Endocyclic *vs* Exocyclic Olefin Formation from 4-Piperidones *via* the Wittig Reaction (1a)

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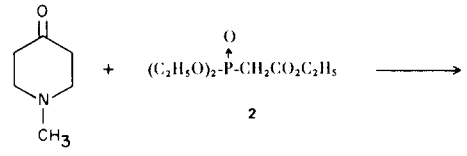
The reaction of 1-methyl-4-piperidone and 1-benzoyl-4-piperidone with triethyl phosphonoacetate in the presence of excess base yields both the endocyclic and exocyclic olefins. However, treatment of 1-methyl-4-piperidone with diethyl cyanomethylphosphonate, even in the presence of excess base, yielded only the exocyclic olefin. Factors affecting isomer distribution during the course of the reaction are presented. The isolation of an exocyclic tetrahydropyridine from the sodium borohydride reduction of the methiodide of 4-pyridylacetonitrile is reported.

A number of isomerizations of exocyclic to endocyclic olefins during the course of Wittig reactions on derivatives 4-piperidone have been previously reported (2-5). The degree and the rate of isomerization appear to depend upon the nature of the base used during the reaction, the amount of base used, and the nature of the solvent employed in the reaction. Until recently, the 4-piperidones studied were derivatives of benzo[*a*]quinolizin-2-one (2,3) and 1-benzoyl-4-piperidone (4,5). The recent report (6) concerning the Wittig reaction of the carbanion of triethyl phosphonoacetate with 1-methyl-4-piperidone, 1-methyl-4-phosphorinanone, and cyclohexanone has prompted us to report our observations of the reactions of 1-methyl-4-piperidone and 1-benzoyl-4-piperidone with various phosphonate ylides. Our results differ in several ways from those previously reported.



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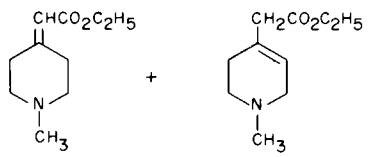

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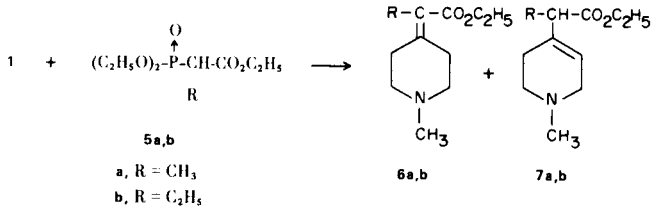
Quin and co-workers (6) reported that 1-methyl-4-piperidone (**1**) on reaction with the phosphorane prepared *in situ* from triethyl phosphonoacetate (**2**) and an equimolar amount of sodium hydride in 1,2-dimethyoxyethane gave only the exocyclic ester **3**. No isomeric endocyclic ester was detected. In an attempt to affect isomerization of the exocyclic double bond, **3** was treated with ethanolic sodium ethoxide at 35° for 64 days. No isomerization was detected. However, when **3** was heated for 5 hours at 170° a mixture consisting of 75% **4** and 25% **3** was obtained. The failure of **3** to undergo base-catalyzed isomerization was surprising to us since our results indicate that isomerization can be readily achieved under basic conditions.

We have carried out the reaction of **1** and **2** using a slight excess of sodium hydride in 1,2-dimethoxyethane and, consistent with the report of Quin (6), obtained only the exocyclic ester **3**. Spectral data were consistent with that expected for the exocyclic isomer, *i.e.*, the ir spectrum indicated an α,β-unsaturated ester (ν C=O 1710 cm^{-1}) and the nmr spectrum contained one vinyl proton at δ 5.70 (W_H = 2 Hz). We were, however, able to easily achieve isomerization by treating **3** with excess sodium ethoxide overnight. The resulting mixture consisting of **3** and **4** in a ratio of approximately 4:7 (as determined by the ratio of vinyl protons in the nmr spectrum) was chromatographed to separate **3** and **4**. The spectral characteristics of **4** were, as one would expect, markedly different from those of **3**. For example, the ir spectrum indicated a non-conjugated ester (ν C=O 1735 cm^{-1}) and the nmr spectrum contained a broad singlet at δ 5.60 (W_H = 8 Hz) for the vinyl proton. The larger W_H of the vinyl proton for the endocyclic ester is obviously due to vicinal coupling with piperidine ring protons. Vicinal coupling is not possible in the exocyclic isomer. Additionally, the physical and spectral properties of **4** obtained from the isomerization were identical in all respects with a sample prepared by the condensation of **1**

