1,5,5-Trimethyl-3-*tert*-butyl-4-methylene-2-imidazolidinone (12b). To 0.3 g (~6.0 mmol) of NaH dispersion in 50 mL of THF was added 1.0 g (5.5 mmol) of *N*-*tert*-butyl-*N'*-(1,1-dimethyl-2-propynyl)urea.[4] The solution was heated to reflux for 2 h and cooled to room temperature, and 0.8 g (5.5 mmol) of iodomethane was added. After the mixture was stirred for 1 h, 50 mL of water was added cautiously, and the THF was removed in vacuo. The residue was distilled to give a liquid which solidified on standing. After recrystallization from $CHCl_3$–hexane, 0.65 g (60%) of **12b** was obtained: bp 137 °C (35 mm); mp 40–41 °C; NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.57 (s, 9 H), 2.72 (s, 3 H), 4.04 (d, 1 H, J = 3 Hz), 4.32 (d, 1 H, J = 3 Hz); mass spectrum m/e 196. The compound was hygroscopic and was analyzed as the hydantoin derivative, mp 81–82 °C, obtained by ozonolysis of **12b**.

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.49; H, 9.04; N, 13.95.

1,4,5,5-Tetramethyl-3-*tert*-butyl-4-hydroxy-2-imidazolidinone (14b). The solid imidazolidinone **12b** (1.0 g, 5.1 mmol) was allowed to stand in an open 50-mL Erlenmeyer flask for 3 days, during which it liquefied and then resolidified. The solid was recrystallized from hexane–$CHCl_3$ to yield 0.8 g (73%) of **14b**: mp 86–87 °C; NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.17 (s, 3 H), 1.55 (s, 12 H), 2.35 (br s, 1 H), 2.63 (s, 3 H); IR ($CHCl_3$) 3400, 1705 cm^{-1}.

Anal. Calcd for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.71; H, 10.44; N, 12.88.

1-Acetyl-3-*tert*-butyl-4,5,5-trimethyl-4-hydroxy-2-imidazolidinone (14c). The imidazolidinone **12c** (3.0 g, 13.2 mmol) was allowed to stand in an open Erlenmeyer flask for 2 weeks. The solid obtained was recrystallized from hexane–$CHCl_3$ to yield 2.9 g (89%) of **14c**: mp 109.5–110.5 °C; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.45 (s, 3 H), 1.55 (s, 3 H), 1.58 (s, 9 H), 2.30 (br s, 1 H), 1.49 (s, 3 H); IR ($CHCl_3$) 3418, 1725, 1686 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.49; H, 9.14; N, 11.40.

1,4,4,5-Tetramethyl-4-hydroxy-2-imidazolidinone (15b). Imidazolidinone **14b** (1.0 g, 4.67 mmol) was heated at 40 °C for 2 days in a solution of 10 mL of concentrated HCl, 95 mL of H_2O, and 100 mL of THF. The mixture was cooled to room temperature, neutralized with $NaHCO_3$, and extracted with three 75-mL portions of $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated to a yellow oil. After chromatography on silica gel with dichloromethane, a white solid was obtained. This solid was recrystallized from pentane to give 0.4 g (54%) of **15b**: mp 93–94 °C; NMR ($CDCl_3$) δ 1.32 (s, 6 H), 2.15 (br s, 1 H), 2.30 (s, 3 H), 2.75 (br s, 1 H), 2.89 (s, 3 H); IR ($CHCl_3$) 3325, 1720, 1610 cm^{-1}.

Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.34; H, 9.01; N, 17.75. Found: C, 53.15; H, 8.92; N, 17.71.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Louisiana Heart Association for partial support of this research.

Registry No. 1b (R_3 = *t*-Bu, R_5 = Me), 59863-61-5; **5**, 57542-27-5; **6**, 72331-02-3; **7**, 72331-03-4; **9**, 72331-04-5; **10**, 72331-05-6; **11**, 72331-06-7; **12b**, 62989-65-1; **12b**, hydantoin derivative, 70540-22-6; **12c**, 63989-66-2; **14b**, 72331-07-8; **14c**, 72331-08-9; **15b**, 72331-09-0.

Supplementary Material Available: Final atomic parameters and anisotropic thermal parameters are available (1 page). Ordering information is given on any current masthead page.

