Amine-Induced Lossen Rearrangements of 3-Hydroxy-5,6-dihydrouracil and *N*-Hydroxysuccinimide Benzenesulfonates

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The reaction of sodium succinohydroxamate with benzenesulfonyl chloride yielded 3-benzenesulfonyloxy-5,6-dihydrouracil, **3**. Treatment of **3** with ammonia, aniline, *t*-butylamine or piperidine yielded a mixture of the requisite 1,2-bis(ureido)ethane and 1-carboxamido-2-imidazolidone. Acylation of *N*-hydroxysuccinimide with benzenesulfonyl chloride furnished *N*-benzenesulfonyloxysuccinimide, **10**. Aniline or *t*-butylamine were used as representative amines to demonstrate their capability of inducing a Lossen degradation on **10** to afford the corresponding β-ureidopropionamide.

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O-Sulfonate esters of hydroxamic acids, $RCONHOSO_2R$, have not been isolated but are postulated intermediates in some extremely fast Lossen rearrangements (2). Although sulfonate esters of *N*-hydroxyimides are isolable, they react quite rapidly with nucleophilic reagents. The reactions of two distinctly different *N*-hydroxyimide sulfonates, namely, 3-benzenesulfonyloxy-5,6-dihydrouracil, **3**, and *N*-benzenesulfonyloxysuccinimide, **10**, with amines were explored.

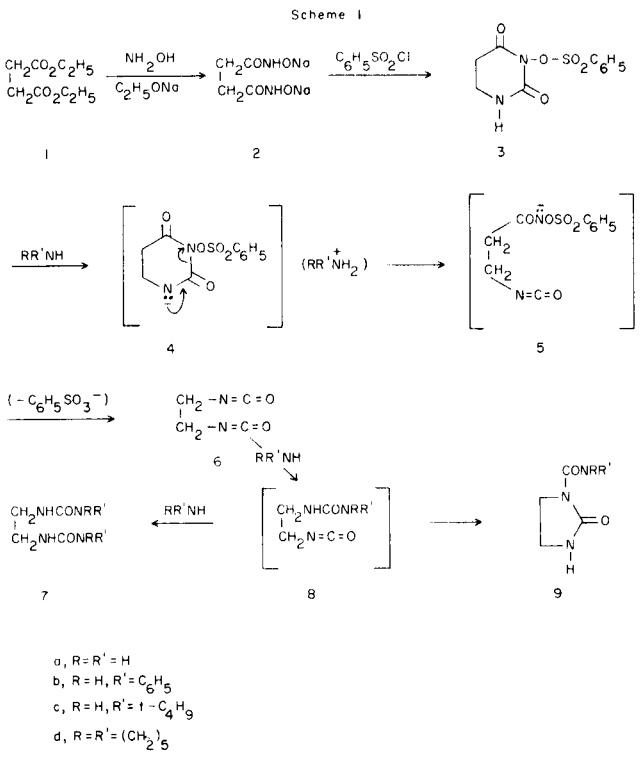
The Reactions of **3** with Amines.

3-Benzenesulfonyloxy-5,6-dihydrouracil was synthesized from ethyl succinate in two steps. The ester, **1** was converted first to the bis-hydroxamate, **2**, and the latter partly degraded (in one pot) to **3** (2). It was found that **3** readily dissolved in aqueous sodium hydroxide solution but was not recovered when such a basic solution was acidified immediately. Apparently, the anion, **4**, underwent a very facile reaction. Such a hydroxide ion initiated Lossen rearrangement of **3** led eventually to ethylenediamine (3).

This study set out to establish if a similar degradative rearrangement of **3** could be brought about by weaker bases, such as amines. The reactions of **3** with ammonia, aniline, *t*-butylamine and piperidine are described. These amines reacted quickly and gave rise to two major products. The products were ureas based on ethylenediamine, and their formation can be rationalized by the pathways in Scheme I. Neutralization of **3** produces the anion, **4**, which opens to the isocyanate and anionic precursor, **5**, which is responsible for a fast subsequent Lossen rearrangement giving rise to ethylene diisocyanate, **6** (2). However, excess amine in the reaction mixture would be expected to add to the isocyanate groups to form ureas. Depending upon the relative rates of competing reactions, the intermediate ureido isocyanate, **8**, could either add more amine to form **7**, or cyclize to give **9**.

