Synthesis of 23 from 25.—A mixture of 130 mg of **25**, 10 ml of MeOH, and 1 drop of concentrated hydrochloric acid was refluxed for 2 hr. Evaporation of the solvent gave 98 mg (81%) of crude **23**, mp 105–110°.

Registry No.—**1**, 35042-51-4; **2**, 35040-15-4; **3**, 35040-16-5; **4**, 35040-17-6; **5**, 35040-18-7; **6**, 35040-19-8; **7**, 35040-20-1; **8**, 35040-21-2; **9**, 35040-22-3; **23**, 35040-27-8; 2-isopropyl-6-nitrobenzotriazole 1-oxide, 35040-23-4; 2-cyclohexyl-6-nitrobenzotriazole 1-oxide, 35040-24-5; 1-(2,4-dinitrophenyl)-2-isopropylhydrazine 35040-25-6; 1-(2,4-dinitrophenyl)-2-cyclohexylhydrazine, 35040-26-7.

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cis-8,9-Dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

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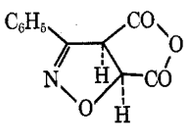
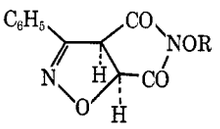
The Lossen rearrangement of *cis*-3-phenyl-2-isoxazoline-*N*-benzenesulfonyloxy-4,5-dicarboximide with aqueous ammonia or methylamine produced a mixture of *cis*-3-phenyl-5-ureido-2-isoxazoline-4-carboxamides and the corresponding 4-carboxylic acids (80–90% yield). Cyclization of these ureido acids with 3.3 *N* hydrochloric acid at 100° furnished the title compounds. Structures of all products were established *via* their pmr and mass spectra; the stereochemistry of the 4,5-disubstituted 2-isoxazolines was shown to be *cis* with $J_{4,5}$ consistently between 9 and 12 Hz. Mechanisms for this selective Lossen degradation are discussed.

As part of our continuing interest in condensed uracils[2] as potential antimetabolites, we explored syntheses of isoxazolo[4,5- and 5,4-*d*]pyrimidinediones.[3] The initial plan to utilize 4,5-isoxazoledicarboxylic esters[4] and to convert these by the standard method[2] to the corresponding bishydroxamates, was thwarted when the latter could not be isolated. Thus, this approach to build the uracil system onto the isoxazole ring *via* the modified Lossen rearrangement of the 4,5-bishydroxamates[2] was abandoned. An alternate route to the isoxazolo pyrimidine system is reported below.

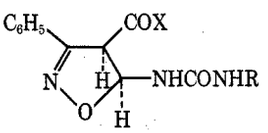
1,3-Dipolar addition of benzonitrile oxide to maleic anhydride produced *cis*-3-phenyl-2-isoxazoline-4,5-dicarboxylic anhydride (**1**).[6,7] It was planned to degrade **1**, *via* the Lossen reaction, to one, or both, of the corresponding β-amino acids[8,9] and then build up, in this instance, the dihydrouracil system. Hydroxylamine smoothly transformed **1** to the corresponding *N*-hydroxyimide, **2a**, which was characterized by an acetate, **2b**, and sulfonate, **2c**. An instantaneous reaction took place between **2c** and ammonia to give the ureido acid and amide, **3a** and **3b**, respectively. The isomers **4a** and **4b** could not be detected. This type of Lossen degradation parallels that of *N*-sulfonyloxyphthalimides with amines reported by Kühle and Wegler.[9] However, these authors found their intermediate *o*-ureidobenzoic acid derivatives spontaneously cyclized to 2,4-quin-



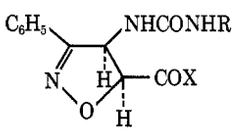
1



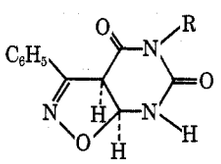
2a, R = H
b, R = $COCH_3$
c, R = $SO_2C_6H_5$



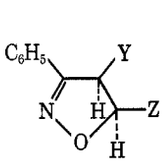
3a, X = OH; R = H
b, X = NH_2; R = H
c, X = OH; R = CH_3
d, X = $NHCH_3$; R = CH_3



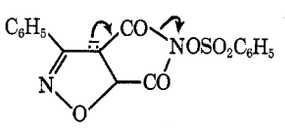
4a, X = OH; R = H
b, X = NH_2; R = H



5a, R = H
b, R = CH_3



6a, Y = CO_2H; Z = $CONH_2$
b, Y = H; Z = $CONH_2$
c, Y = CO_2H; Z = CONHOH



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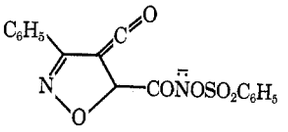

8

(1) Abstracted from the Ph.D. Dissertation of W. J. T., University of Illinois (Medical Center), 1972.

