ max (95% C_2H_5OH), 299 mμ, log ε = 3.86) were considerably different (9) from those of the thiazolo[5,4-*d*]pyrimidine isomer (Vg) (m.p. 197-198°, λ max (water), 282 mμ, log ε = 4.32).

The data from these studies revealed that the modified Lossen rearrangement in IIIb and IIIe took place predominantly at the hydroxamic acid group at C-4 in THF (*vide* Experimental Section). However, in water, IIIb gave Va, a product arising from degradation of the hydroxamate at C-5 while IIIe under these conditions involved the hydroxamate at C-4. Considerable work under a variety of conditions and in a number of different solvent systems would be required before vital factors in this series of consecutive reactions could be established.

EXPERIMENTAL (11)

Ethyl 4,5-Thiazoledicarboxylate (IIIa).

Ethyl bromooxalacetate, $H_5C_2O_2CCOCH(Br)CO_2C_2H_5$, as prepared in chloroform by the literature method (12) apparently contained other compounds (NMR evidence) and gave considerably poorer yields of the thiazole esters in the subsequent steps. The following modification furnished pure starting material.

To an ice-cold stirred solution of bromine (16 g.) in carbon tetrachloride (100 ml.) was added a suspension of sodio ethyl oxalacetate (21 g.) in carbon tetrachloride. After 20 minutes, solids were filtered off and washed with carbon tetrachloride. The filtrate was washed twice with water (100 ml.) and dried (sodium sulfate). Distillation gave ethyl bromooxaoacetate (12.5 g.), b.p. 100-105° (0.5 mm.), n^{24} 1.4660, lit. n^{20} 1.4680 (12); NMR (carbon tetrachloride) δ 5.40 (s, CH), 4.33 (two q, CH_2), 1.35 (two t, CH_3).

An ice-cooled stirred solution of ethyl bromooxalacetate (25 g.) in ether (50 ml.) was mixed with an ethereal solution of thioformamide (13) (15 g.) and allowed to stand at 25° for 2 hours. Solvents were distilled and the residue heated at 100° for 2 hours. The oily product was dissolved in carbon tetrachloride and filtered. The mother liquor was washed with 2% ammonium hydroxide, then with water. Distillation gave IIIa (15 g., 70%), b.p. 115-120° at 0.3 mm., (lit. b.p. 175° at 12 mm. (14)); λ max 247 mμ (log ε 3.82), IR (film) 1750 cm^{-1} (C=O); NMR (deuteriochloroform) δ 8.93 (H-2) 4.46, 4.39 (CH_2) 1.43, 1.39 (CH_3), (DMSO) δ 9.35 (H-2), 4.37, 4.34 (CH_2) 1.33, 1.30 (CH_3), (TFAA)(15) δ 10.05 (H-2) 4.61 (CH_2) 1.50 (CH_3).

Ethyl 2-Methyl-4,5-thiazoledicarboxylate (IIId).

This compound (15 g., 66%) was prepared similarly from ethyl bromooxalacetate (25 g.) and thioacetamide (16 g.), b.p. 125-130° at 0.5 mm., [it was not distilled previously but characterized by the carresponding acid (12)]; λ max 257 mμ (log ε 3.89); IR (film) 1760, 1735 sh cm^{-1} (C=O); NMR (deuteriochloroform) δ 2.72 (2-CH_3) 4.41, 4.32 (CH_2) 1.39, 1.35 (CH_3); (TFAA)(15) δ 3.14 (2-CH_3) 4.70 (CH_2) 1.49 (CH_3).

Anal. Calcd. for $C_{10}H_{13}NO_4S$: N, 5.76. Found: N, 5.63.

Ethyl 5-Amino-4-thiazolecarboxylate (IIIc).

