## Synthesis and Characterization of 5- and 6-(4-Pyridinyl)bicyclo[2.2.1]heptan-2-amines

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The application of $^{13}C$ NMR spectroscopy to the characterization of bicyclo[2.2.1]heptanyl systems is well documented.[1] In this regard, we would like to report the synthesis, characterization, and partial separation of three of the eight possible isomers of 5-(4-pyridinyl)bicyclo[2.2.1]heptan-2-amine and 6-(4-pyridinyl)bicyclo[2.2.1]heptan-2-amine: **2a, 2b,** and **4a,** Scheme I; subsequently, **2** and **4** will be named as 5- and 6-pyridylnorbornan-2-amines.

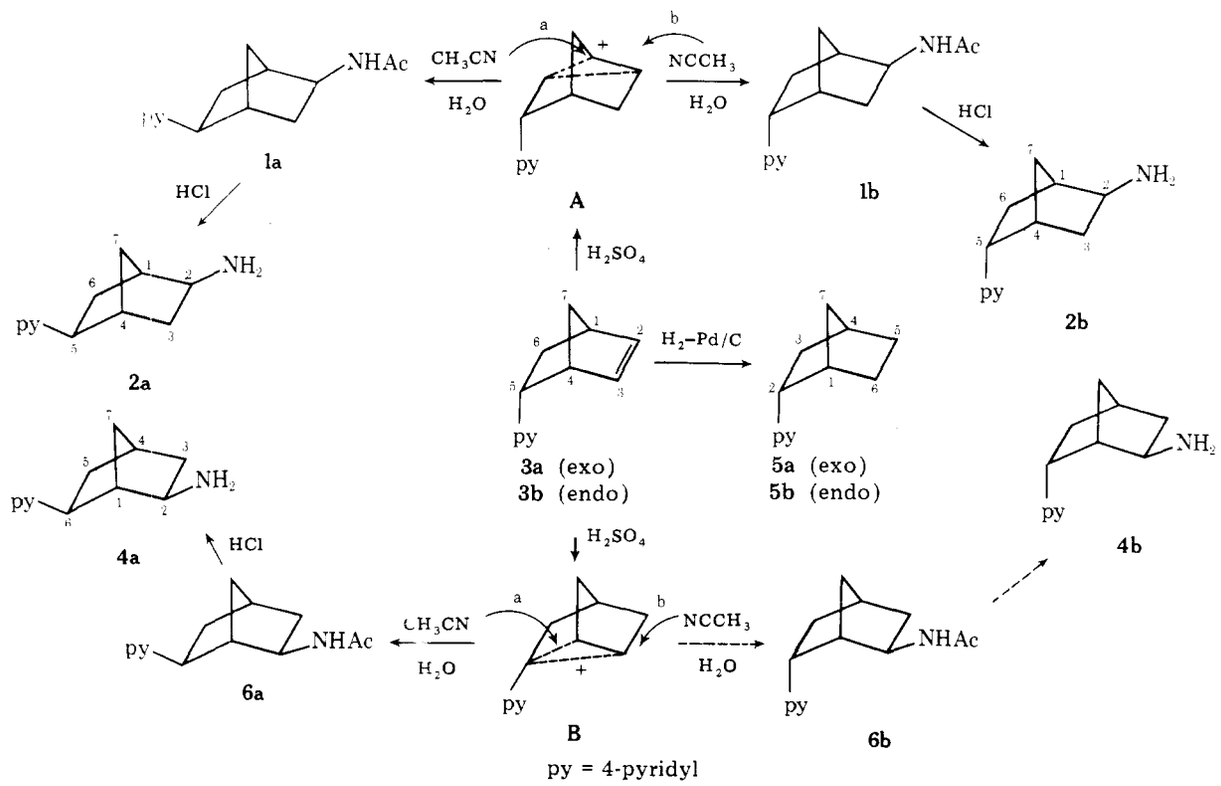
Reaction of 4-vinylpyridine with distilled cyclopentadiene in a sealed tube at 100 °C for 67 h gave a 30% yield of an 85:15 mixture of *endo*-/*exo*-5-pyridyl-2-norbornene (**3**).[2] The ratio was determined from the 100-MHz $^1H$ NMR spectrum by integration of $H_{5x}$ and $H_{5n}$ at $\delta$ 3.40 and 2.70, respectively, and by integration of the $\beta$-pyridyl protons at $\delta$ 7.10 (*endo*-pyridyl) and 7.24 (*exo*-pyridyl). By the use of double resonance $^1H$ NMR experiments, it was possible to assign the proton resonances in **3**; thus, irradiation of $H_1$ at 297.5 Hz resulted in the collapse of $H_2$ (6.31 ppm) to a doublet and the collapse of $H_{6x}$ (2.21 ppm) to a quartet. Irradiation of $H_4$ at 309.5 Hz caused $H_3$ (5.80 ppm) to collapse to a doublet and the observed quintet for $H_{5x}$ (3.37 ppm) to simplify to a quartet. Finally, irradiation of $H_{5x}$ at 333.9 Hz simplified the octet for $H_{6x}$ (2.21 ppm) and the octet for $H_{6n}$ (1.30 ppm).

