dilute HCl and H_2O, dried (anhydrous $MgSO_4$), and concentrated in vacuo. This was chromatographed on Al_2O_3 (neutral, activity I). Compound **7** was obtained as an oil upon elution with 10–40% Et_2O/hexane; continued elution with 50–80% Et_2O/hexane gave **8**, which was recrystallized.

D. 9 and 10. A product mixture which precipitated from the cooled reaction was chromatographed on Al_2O_3 (neutral, activity I). Elution with 10–20% EtOAc/hexane afforded **9**, which was recrystallized; further elution with 10–60% $CHCl_3$/hexane gave **10**, which was purified by recrystallization.

E. 11 and 12. A product mixture which precipitated from the cooled reaction was chromatographed on Al_2O_3 (neutral, activity I). Compound **11** was eluted first with 10–20% Et_2O/hexane and was recrystallized; elution with 40–60% Et_2O/hexane provided **12**, which was further purified by recrystallization.

F. 13 and 14. The cooled reaction mixture provided a mixture of crystalline **13** and **14**. Crystals of **14** are large cubes and dissolve quite slowly in cold $CHCl_3$, whereas crystals of **13** are light, fluffy needles which rapidly dissolve in $CHCl_3$. A rapid wash of the mixture of **13** and **14** with cold $CHCl_3$ leaves the latter behind, which can then be further purified by recrystallization. The filtrate, containing mainly **13**, was concentrated in vacuo and purified by recrystallization.

G. 15 and 16. The cooled reaction gave a mixture of **15** and **16**; several recrystallizations afforded **15**. The combined mother liquors were concentrated in vacuo and the residue was recrystallized to give **16**.

H. 17 and 18. The cooled reaction gave a mixture of **17** and **18**; two recrystallizations afforded **18**. The combined mother liquors were concentrated in vacuo and chromatographed on silica gel; elution with 10% EtOAc/hexane gave **17**, which was further purified by crystallization.

I. 19 and 20. Solvent was removed in vacuo and the residue dissolved in $CHCl_3$ and washed with dilute HCl and H_2O. The organic layer was dried (anhydrous $MgSO_4$) and concentrated in vacuo and the residue was chromatographed on Al_2O_3 (neutral, activity I). Elution with hexane gave **19**, which was further purified by recrystallization. Et_2O elution afforded **20**, which was then recrystallized.

Reaction of 13 with *o*-Chloranil. Preparation of 22–24. To a suspension of **13** (2.0 g, 4.9 mmol) in 100 mL of CCl_4 at ambient temperature was added a solution of *o*-chloranil (1.25 g, 5.1 mmol) in 100 mL of CCl_4 over a period of 2.5 h. The reaction mixture, which became homogeneous near the end of the *o*-chloranil addition, was allowed to stir for another 0.5 h before washing with dilute NaOH and H_2O. The organic layer was dried ($CaCl_2$) and concentrated in vacuo and the residue was chromatographed on Al_2O_3 (neutral, activity I). Elution with CCl_4/$CHCl_3$ (100/0 to 65/35) gave two major fractions as followed by TLC.

The first product to elute was **22** (1.4 g) which was recrystallized from CCl_4/hexane to give 1.1 g: mp 152–154 °C dec; IR (Nujol) 1520, 1570 (C=N), 1130, 1310 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.10–7.22 (m, 8 H, ArH), 5.73 (s, 1 H, OCH), 2.78 (t, 2 H, J = 7 Hz, NCH_2). Anal. Calcd for $C_{30}H_{28}N_2Cl_4SO_4$: C, 55.05; H, 4.31; N, 4.28; S, 4.90; Cl, 21.67. Found: C, 55.34; H, 4.09; N, 4.11; S, 4.84; Cl, 21.43.

The second product to elute was **23** (0.4 g), which was purified by recrystallization from CCl_4/hexane and then from acetone/hexane to give 0.2 g: mp 161–163 °C; m/e 406 (M^+); IR (Nujol) 1450, 1500 (PhCH=CC=N), 1125, 1315 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.68 (br s, 1 H, =CH), 7.18 (s, 8 H, ArH), 4.02 (t, 2 H, J = 7 Hz, NCH_2), 2.43, 2.37 (two s, 6 H, $ArCH_3$). Anal. Calcd for $C_{24}H_{26}N_2O_2S$: C, 70.70; H, 6.45; N, 6.89; S, 7.89. Found: C, 71.03; H, 6.68; N, 6.93; S, 8.00.

When **22** (325 mg, 0.5 mmol) in 15 mL of CCl_4 containing *o*-chloranil (130 mg, 0.5 mol) was heated at reflux temperature for 2 h, the initial red dissipated and a solid separated. After the mixture had cooled overnight, there was collected a small amount of **24**: mp 275.5–277°C dec; m/e 650 (M^+); NMR ($CDCl_3$) δ 7.00–7.38 (m, 8 H, ArH), 5.92 (s, 1 H, OCH_2), 4.13 (t, 2 H, J = 7 Hz, NCH_2), 2.43, 2.35 (two s, 6 H, $ArCH_3$). Anal. Calcd for $C_{30}H_{26}N_2Cl_4SO_4$: C, 55.22; H, 4.02; N, 4.29; S, 4.92; Cl, 21.74. Found: C, 55.35; H, 4.32; N, 4.37; S, 4.70; Cl, 21.53.

Acknowledgments. We thank Mr. J. Alicino and Ms. Mary Young for the microanalyses, Drs. M. S. Puar and A. I. Cohen for the infrared and nuclear magnetic resonance spectra, Dr. P. Funke for the mass spectra, and Mrs. B. Toeplitz for the X-ray data.

Registry No. **1**, 61448-59-7; **4**, 70343-23-6; **5**, 61448-60-0; **6**, 70343-24-7; **7**, 70343-25-8; **8**, 70343-26-9; **9**, 61479-64-9; **10**, 70343-27-0; **11**, 70343-28-1; **12**, 70343-29-2; **13**, 70343-30-5; **14**, 70343-31-6; **15**, 70355-59-8; **16**, 70343-32-7; **17**, 70343-33-8; **18**, 70343-34-9; **19**, 62513-32-0; **20**, 70343-35-0; **22**, 70343-36-1; **23**, 70343-37-2; **24**, 70343-38-3; **25**, 28612-36-4; **26**, 61448-77-9; **27**, 62040-99-7; **28**, 70343-39-4; **29**, 62513-33-1; **30**, 61448-78-0; **31**, 61448-82-6; **32**, 61448-83-7; $C_3H_7NHNH_2$, 5039-61-2; *i*-$C_3H_7NHNH_2$, 2257-52-5; $CF_3CH_2NHNH_2$, 5042-30-8; tetrahydro-4*H*-thiopyran-4-one, 1072-72-6; 4-chlorobenzaldehyde, 104-88-1; 3,4-dichlorobenzaldehyde, 6287-38-3; tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide, 17396-35-9; 3-(trifluoromethyl)benzaldehyde, 454-89-7; tetrahydro-3,5-bis[[3-(trifluoromethyl)phenyl]methylene]-4*H*-thiopyran-4-one, 61448-84-8; *o*-chloranil, 2435-53-2.

Synthesis and Nuclear Magnetic Resonance Spectra of *N*-Carboethoxy-4-spiro-1,4-dihydropyridines

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A series of *N*-carboethoxy-4-spiro-1,4-dihydropyridines (**11**) has been prepared via condensation reactions of glutaraldehydes with ammonia or ethyl carbamate. While ammonia gives substantial amounts of 2-amino-1,2,3,4-tetrahydropyridines as well as some 1,4-dihydropyridines, ethyl carbamate condenses in benzene solution in the presence of catalytic amounts of *p*-toluenesulfonic acid to give **11** exclusively. The latter reaction, run as a one-pot synthesis from diol to *N*-carboethoxy-1,4-dihydropyridine, gives yields of 70–80%. NMR data, both ^1H and ^{13}C, show that in the ground state the rings in these spirourethanes do not interact. NMR investigation of glutaraldehyde isolated from water solution shows it to consist in Me_2SO of a 1:1 mixture of free dialdehyde and polymeric cyclic acetal. In contrast, periodate cleavage of 3,3-tetramethine-1,2-cyclopentanediol gives the monomeric cyclic acetal.

