Synthesis and Characterization of 2-Substituted 6-(Methylthio)bicyclo[2.2.1]heptanes

Richard S. Glass,* John R. Duchek, Usha Devi G. Prabhu, William N. Setzer, and George S. Wilson

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

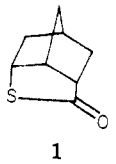
Received March 24, 1980

The synthesis and structure elucidations of several 2-*endo*-substituted-6-*endo*-(methylthio)-, 2-*exo*-substituted-6-*endo*-(methylthio)-, 2-*endo*-substituted-6-*exo*-(methylthio)-, and 2-*exo*-substituted-6-*exo*-(methylthio)-bicyclo[2.2.1]heptanes, **2–5**, respectively, are reported. The structure proofs involved a combination of spectroscopic, X-ray crystallographic, and equilibration studies. The crystal and molecular structures of 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2a**) and 6-*exo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**4a**) were determined by X-ray crystallographic techniques. These compounds crystallize in the space groups *Pbca* and $P2_1/n$, respectively, with a = 13.040 (2) Å, b = 10.877 (3) Å, c = 13.518 (3) Å, Z = 8, and a = 12.740 (2) Å, b = 6.200 (1) Å, c = 13.146 (2) Å, β = 114.81 (1)°, Z = 4, respectively. The nonhydrogen atoms were located in each case by direct methods. Full-matrix least-squares refinement led to conventional R factors of 0.0466 and 0.0389, respectively, after several cycles of anisotropic refinement. These molecular structure determinations revealed an unsymmetrical *contra* twist of the norbornyl skeleton in endo acid **2a** and an unsymmetrical *synchro* twist in endo acid **4a**.

The intermediacy of a phosphorylated sulfonium salt in respiratory chain-linked oxidative phosphorylation has been suggested.[1] To form such a species, oxidation of aliphatic sulfides, e.g., the sulfide moiety present in the side chain of methionine residues in proteins, with facilitation of the oxidation by neighboring groups was postulated.[2] Aliphatic sulfides appended with suitable neighboring groups were required to test this postulate. Suitable geometric constraint was deemed essential to maximize any interaction between a sulfide sulfur atom and potential neighboring groups. Two such molecular arrays have been investigated thus far: substituted medium-size rings[3] and substituted bicyclo[2.2.1]heptane derivatives.[4] An advantage to studying 2-*endo*-substituted-6-*endo*-(methylthio)bicyclo[2.2.1]heptanes **2** is that model systems in which bond formation between the sulfur atom and 2-substituent is geometrically precluded are readily at hand: 2-exo-6-endo-, 2-endo-6-exo-, and 2-exo-6-exo-substituted derivatives **3–5**, respectively. This paper records the synthesis and structure elucidation of a number of 2-substituted-6-(methylthio)bicyclo[2.2.1]heptanes. In addition the crystal and molecular structures, determined by X-ray crystallographic techniques, of **2a** and **4a** are also reported.

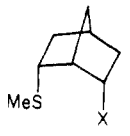
Results and Discussion

Thiolactone **1**, 5-thiatricyclo[4.2.1.$0^{3,7}$]nonan-4-one, was

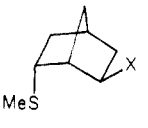


1

prepared by Storm and Koshland,[5] Hershfield and Schmir,[6] and Johnsson and Allenmark[7] from 5-norbornene-2-*endo*-carboxylic acid. This acid was converted to the corresponding acid chloride which, on treatment with potassium hydrogen sulfide in ethanol[5,6] or hydrogen sulfide in pyridine[7] followed by acid, produced thiolactone **1**. Its structure had not been unequivocally proven.[5-7] Since acid-catalyzed cyclization of bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid is known to proceed with rearrangement,[8] it was deemed prudent to verify the structure of thiolactone **1**. Saponification of thiolactone **1** followed by treatment with methyl iodide afforded endo acid **2a**. This transformation should occur without



2a, X = CO_2H
b, X = CO_2Me
c, X = CH_2OH
d, X = $CONH_2$
e, X = $NHCO_2Et$
f, X = COSMe



3a, X = CO_2H
b, X = CO_2Me
c, X = CH_2OH
d, X = $CONH_2$
e, X = $NHCO_2Et$
f, X = COSMe
g, X = $CONHCH_2Ph$

skeletal rearrangement.[9] The crystal and molecular structure of endo acid **2a** was determined by X-ray crystallographic analysis to establish the structures of these compounds (**1** and **2a**) beyond doubt. A stereoscopic view of the molecule is shown in Figure 1. This determination indisputably confirms the structural assignments of endo acid **2a** and thiolactone **1**.

Thiolactone **1** was also converted to 6-*endo*-(isopropylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid

(1) Lambeth, D. O.; Lardy, H. A. *Biochemistry* **1969**, *8*, 3395–3402.
(2) Glass, R. S.; Williams, E. B., Jr.; Wilson, G. S. *Biochemistry* **1974**, *13*, 2800–2805.
(3) Wilson, G. S.; Swanson, D. D.; Klug, J. T.; Glass, R. S.; Ryan, M. D.; Musker, W. K. *J. Am. Chem. Soc.* **1979**, *101*, 1040–1042.
(4) Glass, R. S.; Duchek, J. R.; Klug, J. T.; Wilson, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 7349–7350.
(5) Storm, D. R.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5815–5825.
(6) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, 6788–6793.
(7) Johnsson, H.; Allenmark, S. *Chem. Scr.* **1975**, *8*, 223–227.
(8) Davies, D. I.; Doyle, M. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 227–231 and references therein. The mechanism for cyclization of 5-norbornene-2-*endo*-thiocarboxylic acid to thiolactone **1** has not been investigated. An electrophilic-addition mechanism is reasonable but a radical-addition mechanism is also conceivable: Ohno, A., Oae, S. "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum: New York, 1977; pp 129–142.
(9) Base-catalyzed epimerization of the carboxylate moiety at C(2) is conceivable. Raney nickel desulfurization of endo acid **2a**, following the method of Johnsson and Allenmark (*Chem. Scr.* **1975**, *8*, 216–222) for the Raney nickel desulfurization of 3-*exo*-(benzylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, afforded 2-*endo*-bicyclo[2.2.1]heptanecarboxylic acid. This demonstrates that epimerization did not occur. The X-ray crystallographic structure determination, of course, also confirms this point.