A Ritter reaction between **3** and acetonitrile in concentrated $H_2SO_4$ afforded a regio- and stereoisomeric mixture of the *exo*-amides, **1** and **6,** which was separated into the two regioisomers by careful column chromatography to give 15.5% of **1** as a crystalline solid and 23% of **6** as glass which defied crystallization and yet was homogeneous on TLC. Recrystallization of the stereoisomeric mixture of amides, **1,** gave the pure *endo*-pyridyl isomer, **1b.** The assignment of the *exo*-amide structures rests upon the chemical shift of $H_{2n}$ of $\delta$ 3.90 and 3.80 for **1** and **6,** respectively,[3] and upon the precedented formation of exo adducts to norbornyl carbocations.[4]

Acid-catalyzed hydrolysis of the amides **1** and **6,** followed by vacuum distillation, gave the pure isomeric 5- and 6-pyridylnorbornan-2-amines, **2** and **4,** as low melting solids. The 5-pyridyl regioisomer was a mixture of *endo*- and *exo*-pyridyl steroisomers, **2a** and **2b,** while the only 6-pyridyl regioisomer isolated was the exo stereoisomer, **4a.** Hydrolysis of **1b** gave a single isomer, **2b.** In order to facilitate the structural assignments, 2-(4-pyridyl)norbornane (**5**) was prepared by catalytic reduction of **3.**

The $^{13}C$ NMR chemical shifts (ppm from $Me_4Si$) and the multiplicities (m) from off-resonance decoupled spectra, where obtainable, are listed in Table I for compounds **2a, 2b, 4a, 5a,** and **5b.** The $^{13}C$ NMR spectrum of *exo*-norbornan-2-amine (**7**) was assigned by Roberts et al.[1] and is confirmed in Table I, which lists the chemical shifts we obtained using a commercial sample of **7.** The chemical shifts for norbornane (**8**) are taken from Robert's paper. The assignment of resonances in the $^{13}C$ NMR spectrum of **5b** follows readily from the known chemical shift values for norbornane and the off-resonance decoupled spectrum (Table I). Assignment of carbon atoms in **5a** is less certain since its presence to the extent of ~15% in the mixture allowed us to obtain only chemical shifts and not multiplicities for the carbon atoms in this isomer. Nevertheless, the assignment of resonances for C-2, C-4, C-5, C-6, and C-7 is reasonable, while C-1 and C-3 are perhaps questionable. Of particular relevance to the structural assignments of **2a, 2b,** and **4a** are the upfield shifts of C-7 in **5a** and C-6 in **5b** relative to each other and to norbornane, due to steric compression by the pyridyl group.