Dihydropyridines occupy a central position in metabolism (NAD–NADH oxidation–reduction system), and their analogues have been therapeutically useful in a variety of physiological disorders.[1,2] Also, these com-

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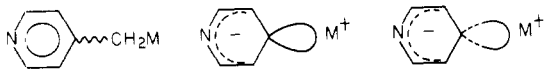
pounds are useful intermediates in heterocyclic synthesis.[3]

We have utilized salts of spirodihydropyridines as models of bridged dihydro aromatic anions.[4] In principle, these systems could exist in open (1), closed (2), or nonclassical (3) forms, and we have investigated the

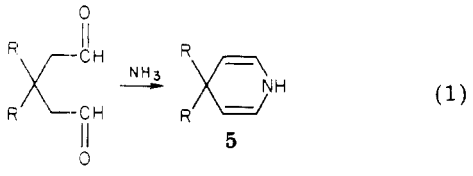


1 2 3

structures of such species by using NMR spectroscopy.[4,5] These spiro anions are readily accessible by cleavage of the corresponding stable *N*-acyl-1,4-dihydropyridines with organometallic compounds.[4] In the course of this work, it became necessary to develop efficient routes to prepare these starting materials. Most preparations of dihydropyridines either are modifications of the Hanzsch synthesis[6] or are metal hydride reductions of pyridinium salts.[3,7] Two recent preparations include the formation of 4-cyano-1,4-dihydropyridines[8] and the use of fragmentation reactions.[9] This paper describes our investigation of the condensation of glutaraldehydes with amine functions.[10] It will be shown how an acid-catalyzed condensation of glutaraldehydes with ethyl carbamate produces the required dihydropyridines in excellent yields.

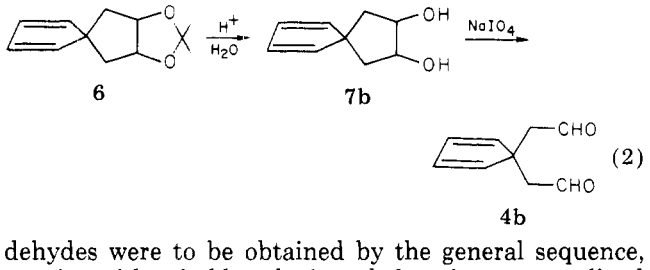
Results and Discussion

We first investigated a classical dihydropyridine synthesis, the condensation of ammonia with a suitably substituted glutaraldehyde (eq 1).[3,10] Glutaraldehyde



4 5 (1)

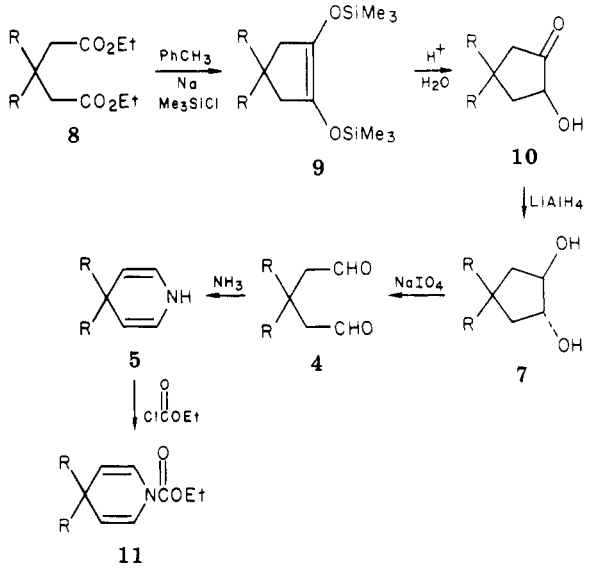
itself, **4a**, is commercially available, while **4b** was accessible by hydrolysis and cleavage of the ketal, as reported by Semmelhack, Katz, and Foos (eq 2).[11] The other al-



6 7b 4b (2)

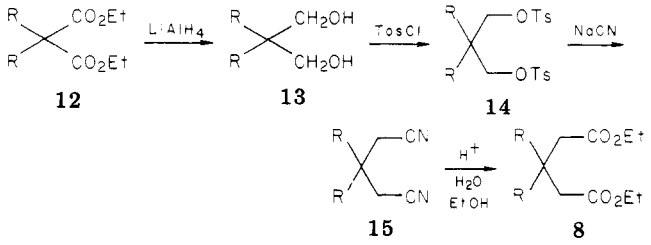
dehydes were to be obtained by the general sequence, starting with suitably substituted glutaric esters, outlined in Scheme I.

Scheme I



R, R = c, CH_3, CH_3; d-h, $(CH_2)_n$ (n = 2-6)

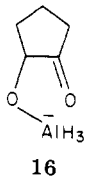
Scheme II



R, R = d, $(CH_2)_2$; e, $(CH_2)_3$

Where glutaric esters were not commercially available, these were obtained from the cycloalkane-1,1-dicarboxylic esters (see Seheme II). This series of reactions functioned smoothly (see Experimental Section). Note, however, that the conversion of ditosylate, **14**, to dinitrile, **15**, proceeds most conveniently by using phase-transfer conditions—"Aliquat 336" in benzene and potassium cyanide in water. The yields of these reactions are superior to those using the dimethyl sulfoxide procedure, and the reactions are easier to work up.

Concerning the steps which follow, in Scheme I, it is appropriate to comment on the reduction of the glutaroins. Kwart reported the lithium aluminum hydride reduction of glutaroin, **10c**, to give the trans diol **7c**.[12] The compound failed to give a cyclic ketal derivative. The reduction products of all the glutaroins reported in this work behaved in the same way and are assigned to be trans diols. Such a result need not be surprising since reducing agent probably bonds to the OH oxygen first, **16**. Then hydride



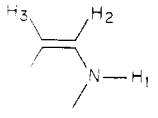
16

transfer to carbonyl carbon takes place from the side cis to the original OH, giving trans diol. In the reduction of alicyclic 2-keto alcohols by $LiAlH_4$, the two oxygens can be closer together and a cisoid intermediate ensues,[13]

(1) See S. P. Colowick, J. van Eys, and J. M. Park, *Enzymes*, **2** (1970).
(2) J. P. Kutney, *Heterocycles*, **7**, 593 (1977); R. E. Masingal and C. G. Skinner, *Arch. Biochem. Biophys.*, **169**, 443 (1975).
(3) A. Eisner and J. Kuthan, *Chem. Ber.*, **72**, 1 (1972), a review of dihydropyridine synthesis.
(4) G. Fraenkel, C. C. Ho, Y. Liang, and S. Yu, *J. Am. Chem. Soc.*, **94**, 4732 (1972).
(5) G. Fraenkel and J. W. Cooper, *J. Am. Chem. Soc.*, **93**, 7228 (1971).
(6) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds", Interscience, New York, 1962, p 163.
(7) F. W. Fowler, *J. Am. Chem. Soc.*, **94**, 5926 (1972); *J. Org. Chem.*, **37**, 1321 (1972).
(8) L. J. Winters, *Chem. Commun.*, 642 (1970).
(9) D. M. Stout, T. Takaya, and A. I. Meyers, *J. Org. Chem.*, **40**, 563 (1975).
(10) E. M. Kosower and T. S. Sorenson, *J. Org. Chem.*, **27**, 3764 (1962); M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1489 (1962).
(11) M. F. Semmelhack, J. S. Foos, and S. Katz, *J. Am. Chem. Soc.*, **95**, 7325 (1973).
(12) H. Kwart and J. A. Ford, *J. Org. Chem.*, **24**, 2060 (1959).

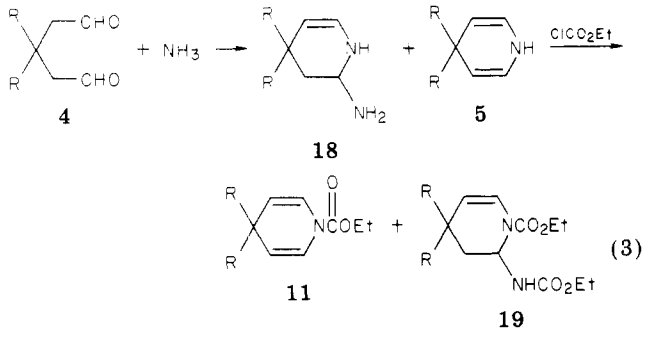
leading to cis diol. Such a cisoid intermediate would be energetically prohibited in the case of the glutaroins reported herein.