1,3-Diazepinones. 1. Synthesis of 5-Hydroxyperhydro-1,3-diazepin-2-one

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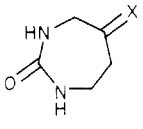
Received April 25, 1979

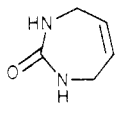
The synthesis of 5-hydroxyperhydro-1,3-diazepin-2-one (**3**) is accomplished by two different routes. The first route involves the reduction of the precursor ketone **2**, which is synthesized in seven steps from levulinic acid (**5**). The second approach makes use of the hydration of the symmetrically unsaturated precursor **4** via the hydroboration–oxidation procedure. This precursor in turn is obtained by direct cyclization of *cis*-1,4-diamino-2-butene (**12**).

As a result of our continued interest in novel cytidine deaminase inhibitors,[1] pyrimidine nucleosides where the base has been both reduced and ring-expanded appeared as interesting target compounds.

The few 1,3-diazepine nucleosides reported in the literature have been prepared by methylene insertion reactions into uridine derivatives followed by ring expansion.[2-4] Our approach, however, consisted in developing independent syntheses of the seven-member-ring heterocycles (**1**–**4**) in order to convert them to the ribofuranosyl analogues via the silyl ether modification of the Hilbert–Johnson reaction.[5-11]



1, X = H_2
2, X = O
3, X = H, OH



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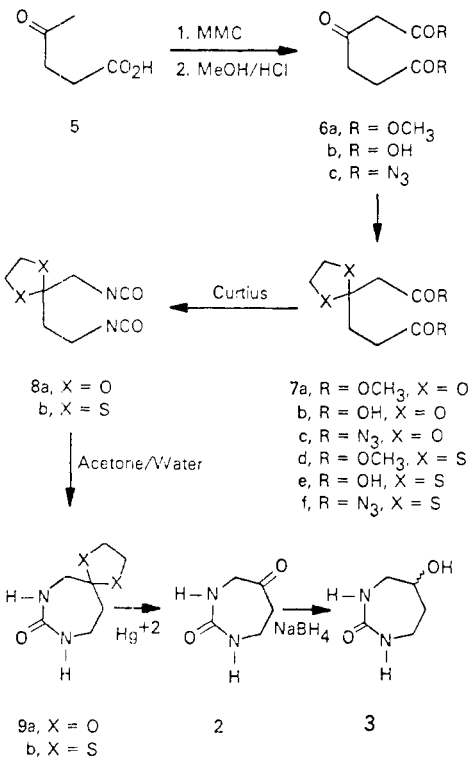
Scheme I



The reported syntheses of functionalized perhydro-1,3-diazepin-2-ones are very specific[12-15] and bear no similarity to the several methods of synthesis of the parent ring system 1 (tetramethyleneurea).[16-21]

In this report we wish to relate the synthesis of heterocycles 2 and 4 via the adapation of the two simplest general methods for the synthesis of tetramethyleneurea (1)[16,21] and the successful conversion of both intermediates to the title compound 3.

Results and Discussion

A tetramethylene diisocyanate derivative (8a or 8b) appeared to be a good candidate for intramolecular cyclization to the previously unreported perhydro-1,3-diazepine-2,5-dione (2). The synthetic plan (Scheme I) required the appropriate diisocyanate to be generated from β-ketoadipic acid (6b) via its corresponding diacyl azide (6c). Dimethyl β-ketoadipate (6a) was obtained from levulinic acid by employing methylmagnesium carbonate (MMC) followed by Fischer esterification.[22] The ester 6a was hydrolyzed in hydrochloric acid[23] to the corresponding

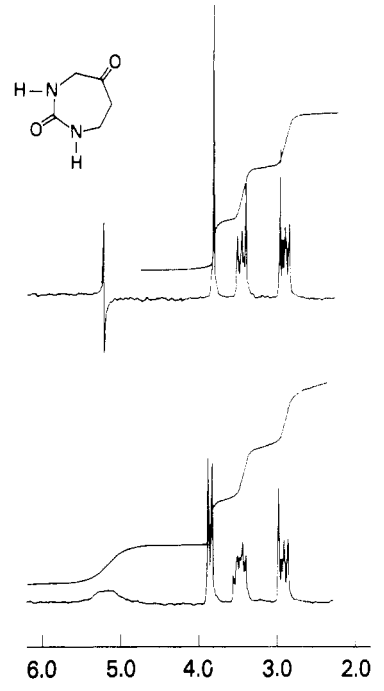


Figure 1. (a, bottom) FT ^1H NMR spectrum (99.6 MHz) of 2 in $CDCl_3$. (b, top) After irradiation of the NH protons.