0022-3263/80/1945-3640$01.00/0

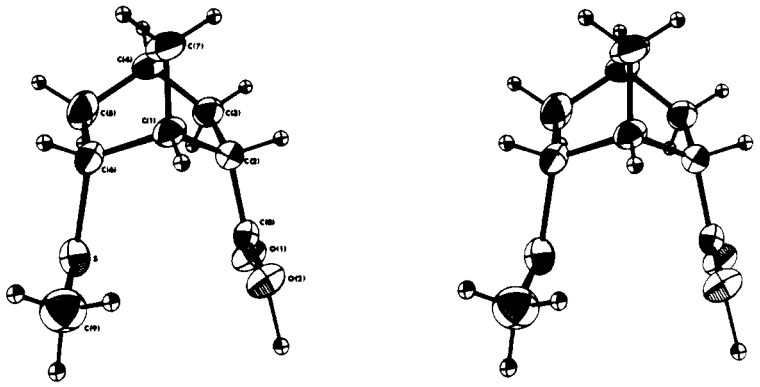


Figure 1. ORTEP[25] stereoview of endo acid **2a**. The hydrogen atoms have been assigned arbitrary thermal parameters. Thermal ellipsoids are drawn to enclose 30% of the probability distribution.

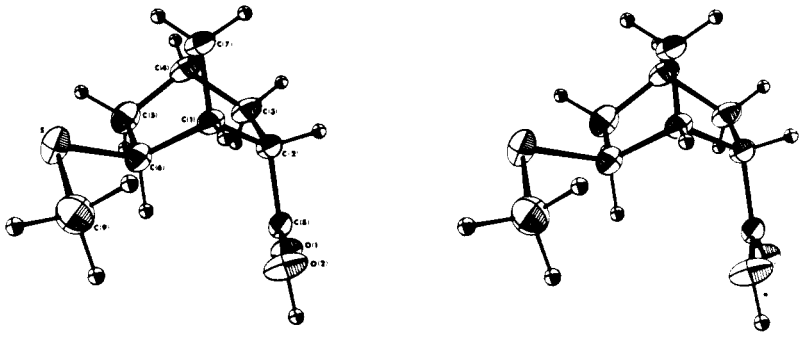


Figure 2. ORTEP[25] stereoview of endo acid **4a**. The hydrogen atoms have been assigned arbitrary thermal parameters. Thermal ellipsoids are drawn to enclose 30% of the probability distribution.

by saponification followed by alkylation. These preparations are similar to the synthesis of 6-*endo*-(benzylthio)-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid reported by Johnsson and Allenmark.[7]

Treatment of endo acid **2a** with methyl *p*-tolyltriazene[10] afforded endo ester **2b**. Reduction of this ester with lithium aluminum hydride produced endo alcohol **2c**. All of these transformations are effected under conditions which preclude skeletal rearrangement and epimerization at C(2).

Exposure of endo ester **2b** to sodium methoxide in methanol afforded a mixture of starting ester and a new ester. The ratio of new ester to endo ester **2b**, after equilibration, was approximately 99:1. This ratio was unchanged on additional exposure to base and was the same whether pure endo ester **2b** or the pure new ester was initially exposed to base. This demonstrates that equilibrium was achieved. The new ester was isolated from this mixture by preparative GC. The new ester must be exo ester **3b**. It is expected that exo ester **3b** is thermodynamically more stable than endo ester **2b**, principally because the steric strain between the methylthio and ester moieties in endo ester **2b** is relieved in exo ester **3b**. Saponification of exo ester **3b** (mixture containing a small amount of endo ester **2b** from equilibration) produced exo acid **3a** free of endo acid **2a** after recrystallization. Lithium aluminum hydride reduction of exo ester **3b** gives exo alcohol **3c**. Ammonolysis of exo ester **3b** produced exo amide **3d**. However, this amide could be more conveniently prepared from exo acid **3a** as follows. Treatment of exo acid **3a** with 1,1′-carbonyldiimidazole afforded the corresponding acylimidazole which, upon ammonolysis, produced exo amide **3d**.[11]

It is interesting to contrast the results found for the preparation of the amide in the exo series with those found for the endo series. Ammonolysis of endo ester **2b** produced the same amide as that obtained by ammonolysis of exo ester **3b**. Clearly, this must be exo amide **3d**. Epimerization occurs during the ammonolysis of endo ester **2b**. Similarly, heating endo acid **2a** or exo acid **3a** with benzylamine afforded the same *N*-benzylamide **3g** assigned the exo configuration at C(2). Ammonolysis of the acylimidazole obtained by reaction of endo acid **2a** with 1,1′-carbonyldiimidazole gave, in addition to exo amide **3d**, an isomeric amide. That this new amide was indeed the endo amide **2d**[12] was demonstrated by epimerizing it with potassium *tert*-butoxide in *tert*-butyl alcohol to produce exo amide **3d**. Thus partial epimerization occurs in the conversion of endo acid **2a** to endo amide **2d** by way of the corresponding *N*-acylimidazole. Since endo amide **2d** did not epimerize in the presence of ammonia and imidazole the epimerization must occur in the ammonolysis of the intermediary *N*-acylimidazole.

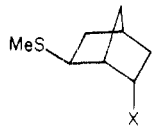
Conversion of endo acid **2a** and exo acid **3a** to their corresponding urethanes **2e** and **3e** via Curtius rearrangement was effected by following the method of Yamada et al.[13] The stereochemistry at C(2) is assigned on the basis of the known stereospecificity of the Curtius rearrangement (and no epimerization in the formation of the intermediary acyl azides), that is, complete retention of configuration of the migrating carbon.[14] Conversion

(10) White, E. H.; Baum, A. A.; Eitel, D. E. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 797.
(11) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367.

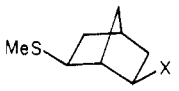
(12) An alternative route to endo amide **2d** may be envisioned: ammonolysis of thiolactone **1** followed by S-methylation. It was reported by Dafford and Koshland (*J. Am. Chem. Soc.* **1977**, *99*, 7246–7257) that ammonolysis of thiolactone **1** gave the desired thioamide. However, this material was not obtained pure and the reported procedure is inconvenient. Thus, this route to endo amide **2d** was not investigated.
(13) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205. Yamada, S.: Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1973**, 2343–2346.

of endo acid **2a** and exo acid **3a** to their corresponding *N*-acylimidazoles followed by treatment with methanethiol gave endo thioester **2f** and exo thioester **3f**, respectively.

Synthesis of the 6-*exo*-methylthio derivatives **4** and **5** was investigated. Attempts to produce endo acid **4a** or

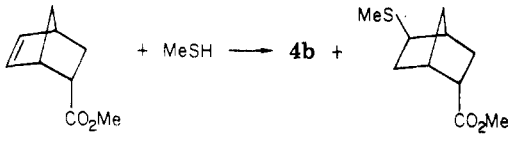


4a, X = CO_2H
b, X = CO_2Me



5a, X = CO_2H
b, X = CO_2Me

endo ester **4b** with positional and stereochemical control proved futile. Therefore, the addition of methanethiol to methyl bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate was studied.[15] This addition afforded a 44:56 mixture of isomeric esters. These isomers could be separated by GC, but there was the problem of structural assignment. This was unequivocally resolved by X-ray crystallographic structure analysis of a single crystal of the acid, obtained by saponification of one of the isomeric esters. This acid proved to be endo acid **4a** and a stereoscopic view of the molecule is shown in Figure 2. The other ester formed in the addition of methanethiol to methyl bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylate was presumably ester **6**.



