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Biologically Oriented Organic Sulfur Chemistry. 19. Synthesis and Properties of 2-Amino-5-mercapto-5-methylhexanoic Acid, a Bishomologue of Penicillamine. Use of Boron Trifluoride Etherate for Catalyzing Markownikoff Addition of a Thiol to an Olefin[1a-f]

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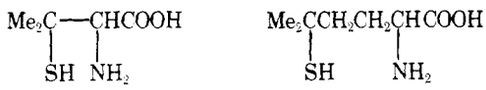
Synthesis is reported of 2-amino-5-mercapto-5-methylhexanoic acid (**2**) as a bishomologue of penicillamine (**1**). In this synthesis, alkylation of diethyl acetamidomalonate gave ethyl 2-acetamido-2-carbethoxy-5-methyl-4-hexenoate (**4**). Addition of α-toluenethiol to **4** using BF_3·Et_2O then gave ethyl 2-acetamido-2-carbethoxy-5-benzylthio-5-methylhexanoate (**6**) in 63–74% yield; this reaction appears to be the first use of BF_3·Et_2O as a catalyst for effecting Markownikoff-type addition of a thiol to an alkene. The bishomologue **2** was obtained from **6** either by decarboxylation to the amide (**5**), debenzylation of **5** to **7**, and hydrolysis, or (preferably) by decarboxylation and hydrolysis to the amino acid **8** in one step and debenzylation. The bishomologue **2** resisted hot strong acid. It reacts with formaldehyde, Fe(III), or Cu(II) much less readily than does **1** and therefore affords a promising means of probing biological properties of **1** where it is unclear whether these properties depend upon ring formation involving SH and NH_2 or upon independent action of functional groups.

Penicillamine (**1**) gives rise to an astonishing multiplicity of significant biomedical and biological effects. Illustratively,



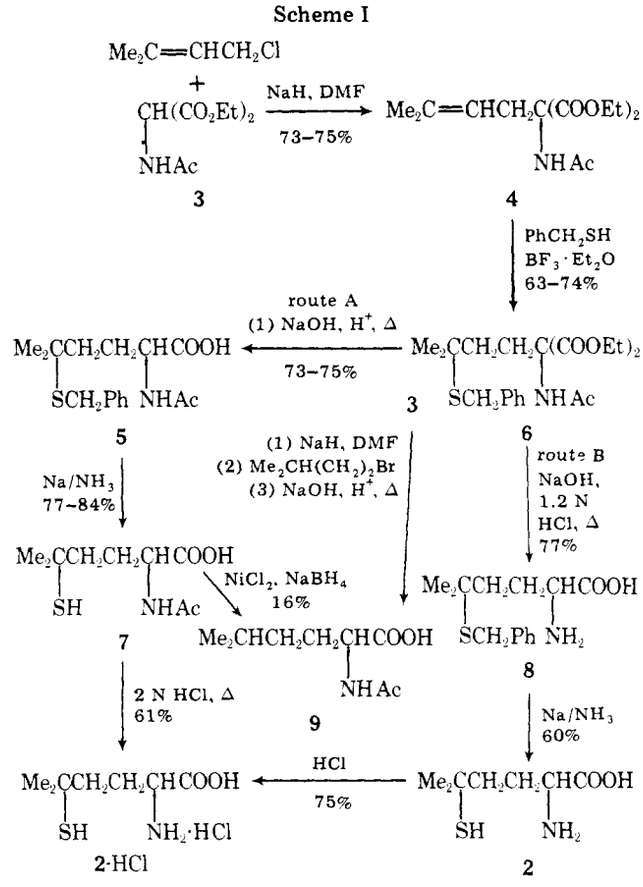
1 **2**

it has been of interest in treating a wide variety of diseases,[2a] inhibits lysyl oxidase,[2b] shows immunological properties,[1b] reduces skin-tensile strength of rats (apparently through formation of thiazolidines with aldehyde groups of collagen),[1a] and is a good chelating agent,[2c] a property that is biomedically important.[2c-e] The last two of these, formation of thiazolidines and chelation, depend on the capability of **1** to form five-membered rings involving SH and NH_2, but whether most other biological functions of **1** depend on this proclivity or simply on independent action of one or more of the functional groups is unknown. A bishomologue of **1** that could lead only to more difficultly formed seven-membered rings would be useful because it could be compared with **1** in the multifold biological activities of **1** and thus could help to clarify the question of five-membered ring involvement vs. independent action of functional groups. This paper reports synthesis of the bishomologue **2**. The key to the synthesis of **2** was a novel BF_3-catalyzed Markownikoff-type addition of a thiol to an alkene that warrants general attention as a new synthetic tool. The bishomologue **2** was indeed found to react much less readily than **1** with a model aldehyde and in forming metal chelates.