(2) L. Bauer and C. S. Mahajanshetti, *J. Heterocycl. Chem.*, **5**, 331 (1968), and references cited therein.

(3) Recent papers in this field are by G. Desimoni and P. Grünanger, *Gazz. Chim. Ital.*, **98**, 25 (1968); *Tetrahedron*, **23**, 687 (1967); P. Rajagopalan and C. N. Talaty, *ibid.*, **23**, 3541 (1967).

(4) These esters are readily available from the addition of acetylenedicarboxylic esters to nitrile oxides; see ref 5.

(5) C. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer-Verlag, New York, N. Y., 1971.

(6) (a) This anhydride was synthesized in somewhat larger scale from the original paper of A. Quilico, G. S. D'Alcontres, and P. Grünanger, *Gazz. Chim. Ital.*, **80**, 479 (1950); N. S. Isaacs, "Experiments in Physical Organic Chemistry," Macmillan, London, 1969, p 261.

(7) A. Quilico, "Five- and Six-Membered Compounds with Nitrogen and Oxygen," Interscience, New York, N. Y., 1962 p 95.

(8) This approach was demonstrated originally by us [L. Bauer and S. Miarka, *J. Amer. Chem. Soc.*, **79**, 1983 (1957)], later by Kühle and Wegler (ref 9). A recent example of this type of degradation is described by V. L. Plakidin, N. M. Zadorozhnyi and Z. I. Krasota, *J. Org. Chem. USSR*, **6**, 1493 (1970).

(9) E. Kühle and R. Wegler [*Justus Liebigs Ann. Chem.*, **616**, 183 (1958)] found that *N*-(*p*-chlorobenzenesulfonyloxy)phthalimide rearranged with gaseous ammonia at 25° in benzene–dioxane and gave *o*-ureidobenzamide (72%), but cyclized in 10% aqueous ammonia solution. It is plausible that the driving force for this cyclization was the formation of the aromatic 2,4-quinazolinedione.

azolinediones.[9] The rearrangement of **2c** with amines stopped at the ureido acid stage and subsequent cyclization to **5** had to be conducted separately.

The reaction of **2c** with ammonia produced both **3a** and amide, **3b**, the proportion depending upon the concentration of ammonia. With concentrated ammonium hydroxide, alone or in tetrahydrofuran, or ammonia gas in *N,N*-dimethylformamide, **3b** proved to be the major product (80–90%). On reducing the concentration of ammonia, the yield of the acid, **3a**, increased over that of the amide, **3b**. Cyclization of the more readily available ureidoamide, **3b**, with dilute acid produced a negligible quantity of **5a**, accompanied by a large quantity of reddish-brown material. As a matter of fact, all 2-isoxazolines in this study turned bright red on boiling with hydrochloric acid and decomposed subsequently. By contrast, the ureido acid, **3a**, cyclized to **5a** with great ease, which is in line with the acid-catalyzed cyclization of β-ureido acids to dihydrouracils.[10]

A similar series of reactions was initiated when **2c** was treated with methylamine to give **3c** and **3d**. Of these, only the acid **3c** cyclized readily to **5b**, while the amide, **3d**, could not be induced to yield any **5b**.

Structure Proof.—Proton magnetic resonance (pmr) spectra readily distinguished between the series based on **3** from isomers **4**, and at the same time established the stereochemistry. It had been demonstrated that in 3-phenyl-2-isoxazolines, in $CDCl_3$, H-5 is the most deshielded proton, irrespective of the type of substituents on C-4 and C-5.[11] A similar anisotropic effect was reported for H-5 in 3-phenylisoxazolidines. Our pmr spectra were all recorded in $(CD_3)_2SO$ due to limited solubilities in $CDCl_3$, and, for each member of series **3** and **5**, the signal furthest downfield consisted of a doublet of doublets, or triplet, readily exchanged with D_2O to a doublet. This pattern arises from the –CHCH(O–)NH– grouping, which proves that the Lossen degradation of the 5-carboxylic acid function in **2** was involved to form **3**. The magnitude of the spin–spin coupling constant, $J_{4,5}$, in **1–6** (9–12 Hz) is in excellent agreement with the cis coupling constant established for a series of 3-phenyl-2-isoxazolines.[11]