with ethylcyanoacetate (7). Thus, we are puzzled by the apparent failure of **3** to undergo isomerization under conditions reported previously (6).

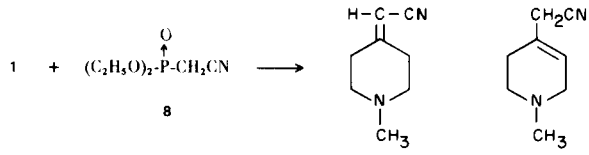
We have extended this study to the reaction of **1** with other phosphonate ylides (Scheme I). Treating **1** with either **5a** or **5b**, using excess sodium ethoxide in ethanol gave only the endocyclic isomers, **7a** or **7b**. None of the exocyclic isomer (**6a** or **6b**) was observed. These results are quite different from the results obtained in the synthesis of **3** using sodium hydride as a base. It appears obvious that the exocyclic esters, presumably the initial products of the Wittig reaction, undergo isomerization in

SCHEME I

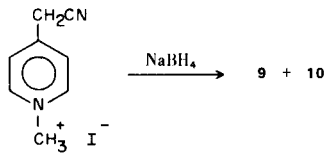


the presence of excess sodium ethoxide. The endocyclic structures were assigned on the basis of ir and nmr spectral data (see Experimental) in a manner similar to that described for the assignment of **4**. These reactions lend further support for the observation of the ease of base catalyzed isomerizations of the exocyclic esters.

Interesting results were obtained when **1** was treated with diethyl cyanomethylphosphonate (**8**). Using an equimolar amount of sodium hydride in 1,2-dimethoxyethane only the exocyclic isomer **9** was obtained. This result was consistent with results obtained using triethyl phosphonoacetate under similar conditions. Based on the results of isomerization of the exocyclic esters in the presence of excess base the condensation of **1** and **8** in



ethanol using an excess of sodium ethoxide was carried out in an attempt to obtain the endocyclic ester **10**. However, only the exocyclic nitrile (**9**) was obtained. Thus, in the case of the nitrile excess base had no effect on isomerization. The enhanced stability of the exocyclic nitrile was verified in another manner. 4-Pyridylacetonitrile methiodide (**11**) was reduced with sodium borohydride in ethanol according to the procedure reported by Lyle, *et al.* (8) for the synthesis of tetrahydropyridines.



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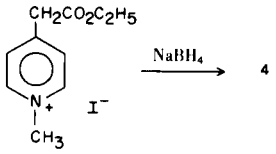
In addition to the expected endocyclic nitrile **10**, the product expected from the borohydride reduction of pyridinium salts, the exocyclic isomer **9** was also obtained. The nmr spectrum of the reaction product indicated a mixture of **9** and **10** in a ratio of approximately 1:2, respectively. Separation was affected by column chromatography to give pure **9** and **10**. The exocyclic isomer **9** obtained from the Wittig reaction was identical in all respects with that obtained from the reduction of **11**. The use of W_H of the vinyl protons of **9** and **10** was again useful in structural assignments. The vinyl proton W_H of **9** is 2 Hz while that of **10** is 8 Hz. To our knowledge this is the first reported isolation of an exocyclic olefin from the borohydride reduction of quaternary salts of pyridine derivatives.