Sodium periodate cleavage of the *trans*-1,2-cyclopentanediols in THF–water was monitored, by using the NMR spectrum. The resonances of diol are replaced by multiplets at τ 0.0 and 7.4, J = 2.5 Hz, characteristic of the CH_2CHO moiety in glutaraldehydes as well as peaks for the glutaraldehyde hydrates at τ 4.9 and 8.3 (see below).[14] The aldehydes from this procedure were used without purification. In each case, the reaction mixture was extracted into ether and the extract concentrated. Typically, when 3,3-dimethylglutaraldehyde was allowed to react slowly with ammonia (method A), the aldehyde resonances were replaced by a triplet at τ 3.82 and a doublet at τ 5.37 (see Figure 1; vinylic hydrogens). This is due to the enamine moiety **17**, with J(1,2) and J(2,3)



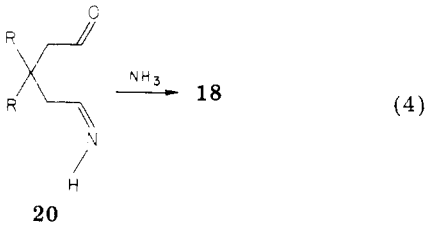
17

both ca. 8.0 Hz. Treatment of the crude products from these reactions with ethyl chloroformate gave only small yields of the expected *N*-carboethoxy-1,4-dihydropyridines, **11**, together with mainly 2-amino-1,2,3,4-tetrahydropyridines (equ 3).[15] Thus, it appears that the spectrum



(3)

in Figure 1 is the vinylic resonance of 3,3-dimethyl-1,2,3,4-tetrahydropyridine, **18c** (R = CH_3). Compounds **18** must have resulted from the intermediacy of immoaldehyde **20** (eq 4).



(4)

20

We next addressed the problem of improving the yield of the condensation–carboethoxylation step. Glutaraldehyde was chosen as a model compound. A sample of glutaraldehyde was obtained by fractionation of 50% glutaraldehyde in water. Two fractions of the glutaraldehyde were collected: one was diluted with ether, and both were stored at −10 °C for several days. At the end of this time, the neat sample had become a glass, and the NMR spectrum of the diluted sample showed broad peaks

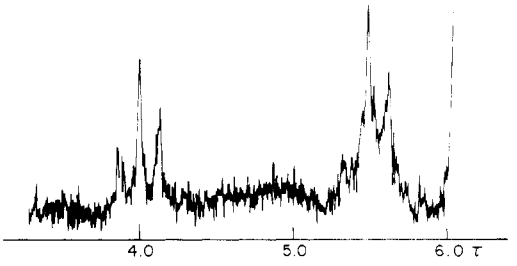
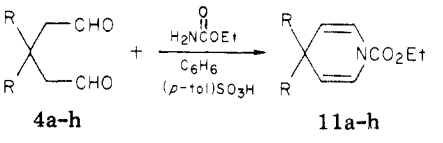


Figure 1. Proton NMR spectrum, 60 MHz, of mainly **18c**, the result of reacting 3,3-dimethylglutaraldehyde in ether with ammonia.

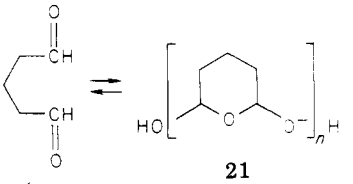
Scheme III



4a-h **11a-h**

R, R = a, H, H; b,  ; c, CH_3, CH_3; d-h, $(CH_2)_n$

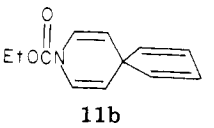
at τ 4.9 and 8.3 which have been assigned to the methine and methylene protons, respectively, of polymer **21**. The



4a **21**

mixture was ca. 1:1 dialdehyde to polymer as calculated from the methine proton resonance. We reasoned that it should be possible to condense ethyl carbamate directly with the glutaraldehyde mixture. The reaction could be catalyzed by acid since ethyl carbamate is not very basic. Finally, use of benzene to azeotrope out water would drive the reaction to completion. When the 1:1 glutaraldehyde mixture was treated with 1 mol equiv of ethyl carbamate in refluxing benzene containing a small amount of *p*-toluenesulfonic acid (method B), 1 mol equiv of water collected in the Dean–Stark trap within 1 h. NMR analysis of the residue after removal of benzene indicated nearly quantitative conversion to the *N*-carboethoxy-1,4-dihydropyridine, **11a**. Distillation of this product resulted in a loss of material and gave a yield of 60% (see Table I). No aminotetrahydropyridine, **19**, was detected in this reaction product (Scheme III).

Spirodiene dihydropyridine **11b** was prepared by a

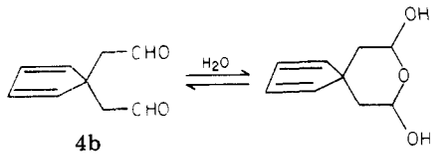


11b

similar procedure starting from ketal **6**. Without purifying any of the intermediates, we obtained a 15–20% yield of **11b**, the only compound in the series which decomposed to an unidentified tar on extended storage at 0 °C. The dialdehyde precursor of **11b** exists in a different form from that of glutaraldehyde. Potassium periodate cleavage of the diol, **7b**, gave (after extraction into ether, removal of solvent, and treatment with benzene) a colorless solid precipitate; mp 97–98 °C. This powdery solid has been assigned structure **22** on the basis of spectral data.

The presence of the diene and hydroxyl groups is confirmed by a λ_{max} of 249 nm (ϵ 2500) in the ultraviolet spectrum and by a broad O–H stretch at 3400 cm^{-1} in the

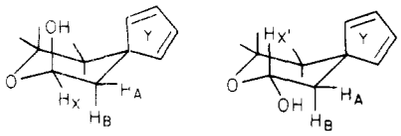
(13) H. O. House, "Modern Synthetic Reactions", 2nd ed., Wiley, New York, 1972, p 57.
(14) P. M. Hardy, A. C. Nichollas, and H. H. Rydon, *J. Chem. Soc., Perkin Trans. 2*, 2270 (1972).
(15) G. Fraenkel, C. C. Ho, H. Stucki, and Y. Liang, *Tetrahedron Lett.*, 300 (1978).



4b 22

IR spectrum, respectively. There is no molecular ion peak in the mass spectrum; however, a peak at m/e 150 (6%) corresponds to structure **23** (and **4b**) which requires only the loss of water, to be expected in the mass spectral environment. Peaks at m/e 108 (47%) and m/e 79 (100%) are rationalized in Scheme IV.

The ^{1}H NMR spectrum of the powder in Me_2SO-d_6 is shown at the bottom of Figure 2. The simplified spectrum after the addition of D_2O is shown above it. The AB part of an ABX system (see partial structures **22a** and **22b**)



22a 22b

centered at τ 8.8 is assigned to the methylene hydrogens. Two X resonances at τ 4.78 and 5.1, in a 3:1 ratio, representing equatorial and axial carbinyl hydrogens, respectively, evidence vicinal coupling constants of 3 and 5 Hz for X (equatorial) and 2.8 and 8 Hz for X′ (axial). From the spectrum (bottom, Figure 2), OH at τ 3.85 shows a value for J(X,OH) of 6.0 Hz. The spectrum clarifies in the expected manner on addition of D_2O to the Me_2SO-d_6 solution. Other solvents give much the same results with the exception that the OH shift varies, τ 4.95, in acetone-d_6. This foregoing partial analysis dose not reveal the relative proportions of the three possible stereoisomers which could be present in the mixture: diaxial cis, diequatorial cis, and diequatorial trans.

Hydrate **22**, like aldehyde **4b**, reacted smoothly with ethyl carbamate and catalytic amounts of toluenesulfonic acid in benzene to give the dihydropyridine **11b**. The acid-catalyzed condensation of glutaraldehydes with ethyl carbamate was applied to the preparation of a whole series of 4,4-spiro-1,4-dihydropyridines, **11a–h**. Cyclopentane-1,2-diols were cleaved with potassium periodate in water–THF, and the resulting dialdehyde was extracted into ether, as before. After removal of the solvent, the dialdehydes were used without further purification in the new condensation step. Table I lists physical data for the dihydropyridines together with a comparison of yields for reactions using the two different condensation procedures. Clearly, the acid-catalyzed reaction is the superior of the two, giving a conversion from diol to dihydropyridine of 70–80% with the exception of **11b** and **11d** which are also unstable compounds.