From each of the reactions of **3** with ammonia or amines, the bis-ureides, **7**, and 2-imidazolidones, **9** were isolated in (combined) good yield. No attempt was made to study how changes in reaction conditions influenced the ratio of **7** to **9**. It has previously been reported that the reactions of ethylene diisocyanate with amines yielded both the linear and cyclic ureas, **7** and **9**, respectively (4). Frequently, the 2-imidazolidone, **9**, was the major product instead of the expected linear bis-ureide, **7** (4). The preponderance of **9** over **7** was attributed to "overwhelming kinetic effects incurred by intramolecular proximity", since it was established independently that

Scheme I



a, R = R' = H
b, R = H, R' = C_6H_5
c, R = H, R' = t-C_4H_9
d, R = R' = $(CH_2)_5$

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amines added to isocyanates usually much faster than do ureas (under similar conditions) (4). Although we did not isolate ethylene diisocyanate, its intermediacy explains the products obtained from **3**.

The physical properties of the crude products (m.p.'s, tlc data, ^{1}H nmr spectra) clearly indicated the presence of mixtures of **7** and **9**. The closeness of the chemical shifts of similar protons (on carbon) of **7** and **9** prevented the use of integration experiments to establish the ratio of these products. The ureides were separated by fractional crystallization but the yields of the pure products do not reflect accurately their percentages in the crude reaction mixtures. Structures of most of the products were established by comparison with literature data and were confirmed by proton nmr and mass spectra.

The proton nmr spectra of **7** and **9** served to distinguish between the two ureides. The ^{1}H nmr spectra for type **9** were as anticipated. The ring methylene proton were considered to be part of an AA'BB'X system, with the X-portion being the ring NH proton. After deuterium oxide addition to effect H-D exchange, the ring methylene protons resonance were seen as a typical symmetrical complex multiplet (AA'BB') centered around 3.4 ppm in DMSO-d_6. The ^{1}H nmr spectra of the linear ureas of type **7** were more perplexing. In dry DMSO-d_6, the signals arising from the methylene and NH protons from the symmetrical $NHCH_2CH_2NH$ system appeared as two complex multiplets. The signals for the methylene protons consisted of two relatively sharp lines some 5-8 Hz apart, with a broader signal of somewhat lesser intensity centered between them. The appearance of this multiplet remained unchanged when solutions of **7** were heated up to 150° in DMSO-d_6, thus eliminating any equilibria due to conformers or rotamers. Furthermore, the separation beween the two sharp outside lines remained constant in 60 or 100 MHz spectra. The ^{13}C nmr spectrum of **7a** showed just two carbon resonances. The signal from the NH's adjacent to the CH_2's resembled a broad triplet and changed when reagents were added which perturbed the N-H bond, such as traces of hydrogen chloride gas, acetic acid or pyridine. The NH signal commenced to sharpen while the CH_2 signal started to coalesce. Finally, both the NH and CH_2 signals became sharp singlets indicative that couplings were no longer visible between adjacent protons. The complex multiplet arising from the CH_2 protons was also converted to a sharp singlet around 3.0 ppm when the NH signal was irradiated, or when deuterium oxide was added to effect NH to ND exchange.

The complex multiplets stemming from the $NHCH_2$-CH_2NH system were not entirely unique in the proton nmr spectra of **7** in DMSO-d_6, but were also observed in the spectra 1,2-di(acetamido) ethane, $(CH_2NHCOCH_3)_2$, and were reported recently for several spectra of bis-ureides of type **7** (R = H or CH_3) (6). The complex ^{1}H nmr pattern for the CH_2 and NH signals arises from the symmetrical six-spin system, $NHCH_2CH_2NH$, of **7**, which can be considered to be of type $A_2A_2'XX'$. A computer-simulated spectrum for the $NHCH_2CH_2NH$ portion of **7a** was generated using the following parameters (assuming a freely rotating system): the experimentally determined chemical shifts of **7a**, spin-spin coupling constants for geminal CH_2's of −12 Hz, vicinal CH_2's of 7.0 Hz, CH_2NH coupling of 6.0 Hz, all other couplings to be 0 Hz, and line width of 2.5 Hz. The simulated spectrum of **7a** was identical to the experimentally observed one.

Reactions of **10** with Amines.

N-Acyloxysuccinimides are used widely in peptide syntheses (8). As "activated" esters, they owe their success as "acyl transfer agents" to preferential nucleophilic attack by an amino group on the exocyclic rather than a ring C=O group. It would seem that during these condensations to create peptides, the Lossen rearrangement does not compete. Other undersirable side reactions have been noted, such as ring opening (of the succinimide) when proline was reacted with *N*-*t*-butoxycarbonyl-L-proline 1-succinimidyl ester to form the expected dipeptide and an amide hydroxamic ester (9).