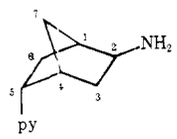
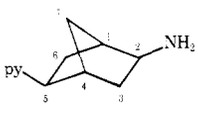
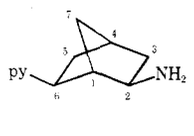
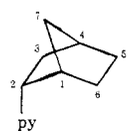
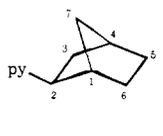
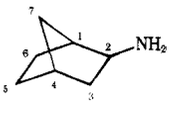
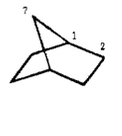
Scheme I




py = 4-pyridyl

0022-3263/79/1944-1889$01.00/0 

**Table I. Chemical Shifts (δ, ppm) and Multiplicities of Carbon Resonances of the Norbornane Derivatives 2, 4, 5, 7, and 8**

| carbon no. |  2b |  2a |  4a |  5b |  5a |  7 |  8[a] |
|---|---|---|---|---|---|---|---|
| 1 | 45.20 (d) | 49.27 (d) | 47.96 (d) | 42.09 (d) | 42.27 | 45.31 | 36.8 |
| 2 | 54.01 (d) | 56.53 (d) | 54.94 (d) | 45.47 (d) | 46.68 | 54.91 | 30.1 |
| 3 | 31.78 (t) | 40.53 (t) | 42.36 (t) | 33.63 (t) | 36.17 | 42.22 | |
| 4 | 42.27 (d) | 37.09 (d) | 38.56 (d) | 37.38 (d) | 38.53 | 36.01 | |
| 5 | 45.50 (d) | 51.81 (d) | 25.77 (t) | 29.96 (t) | 28.67 | 28.24 | |
| 6 | 41.67 (t) | 28.31 (t) | 48.99 (d) | 22.95 (t) | 30.35 | 26.79 | |
| 7 | 35.02 (t) | 28.01 (t) | 24.46 (t) | 40.49 (t) | 23.20 | 34.26 | 38.7 |

[a] Values taken from ref 1.

The $^{13}C$ NMR spectrum of the mixture of **2a** and **2b** shows 14 well-defined alkyl carbon resonances for the two stereoisomers with the assigned chemical shifts and multiplicities given in Table I. The $^{13}C$ NMR spectrum of **2b** is identical with that of the major product from the hydrolysis of **1**. The carbon assignments in Table I follow from **5a, 5b,** and **7**. Assignment of resonances for **2b** proceeds from the upfield shifts of C-3 (31.78 ppm) relative to that of **7** (42.22 ppm). The chemical shift of C-2 (54.01 ppm) precludes assignment of the regioisomeric *endo*-6-pyridyl structure to **2b** since a considerable upfield shift of C-2 would be expected for this isomer. The structure of **2a** rests upon the upfield shift of C-7 (28.01 ppm) relative to C-7 of **2b** (35.02 ppm) and C-7 of **7** (34.26 ppm). The $^{13}C$ NMR spectrum of **4a** shows seven well-defined alkyl carbon resonances. The structure of **4a** follows from the upfield shift of C-7 (24.46 ppm) and the unchanged (relative to **7**) shift of C-2.

Although the $^{1}H$ NMR spectra of **2a, 2b,** and **4a** do not permit differentiation of the three isomers, they do support the structural assignments derived from the $^{13}C$ NMR spectra. For **2a** and **2b,** there is a multiplet centered at 2.97 ppm assignable to $H_{2n}$. The two sets of β-pyridyl protons of **2b** and **2a** resonate at 7.14 and 7.27 ppm, respectively. For **4a,** there is a well-defined quartet at 3.09 ppm assignable to $H_{2n}$ and a broad singlet at 2.62 ppm assignable to $H_{6n}$.