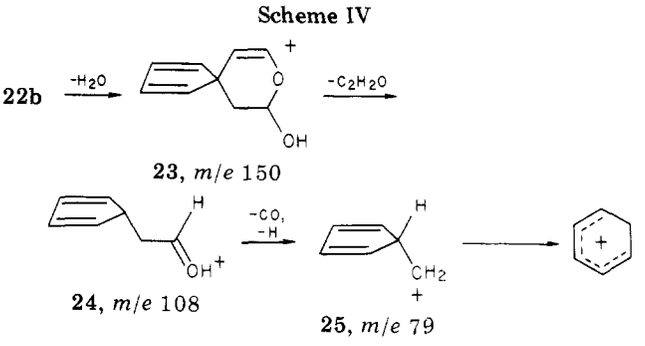
^{1}H and ^{13}C NMR data for the series of urethanes **11a–h** are collected in Tables II and III (see Figures 3 and 4). With the exceptions of R, R = $(CH_2)_2$ and $(CH)_4$, the vinylic proton shifts are very similar. The diene ring in **11b** causes proton shielding at H_3 and H_5 and deshielding at H_2 and H_6 relative to shifts in the other compounds. The bridging loops about the 4 position give proton NMR absorption (not resolved) centered quite close to the shifts for the corresponding cycloalkanes with the exception of the three-membered ring in **11d** which is deshielded with respect to cyclopropane by 0.38 ppm (see the last column in Table II).

In the proton-decoupled ^{13}C NMR spectra of urethanes **11a–h**, the higher field of the two vinylic resonances is always the broader line. Selective proton decoupling established the latter to represent C_3 and C_5.

Of the ^{13}C dihydropyridine ring shifts in **11a–h** (Table III), those for C_2 and C_6 lie in the region 120–124 ppm (measured from Me_4Si) while those for C_3 and C_5 stand around 113–114 ppm with the exception of the shift for C_3 and C_5 in **11b** [R, R = $(CH)_4$] which is 106 ppm, shielded with respect to the others.

Assignments for the spiroalkane ^{13}C shifts in the urethanes were accomplished by use of a combination of intensity ratios and the known alteration of shifts in substituted cycloalkanes and spiroalkanes[16] together with

Scheme IV



22b 23, m/e 150 24, m/e 108 25, m/e 79

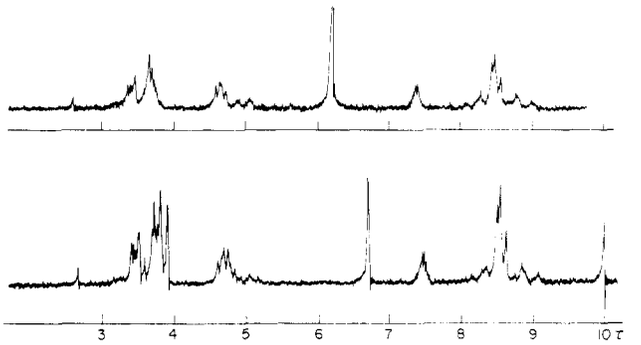


Figure 2. Proton NMR spectra, 60 MHz, of spirodiene acetal **22**: (top) in Me_2SO-d_6 + D_2O; (bottom) in Me_2SO-d_6.

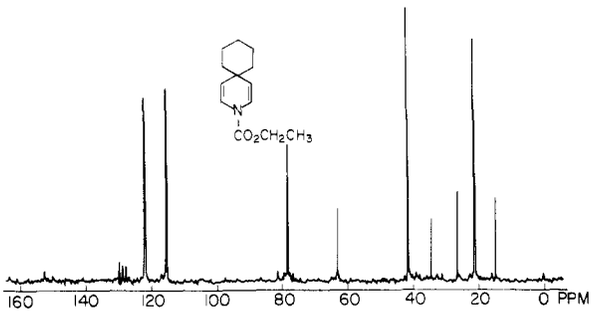


Figure 3. Carbon-13 NMR spectrum, 22.63 MHz, of *N*-carboethoxy-4,4-pentamethylene-1,4-dihydropyridine in $CDCl_3$ with respect to Me_4Si at 40 °C.

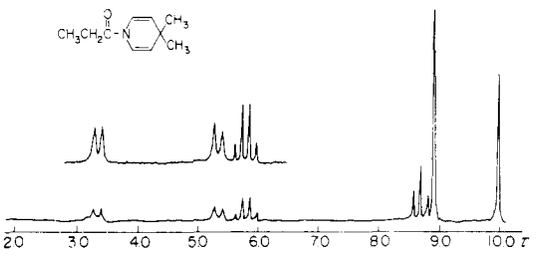


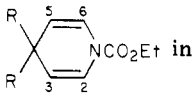
Figure 4. Proton NMR spectrum, 90 MHz, of *N*-carboethoxy-4,4-pentamethylene-1,4-dihydropyridine in $CDCl_3$ at 40 °C.

(16) D. Zimmerman, R. Ottinger, J. Reisse, H. Christol, and J. Brugidon, *Org. Magn. Reson.*, **6**, 346 (1974).

Table I. 1-Carboethoxy-4,4-disubstituted-1,4-dihydropyridines (11)

compd	R, R	yield, % A	yield, % B	bp, °C (torr)	m/e[a]	analysis[a] C	analysis[a] H	analysis[a] N	ν(C-O),[b] cm⁻¹	λmax,[c] nm (ε)
11a	H, H	5	60	52 (0.12)	153.07896				1700	228 (1.8 × 10⁴)
					153.07922					
11b	$(CH)_4$	2	25	100 (0.02)	203.09460				1725	225 (2.6 × 10⁴)
					203.09481					
11c	CH_3, CH_3	14	76	64-70 (0.44)	181.23655	66.27	8.34	7.73	1700	
					181.23679	66.15	8.17	7.74		
11d	$(CH_2)_2$		15	85-95 (0.08)	179.09460				1715	239 (2.4 × 10⁴)
					179.09484					
11e	$(CH_2)_3$	5	70	78-82 (0.15)	165.07897[d]	68.37	8.82	7.25	1720	233 (1.1 × 10⁴)
					165.07914	68.23	8.65	7.26		
11f	$(CH_2)_4$	13	72	85-90 (0.07)	207.12590	69.54	8.27	6.76	1710	232 (1.3 × 10⁴)
					207.12621	69.17	7.74	7.23		
11g	$(CH_2)_5$	19	80	97-100 (0.2)	221.14157	70.55	8.65	6.33	1700	230 (1.74 × 10⁴)
					221.14197	70.13	8.60	5.89		
11h	$(CH_2)_6$	24	75	100-130 (0.3)	235.15722	71.45	8.99	5.95	1725	230 (1.77 × 10⁴)
					235.15749	71.72	9.11	5.78		

[a] Calculated values are listed above observed values for each compound given. [b] Film on KBr plates. [c] Isooctane. [d] M^+ − ethylene.

Table II. Proton NMR Data for  in $CDCl_3$

	R, R	shift, τ 2,6	shift, τ 3,5	shift, τ R_1,R_2	J(2,3), Hz	$(CH_2)_n$[a]
11a	H, H	3.36	5.25	7.14 m	8.5	
11b	$(CH)_4$	3.00	5.67	3.76 m	8.0	
11c	$(CH_3)_2$	3.38	5.37	8.95 s	8.0	
11d	$(CH_2)_2$	3.27	5.72	9.40 s	8.0	9.78
11e	$(CH_2)_3$	3.30	4.90	8.03 m	8.0	8.04
11f	$(CH_2)_4$	3.27	5.17	8.40 m	8.0	8.49
11g	$(CH_2)_5$	3.28	5.17	8.56 m	8.0	8.54
11h	$(CH_2)_6$	3.31	5.11	8.47 m	8.0	8.46

[a] Proton shift for cycloalkane of same size as saturated ring in urethane.

the observation that the most distant carbons from a substituent in a cycloalkane most closely approach the carbon shift of the unsubstituted cycloalkane.