6

Epimerization of endo ester **4b** with sodium methoxide in methanol gave a mixture of a new ester, which could be obtained pure by preparative GC, and endo ester **4b** in an approximately 73:27 ratio at equilibrium.[16] This ratio was unchanged by additional exposure to base and was the same within experimental error whether pure endo ester **4b** or the pure new ester was initially used. This proves that equilibrium has been established. The new ester must be exo ester **5b**. It is expected that exo ester **5b** with both relatively large groups exo is thermodynamically more stable than endo ester **4b** with one relatively large endo group. Furthermore, one expects the difference in free energy between endo ester **4b** and exo ester **5b** to be less than that between endo ester **2b** and exo ester **3b**. In the former pair of esters the endo ester moiety in **4b** encounters less severe 1,3-steric interactions with the 6-*endo*-hydrogen atom than in the latter pair in which the endo ester moiety in **2b** suffers steric interaction with the 6-*endo*-methylthio group. The difference in $\Delta G°$ between the two systems is approximately 2.3 kcal/mol. Saponification of pure exo ester **5b** afforded exo acid **5a**.

The detailed molecular structures of endo acid **2a** and endo acid **4a** determined by X-ray crystallographic techniques present some notable features. Altona and Sundaralingam[17] called attention to the significant distortion of the norbornyl skeleton from the C_{2v} symmetry of the

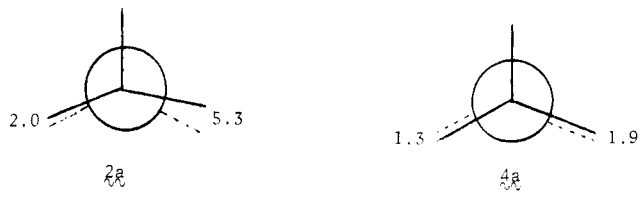


Figure 3. Projection of endo acid **2a** and endo acid **4a** along the C(1)–C(4) vector. The numbers on the right and left of each diagram are the absolute values of the C(1)–C(2)–C(3)–C(4) and C(4)–C(5)–C(6)–C(1) dihedral angles, respectively.

parent hydrocarbon in substituted bicyclo[2.2.1]heptanes. Owing to steric interactions, principally of the relatively large 2-endo and 6-endo substituents in endo acid **2a**, there is an unsymmetrical *contra* twist, C(+−), of the norbornyl skeleton. That is, viewing down the C(1)–C(4) vector, C(3) is located clockwise (+) from C(2) and C(5) is located counterclockwise (−) from C(6), as shown in Figure 3. This twisting can also be seen from the C(1)–C(2)–C(3)–C(4) and C(4)–C(5)–C(6)–C(1) torsional angles of 5.3 and −2.0°, respectively. Relief of steric strain is also achieved by opening the C(2)–C(1)–C(6), C(1)–C(2)–C(8), and S–C-(6)–C(1) bond angles. In addition, the bonds directed in the endo direction from C(2) and C(6) are not coplanar. This is illustrated by the C(8)–S–C(6)–C(2) dihedral angle of 2.8°. The S–C(8) interatomic distance is 3.118 (4) Å. An interesting feature of the packing of racemic endo acid **2a** is that one enantiomer is hydrogen bonded to the other. The O(1)–O(2)′ distance of 2.653 (9) Å and the C(8)–O-(1)–O(2)′ and C(8)–O(2)–O(1)′ angles of 124.7(6)° and 111.9(6)°, respectively, are comparable to those reported for other hydrogen-bonded dimeric carboxylic acids.[18] The C(8)–O(1)–O(2)′–C(8)′ torsion angle of −2.4° indicates that the two carboxyl groups are nearly coplanar.

The geometry of endo acid **2a** obtained by molecular-mechanics optimization using Allinger's force field[19] and additional parameters for carboxylic acids[20] is in qualitative agreement with the experimentally determined solid-state structure. The bonds to C(4), i.e., C(3)–C(4), C(4)–C(5), and C(4)–C(7), are unusually short as determined by X-ray crystallography, but such shortening is not found in the results from the molecular-mechanics calculation. Other quantitative differences between the experimentally determined geometry and the calculated geometry are given in a table in the supplementary material.

In endo acid **4a** there is an unsymmetrical *synchro* twist, S(++), of the norbornyl skeleton as illustrated in Figure 3. This twisting is evident from the C(1)–C(2)–C(3)–C(4) and C(4)–C(5)–C(6)–C(1) torsional angles of −1.9 and −1.3°, respectively. The geometry revealed by X-ray is in qualitative agreement with that calculated by using molecular mechanics. As with endo acid **2a**, one enantiomer of racemic endo acid **4a** is hydrogen bonded to the other enantiomer. The O(1)–O(2)′ distance of 2.698 (2) Å, the C(8)–O(1)–O(2)′ angle of 127.4 (2)°, the C(8)–O(2)–O(1)′ angle of 110.3 (2)°, and the C(8)–O(1)–O(2)′–C(8)′ torsion angle of 0.23° support the proposed hydrogen bonding.[18]

Experimental Section

All melting points and boiling points are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 137 spectrometer.

(14) Jones, L. W.; Wallis, E. S. *J. Am. Chem. Soc.* **1926**, *48*, 169–181. Campbell, A.; Kenyon, J. *J. Chem. Soc.* **1946**, 25–27.

(15) For addition of methanethiol to bicyclo[2.2.1]heptene, see: Davies, D. I.; Parfitt, L. T.; (in part) Alden, C. K.; Claisse, J. A. *J. Chem. Soc. C* **1969**, 1585–1590.

(16) Epimerization of methyl 2-*endo*-bicyclo[2.2.1]heptanecarboxylate with sodium methoxide followed by saponification produces a mixture of acids estimated to consist of 70–80% of the exo isomer: Alder, K.; Stein, G. *Justus Liebigs Ann. Chem.* **1934**, *514*, 211–227.

(17) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1970**, *92*, 1995–1999.

(18) Strieter, F. J.; Templeton, D. H.; Sheuerman, R. F.; Sass, R. L. *Acta Crystallogr.* **1962**, *15*, 1233–1239. Strieter, F. J.; Templeton, D. H. *Ibid.* **1962**, *15*, 1240–1244. Sheuerman, R. F.; Sass, R. L. *Ibid.* **1962**, *15*, 1244–1247.

(19) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637–1648; Wertz, D. H.; Allinger, N. L. *Tetrahedron* **1974**, *30*, 1579–1586.

(20) Allinger, N. L.; Chang, S. H. M. *Tetrahedron* **1977**, *33*, 1561–1567.

