ANOMALOUS 'LOSSEN-TYPE' REARRANGEMENT SYNTHESIS OF FUNCTIONALIZED IMIDAZOLINONES

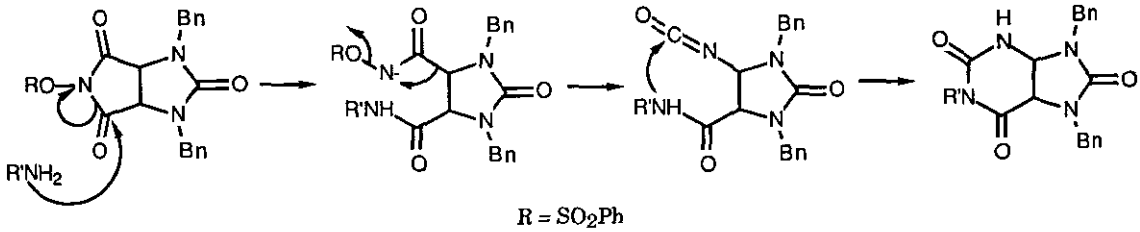
Dee Ann Casteel,* Rebecca S. Gephart, and Tracey Morgan

Division of Medicinal and Natural Products Chemistry,
College of Pharmacy, University of Iowa, Iowa City, Iowa 52242, U.S.A.

Abstract- Reaction of an imidazolinone *N*-sulfonyloxyimide (**3**) with ammonia or methylamine provided carboxy-ureido compounds (**4, 5, 6,** and **7**), products of a Lossen rearrangement in which the intermediate isocyanate is trapped by the amine. Possible mechanism(s) are discussed. Upon heating, the carboxy-ureido materials eliminate urea to form the carboxy substituted imidazolones (**8, 9, 10**).

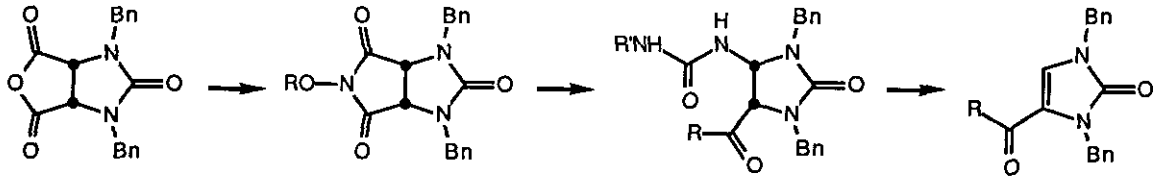
The treatment of *O*-acylhydroxamic acids with base results in a rearrangement to give isocyanates, a reaction known as the Lossen rearrangement.[1] These isocyanate intermediates most commonly suffer either hydrolysis with loss of carbon dioxide yielding the amine or are trapped by nucleophiles such as alcohols or amines to provide the carbamate or urea derivatives, respectively. In a similar manner, *N*-acyloxy- or *N*-sulfonyloxyimides are known to undergo Lossen-type rearrangements; *N*-sulfonyloxyphthalimides are degraded to anthranilic acid derivatives when treated with aqueous sodium hydroxide. The proposed

Scheme 1



R = SO_2Ph

Scheme 2



1 **2**, R=H; **3**, R=SO_2Ph **4**, R=NHMe, R'=Me; **5**, R=OH, R'=H; **6**, R=NH_2, R'=H; **7**,R=OEt, R'=H **8**, R=NH_2; **9**,R=OEt; **10**, R=OH

mechanism for the Lossen rearrangement of *N*-sulfonyloxyphthalimides is outlined in Scheme 1. A heterocyclic example is found in the rearrangement of an isoxazoline imide derivative, which upon reaction with aqueous ammonia, rearranged and subsequently was cyclized to a dihydrooxazolino-pyrimidine.[2] In the course of investigations directed toward the synthesis of dihydropurine analogues, we sought to utilize the Lossen rearrangement reaction of suitably functionalized imidazolinone imides.