^{13}C NMR shifts in cycloalkanes and spiroalkanes have been correlated from linearly additive contributions at different positions due to geminal or spiro substitution.[16] The numbering around the loop about C_4 in **11** is α (4), β, γ, etc., where α (4) is the spiro carbon. Table IV lists these ^{13}C shift contributions for a variety of structures. These parameters are used to qualitatively predict shifts in the spirourethanes (see Table V). The basic ^{13}C NMR shifts for the 4,4 loops were taken to be those of the corresponding cycloalkanes or, for **11b**, of cyclopentadiene. This procedure is necessarily approximate and gives only tentative assignments. However, in each case, a pattern of shifts is seen in the spectrum quite close to that predicted. We are assuming that the alternating arrangement of shifts in spiroalkanes carries over to the spirodihydropyridines. In the case of **11h**, the assignments were made by analogy to shifts in methylcycloheptane.[17]

Finally, it should be mentioned that, for all the spirourethanes reported herein, the carbons in the second ring symmetrically disposed about C_4, e.g., β and β′, are also magnetically equivalent. This equivalence persists to −100 °C. Since puckering about C_4 should induce substantial shifts between C_β and $C_{\beta'}$, one may conclude these dihydropyridines are planar. Further ring flipping should be slow by −100 °C.

Altogether, the NMR data strongly suggest that in their ground states the rings in these urethanes do not interact, with the possible exception of **11b**. The different moieties in these urethanes display very similar NMR parameters. The chemical behavior of these compounds will be described later.

Experimental Section

General Details. 3,3-Dimethyl-, 3,3-tetramethylene-, and 3,3-hexamethyleneglutaric acids were obtained from Aldrich Chemical Co. Elemental analyses were carried out by Galbraith Laboratories and by Scandinavian Analytical Laboratories. Proton NMR spectra were obtained by using Varian HA-100, Varian A-60-A, and Bruker HX-90 spectrometers. ^{13}C NMR was accomplished with the Bruker HX-90 instrument operating at 22.63 MHz in the FT mode. The solvent for NMR samples reported below was $CDCl_3$. Ultraviolet spectra were determined with a Cary Model 14 spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer Infracord.

Bis(*p*-toluenesulfonate) of Cyclopropane-1,1-dimethanol (14d). In an improved procedure, *p*-toluenesulfonyl chloride (260 g, 1.35 mol) was added in portions to a well-stirred solution of 1,1-cyclopropanedimethanol (56 g, 0.64 mol) in pyridine (350 mL) at 0 °C. After the addition was complete, the mixture was kept at 0 °C overnight. Dilution with water resulted in the separation of the ditosylate which was collected and dried. Recrystallization from acetone–water gave colorless crystals (240 g, 92%), mp 112–114 °C (lit.[18] mp 114 °C).

Cyclopropane-1,1-diacetonitrile (15d). In an improved procedure, a mixture of the ditosylate (82 g, 0.2 mol) in benzene (300 mL), potassium cyanide (78 g, 1.2 mol) in water (200 mL), and "Aliquat 336" was stirred at reflux for 16 h. The solution was cooled, diluted with water, and extracted with four 200-mL portions of methylene chloride. The organic extracts were combined, washed with water and saturated sodium chloride solution, and dried with magnesium sulfate. Removal of the solvent and distillation of the residue gave 20.5 g of dinitrile in 85% yield; bp 95–97 °C (0.1 torr) (lit.[18] bp 140 °C (11 torr)).

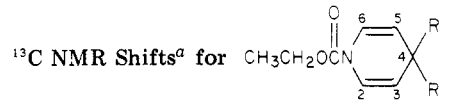
Cyclopropane-1,1-diacetic Acid. Cyclopropane-1,1-diacetonitrile (15 g, 0.125 mol) was boiled with 20% potassium hydroxide solution (200 mL). After 48 h, the mixture was cooled and poured onto ice. After acidification, the solution was extracted with ethyl acetate, dried, and evaporated to give the crude acid, 158 g in 80% yield; mp 107–108 °C (lit.[19] mp 105 °C).

1,1-Cyclobutanedimethanol (13e). Methyl 1,1-cyclobutanedicarboxylate (100 g, 0.58 mol) in 500 mL of ether was

(17) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).

(18) B. Chambraux, Y. Etienne, and R. Palland, *C. R. Hebd. Seances Acad. Sci.*, **254**, 313 (1962).

(19) H. Wertkamp, H. Hasserodt, and F. Korte, *Chem. Ber.*, **95**, 2280 (1962).

Table III. ^{13}C NMR Shifts[a] for  (11) in $CDCl_3$

	R, R	C_2	C_3	C_4[b]	CO	OCH_2	CH_3	β[c]	γ	δ
a	H, H	123.7	105.9	22.5	151.5	62.3	14.5			
b	$(CH)_4$	124.0	106.2	54.1	151.5	62.5	14.5	147.3	130.1	
c	CH_3, CH_3	120.3	115.9	30.8	151.5	62.3	14.5	32.5		
d	$(CH_2)_2$	123.2	113.9	18.7	151.3	62.4	14.5	19.0		
e	$(CH_2)_3$	120.3	114.8	37.7	151.3	62.4	14.5	40.0	14.9	
f	$(CH_2)_4$	120.1	114.8	41.3	151.4	62.3	14.5	44.6	24.1	
g	$(CH_2)_5$	120.6	114.3	33.9	151.4	62.3	14.5	40.8	20.7	25.9
h	$(CH_2)_6$	119.5	115.8	36.4	151.6	62.3	14.5	44.3	30.3	22.0

[a] Shifts in ppm from tetramethylsilane. [b] Spiro carbon C_4 or α. [c] R, R loop, numbered from spiro, α, β, γ.

Table IV. Contributing Geminal and Shiro Substitution to ^{13}C Shifts (ppm) in Cycloalkanes

effect of	on	α	β	γ	δ
gem dimethyl	cyclohexane	3.2	12.8	−4.4	−0.3
$(CH_2)_4$	cyclohexane	15.3	13.0	−2.2	
$(CH_2)_5$	cyclohexane	5.5	10.2	−5.2	0.0
$(CH_2)_4$	cyclopentane	19.2	15.0	−0.9	
$(CH_2)_5$	cyclopentane	11.4	12.7	−0.2	0.0

placed in a 5-L flask containing 2.5 L of refluxing ether and 38 g of lithium aluminum hydride. The mixture was refluxed for 18 h and quenched with a saturated solution of sodium sulfate. The mixture was filtered and dried with anhydrous magnesium sulfate. After removal of solvent, 59 g of **13e** was obtained (87% yield): NMR τ 8.20 (s, 6 H), 6.40 (s, 4 H), 5.54 (s, 2 H).

1,1-Bis(hydroxymethyl)cyclobutanediyl Bis(*p*-toluenesulfonate) (14e). Into a 1-L Morton flask containing a solution of 1,1-cyclobutanedimethanol (59.0 g, 0.50 mol) in 400 mL of pyridine at 0 °C was added *p*-toluenesulfonyl chloride (285 g, 1.5 mol) during 1.5 h. The reaction mixture was stirred for an additional 4 h and then poured into a 4-L beaker which was immersed in an ice bath. While the mixture was stirred, a solution, prepared by adding 2 kg of ice to 600 mL of concentrated hydrochloric acid, was slowly added to the reaction mixture. The mixture was then filtered and the product recrystallized from 1 L of methanol to give 199.5 g of **14e** in 94% yield: mp 93–94 °C; NMR τ 8.20 (s, 6 H), 7.60 (s, 6 H), 6.07 (s, 4 H), 2.75 (d, 4 H), 2.37 (d, 4 H).

1,1-Bis(cyanomethyl)cyclobutane (15e). Into a 1-L flask containing potassium cyanide (122 g, 1.88 mol) in 300 mL of dimethyl sulfoxide was added 1,1-bis(hydroxymethyl)cyclobutanediyl bis(*p*-toluenesulfonate) (100 g, 0.235 mol), and the reaction mixture was stirred for 10.5 h at 90 °C. Three 10-mL portions of the reaction mixture were each added to 1 L of water. The three aqueous solutions were then extracted three times with 300-mL portions of ether. The ethereal extracts were combined, concentrated, and washed with a total volume of 400 mL of water. The ether was dried with anhydrous magnesium sulfate and removed, to give 24 g of **15e** in 94% yield: NMR τ 7.97 (s, 6 H), 7.40 (s, 4 H); IR 2940, 2260 cm^{-1}. The procedure was repeated on the crude product to convert any unreacted ditosylate to dinitrile.