^{1}H NMR spectra were measured at 60 MHz with a Varian T-60 NMR spectrometer on samples containing tetramethylsilane as an internal standard. A Varian Model 1720 gas chromatograph was used for GC studies. Mass spectra were measured with a Hewlett-Packard Model 5930A dodecapole mass spectrometer. Elemental microanalysis was performed by analysts at Spang Microanalytical Laboratory, Ann Arbor, MI, or Atlantic Microlab, Inc., Atlanta, GA. For preparative-layer chromatography, silica gel HF-254 (type 60), supplied by Brinkmann Instruments, Inc. (E. Merck HF-254), was used. All experiments were carried out under oxygen-free dry nitrogen which was obtained by passing commercial nitrogen through activated BTS catalyst (BASF Colors & Chemicals, Inc.) and then through a drying tower filled with potassium hydroxide pellets. Tetrahydrofuran (AR) was distilled from sodium metal and benzophenone.

3-Methyl-1-(*p*-tolyl)triazene obtained from Aldrich was purified by sublimation followed by recrystallization from *n*-hexane. Dry 1,2-dimethoxyethane was prepared by distillation from calcium hydride. Methanol was first refluxed over magnesium methoxide for 2 h and then distilled. Dry ethanol was similarly prepared by using magnesium ethoxide.

6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (2a). Thiolactone **1** (8.5 g, 55 mmol), prepared by a modification of the procedure of Storm and Koshland,[5] was added to degassed 0.420 M potassium hydroxide in 95% ethanol solution (263 mL, 110 mmol). The solution was stirred under a nitrogen atmosphere and, after 10–20 min, a thick, white precipitate formed. Methyl iodide (3.43 mL, 55 mmol) was then added; the precipitate dissolved immediately. After being stirred overnight at room temperature, the reaction mixture was evaporated to dryness with a rotary evaporator. The residue was dissolved in distilled water (50 mL) and extracted once with ether to remove any neutral material. The aqueous layer was acidified with 3 M aqueous hydrochloric acid solution and extracted with ethyl ether (3 × 75 mL). The combined ether extracts were washed sequentially with distilled water, aqueous sodium thiosulfate solution (if the ethereal extracts are yellow), and brine, dried (Na_2SO_4), filtered, and evaporated to give a solid. A second experiment was carried out identical with the one described above. The crude product from both experiments was combined and first sublimed in vacuo and then recrystallized from ethyl acetate–petroleum ether to give pure endo acid **2a** (10.1 g, 49%): mp 114.5–115.5 °C; IR (KBr) 3226–2222 (CO_2H), 1639 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3 H, SMe), 0.72–3.38 (m, 10 H, ring protons), 11.4 (br s, 1 H, CO_2H).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.12; H, 7.53; S, 17.17.

Concentration of the mother liquor from the above recrystallization afforded a second crop of endo acid **2a**: 1 g, mp 110–115 °C.

Raney Nickel Desulfurization of Endo Acid 2a. Endo acid **2a** (186 mg, 1.00 mmol) was dissolved in 10% aqueous sodium hydroxide solution (25 mL). This solution was maintained at 50–55 °C as nickel–aluminum alloy (1.9 g) was added portionwise over 0.5 h. After completion of the addition, the reaction mixture was stirred at 50–55 °C for 2 h, allowed to cool to room temperature, and filtered. The filtrate was acidified with 3 M hydrochloric acid solution with ice-bath cooling and extracted with ethyl ether. The aqueous layer was saturated with sodium chloride and twice more extracted with ethyl ether. The ether extracts were combined and washed with brine, the solvent was evaporated on a rotary evaporator, and the residue was distilled from bulb to bulb under vacuum to give a sticky white solid. Spectral analysis (^{1}H NMR) showed the reaction to be incomplete so the material was again subjected to the reaction conditions for 3.5 h and workup as before. After bulb-to-bulb distillation, a white crystalline solid (117 mg), mp 62–65 °C, was obtained. Recrystallization from petroleum ether gave colorless crystals: 81.9 mg (59%); mp 64–66 °C; mmp (with authentic 2-*endo*-bicyclo[2.2.1]heptanecarboxylic acid)[21] 63.5–66 °C. The IR and ^{1}H NMR spectra obtained for this material were superimposable with those of authentic 2-*endo*-bicyclo[2.2.1]heptanecarboxylic acid.

(21) Berson, J. A.; Ben-Efraim, D. A. *J. Am. Chem. Soc.* **1959**, *81*, 4083–4087.

Table I. Crystal Data[a] for Endo Acid 2a and Endo Acid 4a

compd	endo acid 2a	endo acid 4a
molecular formula	$C_9H_{14}O_2S$	$C_9H_{14}O_2S$
molecular weight	186.26	186.26
space group	$Pbca$ (no. 61)[b]	$P2_1/n$[c]
cell dimensions		
a, Å	13.040 (2)	12.740 (2)
b, Å	10.877 (3)	6.200 (1)
c, Å	13.518 (3)	13.146 (2)
β, deg		114.81 (1)
V, Å^3	1917.4 (8)	943.3 (3)
Z	8	4
d_{obsd}, g cm^{-3}[d]	1.291 (10)	1.313 (10)
d_{calcd}, g cm^{-3}	1.290	1.311
crystal color, shape	colorless, rectangular parallelopiped	colorless, plate
crystal dimensions, mm	0.4 × 0.2 × 0.1	0.5 × 0.5 × 0.1
no. of unique data	1700	1742
no. of data used in the calculations	921	1294
absorption coefficient (μ_λ), cm^{-1}	2.915	2.867

[a] The standard deviation of the least significant figure is given in parentheses in this table and in the following tables. [b] Based upon the systematic absences: $0kl$, $k \neq 2n$; $h0l$, $l \neq 2n$; $hk0$, $h \neq 2n$; $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; $00l$, $l \neq 2n$. [c] Based upon the systematic absences: $h0l$, $h + l \neq 2n$; $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; $00l$, $l \neq 2n$. The space group $P2_1/n$ is an alternative setting of $P2_1/c$ (no. 14). [d] Density was determined by the flotation method using an aqueous sodium iodide solution.

X-ray Single Crystal Structure Study of Endo Acid 2a and Endo Acid 4a. Clear colorless crystals of endo acid **2a** were obtained by vapor diffusion of a solution of the compound in ethyl ether with *n*-hexane. Similarly, crystals of endo acid **4a** were obtained by vapor diffusion of a solution of the compound in chloroform with petroleum ether.

For each compound a well-formed crystal was mounted on a Syntex $P2_1$ auto diffractometer equipped with a scintillation counter and Mo Kα radiation with a graphite monochromator. The automatic centering, indexing, and least-squares routines were carried out on 25 reflections to obtain the cell dimensions which are given in Table I. The data were reduced to F_o^2 and $\sigma(F_o^2)$. Lorenz and polarization factors were applied to all reflections. For each structure, a θ–2θ scan over the range $4° \leq 2\theta \leq 50°$ was used to collect the data of which those with $I \geq 3\sigma(I)$ were considered observed and were used in the calculations.