This compound was prepared by literature methods (16), m.p. 163°, lit. m.p. 163° (16); λ max 279 mμ (log ε 4.00); IR 1675 cm^{-1} (C=O); NMR (deuteriochloroform) δ 7.87 (H-2) 6.17 (NH_2) 4.37 (CH_2) 1.40 (CH_3); (DMSO) 8.00 (H-2) 7.32 (NH_2) 4.24

(CH_2) 1.28 (CH_3); (TFAA) (15) δ 9.02 (H-2) 4.59 (CH_2) 1.50 (CH_3).

Preparation of the Hydroxamates, IIIb and IIIe.

To a stirred solution of hydroxylamine in ethanol [obtained by neutralizing a stirred suspension of dry powdered hydroxylammonium chloride (15.3 g.) in ethanol (100 ml.) with ethanolic sodium ethoxide (5.1 g. of sodium in 200 ml. at 25°, filtered to remove sodium chloride] was added the ester (IIIa) (22.9 g., 0.1 mole) at 0-5°. After 30 minutes an ethanolic solution of sodium ethoxide (4.9 g. of sodium in 200 ml.) was added and the mixture allowed to stand at 25° for 15 hours. The salt (IIIb) (20 g.) was filtered off, washed with ice cold ethanol and dry ether, and dried *in vacuo*. It was used within a few days without further purification. Similarly, the sodium salt, (IIIe) (24 g.) was prepared from the ester (IIId) (24.3 g., 0.1 mole).

5-Hydroxythiazolo[4,5-*d*]pyrimidine-4,6(5*H*, 7*H*)-dione (IVa) and 6-Hydroxythiazolo[5,4-*d*]pyrimidine-5,7-(4*H*, 6*H*)-dione (Va).

To a stirred solution of sodium salt (IIIb) (4.94 g.) in water (75 ml.) was added benzenesulfonyl chloride (3.4 g.) dropwise at 25-30°, maintaining the *p*H between 7.5-8.5 by the addition of 1 *N* sodium hydroxide as required. After 4 hours at 30°, part of the product had separated and (since it was soluble in sodium hydroxide), the *p*H was adjusted to 3. After 12 hours the product (1 g.) was filtered off and washed with water and ethanol (25 ml.). Since its NMR showed it to be pure Va, it was crystallized from aqueous acetic acid (1:1), or aqueous DMF, m.p. > 400°; λ max 253 mμ (log ε 3.96), λ max (water), 254 mμ (log ε 3.96); IR, 1750, 1690, 1670 cm^{-1} (C=O); NMR (DMSO) δ 8.79 (H-2).

Anal. Calcd. for $C_5H_3N_3O_3S$: C, 32.43; H, 1.62; N, 22.70. Found: C, 32.33; H, 1.80; N, 22.74.

Concentration of the original acid mother liquor together with the aqueous and ethanol washings to 5 ml. afforded a mixture of IVa and Va (2:1, by NMR) m.p. 280-290°. Recrystallization of this mixture thrice from aqueous acetic acid (2:1) yielded pure IVa, m.p. 308-310° (dec.); λ max 292 mμ (log ε 3.79); IR, 1750, 1720, 1675 cm^{-1} (C=O); NMR (DMSO) δ 9.47 (H-2), (TFAA) 9.50.

Anal. Calcd. for $C_5H_3N_3O_3S$: C, 32.43; H, 1.62; N, 22.70. Found: C, 32.49; H, 1.73; N, 22.61.

The yield of the two isomers (1.2 g.) represented a 33% conversion from the ester IIIa. The ratio of IVa and Va of 11:89 was estimated from the NMR integrals of the aromatic protons in DMSO. To prove the structure of IVa and Va by using the chemical shift difference of H-2 would have been ideal if the arguments could have been based on NMR data on suitable model compounds (17).

5-Benzenesulfonyloxythiazolo[4,5-*d*]pyrimidine-4,6(5*H*, 7*H*)-dione (IVb) and 6-Benzenesulfonyloxythiazolo[5,4-*d*]pyrimidine-5,7-(4*H*, 6*H*)-dione (Vb).