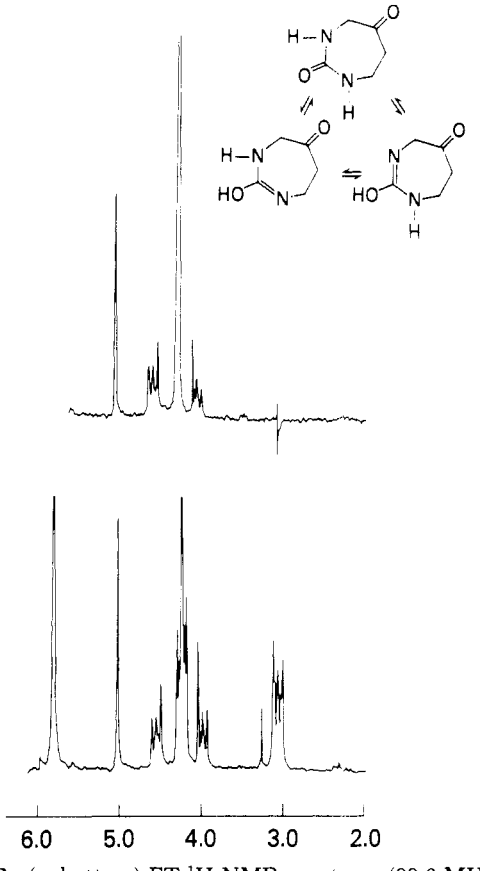


Figure 2. (a, bottom) FT ^1H NMR spectrum (99.6 MHz) of 2 in D_2O. (b, top) After irradiation of the high-field CH_2 protons of the hydroxyimino tautomers of 2.

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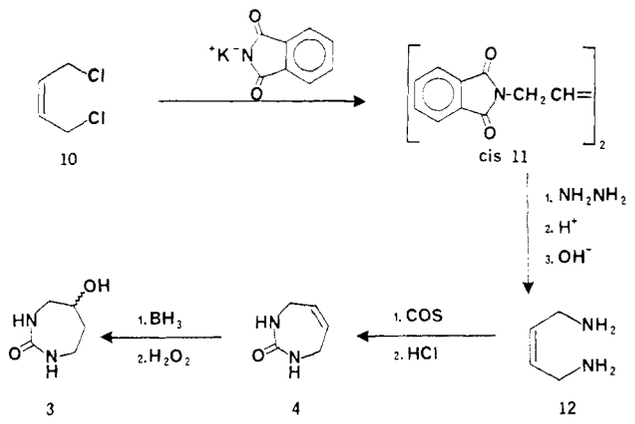
acid **6b**. The reaction of the acid **6b** under modified Curtius rearrangement conditions[24] gave products whose infrared spectra [2150 (azide), 1760 cm^{-1} (C=O)] indicated the formation of an undesired enol lactone. The ketal acid **7b** was therefore prepared and converted by the Curtius rearrangement to the diisocyanate **8a**, which underwent smooth cyclization to the desired perhydro-1,3-diazepin-2-one (**9a**) in an acetone–water mixture at room temperature. However, all attempts to deketalize compound **9a** resulted either in the destruction of the entire molecule or in the isolation of unreacted starting material. Therefore, a different protective group was sought, and the thioketal diester **7d** was synthesized. Following a sequence similar to that for **7a**, the desired cyclic compound **9b** was obtained in 30% overall yield from **6a**. The thioketal derivative **9b** was deprotected with mercuric acetate in water at room temperature,[25] and **2** was isolated in 35% yield.