In the synthesis of **2** (Scheme I), alkylation of **3** produced the requisite carbon skeleton (confirmed below).

For insertion of SH, although Markownikoff addition of H_2S and anti-Markownikoff addition of thiols to alkenes are well known, a report of Ipatieff, Pines, and Friedman that H_2SO_4 catalyzes the requisite Markownikoff addition of thiols was one of a very few guides that were attractive.[3] With α-toluenethiol and **4**, however, the principal or sole product using H_2SO_4 was benzyl disulfide (presumably produced by oxidation of the thiol by H_2SO_4). Use of BF_3·Et_2O at ~25 °C and **4** for several days led to no reaction with α-toluenethiol and led only to intractable mixtures with thioacetic acid. However, use of BF_3·Et_2O as both catalyst and solvent with

Scheme I



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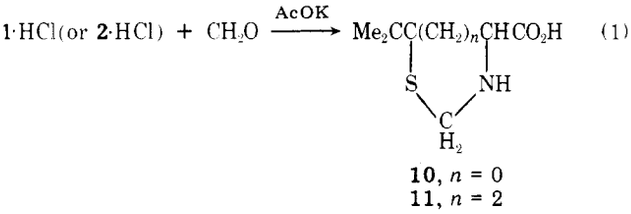
α-toluenethiol at 70 °C for 48 h led to the *S*-benzyl adduct **6**. So far as we know, this is the first use reported of BF_3·Et_2O, or of any acidic catalyst other than H_2SO_4, for effecting clean Markownikoff-type addition of a thiol to an alkene. It is worth recognizing that BF_3·Et_2O will not be a panacea, however; for example in the addition of H_2S to an exo alkylidenecyclodipeptide, catalysis by BF_3·Et_2O led to an intractable mixture, in contrast to $ZnCl_2$ which produced quantitative addition (apparently because of an atypical transannular zinc complex).[4]

Initially, conversion of **6** to the *N*-acetylamino acid **5** was sought (route A, Scheme I), because there was reason to believe that debenzylation might be smoother with the amide **5** than with the amino acid **8**. Conversion to **5** was achieved by using only 0.4 N HCl in the decarboxylation. Ultimately, however, **8** proved to be obtainable in one step and, since **8** proved to be debenzylated nearly as readily as **5**, the sequence of route B is preferred because it is both shorter and affords a somewhat better yield (46% of **2** from **6** by route B vs. 38% of **2**·HCl from **6** by route A). Surprisingly, the amino acid **8** precipitated as such despite the acidic medium, evidently because of very sparing solubility. Early in the studies of deacetylation of **7**, a strong odor of H_2S and an indication of olefinic protons in the NMR led to a suspicion that cleavage of the SH moiety to give a tertiary carbonium ion might be very troublesome. However, once **2**·HCl had been isolated, this suspicion proved unfounded; **2**·HCl could be heated in refluxing 3 N HCl for 8 days with recovery of 79% of pure **2**·HCl after recrystallization (NMR indicated that perhaps 10% of the disulfide formed).

Debenzylation of **5** and **8** was achieved essentially by a procedure of Riegel and du Vigneaud.[5] When **2**·HCl was first synthesized it had a mp of 221–222 °C dec, but this product later changed to an isomorphous form having the same IR and NMR spectra but a mp of 204–206 °C dec, which also was the melting point of all subsequent **2**·HCl encountered. The amino acid **2** was characterized by conversion to **2**·HCl. Both **2** and **2**·HCl gave strong violet colors with alkaline sodium nitroprusside, comparable to that of **1**, showing that SH was present as such and not as a δ-thiolactone (cf. ref 5).