A solution of benzenesulfonyl chloride (8 g.) in THF (25 ml.) was added dropwise to a well-stirred suspension of the sodium salt (IIIb) (4.95 g.) in THF (75 ml.) at 0-5° initially. Since no reaction appeared to take place at 5°, quite contrary to our experience in the imidazole and pyrazole series, the mixture was heated at 35-40° for 3 hours. As a matter of fact, reactions conducted at 5° for several hours gave poorer yields. Sodium acetate trihydrate (2 g.) was then added, stirring continued for 1 hour, and the mixture filtered. The solid so obtained was washed with THF (2-25 ml. portions). The THF insoluble residue proved to be inorganic and soluble in dilute acid. The THF filtrates were concentrated *in vacuo* to 25 ml. and diluted with water (200 ml.) and petroleum ether (50 ml.). After 12 hours, the product (2.45 g., 38%, based on IIIb) was filtered off, washed with petroleum ether. It was shown to be a mixture of IVb and Vb (72:28) by NMR. The mixture was washed 4 times with cold ethanol (10 ml.) and the residue crystallized from 1,4-dioxane to give pure IVb, m.p. 258-259° (dec.); λ max 269 (log ε 3.51)sh, 275 (log ε 3.63)sh, 291.5 mμ (log ε 3.75); IR, 1750, 1700 cm^{-1} (C=O); NMR (DMSO) δ 9.54 (H-2) 8.33-7.50 (C_6H_5), (TFAA) 9.56 (H-2) 8.25-7.42 (C_6H_5).

Anal. Calcd. for $C_{11}H_7N_3O_5S_2$: C, 40.61; H, 2.15; N, 12.92. Found: C, 40.71; H, 2.12; N, 13.00.

The alcoholic washings from the above were concentrated to about 10 ml. and diluted with water (5 ml.) to give the product (0.45 g.) m.p. 190-200° (dec.), which contained Vb as the major component (NMR). The mixture was dissolved in acetone (6 ml.) and chromatographed over neutral alumina (120 g.). Elution with acetone-benzene (9:1) gave in the first 5 fractions (25 ml. each) pure Vb (NMR), which crystallized from ethanol, m.p. 233-235° (dec.); λ max 260 (log ε 3.74) sh, 275 (log ε 3.73) sh and 267 mμ (log ε 3.74); IR, 1760, 1710 cm^{-1} (C=O); NMR (DMSO) δ 8.87 (H-2) 8.30-7.50 (C_6H_5).

Anal. Calcd. for $C_{11}H_7N_3O_5S_2$: C, 40.61; H, 2.15; N, 12.92. Found: C, 40.85; H, 2.34; N, 13.00.

Hydrolysis of IVb (2 g.) with 1 *N* sodium hydroxide (30 ml.) at 100° for 5 minutes furnished after acidification (IVa) (1 g., 88% yield), identical with the sample prepared above.

A similar hydrolysis of Vb produced Va in 88% yield.

2-Methyl-5-hydroxythiazolo[4,5-*d*]pyrimidine-4,6(5*H*,7*H*]-dione (IVd) and 2-Methyl-6-hydroxythiazolo[5,4-*d*]pyrimidine-5,7 (4*H*, 6*H*)-dione (Vd).

A solution of IIIe (5.21 g.) in water (75 ml.) was treated with benzenesulfonyl chloride (3.4 g.) as described above for the preparation of IVa and Va. The product isolated from the solution at *p*H 3 was washed with ethanol (50 ml.) and consisted of IV and Vd (10:1 by NMR in sodium deuterioxide, m.p. 295-300°). Recrystallization from aqueous DMF and then from acetic acid-ethanol, 1:1, furnished IVd, m.p. 328-329° (dec.), λ max 292 mμ (log ε 3.86); IR, 1745, 1700, 1675 (sh) cm^{-1} (C=O); NMR (5%, deuterioxide) δ 2.72 (TFAA) 2.97 (CH_3).