For each compound, the structure was solved by the direct methods program MULTAN.[22] The positions of all nonhydrogen atoms were obtained from an "*E* map" based on the highest combined figure-of-merit value and the lowest residual index. The structures were refined by full-matrix least-squares techniques,[23] using neutral atom scattering factors for all species,[24] leading to isotropic convergence at $R = 0.2135$ for endo acid **2a** and $R = 0.1307$ for endo acid **4a** and anisotropic convergence at $R = 0.0954$ for endo acid **2a** and $R = 0.0754$ for endo acid **4a**. In each case, the hydrogen atoms were located from electron-density difference maps and added to the model in geometrically ideal positions. The hydrogen atom thermal parameters were set according to B_H

(22) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368–376.

(23) The major programs used during the structure determination were FORDAP (Fourier summation program by Zalkin) and NUCLS (structure factor calculations and full-matrix least-squares refinement, by Ibers, adapted from ORFLS by Bussing, Martin, and Levy).

(24) Scattering factors were obtained from the "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 71–98.

(25) ORTEP, Johnson, C. K., Oak Ridge National Laboratory, Oak Ridge, TN.

= B_N + 1, where N is the atom to which H is bonded. The hydrogen atom parameters were not refined. Several cycles of anisotropic refinement led to convergence with R = 0.0466, R_w = 0.0568, and GOF = 2.115 for endo acid **2a** and R = 0.0389, R_w = 0.0501, and GOF = 2.145 for endo acid **4a**.

6-*endo*-(Isopropylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid. Thiolactone 1 (100 mg, 0.65 mmol) was added to a degassed solution of 0.420 M potassium hydroxide in 95% aqueous ethanol (3.1 mL, 1.3 mmol). On stirring the solution, under a nitrogen atmosphere, a thick precipitate formed. Isopropyl bromide (61 μL, 0.65 mmol) was then added and the mixture stirred for 4 h at room temperature. An additional amount of isopropyl bromide (61 μL, 0.65 mmol) was then added and the mixture stirred at room temperature overnight. The reaction mixture was worked up in the same way as in the case of endo acid **2a**. The crude product so obtained was sublimed in vacuo at a bath temperature of 95–105 °C. Recrystallization of the sublimed material from chloroform–petroleum ether gave a colorless solid (89.8 mg, 64%): mp 148.5–150 °C; IR (KBr) 3380–2355 (CO_2H), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1–1.2 (two overlapping d, J = 6 Hz, 6 H, $CHMe_2$), 0.7–3.48 (m, 10 H, ring H), 10.9 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.68; H, 8.41; S, 14.95. Found: C, 61.69; H, 8.47; S, 14.96.

Methyl 6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate (2b). A mixture of endo acid **2a** (1.017 g, 5.46 mmol) and purified 3-methyl-1-(*p*-tolyl)triazene (0.855 g, 5.73 mmol) in dry 1,2-dimethoxyethane (12 mL) was stirred and heated at reflux overnight. The solvent was then removed in vacuo and the residue dissolved in ethyl ether. The ether solution was washed successively with 3 M aqueous hydrochloric acid solution, distilled water, saturated aqueous sodium bicarbonate solution, and distilled water again. The ethereal layer was then dried ($MgSO_4$), filtered, and evaporated to dryness with a rotary evaporator. The resulting oil was distilled to provide endo ester **2b** as a light yellow oil (0.974 g, 89%): IR (neat) 1724 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H, SMe), 0.72–3.25 (m, 10 H, ring H), 3.62 (s, 3 H, CO_2Me).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 59.95; H, 8.17; S, 15.95.

2-*endo*-(Hydroxymethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane (2c). A sample of endo ester **2b** (2.01 g, 10.0 mmol) was added to a suspension of lithium aluminum hydride (0.480 g, 12.6 mmol) in anhydrous ethyl ether (25 mL). The mixture was stirred for 5 h at room temperature. The excess lithium aluminum hydride was destroyed by the addition of wet ether and the reaction mixture was subsequently acidified with 4 M aqueous hydrochloric acid solution. The layers were shaken and the ether layer was separated. The aqueous layer was extracted twice more with ether (2 × 30 mL). The combined ethereal extracts were washed with water (1 × 25 mL) and saturated aqueous sodium bicarbonate solution (1 × 10 mL), dried (Na_2SO_4), and concentrated to an oil by using a rotary evaporator. The oil was distilled to give pure endo alcohol **2c** (1.31 g, 76%): IR (neat) 3448 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H, SMe), 0.65–3.35 (m, 11 H, ring H and OH), 3.8 (d, J = 7 Hz, 2 H, CH_2O).

Anal. Calcd for $C_9H_{16}OS$: C, 62.79; H, 9.30. Found: C, 62.84, H, 9.24.

Methyl 6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxylate (3b). Sodium methoxide in methanol solution was prepared by cautiously adding sodium metal (0.5 g, 22 mmol) to dry methanol (30 mL). To this solution, endo ester **2b** (3.1 g, 15.5 mmol) was added. This solution was stirred and heated at reflux overnight under a nitrogen atmosphere. The solution was then allowed to cool, the solvent was removed by using a rotary evaporator, and the residue was acidifed with ice-cold 3 M hydrochloric acid solution. This mixture was then extracted twice with ethyl ether. The ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to an oil. Distillation of this oil gave a clear liquid (2.75 g, 89%) which, by GC analysis (7-ft 5% DEGS on Chromosorb W at a column temperature of 165 °C), consisted of a 99:1 mixture of exo ester **3b** and endo ester **2b**. Pure exo ester **3b** was obtained by preparative GC: IR (neat) 1739 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, SMe), 0.53–3.4 (m, 10 H, ring H), 3.67 (s, 3 H, CO_2Me).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 60.04; H, 7.96; S, 16.02.

6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (3a). A sample of exo ester **3b** (611 mg, 3.05 mmol) dissolved in 0.42 M potassium hydroxide in 95% ethanol solution (14.5 mL, 6.1 mmol) was stirred and heated at reflux overnight. The solvent was then removed by using a rotary evaporator and distilled water (10 mL) was added to the residue. The water and residue were washed with ethyl ether. The aqueous layer was acidified with 3 M aqueous hydrochloric acid solution and extracted three times with ethyl ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated to a crystalline material by using a rotary evaporator. Recrystallization from hexane yielded large, colorless crystals of exo acid **3a** (455 mg, 80%): mp 68–69 °C; IR (KBr) 3125–2381 (CO_2H), 1709 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H, SMe), 0.52–3.42 (m, 10 H, ring H), 10.8 (br s, 1 H, CO_2H).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.05; H, 7.59; S, 17.26.