The NMR spectral pattern of **2** showed striking differences when recorded in different solvents. With the aid of FT NMR a dilute solution of highly insoluble **2** in $CDCl_3$ was analyzed. This spectrum is shown in Figure 1. The carbonyl group in **2** divides the backbone of the molecule into two spin systems. The doublet at δ 3.85 corresponds to the isolated methylene group which is coupled to the N_3–H hydrogen. Irradiation of the NH signals (Figure 1b, top) causes the doublet to coalesce into a singlet and also simplifies the remaining spin system which consequently appears as an easily diagnosed A_2B_2 system. With this information the unusual NMR spectrum of **2** in D_2O (Figure 2) can be explained as resulting from a mixture of isomers corresponding to structures **2** and the tautomeric pair resulting from the enolization of the 2-carbonyl to the hydroxyimino structures shown in Figure 2. A comparison of the integration of the signals from **2** in a dilute D_2O solution (FT NMR) and in a concentrated D_2O solution (spectrum not shown) indicates that at higher dilution the hydroxyimino forms predominate. These forms would facilitate hydrogen bonding with water molecules. That these signals correspond to different entities is clearly shown by the irradiation of one of the components of the A_2B_2 system of the hydroxyimino tautomers (Figure 2b, top), which only affects its corresponding partner signal. The remainder of the spectrum is similar to the spectrum of **2** in $CDCl_3$ (Figure 1b, top).

Mass spectral analysis, as expected, showed the molecular ion peak at *m/e* 128 together with peaks corresponding to the loss of CO (28 amu) and a rearranged fragment of *m/e* 30, which constitutes the base peak. Compound **2** was also smoothly silylated with excess bis(trimethylsilyl)trifluoroacetamide (BSTFA) at room temperature to give what appeared to be a single product based on GC analysis. However, GC–MS analysis showed that the single GC peak contained both the bis- and tris(trimethylsilyl) derivatives of **2**. Since one still observes a prominent M – 28 peak in the mass spectrum which corresponds to the loss of CO, it appears that the $(Me_3Si)_2$ derivative involving only the urea portion of the molecule is the major product. This peak would not be expected to be present if the carbonyl is silylated as an enol ether. Direct probe analysis confirmed the dominance of the $(Me_3Si)_2$ derivative of **2**.

The reduced analogue of **2** is of major interest as a target compound. It was obtained quantitatively from the borohydride reduction of **2** in water at room temperature.

Scheme II



The isolated heterocycle **3** showed all the spectral characteristics consistent with the proposed structure (see Experimental Section).

When we turned our attention to other possible precursors of **3**, compound **4** appeared as a likely candidate where hydration of the double bond would lead to the desired compound **3**. Indeed, use of another of the general methods for the synthesis of **1**[21] allowed the starting cis diamine **12** to be smoothly cyclized to the desired 1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (**4**) by the reaction with carbonyl sulfide followed by heating in hydrochloric acid (Scheme II). The starting cis diamine was prepared from *cis*-1,4-dichloro-2-butene (**10**) following the method of Feigenbaum and Lehn.[26]

The NMR spectrum of the symmetrical structure **4** showed three distinct resonances corresponding to the NH hydrogens (D_2O exchanged), the vinyl hydrogens (triplet), and the methylene hydrogens (doublet). Catalytic hydrogenation of **4** afforded **1**, which was identical in all respects to an authentic sample of **1** prepared by us according to the procedure of Ulrich et al.[21] Treatment of **4** with diborane in THF followed by aqueous H_2O_2 afforded compound **3** in good yield. This product was identical with the compound previously made by the route shown in Scheme I. Having completed the synthesis of the target heterocyclic aglycons **1**–**4**, we have now directed our attention to the methods of forming the corresponding β-D-ribofuranosyl and β-D-deoxyribofuranosyl derivatives. Our results in this area will be reported in a forthcoming publication.

Experimental Section

General. All chemical reagents are commercially available, and they were purchased from Aldrich Chemical Co. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 727B spectrometer as Nujol mulls unless otherwise specified. Proton NMR spectra were determined on a Varian T-60 instrument. FT ^1H NMR spectra were recorded on a JEOL FX-100 instrument. Chemical shifts are given as δ values with reference to Me_4Si or deuterated sodium 3-(trimethylsilyl)propionate (TSP). Elemental analyses were carried out by the NIAMDD, NIH, and by Galbraith Laboratories, Inc., Knoxville, Tenn. Low-resolution electron-impact mass spectra were obtaied on a Du Pont 21-492 gas chromatograph–mass spectrometer (GC/MS) system interfaced to a VG 2040 data system. Samples were introduced either by direct probe or via a Varian 2740 GC (trimethylsilyl derivatives) coupled to the mass spectrometer by a single-stage glass jet separator. Silylated mixtures were separated on a 1.83 m × 2 mm i.d. glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q and operated isothermally or temperature programmed

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in the range of 90–150 °C. Typical GC operating conditions employed an injector and detector temperature of 260 °C, a 30 mL/min flow rate for both helium carrier gas and hydrogen, and a 300 mL/min flow rate for air. Standard mass spectrometer operating conditions were the following: transfer line and jet separator, 250 °C; ion source, 255 °C; electron energy, 75 eV; ionizing current, 250 μA; and scan speed, 2 s/decade.