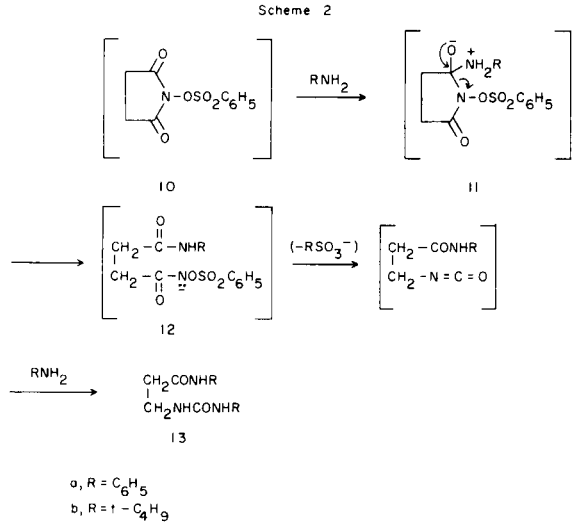
However, when the *N*-acyloxy group was replaced by an *N*-sulfonyloxy group, the electrophilicity of the ring C=O group increases to such an extent that nucleophilic attack prefers to take place on a ring C=O rather than on the exocyclic sulfonate group. Examples of Lossen rearrangements of *N*-sulfonyloxysuccinimides (or substituted succinimides) to β-amino or β-ureido acids, are provided.

The hydroxide ion initiated rearrangement of *N*-benzenesulfonyloxy-1,2-cyclohexanedicarboximide furnished 2-aminocyclohexanecarboxylic acid (10). Ammonia and amines promoted successful Lossen degradations on *cis*-*N*-benzenesulfonyloxy-3-phenyl-2-isoxazoline-4,5-dicarboximide to provide *cis*-3-phenyl-5-ureido-2-isoxazoline-4-carboxamides (11). About the same time, there was a report that *N*-trifluoromethanesulfonyloxysuccinimide underwent a Lossen rearrangement with phenoxide or thiophenoxide ions to produce derivatives of β-alanine (12). In a recent study, *N*-hydroxysuccinimide was degraded to a urethane ester, $C_6H_5O_2CNHCH_2CH_2CO_2C_6H_5$, using phenol in the presence of ethyl azodicarboxylate and triphenylphosphine (13).

We set out to determine how *N*-benzenesulfonyloxysuccinimide, **10**, would react with amines. Indeed, it was found that β-ureido propionamides, which can be considered to be derivatives of β-alanine, were readily formed. While the sequence of events involving **3** and amines was initiated with neutralization, the reaction of **10** with amines commences with covalent bond formation in-

volving one of the ring C=O groups. The driving force for the collapse of tetrahedral intermediate, **11**, is the ring opening to provide the highly energetic Lossen precursor hydroxamate anion, **12**. Loss of the sulfonate ion from **12** generates an isocyanate which adds another equivalent of amine to afford **13** (Scheme 2).

Scheme 2



EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H Nmr (pmr) spectra were recorded on Varian T60A Spectrometer. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane in organic solvents, and from internal sodium 3-(trimethylsilyl)propanesulfonate in deuterium oxide solutions. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak using a Hitachi-Perkin Elmer RMU-6D single focusing spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. The general statement "removal of evaporation of solvents *in vacuo*" implies that relatively low boiling liquids were distilled in a rotary flash evaporator between 40-90° at approximately 20-30 Torr. Thin layer chromatograms (tlc) were obtained on 8 x 4 cm strips of Eastman chromagram silica gel sheets (NO. 13181) mixed with a fluorescent indicator (No. 6060). Developing solvents were ethyl acetate:methanol, 1:1 (solvent A) or ethyl acetate (solvent B). Spots were detected either by uv light and/or iodine stains.

Sodium Succinohydroxamate.