The products from the Ritter reaction of **3** and $CH_3CN$ may be rationalized as shown in Scheme I. Protonation of **3,** in addition to protonating the pyridine nitrogen, affords two carbocations, A and B, which are illustrated in nonclassical form for ease of visualization.[4] The same argument would be valid if A and B were written as a rapid equilibrium of two classical carbocations.[5] Accordingly, exo attack (mode a) by $CH_3CN$ on A will afford the inverted pyridyl isomer **1a,** while exo attack by mode b will afford **1b.** In the same manner, exo attack by $CH_3CN$ via mode a on the regioisomeric carbocation B will give **6a,** and theoretical attack via mode b would give **6b.** In the examples given, **6b** was not isolated; however, the yields of the purified products were low, and conceivably **6b** may have been formed as a minor product. Indeed, the $^{13}C$ NMR spectrum of **4a** suggested the presence of another isomer, but no structural assignment was possible since all of the resonances were not resolved.

## Experimental Section

**General.** Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were obtained on a Varian XL-100-15 Fourier Transform spectrometer. Chemical shifts are reported in parts per million downfield from internal $Me_4Si$. Some $^{1}H$ NMR spectra were obtained on Varian A60A, T60A, and CFT-20 spectrometers. Spin decoupling experiments were carried out on the XL-100 spectrometer. Microanalyses were performed by our Physical and Analytical Research Department.

**5-(4-Pyridinyl)bicyclo[2.2.1]hept-2-ene (3).** A mixture of 13.3 g (0.202 mol) of freshly distilled cyclopentadiene and 26.2 g (0.250 mol) of freshly distilled 4-vinylpyridine was heated for 67 h at 100 °C in a sealed tube. The product was poured into 200 mL of $Et_2O$, the resulting mixture was filtered, and the filtrate was extracted with three cold 50-mL portions of 10% HCl. The acidic extract was diluted with 100 mL of $H_2O$, cooled in an ice bath, and rendered basic with $K_2CO_3$. The basic aqueous solution was extracted several times with a total of 400 mL of $Et_2O$, and the $Et_2O$ was washed with saturated NaCl, dried ($K_2CO_3$), and distilled to give 10.4 g (30%) of **3:** bp 114–120 °C (28 mm); $^{1}H$ NMR ($CDCl_3$) δ 1.30 (octet, 1, $H_{6n}$), 1.45–1.80 (m, 2 $H_7$), 2.21 (octet, 1, $H_{6x}$), 3.01 (broad s, 1, $H_1$), 3.17 (broad s, 1, $H_4$), 3.37 (quintet, $J$ = 4 Hz, 1, $H_{5x}$), 5.80 (q, $J$ = 3 Hz, 1, $H_3$), 6.31 (q, $J$ = 3 Hz, 1, $H_2$), 7.10 (q, *endo*-py β-H), 7.15 (q, *exo*-py β-H), 8.48 (q, 2, py α-H). A 3.0-g sample of **3** in 200 mL of $Et_2O$ was treated with excess HCl in 2-PrOH, and the hydrochloride salt was collected (3.5 g) and recrystallized from 350 mL of acetone to give 1.8 g of **3**·HCl, mp 206–207.5 °C dec.

Anal. Calcd for $C_{12}H_{13}N$·HCl: C, 69.30; H, 6.78; N, 6.73. Found: C, 69.23; H, 6.72; N, 6.67.