Preparation of the necessary precursors was easily accomplished from the known imidazolinone anhydride (**1**) (Scheme 2), prepared as the *cis* isomer in four steps from fumaric acid.[3] Treatment of **1** with hydroxylamine in water provided the *N*-hydroxyimide (**2**) in 85% yield. Activation of the free hydroxyl group with benzenesulfonyl chloride yielded 86% of the sulfonylimide (**3**).

Upon treatment of (**3**) with methylamine, a rearrangement was observed, but the product was not a dihydropurine. Rather, a ureidoamide (**4**) was produced apparently resulting from the interception of the isocyanate by excess amine. The structure of the rearranged product was deduced from ^1H nmr data and elemental analysis which indicated the incorporation of two methyl amine units into the overall structure.

Ammonia itself also caused (**3**) to rearrange. Reaction with dilute aqueous ammonia gave rise to ureidoacid (**5**) instead of the corresponding ureidoamide (**6**) although a large amount of starting

(3) was also recovered. Compound (6) could be formed using more concentrated aqueous ammonia and prolonged heating. Ethanolic ammonia produced ureidoester (7) from (3). In each case, the product was identified by ^{1}H nmr, mass spectrometry, and elemental analysis.

In the case of compound (7), however, it was not possible to determine from the spectroscopic data whether the product was indeed an ester-urea substituted imidazolidinone (structure 7) or whether it was the isomeric amide-carbamate. Treatment of the compound with acid resulted in the elimination of the urea functionality, in a reverse Michael sense, to provide the imidazolone ester (9) proving unambiguously the structure of the precursor as the ester urea (7).

In all cases, a urea moiety is produced, indicating that the intermediate isocyanate is trapped by the amine nucleophile. A puzzling feature relates to the formation of acids and esters in addition to amides as the other substituent on the imidazolinone. If the 'normal' mechanism of the Lossen rearrangement is operating, one would expect that attack of the nucleophile, ammonia or methylamine, on the imide carbonyl initiates the rearrangement leading to the inevitable formation of an amide. One possible explanation would be that, under the reaction conditions, the originally formed amide was hydrolyzed to the ester or acid. However, since forcing conditions lead to an increase in the amide product, not the acid nor ester, the ester and acid do not arise from hydrolysis of the amide.

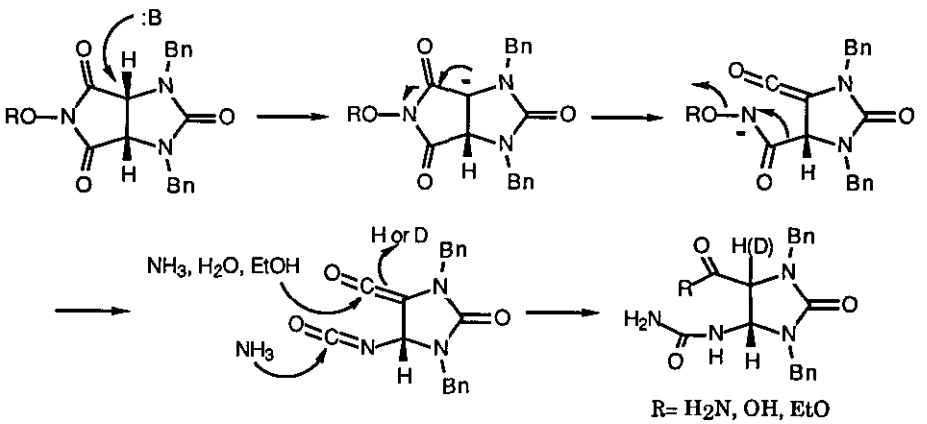
An alternate mechanism has been proposed which might account for the apparent anomalous features of the reaction (Scheme 3).[2] The alternative involves initial deprotonation of the position adjacent to the imide carbonyl, and subsequent formation of a ketene derivative. The ketene must then be trapped by solvent (or excess amine) to form either the acid, ester, or amide. The isocyanate from the rearrangement still is invariably trapped by amine. If deprotonation is involved, deuterium incorporation at the ring juncture position would occur in a deuterated reaction mixture. Reaction of (3) with d_4-ammonium deuteroxide in deuterium oxide yielded

(6), which, after back-washing of exchangeable deuterium with water, gave no indication of deuterium incorporation by ^1H nmr or by mass spectrometry. Any mechanism that involves deprotonation of a ring juncture position is therefore ruled out.