The following procedure provided the salt with the least amount of admixed sodium *N*-hydroxysuccinimide. Sodium (6.9 g., 0.3 g.-atom) was added in several portions to absolute ethanol (150 ml.). During the solution of most of the metal, the solvent boiled, but the final traces of metal were dissolved by heating the mixture on the steam bath for a few minutes. The ethanolic sodium ethoxide solution was then chilled in an ice-water bath to about 5°. Powdered dry hydroxylamine hydrochloride (20 g., 0.29 mole) was dissolved in boiling absolute ethanol (310 ml.). This solution was then cooled to the point of incipient crystallization of the salt (about 40°). At this point, hydroxylamine hydrochloride was neutralized by the previously prepared ice-cold solution of sodium ethoxide. The mixture was swirled continuously in the ice-water bath to maintain the lowest possible temperature during neutralization. In this way, heat-sensitive hydroxylamine was liberated at relatively low temperatures, while co-precipitation of sodium chloride onto crystallizing hydroxylamine hydrochloride was kept to a minumun. After neutralization, sodium chloride was filtered off, and washed with a little absolute ethanol.

Ethyl succinate (17.4 g., 0.10 mole) was now added to the cold ethanolic solution of hydroxylamine (about 5°). Another cold (and previously prepared) solution of sodium ethoxide (from 4.6 g. of sodium in 100 ml. of absolute ethanol) was then added and the mixture permitted to stand for 4 hours at 25°. During that time, most of the product precipitated. To decrease its solubility in ethanol, the mixture was diluted with dry ether (100 ml.) and petroleum ether (b.p. 30-60°, 100 ml.). After another hour, the product was filtered, washed several times with a mixture of ethanol and ether (1:1), and was drained at the pump for just a few minutes since the salt tended to be deliquescent. The rest of adhering solvents were removed in a vacuum desicator (over concentrated sulfuric acid) at room temperature. Most adhering ethanol and ether was removed in about 24-30 hours, with several changes of desiccant. The removal of ethanol was monitored by the ^{1}H nmr spectrum (deuterium oxide). The typical triplet and quartet from the ethyl proton resonances decreased with successive dryings. The major signal arose from the CH_2's of the expected product at 2.38 ppm. A smaller singlet at 2.63 ppm is attributed to the CH_2's of sodium *N*-hydroxysuccinimide. Commercial *N*-hydroxysuccinimide (Aldrich Chemical Co., Milwaukee, Wisc.) in deuterium oxide showed CH_2 resonances at 2.77 ppm and these moved to 2.63 ppm when neutralization was effected by adding sodium hydroxide. Sodium succinohydroxamate prepared in this way contained less than 10% sodium *N*-hydroxysuccinimide as estimated by ^{1}H nmr. Unfortunately, ^{1}H nmr spectra could not be used to detect any sodium succinate in the salt mixture since its CH_2 resonances were found at 2.38 ppm in deuterium oxide. The dry product weighed 19.1 g. and was used as soon as possible in the next step.

3-Benzenesulfonyloxy-5,6-dihydrouracil (**3**).

This preparation is a modification of the literature method (3). Benzenesulfonyl chloride (18.1 ml., 0.14 mole) was slowly added to a cooled, stirred mixture of sodium succinohydroxamate (11.3 g., 0.058 mole) in pyridine (65 ml.) so that the temperature was maintained between 10 and 20°. After the addition, the mixture was stirred at 25° for 30 minutes. Water (250 ml.) and acetic acid (75 ml.) were added and the mixture stored in a refrigerator (5°) for 18 hours. The product (m.p. 171-173°) was filtered and was recrystallized from 2-propanol to produce colorless crystals, (5.4 g., 35%), m.p. 175-178°, lit. (3) m.p. 165-166°; tlc: R_f = 0.39 (solvent B); ^{1}H nmr (DMSO-d_6): δ 2.40-3.20, symmetrical multiplet portion of an AA'BB'X system, the X resonance being downfield due to the NH signal, the upfield portion arose from CH_2CO, the downfield portion of the multiplet was from CH_2NH, and was simplified when decoupled from the NH resonance, 7.60-8.20 (m, arene), 8.30 (broad s, NH, collapsed upon deuterium oxide exchange); ms: (70 eV), m/e (relative intensity), 271 (4), 270 (7, M^+), 269 (26, M^+-1 ion), 206 (3, M-64, m* calcd. 157.0, found 157.0), 158 (5), 143 (10), 142 (15), 141 (90, $C_6H_5SO_2^+$), 125 (7), 98 (16), 94 (14), 93 (10), 78 (20), 77 (100, $C_6H_5^+$) were the major ions' The ion, m/e 112, was less than 5% in intensity and it would appear that there was relatively little thermal or electron-bombardment induced elimination of benzenesulfonic acid concomitant with a Lossen degradation to ethylene diisocyanate (MW = 112).