Related Compounds.—The reaction of **1** with ammonia yielded the acid amide **6a**, which was thermally decarboxylated to the known amide **6b**, and hydrolyzed by concentrated HCl to the acid, 3-phenyl-2-isoxazoline-5-carboxylic acid.[6a] The ease of decarboxylation of the 4 acid in **6a** is attributed to its position in the β-oximino acid system. Ring opening of **1** with aniline also gave anilide analogous to **6a**.[6a] The initial product from **1** and hydroxylamine was isolated (after mild acidification) and was a hydroxamic acid to which structure **6c** was assigned, based on analogous ring opening of **1** with amines. Attempts to decarboxylate **6c** yielded **2a**, and dilute hydrochloric acid produced **2a** in the cold and the 5-carboxylic acid on heating.

The known *cis*-methyl 3-phenyl-2-isoxazoline-4,5-dicarboxylate[6a] was resynthesized and its pmr spectrum in $(CD_3)_2SO$ was compared to the one published in $CDCl_3$.[11] Treatment of this ester with aqueous ammonia produced the bisamide, which possessed the trans configuration as evident from its pmr spectrum. This isomerization of the ring protons on prolonged exposure of the ester or amide to concentrated aqueous ammnonium hydroxide solution was perhaps unexpected, since we had only encountered cis products. However, it had been recorded that the 4,5-dicarboxylic acid and esters are readily epimerized by bases. The active methylene proton at C-4 is thought to be responsible for the ease of such a process and creates the thermodynamically most stable isomer.[12]

Mechanism of Ring Openings.—It is reasonable to assume that ammonia and aniline react most rapidly with the more electrophilic CO group at C-5 to give the identified acid amides of type **6a**. However, during the Lossen rearrangement of **2c**, it would appear that nucleophilic attack on the CO at C-4 initiates the degradation. In the absence of steric factors, an alternate mechanism is suggested. Abstraction of H-4 in **2c** generates **7**, which opens to the ketene hydroxamate ion **8**. To form the products, **3**, the ketene function adds either water or ammonia, while the hydroxamate sulfonate portion of **8** is degraded to the isocyanate,[13] which reacts with ammonia to form the urea. This mechanism explains the formation of the large amount of the ureido acid. This contrasts with the Lossen degradation of *N*-hydroxyphthalimide sulfonates to *o*-ureidobenzamides only.[9] In their mechanism, Kühle and Wegler initiate their Lossen reaction by attack of ammonia on one of the imide CO, followed by ring opening to the amide hydroxamate sulfonate anion, which in turn rearranges to an isocyanate group capable of then adding ammonia or an amine to form the ureidoamide.

This mechanism *via* **8** would encourage the formation of both the cis and trans isomers of **3**. The formation of the cis isomer might well be favored in terms of the highly hydrogen-bonded products **3**, which could account for either stereoselective addition to the intermediate unsaturated systems or epimerization of final products to produce the most stable isomers.

Experimental Section[14]

cis-3-Phenyl-2-isoxazoline-4,5-dicarboxylic anhydride (**1**) was prepared in 62% yield (0.6 mol scale) using Isaac's method.[6] Extreme care must be exercised in handling the intermediate benzohydroximyl chloride, which is a powerful vesicant and lachrymator. The anhydride melted at 161–163° (lit.[6] mp 162°); ir 1800 and 1870 cm^{-1}; pmr δ 4.93 (d, H-4), 5.50 (d, H-5,

(10) I. G. Pojarlieff, R. Z. Mitova-Chernaeva, I. Blagoeva, and B. J. Kourtev, *C. R. Acad. Bulg. Sci.*, **21**, 131 (1968); *Chem. Abstr.*, **69**, 51283b (1968).

(11) R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, **100**, 1802 (1967).

(12) Reference 7, p 107.

(13) C. D. Hurd and L. Bauer, *J. Amer. Chem. Soc.*, **76**, 2791 (1954).