Assurance as to the carbon skeleton of **2**·HCl was sought by desulfurization with W-2 Raney nickel, but no product could be isolated because of strong adsorption on the nickel. Use of the less strongly adsorbed amide in the convenient procedure of Truce and Perry,[6] however (Scheme I), did desulfurize **7** to **9**, which was identical with **9** synthesized from **3** by the conventional independent route shown in Scheme I.

The bishomologue **2**·HCl reacted much less readily than **1**·HCl with formaldehyde. Under conditions that converted **1**·HCl to the pure thiazolidine **10** in 79% yield (eq 1), **2**·HCl led



(1)

10, $n = 0$
11, $n = 2$

only to an intractable mixture from which none of the thiazepane **11** could be isolated; NMR showed a doublet at δ 4.28 that indicated the presence of less than 15% of **11** (**10** has the SCH_2N doublet at δ 4.42). When 1 molar proportion each of **1**·HCl and **2**·HCl were allowed to compete for 1 molar proportion of formaldehyde, relative NMR peak heights for NCH_2S showed the ratio of **10**:**11** to be ~3. The bishomologue **2** showed no indication whatever of the formation of colored coordination compounds with Fe(III)[7a] or Cu(II),[8] despite a variety of conditions where **1** responded well. For example, equimolar amounts of $FeCl_3$ and **1** gave characteristic blue aqueous solutions at 0.5–2.5 mM, but when $FeCl_3$ was slowly added to 0.5–2.5 mM solutions of **2** no color resulted either up to the equimolar concentration of 0.5–2.5 mM or when the proportion of $FeCl_3$ was increased threefold. Addition of $CuSO_4$ to **1** to give an aqueous solution 2.5 mM in each component led to a pale purple solution, but substitution of **2** led to no color at any time as the $CuSO_4$ was added or when the proportion of $CuSO_4$ was increased threefold.

Accordingly, if a biological property of **1** depends on formation of a thiazolidine or a coordination complex, **2** should be considerably less effective. On the other hand, if the biological property depends simply on independent actions of functional groups, such as formation of a disulfide or a redox reaction involving SH, similar results would be expected when **2** is substituted for **1**. Use of **2** thus should afford a useful probe in clarifying a variety of little understood important biological properties of **1**.

Experimental Section

Melting points were determined using a Thomas-Hoover stirred liquid apparatus and are corrected. IR spectra were obtained using a Perkin-Elmer Model 727 spectrophotometer and NMR spectra with a JEOL Model JNM-MH-100 (100 MHz) or a Varian Model EM-360 spectrometer (60 MHz) with Me_4Si as an internal standard [or, in D_2O, $Me_3Si(CH_2)_3SO_3Na$]. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Moist extracts were dried using anhydrous $MgSO_4$ or Na_2SO_4, and solvent then was removed under reduced pressure using a rotary-flask evaporator. TLC was performed on 3 × 10-cm glass plates, prepared by dipping the plates into a stirred mixture of Brinkman Silica Gel G and $CHCl_3$, with solvents as specified and development by I_2 vapor.

Ethyl 2-Acetamido-2-carbethoxy-5-methyl-4-hexenoate (4). Diethyl acetamidomalonate (**3**, 100.0 g, 460 mmol) in a minimum of DMF (~300 mL) was added over 1.5–2 h to NaH (11.06 g, 461 mmol, obtained from a mineral oil dispersion by washing three times with petroleum ether) in DMF (~50 mL) under N_2. The mixture was stirred for 30 min and warmed to 40 °C and 1-chloro-3-methyl-2-butene (48.2 g, 461 mmol, Eastman redistilled) was added dropwise during 30 min. The mixture then was warmed to 60 °C, stirred for 4 h, and allowed to cool. After 4 h, 750 mL of H_2O was added, and the mixture was extracted with five 300-mL portions of ether. The extracts were combined, washed three times with 300 mL of H_2O, and dried (Na_2SO_4). Evaporation of the ether gave an oil that solidified upon cooling. Recrystallization from ethyl acetate–hexane gave 95.5 g (73%) of **4**: constant mp 61.5–63.5 °C; IR (KBr) 3250, 3000, 2950–2900, 1760, 1740, 1650, 1630, 1540, 1440, 1380, 1300, 1200, 1060, 1020, 860, and 800 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, 6 H, $OCH_2\mathbf{CH_3}$), 1.68 [d, 6 H, $(CH_3)_2C=$], 2.04 (s, 3 H, $COCH_3$), 3.10 (d, 2 H, $=CH\mathbf{CH_2}$), 4.29 (q, 4 H, $\mathbf{CH_2}CH_3$), 5.00 (t, 1 H, $=CH-$), and 6.88 (b, 1 H, NH).