2-*exo*-(Hydroxymethyl)-6-*endo*-(methylthio)bicyclo[2.2.1]heptane (3c). The procedure for reduction of exo ester **3b** with lithium aluminum hydride was the same as that for reduction of endo ester **2b**. This method gave exo alcohol **3b** in 78% yield as a colorless oil: IR (neat) 3448 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3 H, SMe), 0.6–3.3 (m, 11 H, ring H and OH), 3.45 (d, J = 7.5 Hz, 2 H, CH_2O).

Anal. Calcd for $C_9H_{16}OS$: C, 62.79; H, 9.30. Found: C, 62.80; H, 9.34.

Ammonolysis of Exo Ester 3b. A solution of exo ester **3b** (60 mg, 0.30 mmol) dissolved in methanol (2 mL) saturated with ammonia gas was sealed in a Pyrex tube and placed in an oven maintained at 120 °C. After 8 days the contents of the tube was assayed by TLC and exo amide **3d** was the predominant constituent (a small amount of starting exo ester **3b** was also present). Evaporation of the solvent left a solid which, on two recrystallizations from dichloromethane–petroleum ether, gave pure exo amide **3d** (identical with exo amide **3d** prepared from exo acid **3a** as outlined below by IR and ^1H NMR spectroscopy and mixture melting point).

Reaction of Endo Acid 2a and Exo Acid 3a with Benzylamine. The reactions of endo acid **2a** and exo acid **3a** with benzylamine were performed similarly. The details for the reaction with endo acid **2a** follow. To endo acid **2a** (480 mg, 2.60 mmol) in a 10-mL round-bottom flask was added benzylamine (2.0 mL, 18.4 mmol). The mixture was stirred and heated at reflux under a nitrogen atmosphere for 2.5 h. The reaction mixture was then allowed to cool to room temperature and dissolved in ethyl ether (40 mL). This solution was then washed successively with 3 M hydrochloric acid solution, distilled water (40 mL), saturated aqueous sodium bicarbonate solution (40 mL), and brine (40 mL). The separated ethereal layer was dried with anhydrous magnesium sulfate, filtered, and concentrated to a white crystalline solid (596 mg). Recrystallization gave a white solid: 480 mg (67.6% yield); mp 92–93.5 °C; IR (KBr) 3333 (NH), 1667 (C=O), 1538 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3 H, SMe), 0.5–3.3 (m, 10 H, ring H), 4.4 (d, J = 6 Hz, 2 H, NCH_2), 5.7 (br, 1 H, NH), 7.26 (s, 5 H, Ar).

Anal. Calcd for $C_{16}H_{21}NOS$: C, 69.82; H, 7.64; N, 5.09; S, 11.64. Found: C, 69.79; H, 7.72; N, 5.08; S, 11.61.

The amide prepared above was identical with that obtained from exo acid **3a** by IR and ^1H NMR spectroscopy and mixture melting point.

Preparation of 6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxamide (3d) via *exo*-Acylimidazole. A mixture of exo acid **3a** (93 mg, 0.50 mmol) and 1,1′-carbonyldiimidazole (85 mg, 0.52 mmol) in dry tetrahydrofuran (3 mL) was stirred under a nitrogen atmosphere for 24 h at room temperature. The reaction mixture was then saturated with gaseous ammonia and stirred at room temperature for 3 days. The reaction mixture was then concentrated on a rotary evaporator. The solid so obtained was purified by preparative-layer chromatography on silica gel (elution with chloroform–methanol, 6:1). Pure exo amide **3d** was so obtained (67 mg, 73%), mp 150–151 °C. Recrystallization from methylene chloride afforded analytically pure exo amide **3d**: mp 151.5 °C; IR (KBr) 3029, 3010, 1615, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, SMe), 0.53–3.26 (m, 10 H, ring

H), 5.2–6 (br s, 2 H, $CONH_2$); mass spectrum, *m/e* 185 (P), 124, 110, 93, 72, 67.

Anal. Calcd for $C_9H_{15}NOS$: C, 58.38; H, 8.11; N, 7.57; S, 17.30. Found: C, 58.20; H, 8.15; N, 7.30; S, 17.28.

Ammonolysis of Endo Ester 2b. Ammonolysis of endo ester **2b** was performed the same way as ammonolysis of exo ester **3b**. TLC analysis of the crude reaction product and subsequent isolation revealed the major product to be exo amide **3d**, identical with that prepared above.

6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxamide (2d). A solution of endo acid **2a** (93 mg, 0.50 mmol) and 1,1′-carbonyldiimidazole (85 mg, 0.52 mmol) in dry tetrahydrofuran (3 mL) under a nitrogen atmosphere was stirred at room temperature for 24 h. The reaction mixture was then saturated with ammonia gas and stirred at room temperature for an additional 72 h. Concentration of the reaction mixture by using a rotary evaporator produced a white solid (166 mg). TLC examination (silica gel HF-254 as adsorbent and elution with ethyl acetate–methanol–concentrated aqueous ammonia solution, 30:1:1) showed this to be a mixture of endo amide **2d**, exo amide **3d**, and imidazole. These amides were separated by preparative-layer chromatography (on silica gel, eluting with ethyl acetate–methanol–concentrated aqueous ammonia, 30:1:1). In one experiment 33 mg of exo amide **3d** and 37 mg of endo-amide **2d** representing 75% combined yield were isolated. However, the ratio of these amides varied from one experiment to another. Pure endo amide **2d** was obtained by repeating preparative-layer chromatography on silica gel, eluting with chloroform–methanol (6:1), and recrystallization from dichloromethane–petroleum ether: mp 150–151 °C; IR (KBr) 3042, 3027, 1652, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3 H, SMe), 0.55–3.25 (m, 10 H, ring H), 5.46–6.06 (br s, 2 H, NH_2); mass spectrum, *m/e* 185 (P), 126, 114, 93.

Anal. Calcd for $C_9H_{15}NOS$: C, 58.38; H, 8.11; N, 7.57; S, 17.30. Found: C, 58.01; H, 8.18; N, 7.28; S, 17.18.

Epimerization of Endo Amide 2d. A mixture of endo amide **2d** (40 mg, 0.22 mmol), freshly sublimed potassium *tert*-butoxide (20 mg, 0.18 mmol), and *tert*-butyl alcohol (6 mL) distilled from calcium hydride under a nitrogen atmosphere was stirred and heated at reflux under a nitrogen atmosphere for 4 days. The solvent was removed in vacuo and the residue was stirred with dichloromethane and filtered. The filtrate was concentrated and purified by preparative-layer chromatography on silica gel and recrystallization from dichloromethane–petroleum ether to give a white crystalline solid (23 mg, 58%), mp 148–150 °C. This material showed an undepressed mixture melting point with exo amide **3d**, and its IR and ^1H NMR spectra were identical with those of exo amide **3d**.

