with ether (3 × 15 ml). The combined ethereal extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and evaporated to dryness to afford a white, crystalline solid. Purification by preparative tlc gave the compound **3** (1.8 g, 85%): mp 100–101°; ν_{max} (Nujol) (3370, 1720 cm^{-1}; nmr (CCl_4) δ 4.36 (br), 4.06 (br) (total 1 H) in ratio 1:4, 3.18 (br, exchangeable, 1 H, OH), 1.45 [s, *ca.* 2.5 H, $OC(CH_3)OH$] superimposed on 2.8–1.0 (complex, methylene envelope) (ratio of 4.06 to 1.45, 1:3); *m/e* 164 ($M^+ - H_2O$). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.32; H, 9.68.

The ketol **3** (70 mg, 0.39 mmol) was stirred with acetic anhydride (0.5 ml) and pyridine (1 ml) for 15 hr under nitrogen. Water (5 ml) was added to the reaction mixture and the resulting solution was extracted with ether (3 × 8 ml). The combined ethereal extracts were washed with HCl (10%, 4 × 5 ml), water (5 ml), and saturated sodium bicarbonate (2 × 5 ml), dried (Na_2SO_4), and evaporated to give a colorless liquid (40 mg, 57%) with the probable structure **5**: ν_{max} (film) 1650 cm^{-1}; nmr δ 4.62 (2 H, s, $C{=}CH_2$), 4.28 (1 H, s, HCOC), and 1.0–2.3 (13 H, complex, methylene envelope).

***endo*-3-Hydroxy-*exo*-7-isopropenylbicyclo[3.3.1]nonane (6) and Its Acetate (9). A.** A suspension of methyltriphenylphosphoniumiodide (1.3 g, 3.3 mmol) and potassium *tert*-butoxide (0.34 g, 3.0 mmol) in anhydrous ether (10 ml) was stirred at 18° under nitrogen for 1 hr. A solution of the ketol **3** (0.18 g, 1 mmol) in dry ether (10 ml) was added and the ethereal layer was separated. The aqueous layer was extracted with ether (2 × 15 ml) and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to leave a pale yellow oil. The crude product was purified by preparative tlc (70% ether–petroleum ether). The band of lower R_f afforded a white, crystalline solid (0.11 g, 58%): mp 34–35°; ν_{max} (Nujol) 3350, 3080, 1640, and 885 cm^{-1}; nmr (CCl_4) δ 4.66 (2 H, s, $C{=}CH_2$), 3.95 (1 H, m, HCOH), 3.14 (1 H, br, exchangeable, OH), 1.68 (3 H, s, $CH_3C{=}C$) superimposed on 1.0–2.2 (13 H, complex, methylene envelope); *m/e* 180 (M^+). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.16. The material of higher R_f showed identical R_f and spectral data with the starting material.

B. A solution of the Ketol **7** (0.18 g, 1 mmol) in dry ether (10 ml) was added to the Wittig reagent prepared as in part A and the mixture was stirred for 15 hr, at which time tlc showed that no starting material was present. Water (50 ml) was added and the ethereal layer was separated. The aqueous layer was extracted with ether and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to leave a pale yellow oil. Purification by preparative tlc (70% ether–petroleum ether) afforded a white, crystalline solid (0.15 g, 84%), mp 35–37°. This compound had identical spectral properties with those of that prepared in part A. The mixture melting point with the compound from part A was 35–37°. Acetylation of compound **6** with acetic anhydride in pyridine for 15 hr at 20° gave the compound **9** (74%): mp 58–59°; ν_{max} (Nujol) 3080, 1730, 1640, 1235, 1020 cm^{-1}; nmr (CCl_4) δ 4.89 (1 H, m, HCOCO), 4.68 (2 H, s, $C{=}CH_2$), 1.92 (3 H, s, CH_3COO), and 1.71 (3 H, s, $CH_3C{=}C$) superimposed on 1.0–2.3 (13 H, complex, methylene envelope); *m/e* 162 (M^+ – AcOH).