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.92; H, 8.14; N, 4.91. Found: C, 59.15; H, 8.12; N, 4.87.

Ethyl 2-Acetamido-2-carbethoxy-5-benzylthio-5-methylhexanoate (6). Freshly distilled BF_3·Et_2O (170.6 g, 1.2 mol, Aldrich) was added to 85.1 g (298 mmol) of **4** and 52.5 g (423 mmol) of α-toluenethiol, and the solution was heated at 70 °C for 48 h under reflux with protection from moisture ($CaCl_2$). The yellow-gold solution was diluted with H_2O (~300 mL) and 15% NaOH (~300 mL) and was extracted with four 200-mL portions of ether. The extracts were combined, washed four times with 150-mL portions of H_2O, and dried ($MgSO_4$). Evaporation of the ether gave an oil, which solidified when rubbed four times with 50 mL of hexane. Two recrystallizations from ether–hexane gave 77.1 g (63%) of **6**: constant mp 63–65 °C; IR (KBr) 3300, 2975, 1760, 1740, 1650, 1500, 1450, 1380, 1300, 1200, 1040, 1020, 860, 760, and 710 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 6 H, $OCH_2\mathbf{CH_3}$), 1.35 [s, 6 H, $(CH_3)_2C$], 1.35 (t, 2 H of CH_2CH_2), 2.03 (s, 3 H, $COCH_3$), 2.45 (m, 2 H of CH_2CH_2), 3.70 (s, 2 H, CH_2S), 4.25 (q, 4 H, $\mathbf{OCH_2}CH_3$), 6.74 (s, 1 H, NH), and 7.35 (s, 5 H, Ph).

Anal. Calcd for $C_{21}H_{31}NO_5S$: C, 61.58; H, 7.64; N, 3.42; S, 7.83. Found: C, 61.71; H, 7.66; N, 3.31; S, 7.65.

2-Acetamido-5-benzylthio-5-methylhexanoic Acid (5). A mixture of **6** (26.7 g, 65.2 mmol) and NaOH (447 mmol) in 179 mL of H_2O was heated under reflux; the mixture became homogeneous in 45–70 min. After 8 h, the solution was cooled to 10 °C and 6 N HCl was added dropwise until a heavy white precipitate resulted and the pH

was 1–2. The solid was added to 200 mL of H_2O and 9 mL of 9 N HCl and heated under reflux for 5 h. When the solution was cooled, an oil appeared that solidified in 12 h at 0 °C. The solid was collected and recrystallized from EtOH–H_2O to give 15.2 g (75%) of **5**: constant mp 127.5–129 °C; IR (KBr) 3340, 2900–1950, 1720, 1640, 1550, 1450, 1380, 1250, 1120, 780, 710, and 700 cm^{-1}; NMR ($CDCl_3$) δ 1.26 [s, 6 H, $(CH_3)_2C$], 1.51 (m, 4 H, CH_2CH_2), 1.98 (s, 3 H, $COCH_3$), 3.60 (s, 2 H, SCH_2), 4.40 (m, 1 H, CH), 6.14 (d, 1 H, NH), 7.14 (s, 5 H, Ph), and 10.06 (s, 1 H, COOH).

Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.10; H, 7.51; N, 4.52; S, 10.36; neut equiv 309. Found: C, 61.97; H, 7.53; N, 4.51; S, 10.37; neut equiv 310.