Ethyl 3,3-Trimethyleneglutarate (8e). To a stirred solution of 63 g of potassium hydroxide in 300 mL of water was added 1,1-bis(cyanomethyl)cyclobutane (29.4 g, 0.22 mol). The reaction mixture was refluxed for 43 h, and then Norite was added. The solution was filtered and acidified to pH 1 with concentrated hydrochloric acid. The diacid was collected, dried, and added to a solution of 450 mL of benzene, 200 mL of ethanol, and 3 g of concentrated sulfuric acid. This solution was refluxed for 24 h while the removal of water was accomplished by using a Dean–Stark trap. After the removal of solvent, water was added, and the mixture was extracted with ether. The ethereal extracts were washed with water, a saturated solution of potassium carbonate, and a saturated solution of sodium chloride. The ether was concentrated and filtered through anhydrous magnesium sulfate. After removal of solvent, 25.7 g of **8e** was obtained in 52% yield: bp 80–82 °C (0.5 torr); NMR τ 8.8 (t, 6 H), 8.07 (d, 6 H), 7.40 (s, 4 H), 5.95 (q, 4 H).

Glutarate Esters. A solution of the substituted glutaric acid (0.25 mol) and 4 mL of concentrated sulfuric acid in 300 mL of absolute alcohol or methanol was refluxed for 24 h. Alcohol was removed and the residue diluted with water (600 mL). The mixture was extracted with ether, and the ether extracts were washed with 10% sodium bicarbonate, water, and saturated sodium chloride solution. After the extracts were filtered through anhydrous magnesium sulfate, the solvent was evaporated. Distillation under reduced pressure gave the esters as colorless liquids.

Table V. ^{13}C NMR Shifts (ppm) in Urethanes Compared with Predicted Values[a]

	α		β		γ		δ	
compd	calcd	obsd	calcd	obsd	calcd	obsd	calcd	obsd
11b	53.0	54.1	145.5	147.3	132.0	130.1		
11f	37.7	41.3	39.0	44.6	26.1	24.1		
11g	32.9	33.9	37.6	40.8	21.9	20.7	27.4	25.9

[a] Cycloalkane shifts taken from J. J. Burke and P. C. Lauterbuhr, *J. Am. Chem. Soc.*, **86**, 1870 (1964); cyclopentadiene shifts from ref 11.

Table VI. $J(^{13}C,H)$ (Hz) Directly Bonded in *N*-Carboethoxy-4-spiro-1,4-dihydropyridines, 40 °C

$(CH_2)_n$	ethoxy		dihydropyridine		cycloalkane		
n	CH_2	CH_3	CH_2	CH_3	β	γ	δ
2	146.2	125.7	180.7	169.7	162.3		
2		147.7[b]	188.0[b]	163.6[b]	161.7[b]		
3	144.0	126.9	183.1	163.6	137.3	133.7	
4	149.0	127.4	181.9	158.7	129.9	129.9	
5	147.7	125.7	184.3	162.3	128.2	130.0	121.5
6	150.2	125.0	184.3	155.0	126.3	125.7	135.8

[a] $CHCl_3$ solutions. [b] *N*-Carbomethoxy derivative, OCH_3.

Dimethyl 3,3-Dimethylglutarate (8c). From 3,3-dimethylglutaric acid (40 g, 0.25 mol) there was obtained 19.3 g of dimethyl 3,3-dimethylglutarate in 41% yield: bp 70 °C (0.14 torr) (lit.[20] bp 111 °C (20 torr)); NMR τ 8.9 (s, 6 H, *gem* dimethyls), 7.58, (s, 4 H, CH_2), 6.37 (s, 6 H, OCH_3).

Diethyl 3,3-Dimethyleneglutarate (8d). From 3,3-dimethyleneglutaric acid (39.5 g, 0.25 mol) there was obtained 42.8 g of the title compound in 80% yield: bp 70–75 °C (0.07 torr); NMR τ 9.47 (s, 4 H, cyclopropyl), 8.77 (t, 6 H, CH_3), 7.62 (s, 4 H, CH_2), 5.89 (q, 4 H, OCH_2).

Dimethyl 3,3-Tetramethyleneglutarate (8f). The corresponding dicarboxylic acid (46.5 g, 0.25 mol) reacted with methanol to give 48.2 g of the title diester in 90% yield: bp 98–99 °C (0.79 torr) (lit.[20] bp 141 °C (17 torr)); NMR τ 8.4 (s, 8 H, cyclopentyl), 7.5 (s, 4 H, CH_2), 6.4 (s, 6 H, OCH_3).

Dimethyl 3,3-Pentamethyleneglutarate (8g). A sample of the diacid (50 g, 0.25 mol) reacted with methanol to give 52.4 g of the title diester in 92% yield: bp 90–95 °C (0.7 torr) (lit.[20] bp 159 °C (21 torr)); NMR τ 8.54 (s, 10 H, cyclohexyl), 7.53 (s, 4 H, CH_2), 6.41 (s, 6 H, OCH_3).

Diethyl 3,3-Hexamethyleneglutarate (8h). The corresponding diacid (53.5 g, 0.25 mol) treated as described above gave 65.5 g of the title compound in 97% yield: bp 118–120 °C (1 torr); NMR τ 8.77 (t, 6 H, $OCH_2\mathbf{CH_3}$), 8.48 (m, 12 H, cycloheptyl), 7.55 (s, 4 H, CH_2), 5.93 (q, 4 H, $\mathbf{OCH_2}CH_3$).

Bis(trimethylsiloxy)alk-2-enes. Sodium (10.2 g, 0.44 g-atom) was dispersed in 700 mL of refluxing toluene in a 2-L Morton flask, by using a Hirschberg stirrer. At reflux, trimethylchlorosilane (55 g, 0.49 mol) was syringed in as rapidly as possible. Then the substituted glutarate ester (0.081 mol) in 150 mL of toluene was added over a period of 4 h. After refluxing for an additional 12 h, the mixture was cooled and filtered through Celite. Evaporation of solvent followed by distillation gave the siloxyalkenes as colorless liquids.

4,4-Dimethyl-1,2-bis(trimethylsiloxy)cyclopent-1-ene (9c). From dimethyl 3,3-dimethylglutarate (17.3 g, 0.081 mol), following the above acyloin reaction procedure, there was obtained 18 g of the title compound in 82% yield: bp 58–60 °C (0.5 torr; NMR τ 9.8 (s, 18 H, trimethylsiloxy), 8.9 (s, 6 H, *gem* dimethyls), 7.95 (s, 4 H, CH_2).

2,3-Bis(trimethylsiloxy)spiro[2.4]hept-2-ene (9d). From diethyl 3,3-dimethyleneglutarate (17.34 g, 0.081 mol) there was obtained 18 g of the title compound in 82% yield: bp 77–80 °C (0.5 torr); *m/e*(obsd) 270.14750, *m/e*(calcd) 270.14710; NMR τ 9.8 (s, 18 H, trimethylsiloxy), 9.53 (s, 4 H, cyclopropyl), 7.77 (s, 4 H, CH_2).

2,3-Bis(trimethylsiloxy)spiro[3.4]oct-2-ene (9e). From diethyl 3,3-trimethyleneglutarate (18.5 g, 0.081 mol) there was obtained 18.4 g of the title compound in 80% yield: bp 55–57 °C (0.3 torr); *m/e*(obsd) 284.16310, *m/e*(calcd) 284.16277; NMR τ 9.87 (s, 18 H, trimethylsiloxy), 8.14 (m, 8 H, cyclobutyl), 7.9 (s, 4 H, CH_2).

2,3-Bis(trimethylsiloxy)spiro[4.4]non-2-ene (9f). From dimethyl 3,3-tetramethyleneglutarate (17.3 g, 0.081 mol) there ensued 22.7 g of the title compound in 94% yield: bp 109–111 °C (7 torr); *m/e*(obsd) 298.1787, *m/e*(calcd) 298.17842; NMR τ 9.89 (s, 18 H, trimethylsiloxy), 8.47 (m, 8 H, cyclopentyl), 7.9 (s, 4 H, CH_2).

2,3-Bis(trimethylsiloxy)spiro[4.5]dec-2-ene (9g). From the improved procedure from 3,3-pentamethyleneglutarate (18.5 g, 0.081 mol) there was obtained 23.6 g of the title compound in 93% yield: bp 78–80 °C (0.1 torr); *m/e*(obsd) 312.19246, *m/e*(calcd) 312.19407; NMR τ 9.87 (s, 18 H, trimethylsiloxy), 8.54 (s, 10 H, cyclohexyl), 7.99 (s, 4 H, CH_2).