(14) Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Microanalysis were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and those for elemental nitrogen by Mr. Richard Dvorak using a Coleman Nitrogen Analyzer, Model 29. Infrared spectra were obtained in Nujol mulls with either Perkin-Elmer Models 337 or 700 recording spectrophotometers. Only strong to medium absorption bands between 1600 and 1900 cm^{-1} are reported. No C=O or C=N stretching band assignments are made, since 2-isoxazolines show a strong band at 1725 cm^{-1}: R. P. Barnes, G. E. Pinkney, and G. M. Phillips, *J. Amer. Chem. Soc.*, **76**, 276 (1954). Pmr spectra were recorded in $(CD_3)_2SO$ (unless otherwise stated) at 60 MHz by means of a Varian A-60 spectrometer or at 100 MHz by Dr. Richard Egan, Abbott Laboratories, on a Varian HA-100 spectrometer. Signals are reported in parts per million (δ) downfield from internal Me_4Si. Only those spin–spin coupling constants (J) are reported which are relevant to the problem. Exchangeable protons were detected on addition of D_2O. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak using a Hitachi Perkin-Elmer RMU-6D mass spectrometer equipped with a Honeywell Visicorder and Hitachi Perkin-Elmer mass marker. Solids were introduced by the direct inlet system at the lowest possible temperature for all parts of the system. Only fragment ions, m/e, present in excess of 5% of the base peak, other than the P + 1, P + 2 ions, are reported. The relative intensities of the ions are shown in parentheses.

$J_{4,5}$ = 11 Hz), 7.25–7.92 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 218 (8), 217 (69), 146 (6), 145 (50), 144 (100), 117 (16), 116 (10), 115 (11), 103 (8), 91 (5), 90 (13), 89 (15), 78 (6), 77 (66), 76 (11), 75 (6), 72 (18), 65 (6), 64 (6), 63 (17), 62 (7), 57 (7), 55 (7), 54 (10), 51 (31), 50 (14), 45 (12), 44 (8), 39 (15), 32 (9).

cis-N-**Hydroxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2a). Method A.**—A stirred solution of hydroxylamine hydrochloride (4.4 g, 0.65 mol) in 25% aqueous tetrahydrofuran (80 ml) was neutralized with sodium carbonate (3.4 g, 0.33 mol) at 25°. Addition of **1** (10.85 g, 0.5 mol) over 1 min produced initially a solution which set to a paste (3–5 min). The mixture was then heated at 60–70° for 0.25 hr and diluted with water (10 ml), pH ≤ 4. The product (8.2 g, 71%) was crystallized from water: mp 206–208°; ir 1720, 1740, 1800 cm^{-1}; pmr δ 5.22 (d, H-4), 5.60 (d, H-5, $J_{4,5}$ = 10 Hz), 7.30–8.05 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 233 (12), 232 (90), 216 (20), 146 (10), 145 (60), 144 (100), 120 (50), 119 (9), 117 (25), 116 (13), 115 (11), 105 (6), 104 (17), 103 (51), 93 (9), 91 (11), 90 (14), 89 (16), 78 (6), 77 (86), 76 (26), 75 (8), 70 (25), 65 (7), 64 (11), 63 (19), 62 (6), 52 (8), 51 (45), 50 (22), 44 (24), 43 (11), 42 (9), 39 (22), 38 (6), 29 (10).

Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.45; N, 12.07. Found: C, 57.12; H, 3.33; N, 12.01.

Method B.—A solution of hydroxylamine hydrochloride (15.8 g, 0.225 mol) in methanol (100 ml) was neutralized by sodium ethoxide solution (5.17 g of Na in 100 ml of methanol). Salt was filtered off and **1** (16.36 g, 0.75 mol) was added to the filtrate over 5 min. After the mixture was stirred for 1 hr, the solid (19.1 g) was filtered. A part of this solid (0.5 g) was dissolved in water (5 ml) and acidified with concentrated HCl to produce **6c** (0.32 g): mp 180–183° (intense purple color with $FeCl_3$); ir 1640 and 1710 cm^{-1}; pmr δ 4.90 (d, H-4) 5.37 (d, H-5, $J_{4,5}$ = 12 Hz), 7.30–8.01 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 232 (16, M − 18), 218 (9), 217 (66), 216 (6), 146 (14), 145 (49), 144 (100), 118 (11), 117 (17), 116 (10), 115 (10), 104 (7), 103 (15), 91 (6), 90 (12), 89 (13), 78 (6), 77 (71), 76 (13), 65 (13), 63 (15), 51 (30), 50 (13), 44 (22), 39 (11), 33 (33).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: N, 11.20. Found: N, 11.31.