The effect of the cyano group on the stability of the exocyclic olefin can also be observed from results obtained from the sodium borohydride reduction of the methiodide derived from ethyl 4-pyridylacetate (**12**). Under the same conditions used for the reduction of **11**, the reduction of **12** gave only the endocyclic ester **4**.



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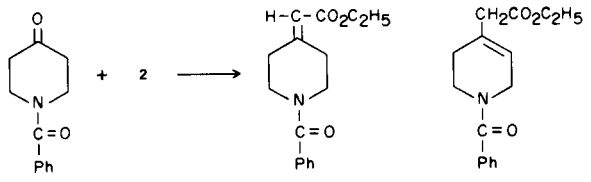
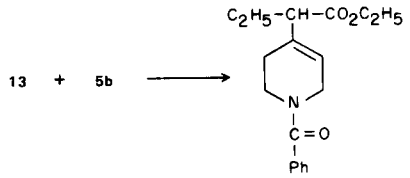
The reaction of phosphonate ylides with 1-benzoyl-4-piperidone (**13**) was also investigated. Sundberg and Holcombe (4) obtained a mixture of **14** and **15** in a 1.3:1 ratio on treating **13** with triethyl phosphonoacetate using excess sodium hydride in 1,2-dimethoxyethane. The effect of the solvent on the degree of isomerization was demonstrated by repeating the above reaction in anhydrous ether and benzene (5). In this case, a mixture of **14** and **15** was again obtained but in a ratio of 1:3. On repeating the



reaction of **13** and **2** with sodium hydride in anhydrous ether and benzene we could isolate only the exocyclic isomer (**14**) in 84% yield. However, using excess sodium ethoxide in ethanol we obtained a mixture consisting of **14** and **15** in a ratio of 1:10, respectively, which was separated by column chromatography. Identification of the exocyclic and endocyclic isomers was again made on comparing ir and nmr spectral data using carbonyl absorption frequencies and W_H of the vinyl protons (see Experimental). Thus, the predominance of the endocyclic isomer under conditions of excess base was again demonstrated. This predominance was observed more conclusively on treating **13** with **5b** using excess sodium ethoxide in ethanol. We were able to isolate only the endocyclic isomer (**16**) in an overall yield of 81% after purification.



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Our results indicate that isomerization of exocyclic esters, resulting from the addition of the ylides of phosphonate esters to 4-piperidone derivatives, in the presence of excess base occurs readily to give the corresponding endocyclic esters. However, the failure of the exocyclic nitrile **9** to undergo base catalyzed isomerization indicates that the stability of the product of Wittig reactions plays an important role in determining the direction of olefin formation.

EXPERIMENTAL

The ir spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were determined on a Jeolco Model C-60-HL spectrometer. Refractive indices were obtained on a Bausch and Lomb refractometer. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. A. Bernhardt, Microanalytisches Laboratorium, Max Planck Institute fur Kohlenfurschung, Mulheim (Ruhr), West Germany. The uv spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Triethylphosphonate (9), triethyl 2-phosphonopropionate (10), triethyl 2-phosphonobutyrate (11), and diethyl cyanomethylphosphonate (11) were prepared according to known procedures.

Ethyl 1-Methyl-$\Delta^{4,\alpha}$-piperidinacetate (**3**) Using Sodium Hydride as a Base.