Anal. Calcd. for $C_6H_5N_3O_3S$: C, 36.17; H, 2.51; N, 21.10. Found: C, 36.36; H, 2.46; N, 21.13.

Concentration of the original acid mother liquor and the original aqueous acid-ethanol washings to 15 ml. gave a mixture of IVd and Vd (1.6 g., 1:1 by NMR, m.p. 275-285°). Fractional crystallization first from aqueous acetic acid (1:1) (until the NMR data showed the considerable diminution of IVd) followed by several crystallizations from dilute aqueous DMF gave Vd which analyzed for the hydrate, m.p. 296-298° (dec.), λ max 253.5 (log ε 3.93), λ max (water), 254 (log ε 3.95); IR, 1715, 1675 cm^{-1} (C=O); NMR (5% sodium deuterioxide) δ 2.56 (TFAA) 3.07 (CH_3).

Anal. Calcd. for $C_6H_5N_3O_3S \cdot H_2O$: C, 33.17; H, 3.22; N, 19.36. Found: C, 33.44; H, 3.24; N, 19.49.

Thus the conversion of the ester IIId to IVd and Vd (in the ratio of 64:36) proceeded in 62% yield.

2-Methyl-5-benzenesulfonyloxythiazolo[4,5-*d*]pyrimidine-4,6-(5*H*, 7*H*)-dione (IVe) and 2-Methyl-6-benzenesulfonyloxythiazolo-[4,5-*d*]pyrimidine-5,7(4*H*, 6*H*)-dione (Ve).

The reaction of IIIe (5.2 g.) in THF (75 ml.) with benzenesulfonyl chloride (8 g.) in THF (25 ml.) was carried out as described for IVb and Vb. The reaction mixture was filtered and washed with THF (2-25 ml. portions). That residue was suspended between water (100 ml.) and petroleum ether (50 ml.) for 12 hours, filtered, washed with ethanol (25 ml.). It weighed

2.4 g. (m.p. 265-266°) and was shown by NMR to consist mainly of IVe. It crystallized from 1,4-dioxane, m.p. 268-270° dec.; λ max 269 (log ε 3.58)sh, 276 (log ε 3.69)sh, 295 mμ (log ε 3.85); IR, 1770, 1725 cm^{-1} (C=O); NMR (TFAA) δ 8.33-7.50 (C_6H_5) 2.97 (CH_3).

Anal. Calcd. for $C_{12}H_9N_3O_5S_2$: C, 42.48; H, 2.65; N, 12.39. Found: C, 42.59; H, 2.74; N, 12.35.

The THF mother liquors and ethanol washings were concentrated *in vacuo* to 25 ml. and the residue partitioned between water and petroleum ether to yield 1.12 g. of IVe and Ve (2:3 by NMR). When 0.8 g. of this mixture was dissolved in DMSO (2 ml.) at 60°, the solution cooled to 0°, some IVe could be filtered off. The mother liquor was diluted with ethanol (2 ml.) to precipitate more IVe which was filtered. Dilution of that filtrate with water (0.5 ml.) afforded a mixture (0.2 g.) rich in Ve, and was crystallized thrice from ethanol to give pure Ve, m.p. 250-251° dec., λ max 274 (log ε 3.87) sh, 254 mμ (log ε 3.94); IR 1750 (sh), 1730, 1710, 1675 (sh) cm^{-1} (C=O); NMR (TFAA) δ 8.30-7.50 (C_6H_5), 3.09 (CH_3).

Anal. Calcd. for $C_{12}H_9N_3O_5S_2$: C, 42.48; H, 2.65; N, 12.39. Found: C, 42.95; H, 3.05; N, 11.98.

The conversion of IIId to IVe and Ve (80:20) took place in 52% yield.