Dimethyl 3-Oxohexanedioate (6a). This compound was prepared according to the procedure of Whitlock and Whitlock;[22] bp 110 °C (0.5 mm) [lit.[22] bp 94–96 °C (0.35 mm)].

3-Oxohexanedioic Acid Ethylene Ketal (7b). A solution of 4.00 g (21 mmol) of **6a** in 100 mL of benzene was refluxed in the presence of 14.5 g (230 mmol) of ethylene glycol and 100 mg of *p*-toluenesulfonic acid while water was azeotropically removed in a Dean–Stark trap. After 2.5 h, the mixture was cooled and washed with equal volumes of saturated sodium bicarbonate solution and water. The benzene layer was dried ($MgSO_4$) and reduced to dryness to leave a clear oil: IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (A_2B_2 multiplet, 4), 2.60 (s, 2), 3.65 (s, 6), and 3.95 (s, 4). The oily ketal was immediately hydrolyzed under reflux for 1.5 h in a solution of 4.4 g of 86% KOH in 50 mL of 95% ethanol. After cooling, the slight precipitate formed was dissolved by adding a small amount of water. Sufficient cation exchange resin AG50W-X8 (H^+) was added to neutralize the base (pH ~6.5), and removal of the resin afforded a filtrate which was reduced to dryness to leave 4.3 g (99%) of **7b** as a yellowish oil which yielded a very hygroscopic solid after trituration with acetone: IR 1720 cm^{-1} (broad); NMR δ (D_2O) 2.20 (A_2B_2 multiplet, 4), 2.60 (s, 2), and 4.0 (s, 4). This compound was not further characterized and used as such in the following step.

5,5-(Ethylenedioxy)perhydro-1,3-diazepin-2-one (9a). The ketal diacid **7b** (4.30 g, 21 mmol) was dissolved in 10 mL of water and 27 mL of acetone. The solution was cooled to 0 °C, 7 mL (50 mmol) of triethylamine in 35 mL of acetone was added, and the solution was cooled again to 0 °C. Ethyl chloroformate (5.3 mL, 55 mmol) dissolved in 12 mL of acetone was added dropwise, the temperature being maintained at 0 °C. Stirring was continued for 0.5 h at 0 °C, followed by the slow addition of 4.27 g (66 mmol) of sodium azide dissolved in 20 mL of water. After the addition, the reaction mixture was stirred at 0 °C for 1 h. Immediately afterward, 75 mL of water was added and the reaction mixture extracted with four 50-mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and reduced to dryness to leave **7c** as a residual oil with the characteristic IR band at 2150 cm^{-1}. The oil was dissolved in 150 mL of benzene and refluxed for 1 h. Evaporation of the solvent yielded **8a** as an oil which showed an intense IR band at 2260 cm^{-1}. This oil was mixed and stirred with 400 mL of a 4:1 acetone–water mixture for 14 h. Evaporation of the solvent produced **9a** as a solid residue which was triturated with acetone. The white solid obtained weighed 0.86 g (23.5% from **6a**), and it was recrystallized from acetone: mp 193–194 °C; IR 3250 and 1680 cm^{-1}; NMR (D_2O) δ 2.10 (m, 2), 3.20 (m, 2), 3.25 (s, 2), and 4.00 (s, 4); mass spectrum *m/e* 172 (M^+·).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.82; H, 7.03; N, 16.27. Found: C, 48.78; H, 7.12; N, 6.10.