**2-*exo*-*N*-Acetyl-5-(4-pyridinyl)bicyclo[2.2.1]heptan-2-amine (1) and 2-*exo*-*N*-Acetyl-6-(4-pyridinyl)bicyclo[2.2.1]heptan-2-amine (6).** A solution of 8.55 g (0.0500 mol) of **3** in 5 mL of $CH_3CN$ was added over 0.75 h, under $N_2$, to a cold (−5 °C) solution of 20 mL of $H_2SO_4$ and 5 mL of $CH_3CN$. During the addition, the temperature of the reaction rose to 25 °C. After being stirred for an additional 1.25 h, the solution was poured over ice and rendered basic with 50% NaOH. Extraction of the aqueous mixture several times with a total of 800 mL of EtOAc, washing the extract with saturated NaCl, drying ($K_2CO_3$), and concentration of the EtOAc on a rotary evaporator gave 10.6 g of an oil which showed two major components on TLC (5% $CH_3OH$–95% $CHCl_3$). This was chromatographed on 410 g of 200 mesh silica gel with 2% $CH_3OH$–98% $CHCl_3$ to separate the product mixture into its two components: **1** (2.4 g) and **6** (5.8 g). Compounds **1** and **6** were each rechromatographed on 200 and 400 g of TLC-grade silica gel, respectively, with 2% $CH_3OH$–98% $CHCl_3$ to give 1.79 g (15.5%) of homogeneous (TLC) **1** (a solid) and 2.67 g (23%) of homogeneous (TLC) **6** (a glass). A 0.6-g sample of **1** was recrystallized from 10 mL of $CH_3CN$ to give 0.23 g of **1b:** mp 168–170 °C; $^{1}H$ NMR ($CDCl_3$) δ 1.98 (s, $CH_3$), 2.25–2.45 (m, 2, $H_1$ and $H_4$), 2.70 (q, 1, $H_{5x}$), 3.90 (m, 1, $H_{2n}$), 5.78 (broad s, 1, NH), 7.16 (q, 2, *endo*-py β-H), 8.50 (q, 2, py α-H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.16. Found: C, 72.74; H, 7.88; N, 12.40.

The $^{1}H$ NMR spectrum of **1** before recrystallization was less well resolved than that of the recrystallized sample and contained, in addition, a small quartet at δ 7.27 assignable to the *exo*-py β-H.

Isomer **6** was an amorphous solid and could not be purified further by crystallization or distillation: $^{1}H$ NMR ($CDCl_3$) δ 1.05–2.95 (m, 9, alkyl H), 1.98 (s, $CH_3$), 3.80 (m, 1, $H_{2n}$), 5.95 (broad d, 1, NH), 7.05 (m, 2, py β-H), 8.45 (q, 2, py α-H).

**2-*exo*-5-(4-Pyridinyl)bicyclo[2.2.1]heptan-2-amine (2).** A solution of unrecrystallized **1** (1.05 g, 0.00435 mol) in 30 mL of EtOH and 30 mL of concentrated HCl was heated under reflux for 43 h. Upon cooling, the solution was poured into 50 mL of saturated $K_2CO_3$ and 50 mL of $H_2O$ and extracted with three 50-mL portions of $CH_2Cl_2$.

The $CH_2Cl_2$ was washed with saturated NaCl solution, dried ($K_2CO_3$), and concentrated on a rotary evaporator to give 0.69 g (84% crude) of **2**. This was distilled to give 0.31 g (38%) of pure **2**: bp 110 °C (0.07 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 0.95–2.02 (m, 8, $H_3$, $H_6$, $H_7$, and $NH_2$), 2.12 (broad s, 1, $H_1$), 2.45 (d, 1, $H_4$), 2.54–3.14 (m, 2, $H_2$ and $H_5$), 7.14 (q, *endo*-py $\beta$-H), 7.27 (q, *exo*-py $\beta$-H), 8.47 (q, 2, py $\alpha$-H).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.56; N, 14.87. Found: C, 76.67; H, 8.58; N, 14.90.

Similarly, hydrolysis of 0.1662 g of **1b** in 5 mL of EtOH and 5 mL of concentrated HCl gave 0.1206 g (89% crude) of **2b**: $^1H$ NMR ($CDCl_3$) $\delta$ 0.95–1.95 (m, 8, $H_3$, $H_6$, H, and $NH_2$), 2.08 (broad s, 1, $H_1$), 2.37 (d, 1, $H_4$), 2.59 (t, 1, $H_{5x}$), 2.99 (1, 1, $H_{2n}$), 7.09 (q, 2, (q, 2, *endo*-py $\beta$-H), 8.45 (q, 2, py $\alpha$-H).