Attempts to ring close compounds (6) or (7) to dihydropurines were not successful. Acidic treatment of any of the ureido materials resulted in the elimination of the urea group to give compounds (8) and (9), respectively. Such an elimination may be considered an example of a reverse Michael addition of urea to the unsaturated carboxyimidazolones. The facile loss of the urea group was also evident from the mass spectra of compounds (4 - 7). In most cases, whether the spectrum was taken by electron impact or by chemical ionization, the molecular ion was missing and fragment peaks attributable to loss of 60 mass units (urea) (or 74 mass units for the methyl urea in 4) were seen. Compound (5) is particularly sensitive to both heat and acidic conditions; no compound (10) was produced but *N,N*-dibenzylimidazolone (11)[4] is isolated, resulting from elimination of the urea group and decarboxylation. Compound (10) could be obtained by hydrolysis of (9), however.

Several five-membered ring heterocyclic nucleosides have been discovered that exhibit interesting anti-tumor and antiviral activities, including ribavirin,[5] pyrazofurin,[6] tiazofurin,[7] and bredinin.[8] These small ring nucleosides offer promising lead compounds for further

Scheme 3



development of therapeutic agents. Other small five-membered heterocycles such as the ones prepared here (when studied as their ribosides) may be worthy of examination for possible antiviral or antitumor activities. Preliminary screening of compounds (**2**, **3**, and **5 - 9**) in antiviral and anticancer tests showed that none of the materials exhibited significant activity.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus in open glass capillaries and are uncorrected. Nmr spectra were recorded with internal tetramethylsilane reference in the solvents indicated on Bruker instruments at the field strengths indicated. Mass spectra were recorded on a Trio-1 (EI) or a Delsi-Nermag R10-10c (CI, NH_3). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

1,3-Dibenzyl-5-hydroxy-2,4,6-trioxopyrrolo[3,4-*d*]imidazoline (**2**)

Hydroxylamine hydrochloride (1.144 g, 16.6 mmol) and sodium carbonate (0.616 g, 5.8 mmol) were dissolved in water (15 ml) and swirled until evolution of carbon dioxide ceased. Anhydride (**1**)[3] (4.4 g, 13.1 mmol) was stirred in boiling water (200 ml) and the hydroxylamine solution was added. The reaction mixture was heated at boiling and additional water was added until all the solids were dissolved. The hot solution was then filtered rapidly and a white crystalline product appeared as the solution cooled. The analytically pure solid was collected by filtration; additional material could be obtained by concentration of the aqueous filtrate and cooling. Total of all crops: 3.91 g (85%). mp 169-170 °C. ^{1}H Nmr ($CDCl_3$, 80 MHz): δ 4.01 (2H, s, CH), 4.19 (2H, d, *J*=15 Hz, benzylic), 5.05 (2H, d, *J*=15 Hz, benzylic), 7.34 (10H, br s, ArH); ms (EI): m/z 351 (M^+). *Anal.* Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.86; H, 5.23; N, 11.85.

1,3-Dibenzyl-5-benzenesulfonyloxy-2,4,6-trioxopyrrolo[3,4-*d*]imidazoline (3)

Compound (2) (1.6 g, 4.54 mmol) was stirred with pyridine (3.4 ml) and dry dimethylacetamide (8.8 ml) in an ice bath for 10 min. Benzenesulfonyl chloride (1.4 ml, 1.92 g, 10.9 mmol) was added by syringe. The reaction mixture was allowed to stir at room temperature for an additional 30 min and was then poured onto 100 ml of an ice/water mixture. The pale yellow precipitate was collected by filtration. The solid was recrystallized from acetonitrile (75 ml)/ methanol (5 ml) to give pure white needles (1.81 g, 81% recovered), mp 237-238 °C. ^{1}H Nmr (DMSO-d_6, 80 MHz): δ 4.03 (2H, d, *J*=16 Hz, benzyl), 4.21 (2H, s, CH), 4.77 (2H, d, *J*=16 Hz, benzyl), 7.16-7.32 (10H, m, ArCH_2), 7.63-7.97 (5H, m, ArS); ms (EI): m/z 491 (M^+), 334 (M-OSO_2Ph^+). *Anal.* Calcd for $C_{25}H_{21}N_3O_6S$: C, 61.09; H, 4.31; N, 8.55; S, 6.52. Found: C, 61.30; H, 4.35; N, 8.65; S, 6.75.