3-Oxohexanedioic Acid Ethylene Thioketal (7e). A mixture of 15.00 g (79 mmol) of **6a** and 9 mL (107 mmol) of ethylenedithiol was treated at room temperature with 21 mL of boron trifluoride etherate. The reaction mixture was stirred for 0.5 h, and then it was extracted with a mixture of benzene and saturated aqueous $NaHCO_3$. The benzene layer was washed further with $NaHCO_3$ and then dried ($MgSO_4$) and reduced to dryness to leave **7d** as a yellow oil: IR (neat) 1740 cm^{-1}. The oily thioketal was immediately hydrolyzed, as in the case of **7a**, with 86% KOH in 95% ethanol. The reaction mixture was reduced to dryness, and 200 mL of 50% aqueous acetone was added. Sufficient cation exchange resin (H^+) was added to reach neutrality, and extra amounts of acetone were required to keep the resulting acid in solution. The resin was removed and the aqueous acetone solution reduced to dryness to yield a white solid, which was recrystallized from ethyl acetate to afford two crops totaling 11 g (58%) of **7e**: mp 178–80 °C; IR 1695 cm^{-1}; NMR (Me_2SO-d_6) δ 2.35 (m, 2), 2.65 (m, 2), 2.95 (s, 2), and 3.20 (s, 4).

Anal. Calcd for $C_{18}H_{12}O_4S_2$: C, 40.65; H, 5.12; S, 27.14. Found: C, 40.88; H, 5.30; S, 26.74.

5,5-(Ethylenedithio)perhydro-1,3-diazepin-2-one (9b). The thioketal diacid **7e** (1.13 g, 4.78 mmol) was dissolved in 30 mL of acetone and cooled to 0 °C. *N,N*-Diisopropylethylamine (1.95 mL, 11.2 mmol) in 5 mL of acetone was added, and the mixture was again cooled to 0 °C. Ethyl chloroformate (1.51 mL, 15.83 mmol) in 2 mL of acetone was added dropwise, the temperature being maintained at 0 °C, and the mixture was stirred further at that temperature for 0.5 h. Dropwise addition of 1.00 g (15.4 mmol) of sodium azide dissolved in 10 mL of water followed, and the mixture was then stirred for 1 h at 0 °C. Following a workup similar to that for **9a**, the ethyl acetate extract was dried ($MgSO_4$) and reduced to dryness to leave **7f** as an oil with the characteristic 2150-cm^{-1} IR band. The oil was rearranged to **8b** in benzene to yield an oil with an intense isocyanate band at 2260 cm^{-1}. The rest of the reaction proceeded as for **9a**, and a 1.13-g (52%) yield of **9b** was obtained as a white solid. The material was recrystallized from acetone to yield **9b** as a crystalline white solid: mp 192 °C; IR 3200, 3050, and 1680 cm^{-1}; NMR (Me_2SO-d_6–D_2O) δ 2.1 (m, 2), 3.0 (m, 2), 3.25 (s, 4), and 3.60 (s, 2); mass spectrum, *m/e* 204 (M^+·).

Anal. Calcd for $C_7H_{12}N_2OS_2$: C, 41.15; H, 5.92; N, 13.71. Found: C, 41.33; H, 6.06; N, 13.34.

Perhydro-1,3-diazepine-2,5-dione (2). A suspension of 2.80 g (13.7 mmol) of **9b** in 80 mL of water was finely dispersed and magnetically stirred while 9.0 g (28 mmol) of mercuric acetate dissolved in 60 mL of water was added in one portion. Stirring was continued for 14 h. Hydrogen sulfide gas was passed through the suspension for 15 min, and all the insoluble materials were removed by filtration. The clear solution obtained was lyophilized to give a tan solid, which was recrystallized twice from acetone (charcoal) to yield 0.580 g (35%) of **2** as white needles: mp 158–160 °C dec; IR 3330, 1720, 1660, and 1620 cm^{-1}; NMR (see Figures 1 and 2); mass spectrum, *m/e* (rel intensity) 128 (M^+·, 21), 100 (15), 57 (6), 56 (7), 55 (5), 43 (8), 30 (100), 29 (15).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.86; H, 6.29; N, 21.86. Found: C, 46.57; H, 6.53; N, 21.60.

***cis*-1,4-Diphthalimido-2-butene (11).** This compound was prepared in 51% yield from commercially available *cis*-1,4-dichloro-2-butene (**10**) following the experimental procedure of Feigenbaum and Lehn;[26] mp 168–169 °C [lit.[26] mp 170 °C].

***cis*-1,4-Diamino-2-butene (12).** This material was also prepared according to the previous reference in 50% yield.[26] The oily amine showed an NMR consistent with the cis stereochemistry: NMR ($CDCl_3$) δ 1.27 (s, 4, D_2O exchanged), 3.26 (m, 4), 5.43 (m, 2).

