2 ml of MeOH saturated with picric acid. The solution was filter to remove polymeric material which had precipitated and then allowed to stand for 2 hr at room temperature. Ether (50 ml) was added to the solution, which was then left in a freezer for 36 hr. During this time, 0.065 g (20%) of orange picrate crystals precipitated: mp 118–119°; nmr (acetone-d_6) δ 8.6 (s, 2 H), 5.79 (m, 2 H), 5.28 (m, 2 H), 5.07 and 4.37 (m, 4 H) (N–H not observed).

Anal. Calcd for $C_{12}H_{12}N_4O_7$: C, 44.44; H, 3.70; N, 17.24. Found: C, 44.69; H, 3.64; N, 17.24.

Polymer (9b) of 1-Methyl-3,4-dimethylenepyrrolidine. Compound **8a** (liquid) polymerized readily upon standing at room temperature to give a water-soluble polymer: nmr (D_2O) δ 4.14 (bs, 4 H), 3.0 (bs, 3 H), 2.34 (bs, 4 H).

Picrate (10b) of 1-Methyl-3,4-dimethylenepyrrolidine. To a solution of the exocyclic diene **8a** (~0.25 g) in 5 ml of methanol was added 5 ml of methanol saturated with picric acid. The solution was allowed to stand for 3 hr at room temperature after which time 60 ml of ether was added. The solution was left in a freezer for 48 hr and during this time 0.52 g (67%) of yellow picrate crystals precipitated: mp 101–103°; nmr (acetone-d_6) δ 8.67 (s, 2 H), 5.74 (m, 2 H), 5.29 (m, 2 H), 4.37 (m, 4 H), 3.18 (s, 3 H) (N–H not observed).

Anal. Calcd for $C_{13}H_{14}N_4O_7$: C, 46.15; H, 4.14; N, 16.56. Found: C, 46.06; H, 4.09; N, 16.36.

1,1-Dimethyl-3,4-dimethylenepyrrolidinium Iodide (11a). Compound **2a** (0.6 g) was decomposed by the same procedure used for the preparation of **8f**. The 1-methyl-3,4-dimethylenepyrrolidine recovered was dissolved in 3 ml of methylene chloride. To this solution was added 3 ml of methyl iodide. The reaction was allowed to stand overnight and 0.52 g (65%) of **11a** was collected by filtration: mp 179° dec; ir max 916 cm^{-1}; nmr (DMSO-d_6) δ 5.78 (m, 2 H), 5.33 (m, 2 H), 4.31 (m, 4 H), 3.12 (s, 6 H).

Anal. Calcd for $C_8H_{14}NI$: C, 38.24; H, 5.60; N, 5.58. Found: C, 37.94; H, 5.54; N, 5.52.

1-Methyl-1-benzyl-3,4-dimethylenepyrrolidinium Iodide (11b). Procedure same as for **11a**: yield 67%; mp 146–147° dec; ir max 907, 750, 696 cm^{-1}; nmr (DMSO-d_6) δ 7.42 (s, 5 H), 5.72 (m, 2 H), 5.26 (m, 2 H), 4.7–3.8 (m, 6 H), 2.8 (s, 3 H).

Anal. Calcd for $C_{14}H_{18}NI$: C, 51.36; H, 5.50; N, 4.28. Found: C, 51.16; H, 5.40; N, 4.10.

1-Methyl-1-isopropyl-3,4-dimethylenepyrrolidinium Iodide (11c). Procedure same as for **11a**: yield 55%; mp 250–252° dec; ir max 1429, 913 cm^{-1}; nmr (DMSO-d_6) δ 5.81 (m, 2 H), 5.30 (m, 2 H), 4.38 (m, 4 H), 3.84 (h, J = 7 Hz, 1 H), 2.75 (s, 3 H), 2.03 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_{10}H_{18}NI$: C, 43.02; H, 6.50; N, 5.01. Found: C, 43.33; H, 6.43; N, 4.91.

Acknowledgment. The authors wish to thank Texaco Incorporated for their fellowship support of P. V. Alston, and the National Science Foundation for their financial support through Grant No. GP 26616.