2-Amino-5-benzylthio-5-methylhexanoic Acid (8). A mixture of **6** (50.05 g, 122 mmol) and NaOH (836 mmol) in 334 mL of H_2O was heated under reflux for 8 h. The cooled solution was treated with 6 N HCl until the pH was 1–2. The heavy white precipitate was separated and heated in 350 mL of H_2O and 40 mL of concentrated HCl under reflux for 9 h. The solution that resulted was cooled (~0–5 °C) overnight, and the resulting **8** was collected. Recrystallization from H_2O gave 25.10 g (77%) of **8** as white crystals: constant mp 202–204 °C; IR (KBr) 3500–2500, 1610, 1500, 1450, 1370, 1080, 760, and 700 cm^{-1}; NMR (CD_3OD) δ 1.32 [s, 6 H, $(CH_3)_2C$], 1.72 [m, 2 H, $(CH_3)_2C\mathbf{CH_2}$], 2.12 (m, 2 H, $CH_2\mathbf{CH_2}CH$), 3.56 (t, 1 H, CH), 3.75 (s, 2 H, SCH_2), and 7.30 (m, 5 H, Ph).

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.93; N, 5.24; neut equiv 267. Found: C, 62.93; H, 7.90; N, 5.28; neut equiv (by formol titration)[9] 263.

2-Acetamido-5-mercapto-5-methylhexanoic Acid (7) from 5. The thioether **5** (14.63 g, 47.3 mmol) was added to 300 mL of liquid NH_3 in a three-necked flask chilled using dry ice and acetone and equipped with a dry-ice condenser and gas-inlet tube. The mixture was stirred for ~15 min to effect dissolution. Sodium (~6.5 g, 0.28 g-atom washed in benzene) then was added portionwise during 20 min until a blue color persisted for 40–45 min. Ammonium chloride was slowly added to discharge the blue color, and the NH_3 was swept away using a steady stream of N_2. The residue was dissolved in a minimum of H_2O, and 6 N HCl was added to the chilled solution until the pH was 1–2. The solid was collected and recrystallized from H_2O to give 7.94 g (77%) of white crystalline **7**: constant mp 173.5–175 °C; IR (KBr) 3350, 3200–2100, 1720, 1690, 1610, 1550, 1450, 1375, 1250, 1120, 960, and 710 cm^{-1}; NMR (CD_3OD) δ 1.36 [s, 6 H, $(CH_3)_2C$], 1.68 (m, 4 H, CH_2CH_2), 1.96 (s, 3 H, $COCH_3$), and 4.36 (t, 1 H, CH).

Anal. Calcd for $C_9H_{17}NO_3S$: C, 49.28; H, 7.83; N, 6.38; S, 14.62. Found: C, 49.11; H, 7.67; N, 6.18; S, 14.49.

2-Amino-5-mercapto-5-methylhexanoic Acid Hydrochloride (2·HCl) from 7. A solution of the *N*-acetyl derivative **7** (3.42 g, 15.6 mmol) in 65 mL of 2 N HCl was heated under reflux for 60 h, and H_2O then was evaporated under reduced pressure. The gummy residue solidified when rubbed with ether. Solid was removed by filtration, dried, and recrystallized from EtOH–ether; yield of **2**·HCl, 2.04 g (61%); constant mp 204–206 °C dec. The first preparation of **2**·HCl had a mp of 221–222 °C dec and the composition shown in the analysis. When the procedure was next repeated (3 months later), the **2**·HCl produced had a constant melting point after recrystallization of 204–206 °C dec (Anal. Found: C, 39.46; H, 7.58). The original **2**·HCl then had changed in mp to 203–205 °C dec and had the same IR and NMR spectra as the new sample. Hence it appears that **2**·HCl with a higher mp of 221–222 °C dec changed to an isomorphous form with mp 204–206 °C dec; all samples of **2**·HCl after the first (which changed) had mp 204–206 °C dec: IR (KBr) 3600–2400, 1960, 1730, 1595, 1480, 1450, 1410, 1370, 1200, 1060, 850, and 760 cm^{-1}; NMR (D_2O) δ 1.38 [s, 6 H, $(CH_3)_2C$], 1.72 [m, 2 H, $Me_2C(SH)\mathbf{CH_2}CH_2$], 2.12 (m, 2 H, $CH_2\mathbf{CH_2}CH$), and 4.12 (t, 1 H, **CH**).

Anal. Calcd for $C_7H_{16}ClNO_2S$: C, 39.32; H, 7.56; Cl 16.60; N, 6.55; S, 15.00. Found: C, 39.31; H, 7.50; Cl, 16.75; N, 6.50; S, 14.84.