1,3,4,7-Tetrahydro-2*H*-1,3-diazepin-2-one (4). Carbonyl sulfide was infused to a solution of 0.5 g (5.8 mmol) of *cis*-1,4-diamino-2-butene (**12**)[26] in 14 mL of 50% aqueous ethanol with stirring over a period of 80–90 min. The salt formed in the reaction began to precipitate after 5–10 min. The reaction mixture was then heated to 70 °C, and 0.7 mL of 1 N HCl was added. Heating at 70 °C was continued overnight and then the mixture evaporated to dryness in vacuo. The residue was extracted with methanol, and the extract was chromatographed on a preparative TLC plate (Analtech silica gel GF, 2000 μm) with CH_2Cl_2–MeOH (93:7). The desired product (R_f 0.44) was isolated as colorless crystals after recrystallization from methanol, yielding 0.35 g (53%) of **4**: mp 182–184 °C; IR (KBr) 3200 and 1660 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ 3.68 (d, J = 3 Hz, 4), 3.82 (s, 2), and 5.83 (t, J = 3 Hz, 2); mass spectrum, *m/e* (rel intensity) 112 (M^+·, 19), 111 (25), 97 (68), 69 (42), 68 (61), 56 (69), 41 (58), 30 (50), 28 (100).

Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; H, 24.98. Found: C, 53.42; H, 7.04; N, 24.75.

(±)-5-Hydroxyperhydro-1,3-diazepin-2-one (3). Method A. A solution of 0.10 g (0.78 mmol) of **2** in 10 mL of water was stirred for 2 h in the presence of 0.10 g (2.6 mmol) of $NaBH_4$. After treating the solution with a strong cation-exchange resin (H^+), the filtrate was reduced to dryness. The residue was dissolved in methanol and reduced again to dryness. This process was repeated three times. Finally, the clear oily residue solidified on standing to give **3** quantitatively as a white solid. This solid was recrystallized from acetone to give pure **3**: mp 133–34 °C; IR (KBr) 3250 and 1650 cm^{-1}; NMR (D_2O) δ 1.90 (m, 2), 3.20 (t, J = 7 Hz, 2), 3.20 (d, J = 7 Hz, 2), and 4.0 (m, 1); mass spectrum *m/e* (rel intensity) 130 (M^+·, 20), 112 (4), 101 (15), 84 (42), 72 (13), 57 (37), 30 (100).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.74; N, 21.53. Found: C, 45.96; H, 7.90; N, 21.28.

Method B. To 0.078 g (0.7 mmol) of **4** placed in a dry, three-necked flask under nitrogen and cooled to 0 °C was added 2 mL (2 mmol) of a 4 °C solution of 1 M BH_3-THF through a septum cap. The mixture was stirred for 15 min at 0 °C and allowed to warm up to room temperature. A colorless gel was formed. After this mixture was allowed to sit for 2.5 h, 1 mL of water was added followed by the dropwise addition of 3 mL of aqueous 1 N NaOH and 3 mL of 30% H_2O_2. The reaction mixture was stirred at room temperature for 1 h, reduced to dryness, and coevaporated several times with methanol. The residue was extracted with methanol and purified on a preparative silica gel TLC plate with CH_2Cl_2–MeOH (4:1) to afford 0.073 g (80%) of **3** (R_f 0.39) as a crystalline material identical in all respects with the compound obtained through method A.

Perhydro-1,3-diazepin-2-one (1). A solution of **4** (0.050 g, 0.446 mmol) in 10 mL of methanol was hydrogenated at 35 psi for 9 h in the presence of 20 mg of 10% Pd/C. The catalyst was removed and the filtrate reduced to dryness to provide colorless crystals of **1** identical with an authentic sample prepared according to ref 21; mp 166–168 °C [lit.[21] mp 166–170 °C].

Acknowledgment. The authors thank Dr. Herman Yeh, NIAMDD, NIH, for his help in providing the FT NMR data. We also thank Mr. Richard Fuller of this department, who synthesized large-scale batches of dimethyl β-ketoadipate, and Dr. R. Richter from the Upjohn Co. for his helpful comments.