Registry No.—**1**, 18214-57-8; **2a**, 35105-72-7; **2b**, 35105-73-8; **2c**, 35105-74-9; **2d**, 50586-20-4; **2e**, 50586-21-5; **2f**, 50586-22-6; **4a**, 50586-23-7; **4b**, 50586-24-8; **4c**, 50586-25-9; **5**, 50586-26-0; **6**, 50586-27-1; **7**, 50586-28-2; **8a**, 50521-42-1; **8b**, 50586-29-3; **8c**, 505086-30-6; **8d**, 50586-31-7; **8e**, 50586-32-8; **8f**, 50586-16-8; **9a**, 50586-17-9; **9b**, 50678-88-1; **10a**, 50586-33-9; **10b**, 50586-34-0; **11a**, 50586-35-1; **11b**, 50586-36-2; **11c**, 50586-37-3; *tert*-butylamine, 75-64-9; isopropylamine, 75-31-0.

References and Notes

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(13) Determined by the Mohr method: D. A. Skoog and D. M. West, "Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1965, p 218.

Synthesis of 1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ols. Novel Fragments of the Morphine Molecule

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Received August 13, 1973

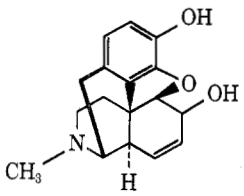
Renewed efforts were made to gain access to the long neglected morphine fragment **2d**, *trans*-1,3,4,5,6,7,8,8a-octahydro-2-methyl-4a-phenylisoquinolin-6-ol. Previous efforts by McElvain involved an unsuccessful attempt at the conjugate addition of phenylmagnesium bromide to the enone **17**, 1,3,4,7,8,8a-hexahydro-2-methylisoquinolin-6-one. Our first attempt involved intramolecular alkylation of the ketal **8b**, which was not successful. Use of diphenylcopper lithium, however, enabled us to achieve conjugate addition to the enone **17**, giving stereospecifically the cis ketone **18**, 1,3,4,7,8,8a-hexahydro-2-methyl-4a-phenylisoquinolin-6-one, whose structure was confirmed by X-ray analysis of the methobromide. The stereochemistry of reduction and methyllithium addition to this ketone **18** is discussed.

In the search for new structural types possessing analgetic activity the pentacyclic structure of morphine (1) has been subjected to many modifications. One of these, compound **2a**, represents an interesting target type, which has been subjected to only one additional study since compound **2a** was reported.[1]

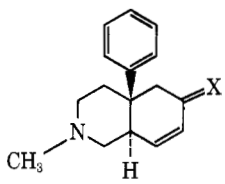
A study by McElvain described an unsuccessful attempt to gain access to this type by a synthetic approach which was quite similar to our successful route.[2]

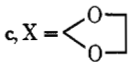
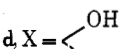
The reason for this apparent neglect of otherwise attractive target compounds such as **2a–d** while other modifications have been extensively explored[3] is perhaps the syn-

thetic difficulties posed by a bridgehead aryl group. This cannot be introduced by an intramolecular process, as in the classical Grewe synthesis of the morphinans.[3] The Boekelheide synthesis of compound **2a**, on the other hand,