***exo*-7-Acetyl-*endo*-3-hydroxybicyclo[3.3.1]nonane (7) and Its Acetate (8).** The ketol **3** (100 mg, 0.55 mmol) was added under nitrogen to a stirred solution of sodium methoxide in dry methanol (15 ml) (from 2 g of sodium) and stirring was continued for 16 hr at 18°. The reaction mixture was poured into water (40 ml) and extracted with ether (3 × 15 ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give a colorless oil. The crude material was purified by preparative tlc plate (20% ether–chloroform). Starting material (49 mg, 55%) was recovered and the ketol **7** (lower R_f) was isolated (40 mg, 45%): mp 69–71°; ν_{max} (Nujol) 3420, 1690, 1060, 1020 cm^{-1}; nmr (CCl_4) δ 4.05 (1 H, m, HCOH), 3.28 (1 H, br, exchangeable, OH), 2.14 (3 H, s, CH_3CO) superimposed on 1.0–2.5 (13 H, complex, methylene envelope); *m/e* 164 ($M^+ - H_2O$). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.29; H, 9.90.

Acetylation of the product with acetic anhydride in pyridine for 15 hr at 20° gave compound **8** (82%): mp 36–37°; ν_{max} (Nujol) 1730, 1700, 1230, 1010 cm^{-1}; nmr (CCl_4) δ 5.05 (1 H, m, CHOCO), 2.12 (3 H, s, CH_3COO), and 2.04 (3 H, s, CH_3CO) superimposed on 1.1–2.2 (13 H, complex, methylene envelope); *m/e* 164 (M^+ – AcOH). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.03; H, 9.22.

Ozonolysis of the Olefin 9. The vinyl acetate **9** (40 mg, 0.18 mmol) in methanol (2 ml) was cooled to −78° (Dry Ice–acetone bath) and treated with ozone (*ca.* 3%, 600 ml/min) for 30 min. The reaction mixture was then poured with stirring into a solution (cooled in a Dry Ice–acetone bath) of methanol (10 ml), acetic acid (3 ml), and sodium iodide (4.8 g). The solution was extracted with ether (2 × 10 ml) and the combined ethereal extracts were washed with 10% sodium thiosulfate solution (2 × 10 ml), saturated sodium bicarbonate (2 × 10 ml), and water (2 × 10 ml). The ether extract was dried (Na_2SO_4) and evaporated to give a colorless oil which crystallized on trituration with ether. Recrystallization from ether–petroleum ether gave a white, crystalline product (33 mg, 82%), mp 37–39°. The mixture melting point with compound **8** was 36–37°.

Registry No.—**2,** 21898-84-0; **3,** 51911-60-5; **5,** 51911-61-6; **6,** 51911-62-7; **7,** 51922-41-9; **8,** 51911-63-8; **9,** 51911-64-9.

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(3) Compound **7** on treatment with sodium methoxide in methanol gave the same approximate ratio of products. This product ratio thus represents the end point of a complex series of equilibria in which presumably the hemiacetal **4** plays an important role. It should be noted that, in the diagrams of the bicyclic structures above, no conformational preference is implied.