2,3-Bis(trimethylsiloxy)spiro[4.6]undec-2-ene (9h). From diethyl 3,3-hexamethyleneglutarate (21.9 g, 0.081 mol) there ensued 18.5 g of the title compound in 70% yield: bp 100–105 °C (0.1 torr); *m/e*(obsd) 326.21017, *m/e*(calcd) 326.20972; NMR τ 9.87 (s, 18 H, trimethylsiloxy), 8.5 (s, 12 H, cycloheptyl), 7.98 (s, 4 H, CH_2).

Glutaroins (10). A stirred solution containing the siloxy-2-alkene (0.065 mol) and 5 mL of 1 N hydrochloric acid in tetrahydrofuran (200 mL) was refluxed for 3 h. After the solution was cooled, calcium carbonate was added. The reaction mixture was filtered and solvent removed by rotary evaporation. The remaining liquid was distilled, giving the glutaroins listed below.

3,3-Dimethylglutaroin (10c). Following the general procedure above, hydrolysis of **9c** (17.65 g, 0.065 mol) yielded 6.7 g of 3,3-dimethylglutaroin: 80%, bp 60–67 °C (1.2 torr) (lit.[12] bp 68–70 °C (2 torr)); *m/e* 128; IR 1750, 3400 cm^{-1}; NMR τ 8.87 and 8.83 (2 s, 6 H, CH_3), 8.32 (m, 2 H, CH_2CO), 7.84 (m, 1 H, $\mathbf{CH_2}CHOH$), 5.71 (m, 2 H, **CH**OH).

3,3-Dimethyleneglutaroin (10d). Hydrolysis of **9d** (17.50 g, 0.005 mol) gave 4.9 g of 3,3-dimethyleneglutaroin, a yellow oil, in 60% yield: bp 66–70 °C (0.08 torr); *m/e*(obsd) 126.06832, *m/e*(calcd) 126.06807; IR 1750, 3400 cm^{-1}; NMR τ 9.4 (s, 4 H, cyclopropyl), 8.9 (m, 2 H, CH_2CHOH), 7.8 (m, 2 H, CH_2CO), 6.17 (br, 1 H, OH), 5.58 (m, 1 H, **CH**OH).

3,3-Trimethyleneglutaroin (10e). Hydrolysis of **9e** (18.5 g, 0.065 mol) gave 8.7 g of 3,3-trimethyleneglutaroin, a yellow oil, in 96% yield: bp 54–55 °C (0.05 torr); *m/e*(obsd) 140.08390, *m/e*(calcd) 140.08370; IR 1750, 3400 cm^{-1}; NMR τ 7.89 (m, 8 H, cyclobutyl and $\mathbf{CH_2}CHOH$), 7.6 (m, 2 H, CH_2CO), 6.00 (m, 1 H, **CH**OH), 4.75 (br s, 1 H, CH**OH**).

3,3-Tetramethyleneglutaroin (10f).[21] Via the above improved procedure, hydrolysis of **9f** (19.4 g, 0.065 mol) gave 9.2 g of the title compound, a yellow oil, in 92% yield: bp 75–78 °C (3 torr); *m/e* 154; IR 1790, 3380 cm^{-1}; NMR τ 8.3 (m, 10 H, cyclopentyl and $\mathbf{CH_2}CHOH$), 7.7 (m, 2 H, CH_2CO), 6.0 (br s, OH), 5.72 (m, 1 H, **CH**OH).

3,3-Pentamethyleneglutaroin (10g).[22] Via the improved hydrolysis, **9g** (20.3 g, 0.065 mol) gave 9.8 g of 3,3-pentamethyleneglutaroin, a colorless oil, bp 85–88 °C (0.2 torr), in 90% yield: *m/e*(obsd) 168.11527, *m/e*(calcd) 168.11502; IR 1750, 3400 cm^{-1}; NMR τ 8.54 (m, 10 H, cyclohexyl), 7.91 (s, 2 H, CH_2CO), 7.82 (m, 2 H, $\mathbf{CH_2}CHOH$), 5.79 (m, 2 H, **CH**OH).

3,3-Hexamethyleneglutaroin (10h). Hydrolysis of **9h** (21.2 g, 0.065 mol) gave 9.5 g of the title compound, a colorless oil, in 80% yield: bp 100–110 °C (0.5 torr); *m/e*(obsd) 182.13069, *m/e*(calcd) 182.13067; IR 1850, 3400 cm^{-1}; NMR τ 8.45 (m, 12 H, cycloheptyl), 7.83 (m, 4 H, CH_2), 5.83 (m, 1 H, **CH**OH), 5.67 (br s, 1 H, OH).

(1,1-Disubstituted)cyclopentane)-3,4-*trans*-diols (7). A solution of the glutaroin (0.064 mol) was slowly added to a suspension of lithium aluminum hydride (2.4 g, 0.065 mol) in 100 mL of tetrahydrofuran. After the reaction mixture was allowed to reflux for 12 h, the mixture was cooled and carefully treated with saturated sodium sulfate solution. Filtration followed by concentration caused part of the diols to crystallize. The crystals were collected, and the filtrate was evaporated to dryness. Distillation of the residual oil gave additional quantities of the diols as white solids. The diols **7d** and **7e** were obtained via lithium aluminum hydride reduction in dioxane instead of tetrahydrofuran.

1,1-Dimethylcyclopentane-3,4-diol (7c). From the reaction of 3,3-dimethylglutaroin (8.2 g, 0.064 mol) with lithium aluminum hydride (see general method) there was obtained 5.8 g of diol in 70% yield: mp 95–95 °C (lit.[12] mp 96–97 °C); *m/e*(obsd) 130.09955, *m/e*(calcd) 130.09937; NMR τ 8.92 (s, 6 H, CH_3), 8.28 (m, 4 H, CH_2), 6.49 (br s, 2 H, OH), 5.95 (m, 2 H, **CH**OH).

Cyclopropanespirocyclopentane-3,4-diol (7d). This compound was obtained in 90% yield, 7.5 g, by the lithium aluminum hydride reduction of **10d** (8.1 g, 0.064 mol). The product was used without distillation: NMR τ 0.43 (s, 4 H, cyclopropyl), 1.80 (m, 4 H, CH_2), 3.67 (br s, 2 H, OH), 4.17 (m, 2 H, **CH**OH).

Cyclobutanespirocyclopentane-3,4-diol (7e). The reduction of 3,3-trimethyleneglutaroin (9.0 g, 0.064 mol) gave 8.2 g of an oil whose properties were consistent with the structure of the title compound, but which could not be crystallized and was unstable to heat. The yield was 90%: NMR τ 8.17 (m, 10 H, cyclobutyl and CH_2), 6.15 (m, 2 H, **CH**OH), 5.75 (br s, 2 H, OH).

Cyclopentanespirocyclopentane-3,4-diol (7f). The glutaroin

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10f (9.9 g, 0.064 mol) was reduced to give 7.8 g of the title compound in 78% yield: mp 102–103 °C; *m/e*(obsd) 156.11522, *m/e*(calcd) 156.11501; IR 3450 cm^{-1}; NMR τ 8.42 (s, 8 H, cyclopentyl), 8.18 (m, 4 H, CH_2), 5.98 (br s, 2 H, OH), 5.65 (m, 2 H, CHOH).

Cyclohexanespirocyclopentane-3,4-diol (7g). Reduction of glutaroin **10g** (10.8 g, 0.064 mol) produced 8.4 g of the title compound in 77% yield: mp 122–123 °C; *m/e*(obsd) 170.13101, *m/e*(calcd) 170.13061; IR 3300 cm^{-1}; NMR τ 8.62 (s, 10 H, cyclohexyl), 8.04 (m, 4 H, CH_2), 6.88 (br s, 2 H, OH), 6.26 (2 H, CHOH).

Cycloheptanespirocyclopentane-3,4-diol (7h). Reduction of glutaroin **10h** (11.7 g, 0.064 mol) gave 10.7 g of the title compound in 90% yield: mp 149 °C; *m/e*(obsd) 184.66100, *m/e*(calcd) 184.14632; NMR τ 8.5 (m, 16 H, cycloheptyl and CH_2), 6.25 (m, 2 H, CHOH), 5.9 (br s, 2 H, OH).