A solution of 28.0 g. (0.125 mole) of triethyl phosphonoacetate (**2**) and 7.2 g. (0.15 mole) of sodium hydride (50% dispersion in mineral oil) in 175 ml. of 1,2-dimethoxyethane (DME) was stirred for 1 hour until the evolution of hydrogen ceased. 1-Methyl-4-piperidone (11.3 g., 0.1 mole), dissolved in 25 ml. of dry DME, was added dropwise. The resulting solution was stirred at room temperature for 5 hours, and the solvent removed under reduced pressure. The residue was acidified with 200 ml. of 20% hydrochloric acid and extracted several times with chloroform. The acidic aqueous layer was rendered alkaline with sodium carbonate, saturated with sodium chloride and extracted with chloroform (3 x 150 ml.). The chloroform extracts were dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure to give 16.5 g. of a residue. Distillation at 72-74° (0.05 mm) yielded 14.3 g. (78%) of a colorless liquid; n_D^{30} 1.4755; picrate (ethanol) m.p. 146-147°; uv λ max (ethanol) 221 mμ (log ε max 3.84); ir (liquid film) 1710 cm^{-1} (C=O α,β unsaturated ester), and 1650 cm^{-1} (C=C); nmr (carbontetrachloride) δ 1.25 (t, 3, CH_3-CH_2-O-CO-), 2.25 (s, 3, N-CH_3), 2.41 and 3.00 (m, 8, -CH_2-of the piperidine ring), 4.10 (q, 2, CH_3-CH_2-O-CO-), and 5.70 (s, 1, olefinic proton, W_H = 2 Hz).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.30; H, 9.22; N, 7.63.

Isomerization of **3** with Sodium Ethoxide.

Ethyl 1-methyl $\Delta^{4,\alpha}$-piperidineacetate (**3**, 9.15 g. 0.05 mole) was dissolved in 25 ml. of ethanol and treated with a solution of sodium ethoxide prepared from 0.23 g. (0.1 g-atom) of sodium metal and 50 ml. of ethanol. The solution was stirred at room temperature for 3 hours, refluxed for 30 minutes, then stirred again at room temperature for an additional 10 hours. The solvent was removed under reduced pressure, the residue treated with 100 ml. of saturated sodium chloride, and extracted with chloroform (3 x 150 ml.). The chloroform extracts were dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give 5.6 g. of a yellow liquid. The ir (liquid film) showed two peaks at 1735 and 1710 cm^{-1} indicating a mixture of the endocyclic and exocyclic isomers, **4** and **3** respectively. The nmr spectrum indicated a mixture of the endocyclic (**4**) and exocyclic (**3**) isomers in a ratio of 4:7 respectively. Separation of isomers was affected by chromatography on silica gel (0.05-0.20 mm E. Merck AG. Germany), using ether-benzene (1:4) as an eluting solvent. The exocyclic isomer (**4**, 3.3 g., 36%) eluted first; ir (liquid film) was identical to an authentic sample, 1710 cm^{-1} (C=O α,β unsaturated ester); nmr (carbon tetrachloride) identical to an authentic sample prepared previously. The endocyclic isomer (**3**, 1.9 g., 21%) eluted later; ir (liquid film) 1735 cm^{-1} (C=O saturated ester); nmr (carbon tetrachloride) was identical to an authentic sample prepared below.

Ethyl [1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]acetate (**4**).

Following the procedure of McElvain and Lyle (7), 113.0 g. (1.0 mole) of 1-methyl-4-piperidone and 169.5 g. (1.5 moles) of ethyl cyanoacetate yielded, after distillation, 54.5 g. (33%) of **4**; n_D^{30} 1.4675 (Lit. (7) n_D^{25} 1.4643); picrate (ethanol) m.p. 105-106°; ir (liquid film) 1735 cm^{-1} (C=O saturated ester); nmr (carbon tetrachloride) δ 1.25 (t, 3, CH_3-CH_2-O-CO-), 4.13 (q, 2, CH_3-CH_2-O-CO-), 2.28 (s, 3, N-CH_3), 2.93 (m, 4, -CH_2CO_2Et and -CH_2- at C_2), 2.46 (m, 2, -CH_2- at C_6), 2.10 (broad signal, 2, -CH_2- at C_5), and 5.60 (broad signal, 1, olefinic H_3, W_H = 8 Hz).

Ethyl 2-[1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]propionate (**7a**) Using Sodium Ethoxide as a Base.