When the above solid from method B was either heated in dilute HCl solution (90° for 0.10 hr) or such a solution was permitted to stand at 25° for 24 hr, **2a** was isolated in 50–65% yield. Also, on heating this solid from B at 110–115° for 0.25 hr *in vacuo* (20 Torr) and treating the residue with cold dilute HCl, **2a** was precipitated immediately in poorer yield.

cis-N-**Acetoxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2b).**—A solution of **2a** (6.96 g, 0.03 mol) in acetic anhydride (80 ml) containing pyridine (3 ml) was heated at 100° for 1 hr. After solvents were removed *in vacuo*, the residue was crystallized from ethanol–ethyl acetate (2:1) to give 7.55 g (92%): mp 156–157°; ir 1700, 1740, 1800 cm^{-1}; pmr δ 5.47 (d, H-4), 5.85 (d, H-5, $J_{4,5}$ = 10 Hz), 7.37–8.11 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 275 (4), 274 (26), 232 (36), 144 (10), 77 (11), 43 (100), 36 (6).

Anal. Calcd for $C_{13}H_{10}N_2O_5$: N, 10.22. Found: N, 10.21.

cis-N-**Benzenesulfonoxy-3-phenyl-2-isoxazoline-4,5-dicarboximide (2c).**—To aqueous 2.5% sodium carbonate (160 ml) was added **2a** (11.6 g, 0.05 mol). The solution was filtered to remove a small amount of insoluble material, and benzenesulfonyl chloride (6.5 ml, 0.05 mol) was added dropwise at 25° over 20 min. The mixture was stirred for 3 hr and the solid (11.3 g, 60%), mp 158–161°, was collected. It was crystallized from ethyl acetate: mp 168–171°; ir 1740, 1775, 1840 cm^{-1}; pmr δ 5.30 (d, H-4), 5.65 (d, H-5, $J_{4,5}$ = 10 Hz), 7.28–8.03 (m, 10 Ar H); mass spectrum *m/e* (rel intensity) 373 (5), 372 (24), 216 (3), 145 (8), 144 (15), 142 (6), 141 (80), 103 (8), 78 (7) 77 (100), 76 (5), 70 (9), 51 (17).

Anal. Calcd for $C_{17}H_{12}N_2O_6S$: C, 54.84; H, 3.23; N, 7.53. Found: C, 54.68; H, 3.42; N, 7.42.

***cis*-3-Phenyl-5-ureido-2-isoxazoline-4-carboxylic Acid (3a) and *cis*-3-Phenyl-5-ureido-2-isoxazoline-4-carboxamide (3b).**—A suspension of **2c** (3.72 g, 0.01 mol) in water (50 ml) containing concentrated NH_4OH (3 ml) was heated in the steam bath for 20 min, cooled, and filtered to give 0.7 g (28%) of **3b**, which is identified below. The filtrate was acidified with concentrated HCl and **3a** was collected. It was recrystallized from methanol to provide 1.28 g (51%): mp 218–220°; ir 1620, 1650, 1730 cm^{-1}; pmr δ 5.08 (d, H-4), 6.10 (d of d, H-5, $J_{4,5}$ = 9.5, $J_{NH,5}$ = 10.5 Hz), 5.45 (broad singlet, NH_2), 6.73 (d, NH at C-5), 7.33–7.88 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (3, M − 18), 159 (5), 158 (74), 145 (7), 144 (8), 141 (8), 135 (9), 128 (6), 119 (11), 104 (8), 103 (28), 95 (7), 94 (86), 93 (8), 91 (5), 78 (9), 77 (100), 76 (18), 75 (8), 74 (9), 66 (15), 65 (22), 57 (7), 55 (7), 51 (56), 50 (25), 44 (21), 43 (7), 41 (6), 39 (12), 36 (7), 32 (24), 29 (6).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.10; H, 4.42; N, 17.13.

When the same reaction was conducted in concentrated NH_4OH (50 ml), **3b** (2.1 g, 85%) was obtained: mp 250–251° (from ethanol); ir 1630, 1660, 1680 cm^{-1}; pmr δ 4.88 (d, H-4), 6.03 (t, H-5, $J_{4,5}$ = $J_{NH,5}$ = 10 Hz), 5.67 (NH_2), 6.48 (d, NH at C-5), 7.30–7.80 (m, C_6H_5 and other NH_2); mass spectrum *m/e* (rel intensity) 248 (2), 231 (6), 205 (13), 204 (100), 160 (8), 144 (7), 133 (8), 105 (16), 104 (94), 103 (81), 101 (14), 77 (38), 76 (33), 75 (14), 74 (7), 73 (7), 71 (10), 70 (10), 69 (8), 59 (30), 58 (48), 57 (19), 56 (8), 55 (12), 51 (10), 50 (15), 45 (9), 44 (45), 43 (18), 41 (13), 39 (10), 30 (24), 29 (15).