Glutaraldehydes. A suspension of sodium *m*-periodate (0.039 mol) in 250 mL of water was allowed to stir with cyclopentanediol (0.037 mol) dissolved in 75 mL of tetrahydrofuran for 24 h at room temperature. The mixture was saturated with sodium chloride and extracted with ether. The ether extracts were dried over magnesium sulfate, concentrated by evaporation of solvent, and used for the next step without further purification. NMR of the ether extract showed a doublet ($J \approx 2.5$ Hz) around τ 6.4–7.4 and a triplet at τ 0.0–0.3, characteristic of glutaraldehydes.

1,4-Dihydropyridines. Method A. Anhydrous ammonia was slowly bubbled through the ethereal solution containing the substituted glutaraldehyde from the previous procedure. NMR analysis of this reaction mixture indicated the glutaraldehyde to be replaced by a substance with resonances at τ 3.82 and 5.37. A syringe was used to add ethyl chloroformate (4.5 mL, 0.04 mol) over a 20-min period. The mixture was stirred overnight, and then an additional 4 mL of ethyl chloroformate was added with stirring for 1 h. The mixture was hydrolyzed with water, and the ether layer was washed with water and dried over anhydrous magnesium sulfate. Removal of ether left an oil which was distilled to give a lower boiling fraction consisting of the expected *N*-carboethoxy-1,4-dihydropyridine and a higher boiling fraction containing the *N,N'*-dicarboethoxy derivative of the corresponding 2-amino-1,2,3,4-tetrahydropyridine.

1,4-Dihydropyridines. Method B. The ether solution containing dialdehyde from the cleavage of 0.037 mol of diol was evaporated to dryness and the residue dissolved in 150 mL of benzene. Ethyl carbamate (2.96 g, 0.037 mol) and *p*-toluenesulfonic acid (0.2 g) were added, and the mixture was refluxed in a round-bottomed flask fitted with a Dean–Stark trap. When the expected amount of water had collected, benzene was evaporated under reduced pressure, and the resulting dihydropyridines were distilled as colorless liquids (Tables I and II).

***N*-Carboethoxy-1,4-dihydropyridine (11a).** A solution was prepared consisting of 5.5 g of glutaraldehyde–glutaraldehyde polymer (1:1) and 4.9 g of ethyl carbamate in 200 mL of benzene. The solution was refluxed under argon in a round-bottomed flask fitted with a Dean–Stark trap. No water was produced after 1.5 h of reflux. At that time, 100 mg of *p*-toluenesulfonic acid was added. After 1 h of continued reflux, 1.5 mL of water had collected in the trap. The solution was allowed to cool and concentrated under reduced pressure to give 8.2 g of **11a** in 98% conversion. Distillation of 53 °C (0.05 torr) gave 5 g of pure **11a**: NMR τ 3.36 (d, 2 H, CHN), 5.25 (m, 2 H, CHCHN), 5.82 (q, 2 H, CH_2CH_3), 7.18 (q, 2 H, CH_2), 8.72 (t, 3 H, CH_3).

Spirodiene Dialdehyde Hydrate 22. A mixture of crude spiro diol (1.2 g, 7.9 mol) and potassium periodate (1.9 g, 8.2 mmol) were added to 60 mL of a 1:1 solution of water–tetrahydrofuran with stirring for 24 h at room temperature. The mixture was extracted with ether and the combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Upon the addition of benzene to the residue, a white solid separated which was washed with benzene and dried to give 0.59 g in 44% yield of **22**; mp 97–98.5 °C.

Spirodihydropyridine-4,1'-2,4-pentadiene, 11b. A solution of spiro ketal **6** (2 g, 10.4 mmol) and 10 mg of *p*-toluenesulfonic acid in 35 mL of methanol, plus 5 mL of water, was reduced under a sweep of argon to approximately one-third the starting volume over a period of 1.5 h. Saturated sodium bicarbonate was added to the residue which was extracted three times with ether; total volume 200 mL. The combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 1.65 g of crude spiro diol **7b**.

The crude spiro diol was dissolved in 60 mL of tetrahydrofuran–water (1:1) and potassium periodate was added (2.5 g, 10.9 mmol). The mixture was allowed to stir at room temperature for 36 h, during which time an additional 1.5 g of potassium periodate and 60 mL of water were added. Sodium chloride was added to the reaction mixture which was extracted with ether. The combined ether extracts were dried, concentrated under reduced pressure, and used immediately in the condensation with ethyl carbamate.

The crude dialdehyde **4b** from the previous step was dissolved in 200 mL of benzene to which was added ethyl carbamate (0.7 g, 7.9 mmol) and 100 mg of *p*-toluenesulfonic acid. The solution was heated in a round-bottomed flask fitted with a Dean–Stark trap for 45 min at reflux. At the end of that time, the solution was allowed to cool and the benzene removed under reduced pressure. Ether was added to this residue, and the ether solution was washed with water containing 0.6 g of sodium bicarbonate and again with water. The ether solution was dried and concentrated to yield 1.25 g of a dark brown liquid residue. A rapid, short-path distillation (50–100 °C; 20 μm) gave 0.64 g of a dark yellow liquid, **11b**. A second similar distillation gave two fractions, the second of which (~100 °C; 20 μm) yielded 330 mg (16% from the ketal **6**) of light yellow liquid: IR 1725, 1405, 1300, 1210, 1130, 1110, 956, 738 cm^{-1}. The UV spectrum (isooctane) showed a λ_{max} at 225 nm (ϵ 26 000). The low-resolution mass spectrum gave the correct molecular ion peak at *m/e* 203 and the parent peak at *m/e* 130 (loss of *m/e* 73, carboethoxy group): *m/e*(obsd) 203.0946, *m/e*(calcd for $C_{12}H_{13}NO_2$) 203.0948. A pure sample of **11b** was stable at −10 °C under argon for a week but showed signs of decomposition when distillation was attempted.

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Registry No. 4a, 111-30-8; **4b**, 70197-47-6; **4c**, 67402-86-2; **4d**, 70197-48-7; **4e**, 70197-49-8; **4f**, 70197-50-1; **4g**, 70197-51-2; **4h**, 70197-52-3; **6**, 70197-53-4; **7b**, 66606-41-5; **7c**, 70197-54-5; **7d**, 70197-55-6; **7e**, 70197-56-7; **7f**, 37778-31-7; **7g**, 70197-57-8; **7h**, 70197-58-9; **8c**, 19184-67-9; **8d**, 70197-59-0; **8e**, 51008-00-5; **8f**, 70197-60-3; **8g**, 70197-61-4; **8h**, 70197-62-5; **9c**, 54851-48-8; **9d**, 70197-63-6; **9e**, 50782-01-9; **9f**, 31297-46-8; **9g**, 70197-64-7; **9h**, 70197-65-8; **10c**, 54639-78-0; **10d**, 70197-66-9; **10e**, 50782-02-0; **10f**, 31297-44-6; **10g**, 70197-67-0; **10h**, 70197-68-1; **11a**, 40339-63-7; **11b**, 66606-49-3; **11c**, 37778-34-0; **11d**, 70197-69-2; **11e**, 70197-70-5; **11f**, 37778-33-9; **11g**, 66606-50-6; **11h**, 70197-71-6; **13e**, 4415-73-0; **14d**, 22308-08-3; **14e**, 22308-09-4; **15d**, 20778-47-6; **15e**, 1073-90-1; **18c**, 70197-72-7; **19a**, 66606-45-9; **19b**, 66606-46-0; **19c**, 66606-44-8; **19d**, 70197-73-8; **19e**, 70197-74-9; **19f**, 66606-47-1; **19g**, 66606-48-2; **19h**, 70197-75-0; **22**, 70197-76-1; 1,1-cyclopropanedimethanol, 39590-81-3; cyclopropane-1,1-diacetic acid, 70197-77-2; dimethyl 1,1-cyclobutanedicarboxylate, 10224-72-3; 1,1-cyclobutanediacetic acid, 1075-98-5; 3,3-dimethylglutaric acid, 4839-46-7; 3,3-tetramethyleneglutaric acid, 16713-66-9; 3,3-pentamethyleneglutaric acid, 4355-11-7; 3,3-hexamethyleneglutaric acid, 4432-18-2; glutaraldehyde polymer, 29257-65-6; ethyl chloroformate, 541-41-3; ethyl carbamate, 51-79-6.