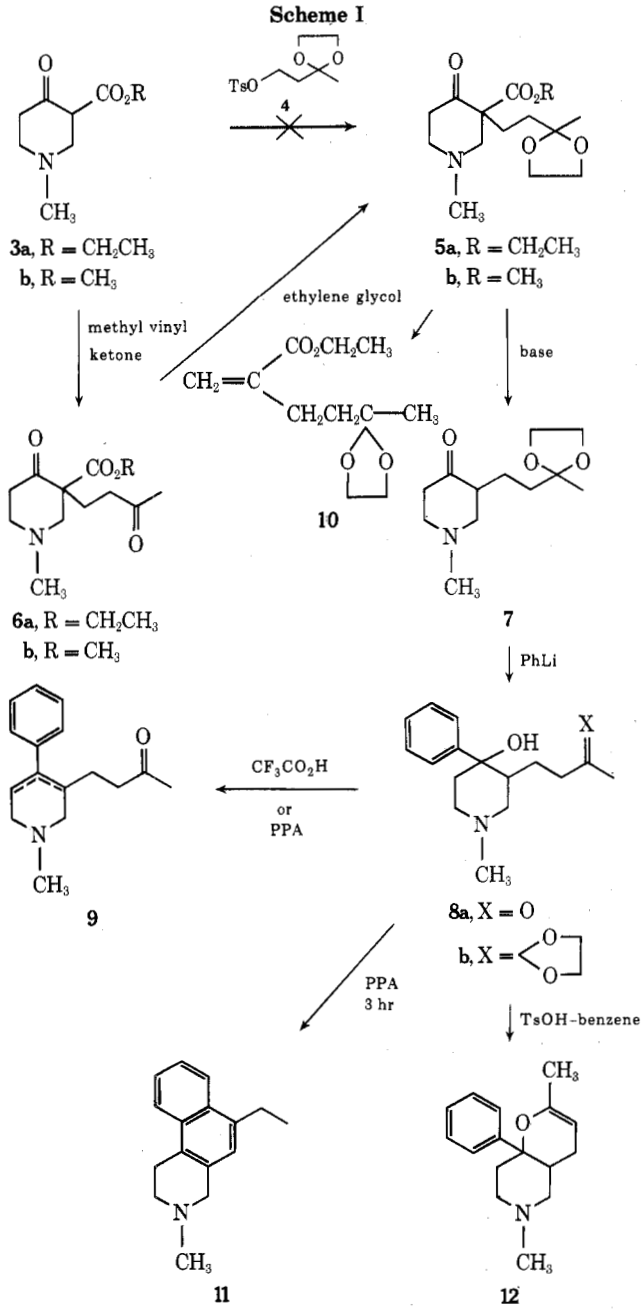
1
morphine



2a, X = H_2
b, X = O
c, X = 
d, X = 

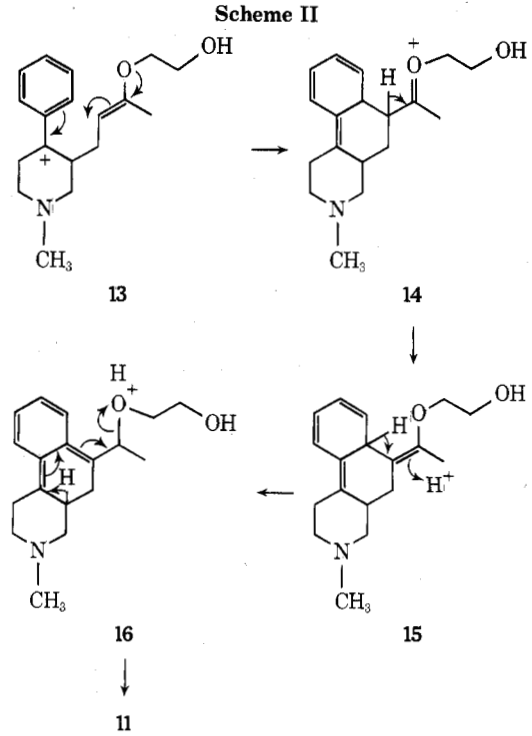
involved six steps and yielded a material of uncertain stereochemistry.[1] Therefore, it seemed appropriate for us to consider application of newer synthetic methodology.