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.17; H, 4.96; N, 22.89.

Concentration of the mother liquor from this reaction and acidification afforded a small quantity of the acid **3a**.

When a solution of **2c** in tetrahydrofuran (1.86 g, 0.005 mol in 15 ml) was treated with 15 ml of concentrated NH_4OH at 90° for 0.5 hr, **3b** was precipitated in 93% yield.

***cis*-3-Phenyl-5-(3-methylureido)-2-isoxazoline-4-carboxylic Acid (3c) and *cis*-3-Phenyl-5-(3-methylureido)-2-isoxazoline-4-(*N*-methylcarboxamide) (3d).**—A suspension of **2c** (1.86 g, 0.005 mol) in water (25 ml) was heated (10 min) with aqueous 40% methylamine (1.15 ml, 0.015 mol). The precipitate of **3d** (0.35 g, 25.2%) was filtered (see below for identification). Acidification of the filtrate afforded a white solid (0.81 g). Crystallization from methanol (5 ml) yielded **3c** (0.62 g, 48%): mp 199–202°; ir 1610, 1640, 1730 cm^{-1}; pmr δ 2.57 (d, CH_3, $J_{CH_3,NH}$ = 4 Hz), 5.05 (d, H-4), 6.11 (t, H-5, $J_{4,5}$ = $J_{NH,5}$ = 10 Hz), 5.68 (q, $NHCH_3$), 6.66 (d, NH at C-5), 7.35–7.78 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 245 (M − 18, 12), 142 (5), 119 (25), 105 (5), 104 (15), 103 (100), 98 (18), 85 (8), 77 (11), 76 (35), 75 (8), 69 (7), 58 (9), 51 (10), 50 (13), 44 (50), 42 (11), 39 (5), 30 (7).

Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.53; H, 4.95; N, 15.80.

Crystallization of **3d** (from above) from 95% ethanol raised the melting point to 255–256° (270 mg, 19.5%). The same product was isolated in 80% yield when a large excess of methylamine was present: ir 1600, 1660, 1680 cm^{-1}; pmr δ 2.52, 2.63 (d, $NHCH_3$, both J = 5 Hz), 4.91 (d, H-4), 6.07 (d of d, H-5, $J_{4,5}$ = 9.5, $J_{NH,5}$ = 10 Hz), 5.86, 7.59 (q, both due to $NHCH_3$), 7.30–7.80 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 276 (4), 245 (4), 218 (64), 188 (4), 161 (5), 146 (7), 133 (7), 116 (6), 115 (19), 105 (6), 104 (48), 103 (44), 89 (6), 88 (5), 77 (18), 65 (16), 70 (6), 59 (40), 58 (100), 57 (6), 51 (9), 50 (7), 42 (6), 30 (25), 29 (6).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.48; H, 5.82; N, 20.19.

***cis*-3-Phenyl-8,9-dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5a).**—A mixture of **3a** (0.24 g, 0.001 mol) and 3.3 *N* HCl (3.0 ml) was boiled for 7 min. On chilling to 5°, the solid 0.21 g) was collected and recrystallized from 35 ml of 2-propanol. There was obtained 0.092 g (40%): mp 254–255°; ir 1700, 1740 cm^{-1}; pmr δ 5.15 (d, H-4), 5.64 (d of d, H-5, $J_{4,5}$ = 10, $J_{NH,5}$ = 4 Hz), 7.40–7.90 (m, C_6H_5), 8.32 (d, NH); mass spectrum *m/e* (rel intensity) 232 (4), 231 (28), 144 (5), 128 (9), 120 (9), 119 (100), 105 (7), 104 (19), 103 (29), 91 (16), 85 (12), 77 (20), 76 (12), 69 (9), 64 (8), 63 (7), 57 (9), 51 (11), 50 (6), 39 (6), 38 (9), 36 (29), 32 (6).

Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.25; H, 4.06; N, 18.08.