A solution of 33.9 g. (0.3 mole) of 1-methyl-4-piperidone dissolved in 50 ml. of absolute ethanol was added dropwise to a solution of 78.6 g. (0.33 mole) of triethyl 2-phosphonopropionate (**5a**) and sodium ethoxide (0.5 mole) in 400 ml. of absolute ethanol. After 45 minutes a solution of sodium ethoxide prepared from 0.15 g. (0.007 g-atom) of sodium metal and 25 ml. of

ethanol was added and the resulting solution refluxed overnight under nitrogen. The solvent was removed, 200 ml. of water was added, the solution saturated with sodium chloride and extracted with ether. The ether extracts were combined, dried (magnesium sulfate) and evaporated. The residue obtained was distilled at 100-104° (0.15 mm) to yield 24.5 g. (42%) of colorless product; n_D^{26} 1.4685; ir (liquid film) 1730 cm^{-1} (C=O saturated ester); nmr (carbontetrachloride) δ 1.13 (d, 3, CH_3-CH-CO_2Et), 1.30 (t, 3, CH_3-CH_2-O-CO-), 2.26 (s, 3, -N-CH_3), 2.90 (m, 3, -CH_2- at C_2 and CH_3-CH-CO_2Et), 2.40 (m, 2, -CH_2- at C_6), 2.06 (m, 2, -CH_2- at C_5), 4.11 (q, 2, CH_3-CH_2-O-CO-), and 5.50 (broad singlet, 1, olefinic proton at C_3, W_H = 8 Hz).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 6.68. Found: C, 66.83; H, 9.81; N, 6.79.

Ethyl 2-[1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]butyrate (**7b**).

The procedure followed was essentially similar to that used to prepare (**7a**) using 19.0 g. (0.17 mole) of 1-methyl-4-piperidone dissolved in 50 ml. of absolute ethanol, 46.5 g. (0.18 mole) of triethyl 2-phosphonobutyrate (**5b**) and a solution of sodium ethoxide (0.3 mole) in 200 ml. of absolute ethanol. After working up the reaction mixture as previously described, 24.5 g. of an oily residue was obtained which was distilled at 80-84° (0.15 mm) to yield 15.3 g. of crude product. Further purification was achieved by chromatography on silica gel (50-200 mesh, The Frederik Smith Chemical Co., Columbus, Ohio) using (1:4) ether-benzene as an eluting solvent. The colorless oil which eluted was distilled at 82-84° (0.15 mm) to yield 14.5 g. (36%) of **7b**; n_D^{28} 1.4693; ir (liquid film) 1735 cm^{-1} (C=O saturated ester); nmr carbon tetrachloride δ 0.87 (t, 3, CH_3-CH_2-CH-), 1.23 (t, 3, CH_3-CH_2-O-CO-), 2.28 (s, 3, N-CH_3), 2.40 (m, 2, -CH_2 at C_6), 2.88 (m, 3, CH_3-CH_2-CH- and -CH_2 at C_2), 1.76 (m, 4, CH_3-CH_2-CH-, and -CH_2- at C_5), 4.03 (q, 2, CH_3-CH_2-O-CO-), and 5.50 (broad singlet, 1, olefinic proton at C_3, W_H = 8 Hz).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.04; H, 10.02; N, 6.52.

1-Methyl-$\Delta^{4,\alpha}$-piperidinylacetonitrile (**9**). Method A Using Sodium Hydride as a Base.

By following the procedure described for the synthesis of **3**. 11.3 g. (0.1 mole) of 1-methyl-4-piperidone was dissolved in 50 ml. of dry DME. This solution was added dropwise to a solution of 6.0 g. (0.125 mole) of sodium hydride (50% dispersion in mineral oil) and 22.1 g. (0.125 mole) of diethyl cyanomethylphosphonate in 100 ml. of DME. The mixture was stirred for 15 hours at room temperature. After working up the reaction mixture as described before, the residue was distilled at 64-68° (0.1 mm) to yield 9.2 g. (68%) of a colorless liquid, n_D^{26} 1.4935; picrate (ethanol) m.p. 177-179°; ir (liquid film) 2220 cm^{-1} (C≡N α,β unsaturated nitrile), and 1640 cm^{-1} (C=C); nmr (carbon tetrachloride) δ 2.35 (s, 3, N-CH_3), 2.51 (s, 4, -CH_2- at C_3 and C_5), 2.63 (s, 4, -CH_2- at C_2 and C_6), 5.40 (s, 1, olefinic proton at $\Delta^{4,\alpha}$ W_H = 2 Hz).