Scheme I

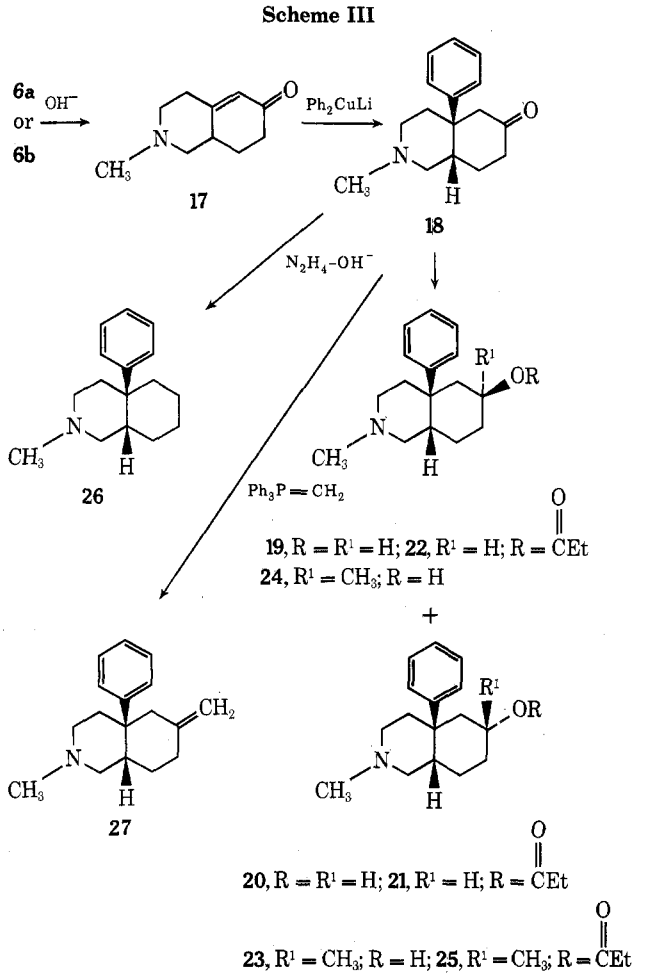


Two schemes were considered. The first was a variant of one used by Wenkert for the synthesis of lupinine.[4] This essentially involves the acid-catalyzed intramolecular alkylation of the α carbon atom of an ethylene ketal. Two routes were selected for the synthesis of an appropriate ketal precursor **8b**. Both routes were designed to provide the 4-piperidone **7** which could be reacted with phenyllithium to give **8b**. The first was an unsuccessful attempt to alkylate 1-methyl-4-oxonipecotate (**3a**) with 3-oxobutyl *p*-toluenesulfonate ethylene ketal (**4**), which had been used by Wenkert.[4] The second provided access to the desired 4-piperidone **7** *via* selective ketalization of the methyl vinyl ketone adduct **6a** of ethyl 1-methyl-4-oxonipecotate (**3a**)[5] followed by basic hydrolysis and decarboxylation (Scheme I). Unfortunately, this decarboxylation process proceeded in very poor yield, the major product **10** being derived by ring cleavage of the nonenolizable β-keto ester and a reverse Michael reaction on the resulting ring-opened product. A better yield (35%) of **7** was obtained from the methyl ester **5b**, derived by methyl vinyl ketone addition to methyl 1-methyl-4-oxonipecotate (**3b**). Use of the more readily hydrolyzable methyl ester **5b** favored the desired pathway. Addition of phenyllithium to the 4-piperidone **7** proceeded well but the ketal in the product **8b** was quite acid sensitive. Merely extraction by 2 *N* hydrochloric acid and rebasification with sodium carbonate was sufficient to deketalize it to give **8a**. A good yield (65%) of the desired ketal **8b** could be obtained by avoiding any treatment with acid. Several attempts to cyclize **8b** to the target compounds **2b** or **2c** were, however, unsuccessful (Scheme I). The most common products were mixtures of the deketalized tetrahydropyridines **9**, *i.e.*, simple dehydration products. Forcing conditions on **8b** with polyphosphoric acid and separation of the products by preparative glc yielded an interesting compound, which was assigned the structure **11** based on spectral evidence. Such a product could be formed by closure not onto the benzylic carbon but the ortho position of the aromatic ring (Scheme II). Unfortunately, complete characterization of this material was not possible, as it yielded consistently unsatisfactory elemental analysis. Conditions similar to those used by Wenkert[4] did give a product **12** derived by alkyla-

Scheme II



Scheme III



tion by the benzylic cation but, alas, this was derived by alkylation on oxygen of an intermediate such as **13** (Scheme II). At this point our efforts were, therefore, directed to another scheme to obtain access to the primary target **2b**, or a derivative thereof. Treatment of the methyl vinyl ketone–piperidone adducts **6a** or **6b** with potassium hydroxide or, better, potassium carbonate yielded 1,3,4,7,8,8a-hexahydro-2-methylisoquinolin-6-one (**17**) which had been obtained previously by McElvain by a slightly different procedure[5] (Scheme III). Conjugate addition of diphenylcopper lithium to the enone **17** should now yield **2b** and/or the cis-fused isomer **18**.[6] High stereoselectivity favoring the cis product had been observed in the copper salt catalyzed conjugate addition of phenylmagnesium bromide to $\Delta^{1(9)}$-2-octalone, which is to our knowledge the only angular arylation of this type reported.[2] Such reaction conditions, when applied by McElvain to the enone **17**, failed to give conjugate addition.[2] However, diphenylcopper lithium in our hands gave a good yield (75%) of a crystalline saturated ketone **18**. This ketone was assigned the cis stereochemistry based on an nmr study of the alcohols **19** and **20** obtained by borohydride reduction and their propionate esters **21** and **22**. In the epimeric pairs, the signal due to the proton attached to the carbon atom bearing the alcohol or propionate functionality was clearly visible in the nmr spectra of these substances. In all the spectra this signal was broadened by the large axial coupling with the neighboring protons. Thus, the substituent is equatorial in both isomers. This is only possible if the ring fusion is conformationally mobile, *i.e.*, cis. In view of the importance of this stereochemical assignment it was confirmed by an X-ray analysis of the methobromide of the ketone **18**.