In order to assess the stability of **2**·HCl, 0.410 g of **2**·HCl (1.9 mmol), 6 N HCl (3.2 mL), and water (3 mL) were heated under reflux for a total of 8 days; periodic TLC showed no changes. Evaporation of H_2O under reduced pressure then left **2**·HCl as white solid with mp 188–195 °C dec. This solid was identical in TLC [two different solvent systems (EtOH, H_2O) although streaking did occur] with the original **2**·HCl and had an IR spectrum nearly superimposable on that of the original **2**·HCl. The NMR spectrum of the product did not show the presence of vinylic hydrogens but did show the appearance of a new peak attributed to the disulfide of **2**·HCl at ~δ 1.2 in about 10% yield, based on its integration ratio to that of all $(CH_3)_2C$ protons. Recrystallization of the crude product gave 0.323 g (79%) of **2**·HCl with mp and mmp 205–206 °C dec.

2-Amino-5-mercapto-5-methylhexanoic Acid (2) from 8. Much as described for the preparation of **7** from **5**, the *S*-benzyl adduct **8** (8.08 g, 30.2 mmol) in 200 mL of liquid NH_3 was stirred ~20 min (homogenous suspension), and sodium (4.2 g, 0.18 g-atom) was added portionwise until the blue color persisted for 45 min. Ammonium chloride was added, the NH_3 was swept away, and the residue was dissolved in a minimum of H_2O. Cooling and acidification with 10% HCl to pH 4.5–5 produced white crystals of **2** which amounted after recrystallization from EtOH–H_2O to 3.19 g (60%) of **2**: mp 240–242 °C dec; IR (KBr) 3650–2300, 2100, 1600, 1500, 1450, 1415, 1360, 1220, 1140, 1080, 850, 800, and 750 cm^{-1}; NMR (D_2O) δ 1.37 [s, 6 H, $(CH_3)_2C$], 1.69 [m, 2 H, $Me_2C(SH)\mathbf{CH_2}CH_2$], 2.01 (m, 2 H, $CH_2\mathbf{CH_2}CH$), and 3.78 (t, 1 H, CH).

Anal. Calcd for $C_7H_{15}NO_2S$: C, 47.42; H, 8.55. Found: C, 47.34; H, 8.49.

For the conversion of **2** to **2**·HCl, 0.108 g (0.61 mmol) of **2** was dissolved in 1.5 mL of hot H_2O and 0.5 mL of 6 N HCl, and the solution was boiled for 5 min. Evaporation of H_2O (reduced pressure) left **2**·HCl, which solidified when rubbed with ether. Recrystallization from EtOH–ether gave 0.098 g (75%) of **2**·HCl, mp and mmp 204–206 °C dec. The TLC and IR spectrum agreed with those of **2**·HCl obtained in the conversion of **7** to **2**·HCl.

Desulfurization of 7 with $NiCl_2$ and $NaBH_4$ to 2-Acetamido-5-methylhexanoic Acid (9). In accordance with the method of Truce and Perry,[6] compound **7** (1.01 g 4.61 mmol), $NiCl_2$·$6H_2O$ (10.91 g, 45.9 mmol), and EtOH (50 mL) were stirred under N_2 for 25 min. The solution then was cooled to 0–5 °C, and 5.21 g (137.7 mmol) of $NaBH_4$ in 40 mL of H_2O was added dropwise during 40 min. After the reaction mixture had been heated under reflux for 10 h, insoluble materials were separated by filtration and washed with absolute EtOH. Evaporation of the solvent gave 6–7 g of crude solid, which was extracted ten times with $CHCl_3$. Evaporation of the $CHCl_3$ and rubbing of the residue with ether gave solid which after recrystallization from H_2O yielded 0.134 g (16%) of **9** as white crystals: constant mp 138–139 °C; IR (KBr) 3350, 3150–2150, 1900, 1700, 1620, 1550, 1440, 1370, 1250, 1160, 1100, 970, and 660 cm^{-1}; NMR (CD_3OD) δ 0.92 [d, 6 H, $(CH_3)_2C$], 1.30 (m, 2 H, $Me_2C\mathbf{HCH_2}CH_2$), 1.54 [m, 1 H, Me_2CH], 1.78 (m, 2 H, $Me_2CHCH_2\mathbf{CH_2}$), 2.00 (s, 3 H, $COCH_3$), and 4.40 (t, 1 H, $Me_2CHCH_2CH_2\mathbf{CH}$).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.72; H, 9.17. Found: C, 57.68; H, 9.16.