Anal. Calcd. for $C_{14}H_{15}N_5O_7$ (picrate): C, 46.03; N, 4.14; N, 19.17. Found: C, 46.22; H, 4.27; N, 19.02.

1-Methyl-$\Delta^{4,\alpha}$-piperidinylacetonitrile (**9**). Method B Using Sodium Ethoxide as a Base.

This procedure used was essentially similar to that described for the synthesis of **7a**, using 11.3 g. (0.1 mole) of 1-methyl-4-piperidone dissolved in 30 ml. of absolute ethanol, 22.1 g. (0.125 mole) of diethyl cyanomethylphosphonate and a solution of sodium ethoxide (0.15 mole) in 150 ml. of absolute ethanol. After working up the reaction mixture as described previously, the residue was distilled at 64-68° (0.1 mm) to yield 5.4 g. (40%) of a colorless liquid, n_D^{27} 1.4955; ir (liquid film) similar to an authentic sample; nmr (carbontetrachloride) identical to the sample prepared using sodium hydride as a base; picrate (ethanol) m.p. 176-178°, no depression on mixed m.p. with a sample from Method A.

1-Methyl-4-(1,2,5,6-tetrahydropyridyl)acetonitrile (**10**) and 1-Methyl-$\Delta^{4,\alpha}$-piperidinylacetonitrile (**9**).

Using the procedure described by Lyle (8), 61.0 g. (0.235 mole) of 4-pyridylacetonitrile methiodide (12-14) was dissolved in 600 ml. of ethanol and cooled, with stirring, to 10°. Sodium borohydride (35.6 g., 0.94 mole) was added at such a rate as to maintain the temperature below 20° throughout the course of addition. After complete addition of the borohydride the reaction mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue dissolved in 150 ml. of water. The aqueous solution was saturated with sodium chloride and extracted several times with chloroform. The extracts were combined, dried (magnesium sulfate), and evaporated. The residue was distilled at 78-80° (0.1 mm) to yield 11.2 g. (35%) of a pale yellow liquid; ir (liquid film) 2220 cm^{-1} (C≡N of α-β unsaturated nitrile) and 2260 cm^{-1} (C≡N saturated alkyl nitrile). The nmr spectrum indicated a mixture of **10** and **9** in a ratio of 2:1. Separation of **10** and **9** was effected by column chromatography on 130 g. of silica gel (Merck AG. 50-200 mesh) using ether-benzene (1:4) as an eluting solvent.

The exocyclic isomer (**9**, 3.4 g., 11%) was eluted first as a colorless liquid; n_D^{27} 1.4938; picrate (ethanol) m.p. 177-179°; ir (liquid film) 2220 cm^{-1} (C≡N α-β unsaturated nitrile), and 1640 (C=C); nmr (carbon tetrachloride) δ 2.30 (s, 3, N-CH_3), 2.46 (s, 4, -CH_2- at C_3 and C_5), 2.56 (s, 4, -CH_2- at C_2 and C_6), and 5.3 (s, 1, olefinic proton at $\Delta^{4,\alpha}$ W_H = 2 Hz).

The endocyclic isomer (**10**, 7.13 g., 22.9%) eluted later as a yellow liquid; n_D^{28} 1.4826; ir (liquid film) 2260 cm^{-1} (C≡N alkyl nitrile); nmr (carbon tetrachloride) δ 2.10 and 2.35 (broad signal and singlet respectively, 5, -CH_2- at C_5 and N-CH_3), 2.56 (m, 2, -CH_2- at C_6), 3.00 (broad signal, 4, -CH_2- at C_2 and -CH_2-CN), and 5.88 (broad signal, 1, olefinic proton H_3, W_H = 8 Hz); picrate (EtOH) 140-141.5°.