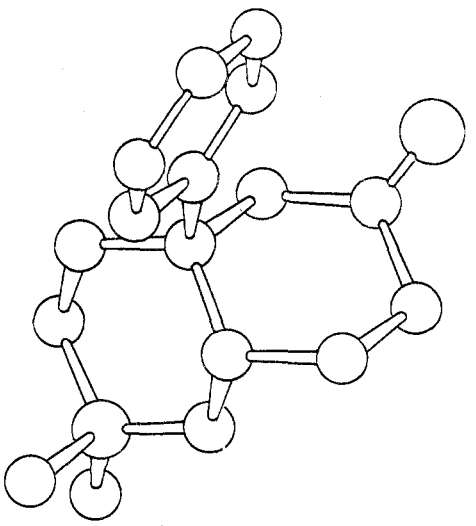


Figure 1. Atomic positions in crystal of methobromide of **18**.

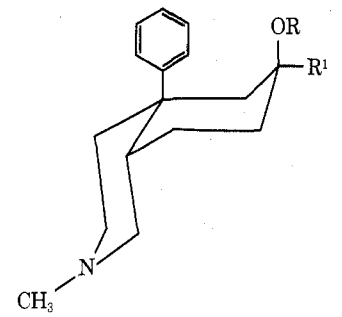
Thin platelet crystals of the quaternary methyl bromide derivative of ketone **18** were obtained from methanol solution. The crystal data for $C_{17}H_{24}BrNO$, mol wt 338.29, are monoclinic, $I2/a$, a = 11.766 (7), b = 9.312 (6), c = 30.46 (2), β = 92.48°, d_{obsd} = 1.34 (2), d_{calcd} = 1.35 g/cm^3 (Z = 8). A total of 1977 reflections were scanned using the θ–2θ technique and Cu Kα radiation on a Picker automated diffractometer; 1577 of these were judged to be above background. There was no significant decay in intensity of the four standard reflections monitored during the course of data collection (see paragraph at end of paper regarding supplementary material).

The bromide ion was located in a straightforward manner from the Patterson synthesis and all other nonhydrogen atoms were evident on an electro-density map phased on the bromide position. Full-matrix least-squares refinement assigning anisotropic thermal parameters to the bromide ion and isotropic parameters to all other atoms resulted in a conventional R factor of 15.8%. Further refinement of the structure was not deemed justifiable in light of the relatively poor quality of the crystals and owing to the fact that the objective of determination of the geometric stereochemistry of the molecule had been achieved. The conformation of the methobromide of ketone **18** as it exists in the crystal is depicted in Figure 1 and clearly agrees with the proposed cis ring fusion.

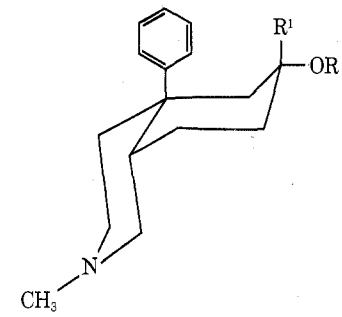
The stereochemical course of the conjugate addition of diphenylcopper lithium to the enone **17** is therefore the same as that observed by McElvain in the copper-catalyzed conjugate addition of phenylmagnesium bromide to $\Delta^{1(9)}$-2-octalone;[2] *i.e.*, addition creates a cis-fused ring system. Analogous results have recently been reported for the addition of dimethylcopper lithium to the enone **17**.[7] The cis ring fusion of the conjugate addition product in this instance was proven by conversion of a derivative to an azatwistane. Wolff–Kishner reduction on ketone **18** yielded a base **26** which could be characterized as a picrate. This picrate was directly compared (tlc, melting point, mixture melting point) with that obtained by Boekelheide,[1,8] and they were not identical. Thus, the compound prepared by Boekelheide[1] has the trans stereochemistry and can be assigned structure **2a**, although a trace of the cis isomer **18** could be detected by tlc.

The chemistry of the diphenylcopper lithium product **18** was explored further. The compound **18** reacted normally with a Wittig reagent, triphenylmethylenephosphorane, to yield **27**.