Registry No. 1, 19055-93-7; **2**, 72331-38-5; **3**, 72331-39-6; **4**, 72331-40-9; **6a**, 5457-44-3; **7a**, 26954-91-6; **7b**, 72331-41-0; **7c**, 72331-42-1; **7d**, 72331-43-2; **7e**, 72331-44-3; **7f**, 72331-45-4; **8a**, 72331-46-5; **8b**, 72331-47-6; **9a**, 72331-48-7; **9b**, 72331-49-8; **11**, 40794-71-6; **12**, 40794-72-7; carbonyl sulfide, 463-58-1.

A Thiol-Containing Ester Side Chain in a Sesquiterpene Lactone from *Eupatorium mikanioides*. Absolute Configuration of Deacetyleupaserrin and Its Congeners[1]

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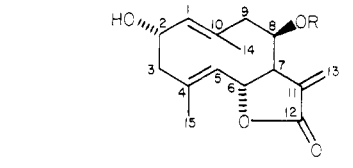
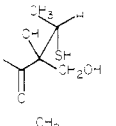
Received September 18, 1979

Extraction of *Eupatorium mikanioides* Chapm. yielded a group of 2-hydroxy-8-(acyloxy)-*trans,trans*-1-(10),4-germacradienolides related to the antileukemic sesquiterpene lactone deacetyleupaserrin (**1c**) which was also isolated. Absolute configurations were established by X-ray crystallography of one of the constituents (**1e**) which had an unprecedented thiol-containing ester side chain. The flavone eupatorin was also isolated.

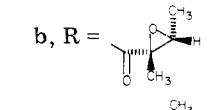
As part of our continuing study[2-4] of *Eupatorium* species *sensu stricto* which elaborates a number of sesquiterpene lactones with cytotoxic and antitumor activity, we have investigated *Eupatorium mikanioides* Chapm., a diploid which is restricted to the coastal areas of peninsular Florida.[5] This has resulted in the isolation of a family of six germacradienolides **1a–f**. **1c**, which was the most abundant lactone constituent (ca. 0.15% of dry weight), is the antileukemic lactone deacetyleupaserrin which has been isolated previously from *E. semiserratum*,[6] *Helianthus pumilus*,[7] and *Helianthus mollis*.[8] X-ray analysis of one of the minor constituents, undertaken to establish the relative stereochemistry of the various ester side chains, led to the discovery of an unusual sulfur-containing ester residue in **1e** and was used to deduce the previously hypothetical absolute stereochemistry of deacetyleupaserrin as well as that of its congeners.



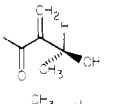
1a, R = H



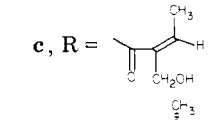
e, R =



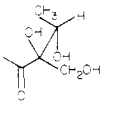
b, R =



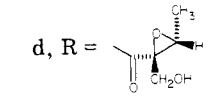
f, R =



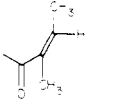
c, R =



g, R =



d, R =



h, R =

We deal first with the sesquiterpene portion common to the various lactones whose nature was deduced by NMR spectrometry at 270 MHz. ^1H chemical shifts and coupling constants are given in Table I and parallel those of desacetyleupaserrin (**1c**)[7,9] for the hydrogen atoms of the ses-

(1) Work at the Florida State University was supported in part by a grant from the U.S. Public Health Service through the National Cancer Institute (CA-13121).

(2) Herz, W.; de Groote, R; Murari, R.; Kumar, N.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 2784. This article contains references to earlier work.

(3) Herz, W.; Govindan, S. V.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 2999.

(4) Herz, W.; Murari, R.; Govindan, S. V. *Phytochemistry* **1979**, *18*, 1337.

(5) Sullivan, V. I. Ph.D. Dissertation, Florida State University, Aug 1972.

(6) Kupchan; S. M.; Fujita, T.; Maruyama, M.; Britton, R. W. *J. Org. Chem.* **1973**, *38*, 1260.

(7) Herz, W.; de Groote, R. *Phytochemistry* **1977**, *16*, 1307. In formulas **1a–c** of this reference the configuration of deacetyleupaserrin and its derivatives at C-6 and C-8 is reproduced incorrectly.

(8) Ohno, N.; Mabry, T. J. *Phytochemistry* **1979**, *18*, 1003.

(9) In Table I of ref 7, assignments of H-14 and H-15 were inadvertently interchanged.

0022-3263/80/1945-0489$01.00/0