A solution of endo amide **2d** (30 mg, 0.16 mmol) and imidazole (30 mg, 0.44 mmol) in dry tetrahydrofuran (4 mL) was saturated with ammonia gas. After being stirred for 72 h at room temperature, the solution was concentrated on a rotary evaporator to give a colorless solid. Assay of this material by TLC revealed the presence of only starting endo amide **2d** and the absence of exo amide **3d**.

Preparation of Endo Urethane 2e. A solution of endo acid **2a** (267 mg, 1.45 mmol) and diphenyl phosphorazidate (398 mg, 1.45 mmol) in dry 1,2-dimethoxyethane (7 mL) was treated with triethylamine (200 μL, 1.45 mmol). This mixture was stirred and heated at reflux under a nitrogen atmosphere for 3.5 h. Absolute ethanol (1.5 mL) was then added. Subsequently, 0.42 M potassium hydroxide in 95% ethanol solution (3.45 mL, 1.45 mmol) was added and the resulting solution stirred and heated at reflux overnight. Concentration on a rotary evaporator produced an oil which was partitioned between distilled water and ethyl ether. The aqueous phase was extracted with additional portions of ether. The combined ethereal extracts were washed sequentially with 2 M aqueous hydrochloric acid solution, distilled water, saturated aqueous sodium bicarbonate solution, and brine. The ether layer was then dried ($MgSO_4$), filtered, and concentrated, using a rotary evaporator, to a yellow oil which was distilled from bulb to bulb under oil-pump vacuum to yield endo urethane **2e** as a colorless oil (240 mg, 72%): IR (neat) 3333 (NH), 1709 (C=O), 1515 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, CCH_3), 2.15 (s, 3 H, SMe), 0.73–3.7 (m, 10 H, ring H), 4.08 (q, J = 7 Hz, 2 H, OCH_2), 6.35 (br, 1 H, NH).

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.64; H, 8.30; N, 6.11; S, 13.97. Found: C, 57.62; H, 8.37; N, 6.07; S, 13.98.

Preparation of Exo Urethane 3e. To a solution of exo acid **3a** (179 mg, 0.968 mmol) and diphenyl phosphorazidate (266 mg, 0.968 mmol) in dry 1,2-dimethoxyethane (5 mL) was added triethylamine (135 μL, 0.968 mmol). The reaction mixture was stirred and heated at reflux under a nitrogen atmosphere for 2.5 h. Absolute ethanol (4 mL) was then added and the reaction mixture heated at reflux for 1 h. Then, 0.42 M potassium hydroxide in 95% ethanol solution (2.3 mL, 0.97 mmol) was added and the reaction mixture heated at reflux overnight. The workup was the same as that for the preparation of the endo urethane **2e**. The crude product was distilled from bulb to bulb under oil-pump vacuum to produce exo urethane **3e** as a colorless oil (173 mg, 78%): IR (neat) 3448 (NH), 1709 (C=O), 1515 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, C-CH_3), 2.12 (s, 3 H, SMe), 0.52–3.68 (m, 10 H, ring H), 4.07 (q, J = 7 Hz, OCH_2), 4.4 (br, 1 H, NH).

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.64; H, 8.30; N, 6.11; S, 13.97. Found: C, 57.62; H, 8.35; N, 6.10; S, 14.01.

***S*-Methyl 6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*endo*-thiocarboxylate (2f).** A solution of endo acid **2a** (698 mg, 3.75 mmol) and 1,1′-carbonyldiimidazole (639 mg, 3.94 mmol) in dry *N*,*N*-dimethylformamide was stirred at room temperature under a nitrogen atmosphere for 24 h. The reaction mixture was then saturated with methanethiol and stirred at room temperature for an additional 70 h. Excess methanethiol was then removed by water aspirator and the reaction mixture was diluted with distilled water and extracted (3 × 20 mL) with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and then with distilled water. The organic layer was dried (Na_2SO_4), filtered, and concentrated to a pale yellow liquid which was distilled from bulb to bulb at 100–105 °C under oil-pump vacuum to give endo-thioester **2f** as a colorless liquid (746 mg, 92%): IR (neat) 1680, 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, SMe), 2.3 (s, 3 H, COSMe), 0.83–3.36 (m, 10 H, ring H); mass spectrum, *m/e* 216 (P), 168, 141, 93, 67, 61.

Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.55; H, 7.41; S, 29.63. Found: C, 55.55; H, 7.45; S, 29.60.

***S*-Methyl 6-*endo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-thiocarboxylate (3f).** Transformation of exo acid **3a** (542 mg, 2.91 mmol) into exo thioester **3f** was accomplished in the same manner as that described above for the conversion of endo acid **2a** into endo thioester **2f**. Exo thioester **3f** was so obtained as a colorless liquid (610 mg, 97%): IR (neat) 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, SMe), 2.27 (s, 3 H, COSMe), 0.48–3.58 (m, 10 H, ring H); mass spectrum, *m/e* 216 (P), 169, 141, 103, 93, 91, 67, 61.

Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.55; H, 7.41; S, 29.63. Found: C, 55.58; H, 7.45; S, 29.61.

Addition of Methanethiol to Methyl Bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate. Methanethiol (10–12 mL) was condensed into a Fischer–Porter medium-pressure reaction bottle containing methyl bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate (2.59 g, 17.1 mmol) and cooled with an ice bath. The bottle was sealed and allowed to warm to room temperature. After standing at room temperature for 2 days, the excess methanethiol was removed under reduced pressure and the residue dissolved in ethyl ether. This solution was washed successively with aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator, and the residue was distilled from bulb to bulb under oil-pump pressure and at bath temperature of 120 °C. A colorless liquid was so obtained in quantitative yield. Analysis of this material by GC on 0.25 in. × 5 ft Carbowax 20M on Chromosorb W (DMCS treated) column at 220 °C showed that it was a mixture of two compounds in a 44:56 ratio. The compound of shorter retention time which was the lesser component was assigned structure **4b** on the basis of the X-ray crystal structure analysis performed on the acid **4a** obtained by saponifying **4b**. The compound of longer retention time which was formed to a slightly greater extent than **4b** was assigned structure **6**. Endo ester **4b**: IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H, SMe), 0.9–3.13 (m, 10 H, ring H), 3.73 (s, 3 H, OMe).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 59.82; H, 8.04; S, 16.04.

Ester 6: IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H, SMe), 0.78-3.08 (m, 10 H, ring H), 3.72 (s, 3 H, OMe).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 59.94; H, 8.04; S, 16.01.

6-*exo*-(Methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (4a). A sample of endo ester **4b** (350 mg, 1.75 mmol) was dissolved in 0.42 M potassium hydroxide solution in 95% ethanol (20 mL, 8.4 mmol). The solution was stirred at room temperature for 24 h. At the end of this time the solvent was removed by rotary evaporation and the residue dissolved in water (5 mL). After extraction with ethyl ether, the aqueous phase was acidified with 3 M hydrochloric acid solution with ice-bath cooling. The mixture was filtered and the precipitate washed with cold water and dried to give a colorless solid, 243 mg, mp 124-126.5 °C. This solid was recrystallized from ethyl acetate-petroleum ether to afford pure endo acid **4a** (201 mg, 62%): mp 127-130 °C; IR (KBr) 3600-2200 (OH), 1675 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H, SMe), 0.88-3.22 (m, 10 H, ring H), 10.15-10.75 (br s, 1 H, CO_2H).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.11; H, 7.60; S, 17.15.