The desulfurization product (**9**) was independently synthesized by a procedure similar to that for the preparation of **4**. Diethyl acetamidomalonate (**3**, 20.0 g, 92.1 mmol) in DMF (75 mL) was added to NaH (2.21 g, 92.1 mmol) in DMF (50 mL) under N_2, and the mixture was stirred for 1 h at ~25 °C. Redistilled 1-bromo-3-methylbutane (18.2 g, 120 mmol, Eastman) then was added dropwise with stirring and the mixture heated at 80 °C for 12 h, cooled, diluted with 200 mL of H_2O, and extracted with three 300-mL portions of ether. The ether extracts were combined and washed successively with two 50-mL portions each of 15% aqueous NaOH and H_2O. Drying of the extract ($MgSO_4$) and concentration gave 23.53 g (89% crude) of ethyl 2-acetamido-2-carbethoxy-5-methylhexanoate as a light-tan oil that had an appropriate NMR spectrum. Without further purification, this product (4.0 g, 13.9 mmol) and NaOH (100 mmol) were heated in 30 mL of H_2O under reflux for 8 h. The solution was cooled to 5 °C, 6 N HCl was added to pH 1–2, and the resulting mixture was kept at 0 °C for 48 h; yield of the crude malonic acid was 2.8 g (87%). This crude diacid (2.0 g, 8.64 mmol) was heated in 40 mL of H_2O and 0.5 mL of 6 N HCl under reflux for 7 h. The solution was cooled to 0 °C for 12 h, and solid which separated was removed and recrystallized from H_2O to give 0.409 g (25%) of pure **9**, mp and mmp 138–139 °C. Spectra (IR and NMR) and TLC (EtOH) were identical with those of product **9** from the desulfurization of **7**.

Competitive Studies of the Formation of Thiazolidine 10 vs. Thiazepane 11. Authentic D,L-4-carboxy-5,5-dimethylthiazolidine (**10**) was prepared by a reported method.[7b] Recrystallization from H_2O and EtOH–H_2O gave **10** in 79% yield: mp 199–201 °C dec (lit.[7b] mp 200–201 °C dec); NMR (D_2O) δ 1.40 [s, 3 H of $(CH_3)_2C$], 1.65 [s, 3 H of $(CH_3)_2C$], 3.96 (s, 1 H, CH), and 4.42 (d, 2 H, CH_2).

In the same manner used for preparing **10**, a mixture of D,L-penicillamine hydrochloride (**1**·HCl, 0.317 g, 1.71 mmol) and **2**·HCl (0.365 g, 1.71 mmol) in 15 mL of 50% EtOH–H_2O was heated for a few minutes to effect solution. The solution was buffered with potassium acetate to pH 6 and formaldehyde (40% aqueous solution, 0.051 g, 1.71 mmol) was added. After 48 h at ~25 °C, the solvent was removed under reduced pressure to give 1.3 g of a white solid; this solid was extracted with hot EtOH, inorganic salts were separated by filtration, and the EtOH was removed under reduced pressure. The NMR spectrum of the resulting solid showed presence of the peaks at δ 4.42 corresponding to the thiazolidine (**10**; peak enhancement upon addition of authentic **10**) and of new peaks at δ 4.38 (d) presumed by analogy with **10** to correspond to the thiazepane **11**. The ratio of the integrals of δ 4.42 (for **10**)/δ 4.38 (for **11**) was ~3.

Registry No.—1·HCl, 22572-05-0; **2**, 67688-61-3; **2**·HCl, 67688-62-4; **3**, 1068-90-2; **4**, 67688-63-5; **5**, 67688-64-6; **6**, 67688-65-7; **7**, 67688-66-8; **8**, 67688-67-9; **9**, 67737-47-7; **10**, 39254-94-9; **11**, 67688-68-0; 1-chloro-3-methyl-2-butene, 503-60-6; α-toluenethiol, 100-53-8; 1-bromo-3-methylbutane, 107-82-4; ethyl 2-acetamido-2-carbethoxy-5-methylhexanoate, 67688-69-1; 2-acetamido-2-carboxy-5-methylhexanoic acid, 67688-70-4.