***cis*-3-Phenyl-5-methyl-8,9-dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (5b).**—A suspension of **3c** (0.263 g, 0.001 mol) in 3.3 *N* HCl (3 ml) was heated at reflux for 2 min. A purple solution resulted. On cooling, the product was filtered off and washed with cold 3.3 *N* HCl. It weighed 0.24 g, mp 264–265°. Recrystallization from acetic acid (70% recovery) raised the melting point to 268–270°: ir 1680 and 1720 cm^{-1}; pmr δ 3.00 (NCH_3), 5.27 (d, H-4), 5.65 (d of d, H-5, $J_{4,5}$ = 10, $J_{NH,5}$ = 3 Hz), 7.40–7.85 (m, C_6H_5), 8.60 (d, NH, $J_{NH,5}$ = 3 Hz); mass spectrum *m/e* (rel intensity) 246 (5), 245 (36), 144 (10), 142 (20), 126 (15), 120 (8), 119 (100), 113 (7), 105 (24), 104 (22), 103 (32), 91 (17), 85 (32), 77 (20), 76 (14), 69 (16), 64 (7), 59 (18), 57 (13), 51 (10), 32 (18), 29 (7).

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.49; H, 4.54; N, 16.91.

Prolonged heating or an increase in the concentration of HCl diminished the yield of **5b**.

***cis*-5-Carboxamido-3-phenyl-2-isoxazoline-4-carboxylic Acid (6a).**—To concentrated ammonium hydroxide (10 ml) at 10° was added **1** (1.08 g, 0.005 mol) in small portions, keeping the temperature below 10°. The reaction mixture was filtered and acidified with cold concentrated hydrochloric acid in an ice bath. The colorless solid (0.86 g, 73.5%) was collected and dried: mp 165–166°; ir 1650 and 1725 cm^{-1}; pmr δ 4.84 (d, H-4), 5.25 (d, H-5, $J_{4,5}$ = 12 Hz), 6.5–7.18 (m, 5, Ar H); mass spectrum *m/e* (rel intensity) 234 (1), 218 (8), 217 (62), 191 (5), 190 (6), 159 (16), 147 (7), 146 (64), 145 (40), 144 (76), 119 (7), 118 (32), 117 (19), 116 (11), 115 (12), 104 (15), 103 (20), 91 (19), 90 (12), 89 (15), 78 (10), 77 (100), 76 (16), 75 (7), 66 (7), 65 (6), 64 (16), 63 (6), 57 (8), 52 (6), 51 (40), 50 (15), 44 (62), 43 (9), 41 (8), 39 (15), 36 (10), 32 (19), 29 (5).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: N, 11.96. Found: N, 11.82.

3-Phenyl-2-isoxazoline-5-carboxamide (6b).—On heating 5-carboxamido-3-phenyl-2-isoxazoline-4-carboxylic acid (**6a**) (0.75 mg, 0.0032 mol) for 15 min *in vacuo* until the oil bath temperature had risen to 190°, a solid material formed which was triturated with saturated aqueous sodium bicarbonate solution (10 ml), collected, and washed with three portions of cold water (5 ml). The solid was extracted with boiling benzene to afford 0.2 g (33%) of **6b**: mp 200–201° (lit.[6] mp 204°); ir 1650 and 1660 cm^{-1}; pmr δ 3.1–3.6 (m, 2 H at C-4), 4.67–5.13 (m, H-5, the X part of an ABX pattern), 7.1–7.84 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 190 (13), 159 (33), 147 (10), 146 (100), 119 (10), 118 (75), 117 (13), 115 (6), 104 (14), 103 (9), 91 (30), 78 (15), 77 (95), 76 (10), 63 (6), 51 (32), 50 (10), 44 (19), 32 (7).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: N, 14.73. Found: N, 14.45.

3-Phenyl-2-isoxazoline-5-carboxylic Acid.—To concentrated hydrochloric acid (10 ml) was added **6a** (0.468 g, 0.002 mol), and the solution was warmed on a steam bath for 20 min. The reaction mixture was allowed to stand for 12 hr to furnish **6c**: 0.21 g (55%); mp 140–143° (lit.[6] mp 143°); ir 1720 cm^{-1}; pmr, computer-checked spectrum for ABX pattern of ring protons offers this solution:[15] δ 5.203 (H-5), 3.745, 3.613 (H-4, J_{gem} = −17.27, $J_{4,5}$ = 11.83 and 6.77 Hz), 7.20–7.80 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 191 (30), 147 (8), 146 (64), 119 (10), 118 (86), 117 (12), 115 (7), 104 (14), 103 (19), 91 (32), 89 (8), 78 (13), 77 (100), 76 (16), 75 (6), 74 (5), 65 (6), 63 (11), 52 (6), 51 (40), 50 (17), 46 (7), 39 (11).

Anal. Calcd for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.51.