Reaction of 3-Benzenesulfonyloxy-5,6-dihydrouracil with Amines.

A. With Ammonia.

A solution of **3** (0.4 g., 0.0015 mole) in concentrated ammonium hydroxide (40 ml.) was heated on a steam bath for 15 minutes and then evaporated to dryness *in vacuo*. The residue was extracted wtih acetonitrile at 25° (3 x 10 ml.). Evaporation of these combined extracts *in vacuo* yielded a solid which was triturated with hot ethanol (3 ml.). Upon cooling this ethanol extract, 1-carboxamido-2-imidazolidone, **9a**, (0.05 g., 26%) crystallized out, m.p. 196-198°, lit. (14) 195°; tlc: R_f = 0.30 (solvent A); ^{1}H nmr (DMSO-d_6): complex multiplet, δ 3.00-4.00, [the AA'BB' portion of an AA'BB'X system, 7.00 (broad s, NH), 7.45 (v. broad s, NH_2), identical to the spectrum reported after the completion of this work (4c), in deuterium oxide, δ 3.40-4.00 (CH_2CH_2); ms: m/e (relative intensity), 129 (M^+, 11), 86 (2-imidazolidone ion, 100), 85 (46), 44 (36), 42 (23), 30 (70).

The solid remaining after the acetonitrile extraction above was boiled with 2-propanol (3 x 10 ml.), decanting after each extraction. The combined extracts were concentrated *in vacuo* to one half of the original volume. Upon cooling, there appeared 1,2-diureidoethane (0.01 g., 46%), m.p. 202-204°, lit. m.p. 192-194° (15), 192-195° (6); tlc: R_f = 0.16 (solvent A); ^{1}H nmr (DMSO-d_6): δ 2.93-3.02 (m, CH_2CH_2), 5.44 (NH_2), 5.94 (NH), almost identical to that published after the completion of this work (6), in deuterium oxide, δ 3.19 (s, CH_2CH_2). The sample had identical properties to the one made by a literature method from ethylenediamine hydrochloride and potassium cyanate (15).

The ^{13}C nmr spectrum (DMSO-d_6) showed the CH_2 carbon resonance at 39.9 and the C=O resonance at 158.9 ppm, respectively. Its mass spectrum (at 380° inlet temperature) showed m/e (relative intensity), 146 (m^+, 2), 129 [M-17, (NH_3), 2], 103 (5), 86 (66), 85 (7), 74 (75), 61 (21), 44 (34), 43 (54), 31 (22), 30 (100).

B. With Aniline.

A mixture of **3** (2.7 g., 0.01 mole) was heated with aniline (7.5 ml., 0.08 mole) at 95° (steam bath) for 1 hour. Aqueous acetic acid (50%, 10 ml.) was added to the cooled reaction mixture and the product consisting of **7b** and **9b** (1.83 g.) was collected after 24 hours, m.p. 160-220°. Recrystallization from aqueous acetic acid yielded 1,2-bis(3-phenylureido)ethane, **7b** (0.89 g., 30%), m.p. 262-264°, identical to a sample made by the literature procedure (16); tlc: Rf = 0.19 (solvent B); ^{1}H nmr spectrum (DMSO-d_6): δ 3.15-3.23 (m, CH_2CH_2), 6.15 (m, NH, coupled to CH_2, irradiation) 6.85-7.40 (m, C_6H_5), 8.46 (s, NH, next to C_6H_5); ms: (400° inlet temperature), m/e (relative intensity), 298 (M^+, 0.1), 212 (10), 205 (20), 119 (40), 93 (100).

From the original aqueous acetic acid filtrate, there crystallized after 24 hours, 1-(phenylcarboxamido)-2-imidazolidone, **9b**, which was further purified by crystallization from aqueous acetic acid, (0.2 g., 10%), m.p. 166-168°, lit. (5) m.p. 168° and otherwise identical to a sample made by the literature method (5); tlc: R_f = 0.40 (solvent B).