Anal. Calcd. for $C_{14}H_{15}N_5O_7$ (picrate); C, 46.03; N, 4.14; N, 19.17. Found: C, 45.97; H, 4.16; N, 19.33.

Ethyl [1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]acetate (**4**).

A modified procedure of Lyle (8) was followed. A solution of 6.7 g. (0.22 mole) of ethyl 4-pyridylacetate methiodide (15,16) in 200 ml. of ethanol was cooled with stirring to 10°. Sodium borohydride (3.3 g., 0.087 mole) was added slowly at such a rate as to maintain the temperature of the reaction below 20° throughout the course of addition. Upon complete addition of the borohydride the reaction mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue dissolved in 150 ml. of water. The aqueous solution was saturated with sodium chloride and extracted with chloroform (2 x 150 ml.). The combined chloroform extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was distilled at 68-69° (0.075 mm) [Lit. (7) b.p. 105-110° (11 mm)] to yield 2.2 g. (55%) of product; n_D^{29} 1.4665 [Lit. (7) n_D^{25} 1.4643]; ir (liquid film) 1735 cm^{-1} (C=O saturated ester), and 1680 cm^{-1} (shoulder, C=C); nmr (carbon tetrachloride) identical with samples of **4** prepared by routes previously described.

Ethyl 1-Benzoyl-$\Delta^{4,\alpha}$-piperidineacetate (**14**) Using Sodium Hydride as a Base.

Using the method of Sundberg (5) a solution of 19.5 g. (0.091 mole) of triethyl phosphonoacetate (**2**) in 150 ml. of ether was added slowly to 3.8 g. (0.06 mole) of sodium hydride in 100 ml. of ether. When hydrogen evolution ceased, a solution of 15.0 g. (0.074 mole) of 1-benzoyl-4-piperidone in 350 ml. of ether and 100 ml. of dry benzene was added in one portion and the resulting solution refluxed for 20 hours under nitrogen. The organic solution was decanted and the gummy precipitate was washed with additional ether. The combined organic solutions were filtered, washed with dilute hydrochloric acid, dilute sodium bicarbonate and then saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and the solvent was evaporated to yield 18.4 g. of a solid which was recrystallized from ether-*n*-hexane to give 17.0 g. (84%) of product, m.p. 99-101° [Lit. (4) m.p. 104-106°]; uv λ max (ethanol) 230 mμ (log ε max 4.44); ir (potassium bromide) 1710 cm^{-1} (C=O ester), 1650 cm^{-1} (C=C), and 1620 cm^{-1} (C=O amide); nmr (deuteriochloroform) 1.26 (t, 3, CH_3-CH_2-O-CO-), 2.4 (broad signal, 2H), 3.00 (broad signal, 2H), 3.70 (m, 4H), 4.2 (q, CH_3-CH_2-O-CO), 5.86 (s, 1, olefinic proton at $\Delta^{4,\alpha}$, W_H = 2 Hz), and 7.50 (s, 5, phenyl).

Ethyl [1-Benzoyl-1,2,5,6-tetrahydropyridine]-4-acetate (**15**) and Ethyl 1-Benzoyl-$\Delta^{4,\alpha}$-piperidineacetate (**14**) Using Sodium Ethoxide as a Base.