Methyl *cis* 3-Phenyl-2-isoxazoline-4,5-dicarboxylate.—This ester was prepared in 44% yield by the literature[6] method: mp 89–92° (lit.[6] mp 91°); pmr ($CDCl_3$) δ 3.73, 3.87 (OCH_3), 4.80 (H-4), 5.43 (H-5, $J_{4,5}$ = 12 Hz); lit.[11] pmr ($CDCl_3$) δ 3.65, 3.80 (OCH_3), 4.81 (H-4), 5.29 (H-5, $J_{4,5}$ = 12 Hz), pmr (CD_3)$_2$SO δ 3.65, 3.77 (OCH_3), 5.23 (H-4), 5.66 (H-5, $J_{4,5}$ = 12 Hz); mass spectrum *m/e* (rel intensity) 264 (11), 263 (62), 231 (5), 204 (27), 178 (21), 177 (14), 176 (100), 172 (23), 160 (14), 146 (6), 144 (85), 134 (18), 119 (11), 118 (9), 117 (12), 116 (12), 115 (6), 113 (16), 105 (8), 104 (6), 103 (15), 91 (18), 89 (9), 77 (51), 76 (9), 59 (31), 51 (22), 39 (6), 31 (11), 29 (5).

***trans*-3-Phenyl-2-isoxazoline-4,5-dicarboxamide.**—A mixture of methyl *cis*-3-phenyl-2-isoxazoline-4,5-dicarboxylate (2.61 g) and concentrated NH_4OH (20 ml) was allowed to react for 8 hr at 25°. The solid (2.1 g, 91%) was collected and dried: mp 250–252°; ir 1660 cm^{-1}; pmr δ 4.73 (d, H-4), 5.07 (d, H-5, $J_{4,5}$ = 6 Hz), 7.33–7.92 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 234 (3), 233 (13), 190 (10), 189 (80), 172 (29), 147 (10), 146 (100), 145 (5), 144 (24), 130 (16), 118 (12), 117 (7), 116 (7), 115 (6), 104 (17), 103 (10), 91 (30), 89 (7), 87 (6), 86 (74), 78 (7), 77 (58), 76 (7), 63 (6), 51 (23), 50 (5), 44 (31), 39 (5) ir (Nujol) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}N_3O_3$: N, 18.02. Found: N, 18.20.

Registry No.—**2a**, 35053-65-7; **2b**, 35053-66-8; **2c**, 35053-67-9; **3a**, 35053-68-0; **3b**, 35053-69-1; **3c**, 35053-70-4; **3d**, 35053-71-5; **5a**, 35053-72-6; **5b**, 35053-73-7; **6a**, 35053-74-8; **6b**, 35053-75-9; **6c**, 35053-76-0; 3-phenyl-2-isoxazoline-5-carboxylic acid, 4872-58-6; *trans*-3-phenyl-2-isoxazoline-4,5-dicarboxamide, 35053-78-2.

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The Synthesis of 2,5- and 4,5-Dihydroxyxanthone[1]

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The photo-Fries rearrangement of *p*-methoxyphenyl 2,3-dimethoxybenzoic acid was advantageously employed in the preparation of 2-hydroxy-2′,3′,5-trimethoxybenzophenone which, after demethylation and cyclodehydration, provided the previously unknown 2,5-dihydroxyxanthone. Similarly, the irradiation of *o*-methoxyphenyl 2,3-dimethoxybenzoate provided the Fries rearrangement products 4-hydroxy- and 2-hydroxy-2′,3,3′-trimethoxybenzophenone. Demethylation and cyclization of the latter yielded 4,5-dihydroxyxanthone, also previously unknown.

We have already described research on the constituents of *Mammea americana* L. which led to the isolation of some simple mono- and dihydroxyxanthones.[4] Among the 16 possible dihydroxyxanthones, we noted that the 1,5, 2,5, and 4,5 isomers were unknown in the literature. The 1,5 isomer was synthesized and shown to be identical to one of the *Mammea* constituents.[4] Here we report the synthesis of the remaining two isomers and describe two new examples of the photo-Fries reaction.

2,5-Dihydroxyxanthone (Ia).—A simple and obvious pathway to Ia would involve treatment of the tetramethoxybenzophenone II with a Lewis acid in order to

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(3) The experiments on which this article is based were taken from the Ph.D. thesis of K. E. M., presented to the Department of Medicinal Chemistry, State University of New York at Buffalo, April 1970.

(4) R. A. Finnegan and J. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, (1972); see also R. A. Finnegan, J. K. Patel, and P. L. Bachman, *Tetrahedron Lett.*, 6087 (1966).