**2-*exo*-6-(4-Pyridinyl)bicyclo[2.2.1]heptan-2-amine (4).** A solution of 2.17 g (0.00943 mol) of **6** in 30 mL of EtOH and 30 mL of concentrated HCl was heated under reflux for 66 h. Workup in the same manner as the previous experiment gave 1.02 g (58% crude) of an oil which was distilled to give 0.21 g (12%) of **4a**: bp 111 °C (0.07 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 0.95–2.15 (multiplets, 8, $H_3$, $H_5$, $H_7$, and $NH_2$), 2.35 (broad s, 1, $H_4$), 2.62 (broad s, 1, $H_{6n}$), 3.09 (1, $J$ = 5 Hz, 1, $H_{2n}$), 3.19 (s, 1, $H_1$), 7.20 (q, 2, py $\beta$-H), 8.52 (q, 2, py $\alpha$-H).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.56; N, 14.87. Found: C, 76.41; H, 8.71; N, 14.80.

**2-(4-Pyridinyl)bicyclo[2.2.1]heptane (5).** A solution of 10.24 g (0.0602 mol) of **3** in 300 mL of EtOH was hydrogenated with 5% Pd/C on a Parr apparatus at 60 psi. After 1 h, $H_2$ uptake had ceased and the solution was filtered and concentrated on a rotary evaporator to give 10.14 g of a liquid which was distilled to give **5**: bp 63–83 °C (0.03–0.05 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 1.00–1.70 (m, 7, $H_{3x}$, $H_5$, $H_6$, and $H_7$), 2.00 (m, 1, $H_{3n}$), 2.40 (m. 2, $H_1$ and $H_4$), 3.20 (m, 1, $H_2$), 7.14 (q, 2, py $\beta$-H), 8.50 (q, 2, py $\alpha$-H).

Anal. Calcd for $C_{12}H_{15}N$: C, 83.18; H, 8.72; N, 8.08. Found: C, 83.04; H, 8.79; N, 8.26.

**Registry No.**—**1b**, 69631-86-3; **2a**, 6963-87-4; **2b**, 69631-88-5; **3a**, 69631-89-6; **3a** hydrochloride, 69631-90-9; **3b**, 69631-91-0; **3b** hydrochloride, 69631-92-1; **4a**, 69668-79-7; **5a**, 69631-93-2; **5b**, 69631-94-3; **6a**, 69631-95-4; **7**, 7242-92-4; cyclopentadiene, 542-92-7; 4-vinylpyridine, 100-43-6; acetonitrile, 75-05-8.

## References and Notes


(1) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).
(2) C. J. Cavallito and A. P. Gray, U.S. Patent 3 409 626, 1968.
(3) The chemical shifts for $H_{2n}$ and $H_{2x}$ of the *exo*- and *endo*-*N*-acetylnorbornan-2-amines are $\delta$ 3.75 and 4.10.
(4) G. D. Sargent, *Q. Rev., Chem. Soc.*, **20**, 301 (1966).
(5) H. C. Brown, "The Non-Classical Ion Problem", Plenum Press, New York, 1977.


## Synthesis and Structure Proof of Diethyl Diacetylmaleate and Diethyl Diacetylfumarate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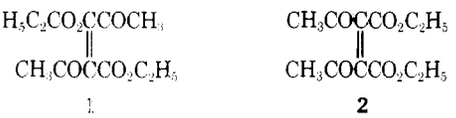
*Received November 20, 1978*

When we became interested in obtaining diethyl diacetylfumarate (**1**) as a synthetic intermediate, we found that it was first reported in 1885[1] and in three subsequent publications.[2-4] All of these procedures involved the dimerization of an ethyl acetoacetate moiety, usually via an $\alpha$-monosubstituted or a $\alpha,\alpha$-disubstituted intermediate. In all of these syntheses, yields were quite low and no support was offered for the assigned trans stereochemistry. We therefore undertook the task of repeating the synthesis of this alleged fumarate, of synthesizing the previously unreported diethyl diacetylmaleate (**2**), and of obtaining proof of the stereochemistry of these compounds from their vibrational spectra.