Its ^{1}H nmr spectrum (DMSO-d_6) showed resonances at δ 3.28-3.93 (complex m, CH_2CH_2), 7.00-7.55 (complex m, C_6H_5), 7.8 and 10.4 (broad s, exchangeable NH protons); ms: [A.E.I. MS-9 mass spectrometer, courtest of Dr. R. S. Egan, Abbott Labs.], calcd. M^+ for $C_{10}N_{11}N_3O_2$, 205.0851 (found, 205.0847, 95), calcd. for C_7H_5NO, C_6H_5NCO, 119.0371 (found, 119.0369, 25), calcd. for C_6H_7N, $C_6H_5NH_2$, 93.0579 (found, 93.0577, 35), calcd. for $C_3H_6N_2O$,  86.0480, (found, 86.0469, 100); in addition there were prominent ions at m/e 85 (80) and 77 (C_6H_5, 15).

The reaction of **3** with aniline was also carried out in boiling ethanol and in dimethylformamide at 95°. The products were **7b** and **9b** and were separated and identified as described above.

C. With *t*-Butylamine.

3-Benzenesulfonyloxy-5,6-dihydrouracil (2.7 g., 0.01 mole) was added to freshly distilled *t*-butylamine (15 ml., 0.14 mole). An immediate and almost violent reaction ensued and **3** dissolved within a few minutes. When the initial reaction had subsided the solution was refluxed on a steam bath for 10 minutes and then more *t*-butylamine (2 ml., 0.019 mole) was added. After an additional 20 minutes reflux, most of the *t*-butylamine was removed *in vacuo*. The residue was diluted with water (20 ml.) and a solid (1.51 g.) was collected, and was recrystallized from aqueous acetic acid (8 ml.) to provide 1,2-bis(3-*t*-butylureido)ethane, **7c**, (0.2 g., 23%), m.p. 225-227°; ^{1}H nmr (DMSO-d_6): δ 136 [s, $C(CH_3)_3$], 2.86-2.97 (m, CH_2CH_2), 3.26, 5.61 (broad s, 2NH's); ms: m/e (relative intensity) 258 (M^+, 10), 243 (4), 186 (10), 170 (8), 159 (6), 142 (20), 130 (23), 117 (40), 115 (35), 87 (35), 74 (26), 58 (100), 57 (25), 43 (20), 30 (25).

Anal. Calcd. for $C_{12}H_{26}N_4O_2$: C, 55.79; H, 10.14; N, 21.68. Found: C, 55.87; H, 10.07; N, 21.66.

Solids which appeared in various filtrates from these recrystallizations were examined carefully. These was isolated 1-(*t*-butylcarboxamido)-2-imidazolidone, **9c**, (0.8 g., 43%), m.p. 155° (from hot water); ^{1}H nmr (DMSO-d_6): δ 1.28 [s, $C(CH_3)_3$], 3.06-3.86 (m, CH_2CH_2), 7.42, 8.10 (broad s, NH's); ms: m/e (relative intensity) 185 (M^+, 2), 170 (100), 130 (6), 127 (10), 113 (10), 87 (23), 86 (12), 85 (16), 84 (8), 70 (8), 58 (20), 42 (8).

Anal. Calcd. for $C_8H_{15}N_3O_2$: C, 51.88; H, 8.16; N, 22.69. Found: C, 52.08; H, 7.93; N, 22.82.

D. With Piperidine.

3-Benzenesulfonyloxy-5,6-dihydrouracil (2.7 g., 0.01 mole) was added to freshly distilled piperidine (14 ml., 0.14 mole) over a 5 minute interval. A vigorous reaction took place upon the addition of the solid and the temperature rose to 50°. More piperidine (2 ml., 0.02 mole) was added and the solution was refluxed on a steam bath for 30 minutes. After removing excess piperidine *in vacuo*, a solid residue remained. The addition of water (10 ml.) caused some of this residue (mainly piperidine benzenesulfonate) to dissolve. The insoluble product (2.0 g.) was filtered off after 24 hours, m.p. 178-215°. Recrystallization of the crude product from aqueous acetic acid produced 1,2-bis(3,3-pentamethyleneureido)ethane, **7d**, (1.8 g., 64%), m.p. 220-222°, lit. (5) m.p. 222°; ^{1}H nmr (DMSO-d_6): δ 1.45 (broad s, protons on C-3, C-4 and C-5 of piperidine rings), 3.21 (broad s, protons on C-2 and C-6 of piperidine rings), 3.06-3.20 (m, CH_2's between ureas), 6.48 (s, NH); ms: m/e (relative intensity), 283 (10), 282 (M^+, 45), 198 (15), 197 (5), 155 (12), 154 (22), 142 (35), 141 (20), 139 (18), 129 (50), 112 (80), 86 (23), 85 (21), 84 (100), 83 (18), 70 (20), 69 (48), 57 (18), 56 (23), 55 (21), 41 (30).