Condensation of Cyclic Nitrones with 3,5-Dicarbomethoxypyridinium Tosylate

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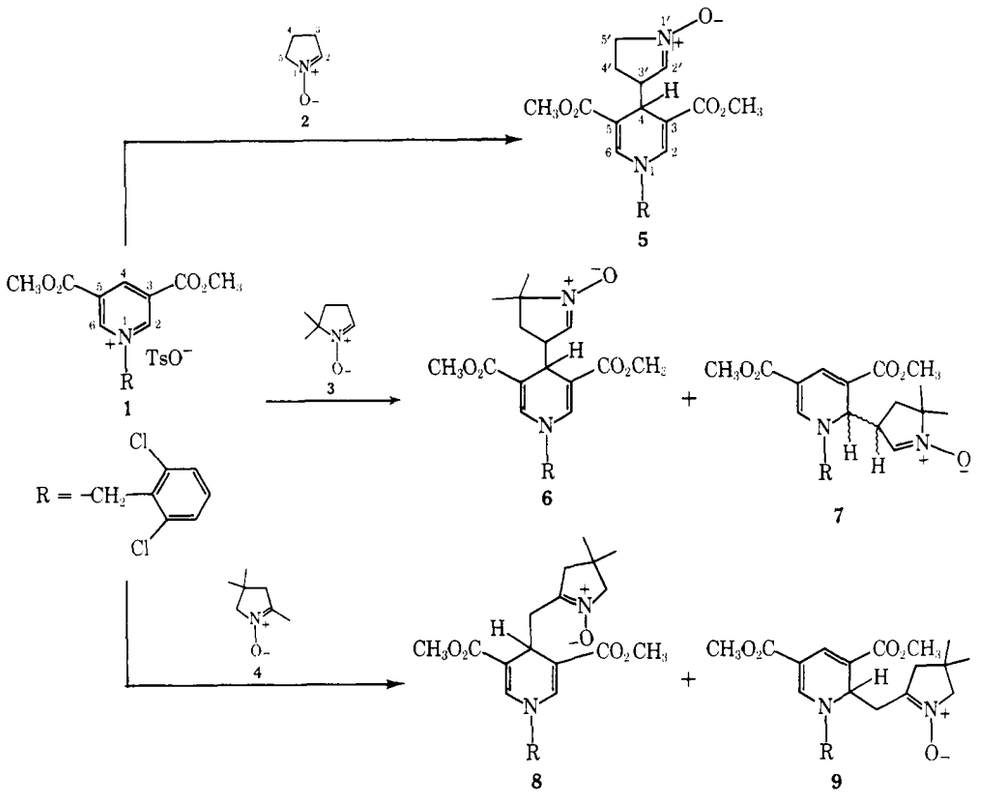
While a wide variety of nucleophiles will condense with pyridinium salts,[1] there are relatively few reported examples of condensations involving carbon nucleophiles which form stable dihydropyridines.[1,2] Since nucleophilic attack by carbon nucleophiles leads to the formation of new carbon–carbon bonds, these reactions are of potential synthetic utility. We would like to report an unusually facile condensation between the pyridinium nucleus and cyclic nitrones.

A single product **5** was formed when the pyridinium salt **1** was allowed to stand for 2 days at room temperature in an excess of the nitrone **2** (Scheme I). Spectroscopic data indicated that **5** was a 1,4-dihydropyridine formed through the condensation between **1** and **2** with the loss of toluenesulfonic acid: mass spectrum *m/e* 438 (M^+); nmr δ 4.20 ppm (1 H, doublet, J = 3 Hz, proton at C_4 in the dihydropyridine nucleus); λ_{max} (MeOH) 220 nm (ϵ 30,900), 265 (15,100), and 353 (8750).[1,3] These data, when interpreted within the framework of known nitrone chemistry,[4] suggest that the position of attachment to the nitrone ring is at the 3′-carbon atom rather than the 5′-carbon atom, which cannot be excluded on the basis of the spectroscopic data alone.

Support for this structure assignment was provided by the condensation between 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**3**) and **1**. This reaction afforded a mixture of dihydropyridine isomers. The major isomer was the crystalline 1,4-dihydropyridine **6** which was analogous to **5**. **6** had mass spectrum *m/e* 466 (M^+); nmr δ 4.20 ppm (1 H, doublet, J = 3 Hz); λ_{max} (MeOH) 223 nm (ϵ 32,300), 250 sh (14,300), and 358 (7430). The minor component was an oil that appeared to be a mixture of the 1,2-dihydropyridine diastereomers **7** which could not be resolved even after extensive chromatography.