1,3-Dibenzyl-4-(*N*-methylcarboxamido)-5-(*N'*-methylureido)-imidazolin-2-one (4)

Compound (3) (113 mg. 0.22 mmol) was stirred in 40% aqueous monomethylamine (5 ml, 58.1 mmol) overnight at room temperature. A precipitate had formed which was collected by filtration and washed with water (80 mg, 88%). The solid was recrystallized from acetonitrile to give pure product (39 mg, 49%), mp 225-226 °C. ^{1}H Nmr (DMSO-d_6, 360 MHz): δ 2.51 (3H, d, *J* = 3.6 Hz, NCH_3), 2.59 (3H, d, *J* = 3.6 Hz, NCH_3), 3.77, 3.93, 4.47, 4.80 (1H each, 4d, *J* = 14.4 Hz, benzyl), 3.91 (1H, d, *J* = 7.2 Hz, C<u>H</u>CONMe), 5.49 (1H, dd, *J* = 7.2, 10.8 Hz, HNC<u>H</u>N), 6.12 (1H, d, *J* = 10.8 Hz, urea NH), 6.13 (1H, m, urea N<u>H</u>CH_3), 7.14-7.35 (10H, m, ArH), 8.02 (1H, d, *J* = 3.6, amide NH); upon deuterium oxide shake, the peaks at δ 6.12, 6.13, and 8.02 disappeared; the peak at δ 5.49 simplified to a doublet; ms (EI, 10 eV): m/z 337 (42.3), 321 (100), 304 (26.5), 280 (14.5), 263 (50.4), 247 (47.1); hrms (CI, CH_4): $(M-H)^+$ Calcd for $C_{21}H_{24}N_5O_3$, 394.187915, found 394.188800.

1,3-Dibenzyl-4-carboxy-5-ureidoimidazolin-2-one (5)

Method A: Compound (3) (2.46 g, 5 mmol) was swirled in water (35 ml) on a steam bath. Concentrated ammonium hydroxide (1.5 ml, 11.5 mmol) was added and the mixture was heated for 30 min and then allowed to cool. The undissolved solid was removed by filtration (1.87 g) and was determined to be unreacted (3). The filtrate was acidified with concentrated hydrochloric acid and the precipitate was collected by filtration. The white solid (403 mg, 91% based on unrecovered starting material) had a melting point of 152-154 °C.

Method B: To compound (3) (100 mg, 0.20 mmol) dissolved in a mixture of water (5 ml) and acetonitrile (5 ml) at room temperature was added dropwise concentrated ammonium hydroxide (0.5 ml, 0.38 mmol) at the rate of 1-2 drops/min. The solution was allowed to stir for 10 min and was then filtered, acidified with concentrated hydrochloric acid, and concentrated under vacuum. The precipitate was collected by filtration, washed with water, and air dried (58 mg, 77%).

Solid (720 mg) prepared by either method could be recrystallized from hot methanol to give pure compound (326 mg, 45%, mp 150-150.5 °C). ^{1}H Nmr (DMSO-d_6, 360 MHz): δ 3.90 (1H, d, J = 15.4 Hz, benzyl), 3.98 (1H, d, J = 8.8 Hz, C<u>H</u>COOH), 3.99 (1H, d, J = 14.2 Hz, benzyl), 4.56 (1H, d, J = 15.5 Hz, benzyl), 4.82 (1H, d, J = 15.1 Hz, benzyl), 5.49 (1H, dd, J = 8.7, 9.8 Hz, NHC<u>H</u>N), 5.74 (2H, br s, NH_2), 6.64 (1H, d, J = 10.3 Hz, NH), 7.17 - 7.41 (10H, m, ArH); ms (EI, 10 eV): m/z 307 (21.5), 264 (100), 91 (38.6). *Anal.* Calcd for $C_{19}H_{20}O_4N_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.27; H, 5.35; N, 15.46.