The filtrates from the bis-ureide were concentrated to a syrup *in vacuo* and permitted to stand. After a week, upon the addition of a small quantity of cold water, the product, 1-(pentamethylenecarboxamido)-2-imidazolidone, **9d**, crystallized in

the viscous residue. The product was filtered off (0.05 g., 2.5%), m.p. 175-179°, lit. (5) m.p. 181°; ^{1}H nmr (DMSO-d_6): δ 1.51 (broad s, CH_2 protons of piperidine ring on carbon atoms 3, 4 and 5), 3.28-3.77, (complex multiplet, consisting of a broad singlet at 3.12 ppm for the methylene protons on carbons 2 and 6 of piperidine, superimposed on the AA'BB' portion of the 4 CH_2 protons of imidazolidone ring), 7.09 (broad s, NH).

Sodium *N*-Hydroxysuccinimide.

Although good procedures to synthesize *N*-hydroxysuccinimide from succinic anhydride are available (17), the following method leads directly to its sodium salt.

Hydroxylamine hydrochloride (30 g., 0.43 mole) was dissolved in boiling methanol (150 ml.) and the solution cooled. Neutralization was achieved by adding a cold solution of sodium methoxide (9.9 g. of sodium in 150 ml. methanol). Sodium chloride was filtered off and the filtrate concentrated by removing about 200 ml. of methanol *in vacuo*. Ethyl succinate (36.58 g., 0.21 mole) was added to the methanolic solution of hydroxylamine, followed by a solution of sodium methoxide (9.9 g. sodium in 150 ml. methanol). The mixture was warmed at 60° for 0.5 hour and then cooled. The product was filtered and dried *in vacuo* (24 hours over concentrated sulfuric acid). The product weighed 28.4 g. (98%) and its ^{1}H nmr spectrum showed a singlet at 2.63 ppm.

N-Benzenesulfonyloxysuccinimide.

Method A.

Benzenesulfonyl chloride (17.66 g., 0.1 mole) was slowly added to a cooled suspension (5°) of sodium *N*-hydroxysuccinimide (13.7 g., 0.1 mole) and sodium acetate trihydrate (0.8 g.) in tetrahydrofuran (20 ml.). The temperature was kept below 30°. Insoluble material was filtered off and the filtrate concentrated *in vacuo*. The residue was diluted with 2-propanol (50 ml.) and petroleum ether (b.p. 30-60°, 100 ml.). The sulfonate (14.9 g., 58%, m.p. 93-97°) was filtered and recrystallized from 2-propanol, m.p. 96-98°; tlc: R_f 0.66 (solvent B); ^{1}H nmr (deuteriochloroform): δ 2.81 (s, CH_2), 7.62-8.23 (m, arene); ms: m/e (relative intensity), 255 (M^+, 5), 158 (40), 141 (54), 101 (20), 100 (35), 94 (43), 77 (100), 74 (45), 73 (32), 55 (47).

Anal. Calcd. for $C_{10}H_9NO_5S$: C, 47.07; H, 3.55; N, 5.49. Found: C, 47.08; H, 3.56; N, 5.52.

Method B.

Benzenesulfonyl chloride (3.7 ml., 0.03 mole) was added to a stirred solution of *N*-hydroxysuccinimide (3.0 g., 0.026 mole) in pyridine (30 ml.). After 0.5 hour, the solution was poured into ice-water (50 ml.) and the product (4.99 g., 75%, m.p. 95-97°) collected.

Reactions of *N*-Benzenesulfonyloxysuccinimide with Amines.

A. With Aniline.

A mixture of *N*-benzenesulfonyloxysuccinimide (2.16 g., 0.0085 mole) and aniline (6 ml., 0.066 mole) was heated on a steam bath for 1 hour. Aqueous acetic acid (50%, 30 ml.) was added and the solid collected (1.57 g., 66%); m.p. 220-225°; tlc: R_f = 0.32 (solvent B). The product was recrystallized from acetic acid (35 ml.) and yielded 3-(3-phenylureido)propionanilide, **13a**, (1.02 g., 42%, m.p. 233-235°; tlc: R_f = 0.34, (solvent B); ^{1}H nmr (DMSO-d_6): δ 2.55 (t, CH_2CO), 3.43 (q, CH_2NH, J_{CH_2,CH_2} = $J_{CH_2,NH}$ = 5.8 Hz, t after deuterium oxide exchange), 6.26 (t, CH_2NH, collapses on deuterium oxide exchange), 6.80-7.70 (m, arene), 8.53 and 9.95 (s, NH's, collapse on deuterium oxide exchange); ms: m/e (relative intensity), 283 (M^+, 6), 191 (6), 190 (5), 212 (12), 164 (10), 135 (9), 119 (16), 93 (100).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.99; H, 6.06; N, 14.98.