The condensation of **1** with nitrone **4** also yielded both the 1,4- (**8**) and the 1,2-dihydropyridines (**9**). In this case

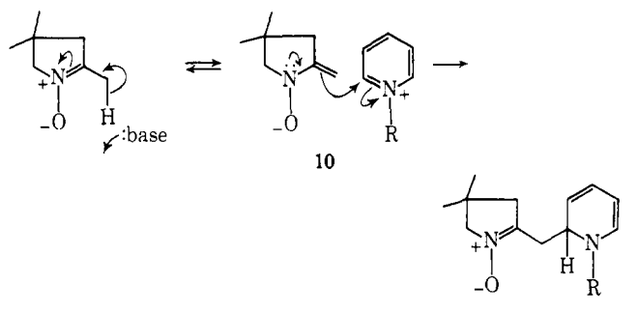
Scheme I



reaction took place at the 2-methyl group rather than the 3 position of the pyrroline ring of **4**. Thus, only a single 1,2-dihydropyridine was formed, since only one asymmetric center is generated in the condensation.

These condensations most probably proceed through the nitrone anion **10** (Scheme II).[4] Since no external base is required, the nitrone itself must serve in this capacity.

Scheme II



Experimental Section

Melting points were determined with a Mettler FP2 melting point apparatus. Spectroscopic studies were conducted with the following instruments: mass spectra, Hitachi Perkin-Elmer RMU-7; uv–visible, Cary 14; ir, Perkin-Elmer 337; nmr spectra, a Brüker HFX-90 and a Varian T-60. Proton assignments were made on the basis of decoupling experiments. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of the Dihydropyridines. General Procedure. The pyridinium salt **1**[5] was dissolved in an excess of the neat nitrone (1:3 molar ratio) and the homogeneous mixture was allowed to stand at room temperature for 2 days. The resulting homogeneous, viscous, yellow-brown oil was dissolved in chloroform and resolved by chromatography on thick layer plates (Brinkmann $PF_{254+366}$ silica gel) developed with chloroform–methanol.

The dihydropyridines were recrystallized from chloroform–ether to afford pale yellow crystals in the case of the 1,4 isomers and bright yellow crystals in the case of the 1,2 isomer.

1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-4-[3′-(Δ¹′-pyrrolinyl 1′-oxide)]-1,4-dihydropyridine (5). Condensation of **1** and **2**[6] afforded **5** in 53% yield (149 mg): mp 176.3–176.4°; ir ($CHCl_3$) 2920, 1700, 1570, 1420, 1400, 1225, 1200, 1160, 1085 cm^{-1}; λ_{max} (MeOH) 220 nm (ε 30,900), 265 (15,100), and 353 (8570); nmr ($CDCl_3$) δ 1.94 (m, 2 H), 3.16 (br, 1 H), 3.73 (m, 2 H), 3.73 (s, 6 H), 4.20 (d, J = 3 Hz, 1 H), 4.90 (s, 2 H), 6.73 (m, 1 H), 7.48 ppm (m, 5 H); mass spectrum m/e M^+ 438, base 354.

Anal. Calcd for $C_{20}H_{20}N_2O_5Cl_2$: C, 54.68; H, 4.59; N, 6.38; Cl, 16.14. Found: C, 54.44; H, 4.86; N, 6.29; Cl, 16.25.

1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-4-[3′-(5′,5′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide)]-1,4-dihydropyridine (6). Condensation of **1** and **3**[7] afforded a mixture of dihydropyridine isomers which could be partially resolved in one elution with chloroform–methanol (90:10). The material derived from the more polar colorless band was **6**: 15% yield (32 mg); mp 162.5–162.8°; ir ($CHCl_3$) 2930, 1700, 1570, 1430, 1400, 1230, 1197, 1163, 1085 cm^{-1}; λ_{max} (MeOH) 223 nm (ε 32,300), 250 sh (14,300), and 358 (7430); nmr ($CDCl_3$) δ 1.17 (s, 3 H), 1.23 (s, 3 H), 1.57 (d, J = 3 Hz, 1 H), 1.83 (d, J = 6 Hz, 1 H), 3.03 (b, 1 H), 3.73 (s, 6 H), 4.20 (d, J = 3 Hz, 1 H), 4.83 (s, 2 H), 6.60 (d, J = 3 Hz, 1 H), 7.33 (s, 2 H), 7.40 ppm (m, 3 H); mass spectrum, m/e M^+ 466, base 354.