Basic hydrolysis of IVe and Ve (as described above for IVb and Vb) furnished IVd and Vd in 95 and 68% yield, respectively.

2,5,7-Trimethylthiazolo[4,5-*d*]pyrimidine-4,6(5*H*, 7*H*)-dione (IVg).

Zinc dust (0.5 g.) was added in four portions over 10 minutes to a boiling solution of IVd (1 g.) in aqueous acetic acid (1:1, 50 ml.) and the mixture was heated gently under reflux for 8 hours. Some hydrogen sulfide [lead acetate test paper] was detected. The mixture was filtered hot, concentrated *in vacuo* to 20 ml. and chilled to 5° for 12 hours to give IVf (0.3 g., 33%) m.p. > 400° (lit. m.p. > 360° (7)), λ max 293.5 mμ (log ε 3.85), similar to one in the lit. (7); IR, 1645, 1600 cm^{-1} (C=O); NMR (5% sodium deuterioxide) δ 2.69 (TFAA) δ 2.96 (CH_3).

A solution of IVf (0.2 g.) in 1 *N* sodium hydroxide (10 ml.) was treated with methyl sulfate (1 ml.) at 5° and allowed to warm to 25° (*p*H > 8). After 2 hours at 25°, the mixture was extracted with chloroform and the product (IVg, 0.075 g.) crystallized from methanol, m.p. 124-126°, λ max 299 mμ (log ε 3.86); IR, 1725, 1675 cm^{-1} (C=O); NMR (deuteriochloroform) δ 2.75 (C-CH_3) 3.40, 3.67 (N-CH_3, (TFAA) δ 2.92 (C-CH_3) δ 3.59, 3.85 (N-CH_3).

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.50; H, 4.26; N, 19.90. Found: C, 45.59; H, 4.39; N, 19.98.

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(1) Support for this project through Research Grant CA-04661 from the National Cancer Institute, U. S. Public Health Service is most gratefully acknowledged.

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(3) L. Bauer, D. Dhawan and C. S. Mahajanshetti, *J. Org. Chem.*, 31, 2491 (1966); L. Bauer and C. S. Mahajanshetti, *J. Heterocyclic Chem.*, 4, 325 (1967).

(4) A number of compounds of this type are currently being screened by the Cancer Chemotherapy National Service Center, Bethesda, Maryland.

(5) D. Samuel and B. L. Silver, *J. Am. Chem. Soc.*, 85, 1197 (1963) and references quoted therein.

(6) A congruence between the Lossen and Hofmann degradation of comparable systems has seldom been observed. For example, the Hofmann reaction of 1-alkyl-4,5-imidazole-dicarboxamides produced 9-substituted xanthines exclusively, which involved degradation of the 5-amide group [R. A. Baxter, A. C. McClean, and F. S. Spring, *J. Chem. Soc.*, 523 (1948) and references quoted therein]while the Lossen reaction of the corresponding hydroxamates yielded 7-alkylxanthines which involved degradation of the 4-hydroxamate [Ref. 2]. In that respect, the recent report by G. Desimoni, P. Grünager and P. V. Finzi [*Tetrahedron*, 23, 675 (1967); *Gazz. Chim. Ital.*, 97, 25 (1967)] should be noted. It was found that the Hofmann reaction of 3-phenyl-4,5-isoxazoledicarboxamide involved only the 4-amide to give 3-phenylisoxazolo[4,5-*d*]pyrimidine-5,7(4*H*, 6*H*)-dione (77%) or related compounds. No comparable study using the Lossen degradation is available to date. Again, the Hofmann degradation of 3,4-pyrazoledicarboxamide appeared selective in that only one isomeric pyrazolo-uracil was isolated. Irrespective of the tautomeric species involved in the pyrazole system, the amide at C-3 only was degraded, and the other isomeric product could not be detected. [E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, 78, 3143 (1956)]. However, it was found that in 1-methyl- and 1-phenyl-3,4- and 4,5-pyrazoledicarbohydroxamic acids either one of the hydroxamic acids could be degraded to give a mixture of pyrazolo-*N*-hydroxyuracils [Ref. 3].