Methyl 6-*exo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxylate (5b). A solution of sodium methoxide was prepared by cautiously adding sodium metal (124 mg, 5.40 mmol) to freshly dried, distilled methanol (5 mL). A solution of endo ester **4b** (504 mg, 2.52 mmol) in dried, distilled methanol (6 mL) was added to the sodium methoxide solution. The solution was stirred and heated at reflux under a nitrogen atmosphere for 19 h. The solution was allowed to cool to room temperature and the solvent removed by rotary evaporation under vacuum. To the residue was added ice cold 3 M hydrochloric acid solution (2-3 mL) and the resulting mixture was twice extracted with ethyl ether. The combined extracts were washed successively with water and brine and dried over anhydrous sodium sulfate, the solvent was evaporated, and the residue was distilled from bulb to bulb under oil-pump vacuum at bath temperature of 115 °C. The colorless, mobile liquid (483 mg) so obtained was analyzed by GC and found to be a 27:73 mixture of **4b** and **5b**. There was no change in the composition of the material on an additional 15 h of exposure to sodium methoxide in methanol. Pure exo ester **5b** was secured by preparative GC on a 0.25 in. × 5 ft Carbowax 20M on Chromosorb W (DMCS treated) column at 220 °C: IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H, SMe), 0.7-3.0 (m, 10 H, ring H), 3.53 (s, 3 H, OMe).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05; S, 16.01. Found: C, 59.90; H, 8.07; S, 15.95.

6-*exo*-(Methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (5a). Exo ester **5b** (109 mg, 0.545 mmol) was dissolved in a 0.420 M solution of potassium hydroxide in 95% ethanol (8 mL, 3.36 mmol). The solution was stirred at room temperature for 20 h. The solvent was then removed on a rotary evaporator. The residue was acidified with 3-4 mL of ice-cold 3 M hydrochloric acid solution and extracted with ethyl ether. The extracts were concentrated to a liquid which was distilled from bulb to bulb under oil-pump pressure at a bath temperature of 155 °C. A colorless viscous liquid (92.5 mg, 91%) was so obtained which was greater than 99% pure by GC analysis on a 0.25 in. × 5 ft 10% SE-30 on Chromosorb W (DMCS treated) column at 220 °C: IR ($CHCl_3$) 3680-2340 (OH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H, SMe), 0.57-2.9 (m, 10 H, ring H), 11.0-11.4 (br s, 1 H, CO_2H).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58; S, 17.21. Found: C, 58.19; H, 7.12; S, 17.25.

Acknowledgment. We gratefully acknowledge support of this work by the U.S. Public Health Service, National Institutes of Health, Grant No. HL 15104.

Registry No. 1, 38347-95-4; **2a**, 64887-93-0; **2a** benzylamide, 74036-64-9; **2b**, 64887-94-1; **2c**, 64887-95-2; **2d**, 74036-60-5; **2e**, 64887-96-3; **2f**, 74036-61-6; **3a**, 64937-41-3; **3b**, 64937-42-4; **3c**, 64937-43-5; **3d**, 74080-75-4; **3e**, 64937-44-6; **3f**, 74080-76-5; **4a**, 74080-77-6; **4b**, 74080-78-7; **5a**, 74080-79-8; **5b**, 74080-80-1; **6**, 74036-62-7; methyl iodide, 74-88-4; 2-*endo*-bicyclo[2.2.1]heptanecarboxylic acid, 934-28-1; *endo*-6-(isopropylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, 74036-63-8; isopropyl bromide, 75-26-3; benzylamine, 100-46-9; methanethiol, 74-93-1; methyl bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate, 2903-75-5.

Supplementary Material Available: Stereoscopic view of the packing of the molecules in the unit cell of endo acid **2a** and endo acid **4a**; tables of additional crystal data, final atomic positional and thermal parameters, bond length, bond angle, and selected torsion angle data for endo acid **2a** and endo acid **4a**; listings of structure factor amplitudes for endo acid **2a** and endo acid **4a**; table comparing molecular structure of endo acid **2a** and endo acid **4a** determined by X-ray crystallographic techniques with the geometry calculated by molecular-mechanics method (12 pages). Ordering information is given on any current masthead page.

1,3-Dipolar Cycloadditions of Diazoalkanes with Thiete 1,1-Dioxide

Pier G. De Benedetti,[1a] Carlo De Micheli,*[1b] Remo Gandolfi,[1c] Pierluigi Gariboldi,[1d] and Augusto Rastelli*[1a]

Institute of Physical Chemistry, 41100-Modena, Italy, Institute of Pharmaceutical Chemistry, 42-Milano, Italy, Institute of Organic Chemistry, 10-Pavia, Italy, and Laboratory of Organic Chemistry, 50-Milano, Italy

Received January 21, 1980

Cycloadditions of diazoalkanes with thiete 1,1-dioxide have been reinvestigated; diazomethane, diazoethane, phenyldiazomethane, and 2-diazopropane yielded similar amounts of two regioisomers, whereas the reaction of diphenyldiazomethane was regiospecific and gave an adduct with regiochemistry opposite to that previously reported. Structures were assigned on the basis of ^1H and ^{13}C NMR spectra. The mass spectra of the adducts are also briefly discussed. Results are rationalized on the basis of a simple model of perturbation theory.

Introduction

Thiete 1,1-dioxide (**2**) is a reactive compound and owing to its planar structure is a suitable substrate for studying endo-exo selectivity in reactions with dienes[2] and regioselectivity in reactions with 1,3-dipoles.[3,4] Nevertheless the 1,3-dipolarophilic reactivity of thiete 1,1-dioxide has been

(1) (a) Institute of Physical Chemistry. (b) Institute of Pharmaceutical Chemistry. (c) Institute of Organic Chemistry. (d) Laboratory of Organic Chemistry.

(2) Dittmer, D. C.; Christy, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 399. Paquette, L. A.; Phillips, T. R. *J. Org. Chem.* **1965**, *30*, 3883. Dittmer, D. C.; Takashina, N. *Tetrahedron Lett.* **1964**, 3809. Martin, H. D.; Iden, R.; Schiwek, H. *J. Tetrahedron Lett.* **1978**, 3337.

(3) Dalla Croce, P.; Del Buttero, P.; Maiorana, S.; Vistocco, R. *J. Heterocycl. Chem.* **1978**, *15*, 515.

0022-3263/80/1945-3646$01.00/0