Anal. Calcd for $C_{22}H_{24}N_2O_5Cl_2$: C, 56.54; H, 5.18; N, 5.99. Found: C, 56.80; H, 5.32; N, 5.92.

An oily mixture of diastereomers **7** was obtained from the less polar yellow band immediately above the band due to **6**. That the material isolated from this band was probably a mixture of the 1,2-dihydropyridine diastereomers **7** was indicated by the chromatographic behavior (*vide infra*) and the nmr spectrum, which exhibited four methyl singlets centered at δ 1.30 ppm and two overlapping benzyl AB patterns centered at δ 4.90 ppm. Both of these nmr features must arise from the proximity of chiral centers such as those present in **7**. Unfortunately, extensive thick layer chromatography failed to separate this oil into its constituents.

4-[1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-1,4-dihydropyridyl]-2′-[4′,4′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide]methane (8) and 2-[1-(2,6-Dichlorobenzyl-3,5-dicarbomethoxy-1,2-dihydropyridyl]-2′-[4′,4′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide] methane (9). Condensation of **1** and **4**[7] afforded a mixture of dihydropyridine isomers which could be resolved in two elutions with chloroform–methanol (93:7). The material derived from the more polar, colorless band was **8**: 16% yield (100 mg); mp 135.5–136.0°; ir ($CHCl_3$) 2930, 1700, 1575, 1430, 1400, 1230, 1160, 1079 cm^{-1}; λ_{max}

(MeOH) 221 nm (ε 27,700), 260 (9530), and 361 (9190); nmr ($CDCl_3$) δ 1.17 (s, 6 H), 2.60 (d, J = 5 Hz, 2 H), 2.65 (s, 2 H), 3.63 (s, 2 H), 3.73 (s, 6 H), 4.03 (t, J = 5 Hz, 1 H), 4.83 (s, 2 H), 7.33 ppm (m, 5 H); mass spectrum m/e M^+ 480, base 354.

Anal. Calcd for $C_{23}H_{26}N_2O_5Cl_2$: C, 57.39; H, 5.44; N, 5.82; Cl, 14.73. Found: C, 57.44; H, 5.16; N, 5.78; Cl, 14.84.

The less polar, yellow band immediately above the band due to 8 provided **9:** 37% yield (202 mg); mp 175.5–175.6°; ir ($CHCl_3$) 2935, 1675, 1620, 1535, 1425, 1228, 1143 cm^{-1}; λ_{max} (MeOH) 223 nm (ε 32,400), 274 (13,800), and 380 (8420); nmr ($CDCl_3$) δ 1.10 (s, 3 H), 1.17 (s, 3 H), 2.50 (m, 2 H), 3.27 (br d, J = 5 Hz, 1 H), 3.50 (br d, J = 5 Hz, 1 H), 3.67 (s, 2 H), 3.73 (s, 6 H), 4.97 (m, 1 H), 5.09 (d, J = 7.5 Hz, 1 H), 5.45 (d, J = 7.5 Hz, 1 H), 7.37 (m, 3 H), 7.67 ppm (m, 2 H); mass spectrum m/e M^+ 480, base 354.

Anal. Calcd for $C_{23}H_{26}N_2O_5Cl_2$: C, 57.39; H, 5.44; N, 5.82; Cl, 14.73. Found: C, 57.48; H, 5.11; N, 5.79; Cl, 14.86.

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Registry No.—**1,** 51898-97-6; **2,** 24423-88-9; **3,** 3317-61-1; **4,** 6931-11-9; **5,** 51849-12-8; **6,** 51849-13-9; **8,** 51849-14-0; **9,** 51849-15-1.