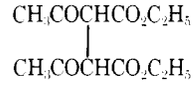


**1**



**2**

The alleged fumarate (**1**) was readily obtained by the method of Tronov et al.,[4] and its trans stereochemistry was verified and will be discussed shortly. The maleate (**2**) was synthesized quite by accident by the oxidation of diethyl diacetylsuccinate (**3**). The latter compound, prepared as a possible precurser for **1** and **2**, surprisingly showed no evidence of enolization in the IR or NMR. In order to see whether a degree of enolization too small to show in the IR and NMR spectra was occurring, an attempt was made to induce H/D exchange for the methine hydrogens by adding a small amount of $D_2O$ and $H_2SO_4$ to the $CCl_4$ solution used for the NMR spectrum. Although this did result in the disappearence of the methine signal from the NMR spectrum, a repetition of the experiment using $H_2O$–$H_2SO_4$ also caused the methine signal to disappear! Further investigation revealed that oxidation of the diethyl diacetylsuccinate (**3**) to diethyl diacetylmaleate (**2**) and not H/D exchange was the cause of the methine hydrogens' disappearence. Evidence for the structure of **2** included readily rationalized IR, Raman, mass, and NMR spectra and elemental analysis. This unusual acid-catalyzed oxidation would not occur in ether–$H_2SO_4$ or in $CCl_4$–concentrated HCl. Thus the strong acid $H_2SO_4$ and not the weaker $H_3O^+$ or protonated ether is needed. Normal dehydrogenation conditions such as heating with platinum or palladium failed to induce the reaction.



**3**

The vibrational spectra of **1** and **2** corroborated their stereochemistries. Comparing the C=C stretching peaks at 1600–1645 $cm^{-1}$ gave the expected results; i.e., this peak was much more intense in **2**, which has no center of symmetry, than in **1** which has a center of symmetry. In the Raman spectra this peak was intense for both compounds. A similar result occurred in the 900–1050 $cm^{-1}$ region. **2** shows moderate skeletal absorptions at 940 and 1030 $cm^{-1}$ in both the IR and Raman spectra. **1** also shows moderate peaks at 940 and 1030 $cm^{-1}$ in the Raman spectrum, but these peaks are extremely weak in the IR specturm. Another tetrasubstituted ethylene, diethylstilbesterol, has been reported to show similar results in the 900–1050 $cm^{-1}$ region when its cis and trans isomers are compared.[5]

### Experimental Section

**Instrumentation.** Melting points are uncorrected and were determined on a Mel-Temp instrument. IR spectra were recorded on Beckman Models IR-8 and IR-12, NMR spectra on a JEOL C-60 HL, Raman spectra on a Cary-83, and mass spectra on a Dupont 21-490. Elemental analyses were obtained from Spang Microanalytical Laboratory, Eagle Harbor, Mich.

**Diethyl Diacetylsuccinate (3).** This compound was synthesized by a modification of the method reported by Dann et al.[3] Sodium ethyl acetoacetate was prepared by reacting sodium metal (2.2 g, 0.096 mol) with freshly distilled ethyl acetoacetate (13.0 g, 0.1 mol) in dry benzene at 6 °C. The contents were warmed until the benzene solution was clear, and ethyl 2-chloroacetoacetate (16.5 g, 0.1 mol) was added dropwise with stirring over a 15-min period. The reaction mixture was then refluxed overnight. The sodium chloride precipitate that formed during the reaction was filtered off. The filtrate was allowed to sit in an open beaker, and after several days crystals of **3** separated and were recrystallized from petroleum ether. The yield was 3.5 g (13.5%): mp 89 °C (lit.[6] mp 88–89 °C); NMR ($CCl_4Me_4Si$) $\delta$ 1.28 (t, 6 H, $J$ = 7.8 Hz), 2.33 (s, 6 H), 4.15 (q, 4 H, $J$ = 7.8 Hz), 4.6 (s, 2 H); IR (mineral oil) 1725, 1360, 1282, 1242, 1169, 1136 (sh), 1031, 1014, 866 $cm^{-1}$; MS *m/e* (rel intensity) 258 (3), 213 (18), 174 (20), 173 (100), 167 (62), 166 (56), 145 (42), 128 (20), 127 (100), 125 (28), 117 (22), 99 (59), 97 (20).

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