B. With *t*-Butylamine.

N-Benzenesulfonyloxysuccinimide (2.55 g., 0.01 mole) was added to *t*-butylamine (10 ml., 0.095 mole). After stirring the mixture for 5 minutes, the solid dissolved and the solution began to reflux spontaneously. To complete the reaction, the solution was heated on a steam bath for 5 minutes, and then *t*-butylamine was removed *in vacuo*. Water (15 ml.) was added to the solid residue to dissolve *t*-butylamine benzenesulfonate and other water-soluble products. The precipitate (0.67 g.) was collected and was recrystallized from water. Although the solid was reluctant to dissolve in boiling water, unless a large volume was used, it was reluctant to crystallize out. Upon concentration of the solution to about one third of its volume, 3-(3-*t*-butylureido)-*N*-*t*-butylpropanamide, **13b**, (0.39 g., 16%) was obtained, m.p. 248-250; ^{1}H nmr (DMSO-d_6): δ 1.20, 1.23 [s, two $C(CH_3)_3$], 2.14 (t, CH_2CO); 3.11 (q, J_{CH_2,CH_2} = $J_{CH_2,NH}$ = 6.0 Hz, t upon deuterium oxide exchange), 5.61 (t, CH_2NH), 7.37-7.73 (s, NH's, collapses upon deuterium oxide exchange); ms: m/e (relative intensity) 243 (M^+, 7), 228 (6), 171 (12), 144 (9), 115 (20), 58 (100).

Anal. Calcd. for $C_{12}H_{25}N_3O_2$: C, 59.23; H, 10.36; N, 17.27. Found: C, 59.09; H, 9.88; N, 17.24.

REFERENCES AND NOTES

(1) Taken in part from the Master's Thesis by M. VanVerst, August, 1977.

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

(3) C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955).

(4a) J. N. Tilley and A. A. R. Sayigh, *ibid.*, **29**, 3347 (1964); (b) N. G. Ostroumova, Yu. V. Markova and M. N. Shchukina, *Probl. Organ. Sinteza, Akad. Nauk SSSR, Otd. Obshch. Tekhn. Khim.*, 140 (1965); *Chem. Abstr.*, 64, 6421b (1966); (c) Ma. Miyahara, M. Nakadate, Mi. Miyahara and I. Suzuki, *Chem. Pharm. Bull.*, **26**, 2635 (1978).

(5) H. J. Schaeffer and P. S. Bhargava, *J. Pharm. Sci.*, **53**, 137 (1964).

(6) S. J. Cristol, R. P. Evans and K. L. Lockwood, *J. Org. Chem.*, **42**, 2378 (1977).

(7) The NMRCAL program of Nicolet Technology, Inc. in the TT-7 F-T accessory on a Varian A-60 spectrometer, was used to generate the simulated ^{1}H nmr spectrum of **7a**.

(8) E. Wünsch, in "Methoden der Organischen Chemie", Houben-Weyl, Vol. 15/2, Georg Thieme Verlag, Stuttgart, 1974, pp. 149-166.

(9) J. Šavrda, *J. Org. Chem.*, **42**, 3199 (1977).

(10) L. Bauer and S. V. Miarka, *ibid.*, **24**, 1293 (1959).

(11) W. J. Tuman and L. Bauer, *ibid.*, **37**, 2983 (1972).

(12) T. M. Chapman and E. A. Freedman, *ibid.*, **38**, 3908 (1973).

(13) E. Grochowski and J. Jurczak, *ibid.*, **43**, 2541 (1978).

(14) T. P. Johnston and P. S. Opliger, *J. Med. Chem.*, **10**, 675 (1967).

(15) A. W. Dox, *J. Am. Chem. Soc.*, **55**, 1230 (1933).

(16) O. Stoutland, L. Helgen and C. L. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(17a) K. T. Wang, D. N. Brattesani and B. Weinstein, *J. Heterocyclic Chem.*, **3**, 98 (1966); (b) H. Gross and I. Keitel, *J. Prakt. Chem.*, **311**, 692 (1969).