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(11) All melting points and boiling points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Petroleum ether refers to the fraction, b.p. 30-60°. NMR spectra were recorded at 60 Mc by a Varian A-60 spectrometer at ambient temperature. All signals are recorded in p.p.m. (δ) downfield from tetramethylsilane (TMS) in organic solvents or sodium 3-(trimethylsilyl)propanesulfonate (TPS) in deuterium oxide or aqueous solvents. All signals reported were singlets or exhibited the multiplicity expected by first order analysis. Abbreviations used for a number of solvents are: THF (tetrahydrofuran), DMSO (dimethyl sulfoxide), DMF (*N,N*-dimethylformamide), TFAA (trifluoroacetic acid); 5% sodium deuterioxide was prepared by dissolving sodium in deuterium oxide. UV spectra were recorded in 95% ethanol (unless otherwise stated) by means of a Beckman DK-1 spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer 337 spectrophotometer, usually in a Nujol mull, unless otherwise stated.

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(15) The unusually large downfield shift of the proton resonance in TFAA of the substituent at C-2 of the thiazole ring is attributed to the fact that the protonated species exists in that solvent. This effect has been described previously for that ring system [P. Haake and W. B. Miller, *J. Am. Chem. Soc.*, 85, 4044 (1963)].

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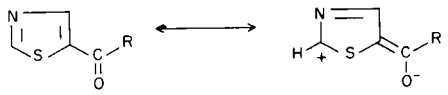
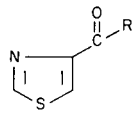
(17) The chemical shift of H-2 in DMSO of IVa and IVb are both downfield from those in Va and Vb (in the same solvent) by

some 0.67 p.p.m. In both IVa and IVb, there is attached a C=O group at position 5 of the original thiazole ring. Since the substituents on that thiazole ring are identical in the pairs, IVa and Va, IVb and Vb, one would expect the similar inductive and anisotropic effects are exerted on H-2. However, since the H-2 resonances of IVa, IVb are so much further downfield than those of Va, Vb, some additional ones might operate in that series. It could be argued that a C=O group at what would be position 5 in the thiazole nomenclature exerts a deshielding effect on H-2 by virtue of the inductive effect expressed by resonance hybrids, A and B. Such an effect would not be felt by H-2 for a comparable 4-carbonyl



A B



C

substituted thiazole, C. However, the NMR spectra of relatively few model compounds have been examined in DMSO. The chemical shifts of the closest related structures are 4- and 5-thiazolecarboxylic acids, which showed (DMSO) H-2 at δ 9.24 and 9.35 respectively. For this pair of isomers, in acetone, the same chemical shifts were found to be at δ 9.21 and 9.26 and the corresponding 4- and 5-thiazolecarboxylic esters had the H-2 resonances at δ 9.03 and 9.28. Similarly, in acetone, 4- and 5-thiazolecarboxaldehydes exhibited δ H-2 at 9.24 and 9.30 respectively. [G. Borgen, S. Gronowitz, R. Dahlbom and B. Holmberg, *Acta Chem. Scand.*, 20, 2593 (1966)]. These differences may perhaps be not as convincing as those found in the two pairs of IVa, Va and IVb, Vb. One other difference in the chemical shift differences of H-2 is noteworthy, *viz.*, the one between ethyl 4,5-thiazoledicarboxylate (IIIa) and ethyl 5-amino-4-thiazolecarboxylate (IIIc) 1.35 p.p.m. in DMSO, 1.06 p.p.m. in deuteriochloroform. Part of this large difference could be attributed to the C=O of the ester at position 5 in IIIa compared to the presence of an NH_2 substituent in IIIc at the same position, with all other parts of IIIa and IIIc being the 4-thiazole carboxylic ester system.

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