A modified procedure of Sundberg and Holcombe (4) was used. 1-Benzoyl-4-piperidone (19.5 g., 0.096 mole) was dissolved in 20 ml. of absolute ethanol and added dropwise to a solution of 23.5 g. (0.105 mole) of triethyl phosphonoacetate and sodium ethoxide (0.1 mole) in 100 ml. of absolute ethanol. After 45 minutes a solution of sodium ethoxide prepared from 0.15 g. (0.007 g-atom) of sodium metal and 25 ml. of ethanol was added, and the resulting solution refluxed overnight under nitrogen. The solvent was removed under reduced pressure, 200 ml. of water was added, the solution was saturated with sodium chloride and extracted with ether. The ether extracts were dried over magnesium sulfate, filtered, and the filtrate was concentrated at reduced pressure to give a mixture of **14** and **15**. The mixture was purified by chromatography on 170 g. of silica gel (0.05-2mm-E. Merck. AG. Germany) using ether-benzene (1:4) as an eluting solvent.

The exocyclic isomer (**14**) eluted first and solidified on treatment with ether-*n*-hexane mixture. Recrystallization from ether-*n*-hexane gave 1.1 g. (4%) of a white crystalline solid, m.p. 99-101° [Lit. (4) 104-106° ether-*n*-hexane]; ir (potassium bromide) 1710 cm^{-1} (C=O α-β unsaturated ester), 1650 cm^{-1} (C=C); and 1625 cm^{-1} (C=O amide); nmr (deuteriochloroform) similar to the product prepared using sodium hydride as a base.

The endocyclic isomer (**15**) separated later as an oil (10.2 g., 39%); n_D^{27} 1.5382; ir (liquid film) 1735 cm^{-1} (C=O saturated ester), 1630 cm^{-1} (C=O amide); nmr (deuteriochloroform) δ 1.23 (t, 3, CH_3-CH_2-O-CO-), 2.23 (broad signal, 2, -CH_2- at C_5), 3.00 (s, 2, -CH_2-CO_2Et), 3.53 (broad signal, 2, -CH_2- at C_6), 4.06 (quartet superimposed by a broad signal, 4, CH_3-CH_3-O-CO-, and -CH_2- at C_2), 5.48 (broad singlet, 1, olefinic H_3 proton, W_H = Hz), and 7.33 (s, 5, phenyl).

Ethyl 2-[1-Benzoyl-1,2,5,6-tetrahydropyridine]-4-butyrate (**16**).

The title compound was prepared by following the procedure described for the synthesis of **15**, using 5.5 g. (0.27 mole) of 1-benzoyl-4-piperidone in 15 ml. of ethanol, 7.8 g. (0.031 mole) of triethyl 2-phosphonobutyrate (**5b**) and sodium ethoxide (0.032 mole) in 20 ml. of ethanol. After 1 hour a solution of sodium ethoxide prepared from 0.23 g. (0.01 g-atom) sodium and 10 ml. of absolute ethanol was added and the resulting solution was stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and 150 ml. of water was added to the residue. The solution was saturated with sodium chloride and extracted with chloroform (3 x 200 ml.). The chloroform extracts were dried over magnesium sulfate, filtered, and the filtrate was evaporated under reduced pressure to give 6.9 g. of an oily residue. The crude substance was purified by chromatography on 100 g. of silica gel (0.05-0.20 mm E. Merck. AG. Germany) using ether-benzene (1:4) as an eluting solvent. Thus, 6.54 g. (81%) of an oil was obtained; n_D^{30} 1.5292; ir (liquid film) 1735 cm^{-1} (C=O saturated ester), 1640 cm^{-1} (C=O amide); nmr (carbon tetrachloride) δ 0.86 (t, 3, CH_3-CH_2-CH-), 1.25 (t, 3, CH_3-CH_2-O-CO-), 1.73 (m, 2, CH_3-CH_2-CH-), 2.2 (broad signal, 2, -CH_2- at C_5) 3.6 (broad signal, 2, -CH_2- at C_6), 4.10 (quartet superimposed by a broad signal, 4, CH_3-CH_2-O-CO-, and -CH_2- at C_2), 5.65 (broad singlet, 1, olefinic proton at C_3, W_H = 8 Hz) and 7.53 (s, 5, phenyl).

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.84; H, 7.65; N, 4.84.

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