1,3-Dibenzyl-4-carbamido-5-ureidoimidazolin-2-one (6)

Compound (3) (290 mg, 0.59 mmol) was heated in acetonitrile (3.9 ml). Concentrated ammonium hydroxide (6 x 5 ml) was added over the course of 1 h. Additional ammonium hydroxide (2 x 5 ml) was added over 2h. The suspension was cooled and filtered to provide 160

mg (74%) of a solid, mp 230-234 °C. The solid (0.58 g) could be recrystallized from methanol/water to give pure material in three crops (426 mg, 73%), mp 236-238 °C. ^{1}H Nmr (DMSO-d_6, 360 MHz): δ 3.83, 3.87, 4.54, 4.83 (1H each, 4d, J = 15 Hz, benzyls), 3.92 (1H, d, J = 8.5 Hz, $H_2NCOC\underline{H}$), 5.45 (1H, dd, J = 9, 10 Hz, NHC$\underline{H}$N), 5.80 (2H, br s, urea NH_2), 6.37 (1H, d, J = 10 Hz, NH), 7.15 - 7.36 (10H, m, ArH), 7.52 (2H, br s, amide NH_2); upon deuterium oxide shake, the signals at δ 7.52, 6.37, and 5.80 disappeared; the signal at δ 5.45 simplified into a doublet, J = 8.5 Hz; ms (CI): 385 (11.4), 368 (15.5), 325 (25.3), 308 (41.3), 78 (100). *Anal.* Calcd for $C_{19}H_{21}O_3N_5$: C, 62.11; H, 5.76; N, 19.06. Found: C, 61.73; H, 5.75; N, 19.24.

Preparation of 1,3-Dibenzyl-4-carbamido-5-ureidoimidazolin-2-one (6) in Ammonium-d_4 Deuteroxide

The preparation of (6) was repeated as above except that instead of concentrated ammonium hydroxide, a solution of 26 wt % ammonium-d_4 deuteroxide in deuterium oxide (Aldrich) was used. The compound had an ^{1}H nmr spectrum virtually identical to that of (6) in dimethyl sulfoxide-d_6/deuterium oxide. No deuterium incorporation was detectable at either the CH adjacent to the amide or at the CH adjacent to the urea.

1,3-Dibenzyl-4-carbethoxy-5-ureidoimidazolin-2-one (7)

Compound (3) (0.21 g. 0.43 mmol) was stirred in ethanol (8 ml) to which concentrated ammonium hydroxide (0.3 ml) was added at room temperature. The reaction stirred for 2 h at which time the precipitated solid was collected by filtration; additional material was isolated from the concentrated filtrate (total 142 mg, 87%). The solid (101 mg) was crystallized from hot acetonitrile (80 mg, 79% recovered), mp 200-202 °C. ^{1}H Nmr (DMSO-d_6, 600 MHz): δ 1.13 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.92, 4.03, 4.54, 4.74 (1H each, 4d, J = 15 Hz, benzyls), 4.03, 4.15 (1H each, 2dq, J = 7.1, 10.7 Hz, diastereotopic $C\underline{H}_2CH_3$), 4.14 (1H, d, J = 8.5 Hz, $C\underline{H}CO_2Et$), 5.50 (1H, dd, J = 8.4, 10.2 Hz, HNC$\underline{H}$N), 5.73 (2H, br s, NH_2), 6.55 (1H, d, J = 10.2 Hz, NH), 7.19-7.35 (10H, m,

ArH); ^{13}C Nmr (DMSO-d_6, 90 MHz): 13.74, 43.52, 45.90, 59.54, 60.34, 60.88, 127.00, 127.29, 127.48, 127.90, 128.29, 128.41, 136.18, 158.42, 167.47; ms (EI, 10 eV): m/z 379 (1.9), 350 (12.6), 336 (100), 305 (74), 264 (22.7), 91 (34.6). *Anal.* Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.53; H, 6.01; N, 14.37.