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A New Furan Synthesis

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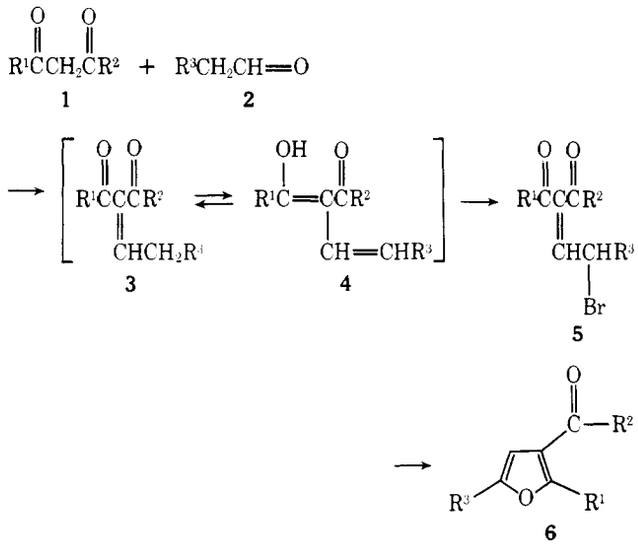
A new furan synthesis is described which comprises reacting an α,β-unsaturated ketone having either an α-carboalkoxy or α-acyl group with *N*-bromosuccinimide and thermally cyclizing the resulting bromine-containing intermediate at a temperature between about 90 and 160 °C. The method is of wide applicability and affords yields in excess of about 70%.

Currently available general methods for the synthesis of furans are essentially limited to the Paal–Knorr synthesis,[2] the condensation of β-keto esters with α-hydroxycarbonyl compounds,[3] and the Feist–Benary method.[4] Unfortunately, these three methods are frequently unsatisfactory. The 1,4-dicarbonyl compounds utilized as starting material in the Paal–Knorr synthesis are often not readily available. Similarly, α-hydroxycarbonyl compounds are frequently unavailable. Finally, the Feist–Benary method requires the use of α-halocarbonyl compounds which are lachrymatory and often not readily available. Although other methods have been reported for the synthesis of furans, these methods appear to be either of relatively limited utility or are inadequately developed.[5]

We now wish to report a new furan synthesis (Scheme I) which is of wide applicability, is simple to carry out, proceeds in high yield, and utilizes readily available starting materials. The required starting material, α,β-unsaturated dicarbonyl compound **3**, is readily available through the Knoevenagel condensation of 1,3-dicarbonyl compound **1** with aldehyde **2**.[6] This α,β-unsaturated compound is not homogeneous, however, and consists of a mixture of geometric isomers in combination with a substantial amount of the corresponding dienol **4**. The Knoevenagel product **3** undergoes an unusually facile allylic bromination upon treatment with an equimolar amount of *N*-bromosuccinimide in carbon tetrachloride at reflux temperature to yield allylic bromide **5**.[7] This material **5**, like its precursor **3**, also consists of a mixture of geometric isomers together with a substantial amount of the corresponding dienol. Carbon tetrachloride is a particularly suitable solvent for this bromination since the succinimide byproduct is relatively insoluble in it and can be easily removed by filtration. The resulting allylic bromide **5** is thermally unstable and undergoes rapid cyclization to yield furan **6** at temperatures in excess of about 80 °C. A variety of substituted furans

Scheme I



were synthesized by this method, and the results are set forth in Table I.

The reaction of **3b** ($R^1 = R^3 = CH_3$; $R^2 = OC_2H_5$) with an equimolar amount of *N*-bromosuccinimide in carbon tetrachloride at reflux temperature (77 °C) was followed by NMR. Under these conditions, the formation of allylic bromide **5b** ($R^1 = R^3 = CH_3$; $R^2 = OC_2H_5$) was complete in approximately 15 min. After 12 h, 60% of the allylic bromide **5b** was converted to ethyl 2,5-dimethyl-3-furoate (**6b**), and after 24 h the only detectable product was furan **6b**. In general, however, such a prolonged reflux period was not utilized to effect cyclization of the intermediate allylic bromide **5**. Since the formation of allylic bromide **5** is very rapid, it was found to be more satisfactory to isolate and distil the crude allylic bromide **5** after

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