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Structural Analysis by Lanthanide-Induced Shifts. V.[1] Influence of Steric and Conjugative Effects on the Barriers to Rotation in *N,N*-Dimethylamides

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Dynamic nuclear magnetic resonance (dnmr) is one of the most powerful tools for the evaluation of rate constants and of the free-energy barriers to rotation (ΔG^*),[2] and the relative simplicity of this technique encourages a systematic search in order to assess the relative merits of steric and conjugative effects on the barriers to internal rotation in *N,N*-dimethylamides.[3-7]

However, this task is somewhat hampered by the necessity of using different solvents in dnmr work, in order to overcome solubility problems and the accidental isochrony of signals in a given solvent. Solvent effects on the barrier height are in fact of an order of magnitude comparable to steric or conjugative effects.[7]

The latter difficulty represented a serious problem also in our case since, in our hands, several of the amides studied by us yielded $CDCl_3$ spectra unsuitable for the measurement of ΔG^* at the coalescence point.

The use of lanthanide shift reagents (LSR) to simplify the amide spectra[8,9] offers a convenient way to avoid uncertainties caused by comparing data obtained in different solvents. Our results, in agreement with those of other authors,[10,11] show that the use of $Eu(fod)_3$ at low shift reagent/substrate molar ratios does not affect sensibly the ΔG^*. This fact allowed us to measure the ΔG^* of a series of structurally related *N,N*-dimethylamides in the same solvent ($CDCl_3$), even if some of the compounds studied exhibited accidental isochronous methyl signals in the undoped spectra.

The resulting set of immediately comparable data has provided detailed information on the relative strength of conjugative effects of some unsaturated amides. For instance, it can be inferred that the conjugative power of the phenyl group is intermediate between that of furan and thiophene, and that the vinyl and cyclopropyl groups are about as "strong" as furan. Furthermore, in some cases, differences in ΔG^* could be attributed to finer conformational effects.

Results

In Tables I and II are reported the results of our measurements, performed on two series of structurally related amides and diamides.

For some compounds in Table I, our ΔG^* estimates in the absence of LSR are in good agreement with data already available in the literature (references in the last column in Table I). The addition of $Eu(fod)_3$ at low shift reagent/substrate molar ratios does not affect sensibly the ΔG^*, but it does increase the separation of the diastereotopic *N*-methyl signals.

The advantage of performing coalescence measurements on peaks well resolved at low temperature is obvious. However, although the peak separation may be varied at will by increasing the amount of LSR, in our experience the optimal separation ranges between 15 and 60 Hz, corresponding to a molar ratio $Eu(fod)_3$/amide of *ca.* 0.1–0.2. Higher separations cause expand of uncertainties in the T_c estimates.

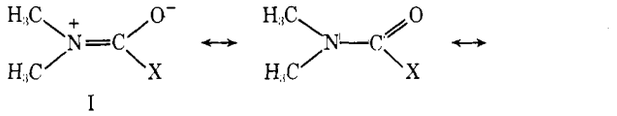
Despite the experimental evidence produced here that, in several cases, measurements of barriers with and without the LSR produces sensibly the same result, *it cannot be inferred that the LSR does not affect the barrier to rotation in the complexed substrate.* In fact, quite recently, in the case of trimethyl carbamate,[11] experiments performed at increasing shift reagent/substrate molar ratios have shown that the observed rate constant is the weighted average for isomerization of free and complexed substrate and, by extrapolation, it was possible to estimate the ΔG^* for both processes (the free-energy difference is about 2.5 kcal/mol.[11]

Of course, using *low* shift reagent/substrate molar ratios, only a small amount of complex is formed (most of the amide being present in the free state), so that our findings seem quite reasonable.

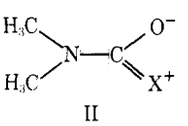
Discussion

Structural effects on the barrier to internal rotation in amides have been acknowledged in the recent literature.[3-7]

Considering the resonance structures I and II as possible contributors to the planar ground state of *N,N*-dimethyl-



I



II