1,3-Dibenzyl-4-carboxamidoimidazol-2-one (8)

Dry hydrogen chloride gas was bubbled through dry methanol (10 ml) for 10 min. Compound (**6**) (50 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure and the residue was taken up in methanol (1 ml) and the product was precipitated by the addition of water (40 mg, 96%). The solid (80 mg) could be recrystallized from methanol/water to give pure (**8**) (50 mg in two crops, 63%), mp 166-167 °C. ^{1}H Nmr ($CDCl_3$, 360 MHz): 4.83 (2H, s, benzyl), 5.27 (2H, s, benzyl), 5.30 (br s, NH_2), 6.65 (1H, s, vinyl), 7.23-7.37 (10H, m, ArH); ms (EI): 307, 91. *Anal.* Calcd for $C_{18}H_{17}O_2N_3$: C, 70.34; H, 5.57; N, 13.67. Found: 70.42; H, 5.71; N, 13.51.

1,3-Dibenzyl-4-carbethoxyimidazol-2-one (9)

Compound (**7**) (150 mg, 0.38 mmol) was stirred at room temperature for 2 days in 2.26 *M* hydrogen chloride in methanol (26 ml, 59 mmol). After removal of the solvent under reduced pressure, water was added to the residue and a white solid precipitated. The solid was collected by filtration, washed with water, and dried under vacuum to give 100 mg (87%). The product could also be prepared by heating (**7**) in dry diglyme at reflux overnight. After cooling the solvent was removed under reduced pressure. The residue was triturated with methylene chloride, filtered, and evaporated. The resulting oil was crystallized from ethanol. mp 115-117 °C. A portion of the solid (22 mg) was then recrystallized from methanol/water to give 18 mg (82%) pure product, mp 119-120 °C. ^{1}H Nmr ($CDCl_3$): δ 1.22 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.18 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 4.86 (2H, s, benzyl), 5.25 (2H, s, benzyl), 6.96 (1H, s, CH), 7.32 (10H, s,

ArH); ms (EI, 70 eV): m/z 336 (13.5), 91 (100). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.29; H, 5.91; N, 8.39.

1,3-Dibenzyl-4-carboxyimidazol-2-one (**10**)

Compound (**9**) (120 mg, 0.36 mmol) was stirred at room temperature overnight in H_2O (3 ml) and EtOH (3 ml) containing 10% aq. KOH (0.5 ml). The solution stirred overnight and was then heated at 55-60 °C for 8 h. After cooling to room temperature and standing one day, the reaction mixture was acidified with conc. HCl, partitioned between satd NaCl (12 ml) and EtOAc (12 ml). The aqueous layer layer was washed with EtOAc (3 x 12 ml), dried over $MgSO_4$, and filtered. Evaporation of the filtrate provided 140 mg of an oily residue. The oil (90 mg) was crystallized from $CHCl_3$ to give pure product (32 mg, 36%, mp 136-138 °C). ^{1}H Nmr ($CDCl_3$): δ 4.87 (2H, s, benzyl), 5.22 (2H, s, benzyl), 7.08 (1H, s, CH), 7.29 (10H, s, ArH); HRms Calcd for $C_{18}H_{16}N_2O_3$: 308.116093. Found: 308.1164.

1,3-Dibenzylimidazol-2-one (**11**)

Compound (**5**) (46 mg, 0.13 mmol) was dissolved in a mixture of concentrated hydrochloric acid (2 ml) and water (4 ml) and heated to boiling for 10 min. Upon cooling, an oily residue had formed. The aqueous layer was removed by pipette and the oil was purified by preparative tlc on silica gel using 70% EtOAc/hexanes as eluant to provide 30 mg (91%) of the product as an oil. The oil could be crystallized from acetone (18 mg, 60%, mp 151-155 °C). ^{1}H Nmr ($CDCl_3$): δ 4.81 (4H, s, benzylic), 6.08 (2H, s, olefinic), 7.29 (10H, s, ArH). ms (EI): m/z 264 (M^+), 91.

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