The remaining problem for us was to make stereochemical assignments to the two alcohols **19** and **20** which had

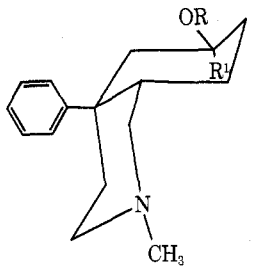


19a, R = R¹ = H; **22a**, R¹ = H, R = CH_3CH_2CO;
24a, R¹ = CH_3, R = H; **25a**, R¹ = CH_3, R = CH_3CH_2CO

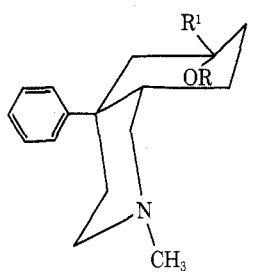


20a, R¹ = R = H; **21a**, R¹ = H, R = CH_3CH_2CO;
23a, R¹ = CH_3; R = H

a conformations



19b, R¹ = R = H; **22b**, R¹ = H, R = CH_3CH_2CO;
24b, R¹ = CH_3, R = H; **25b**, R¹ = CH_3, R = CH_3CH_2CO



20b, R¹ = R = H; **21b**, R¹ = H, R = CH_3CH_2CO;
23b, R¹ = CH_3; R = H

b conformations

been obtained from sodium borohydride reduction of the ketone **18** (Scheme III).

Catalytic reduction in acetic acid of the ketone **18** gave a single product identical (tlc, vpc) with compound **19**, the major product of the borohydride reduction. The identity of the alcohol was also confirmed by comparison of the crystalline propionate hydrochloride **22**. Catalytic reduction of cyclohexanones under acidic conditions has been shown to generate the axial alcohol and the addition of hydrogen can generally be expected to take place from the less hindered side.[9] If we assume that the conformation of **18** on the catalyst is that with the phenyl axial to the carbocyclic ring, *i.e.*, an **a** conformation, then the initial product would be **19a**, which conformationally flips to **19b**.[10] With the assignment of the major borohydride product as the all-cis compound **19b**, the minor product is then necessarily the cis–trans compound **20a**.

Assignment of configuration to the methyllithium adducts **23** and **24** of ketone **18** has been made tentatively by comparison of their nmr spectra with those of the borohydride products **19** and **20**. The major differences in the nmr spectra of **19b** and **20a** are in the pattern of the aromatic protons. The spectrum of compound **19b** shows a multiplet for the five aromatic protons, whereas compound **20a** shows a singlet. If this is assumed to be due to the fact that the compounds have different conformations, then the nmr spectrum of the major methyl carbinol **24** suggests that it has a **b** conformation predominantly whereas the minor methyl carbinol **23** has an **a** conformation. As **24b** readily forms a propionate **25b** it can be assumed to be an equatorial tertiary alcohol; therefore it has an all-cis configuration and the isomeric carbinol **23a** is cis–trans. It had been hoped to confirm these tentative stereochemical assignments by an X-ray crystallographic analysis. Several unsuccessful attempts to grow suitable crystals of an appropriate derivative were made.

An attempt to extend the similarity with the morphine skeleton was thwarted by our inability to prepare *m*-anisyllithium. As were those of McElvain,[2] our attempts to achieve conjugate addition of *m*-anisylmagnesium bromide to the ketone **18** by means of copper catalysis were unsuccessful.

Experimental Section[11]

Attempted Preparation of Ethyl 1-Methyl-4-oxo-3-(3-oxobutyl)nipecotate Monoketal (5a) with Ethylene Glycol. To a suspension of 2.11 g of 57% NaH in 100 ml of toluene and 25 ml of DMF, a solution of 9.1 g (0.049 mol) of ethyl 1-methyl-4-oxonipecotate (**3a**) in 50 ml of toluene was added. After stirring for 2 hr a solution of 0.049 mol of 3-oxobutyl *p*-toluenesulfonate ethylene ketal (**4**) in toluene was added and the mixture was heated for 18 hr to 80°. After cooling, the reaction mixture was poured into water. The toluene layer was repeatedly washed with water and dried. The solvent was removed *in vacuo*, leaving 4.5 g of an oil. The mass spectrum showed no molecular ion for **5a** present. Tlc showed that it was a mixture.

Ethyl and Methyl 4-Oxo-3-(3-oxobutyl)nipecotate (6a and 6b). A mixture of 129 g (0.697 mol) of ethyl 1-methyl-4-oxonipecotate (**3a**), 1 g of 57% NaH, and 550 ml of benzene was stirred at 25° for 1 hr. A solution of 48.7 g (0.697 mol) of methyl vinyl ketone was added dropwise over 30 min. The temperature was kept below 30°. After an additional 45 min the reaction mixture was washed twice with 25 ml of water, dried over Na_2SO_4, and concentrated and the residue was distilled *in vacuo*. The fraction boiling at 142–146° (0.5 mm) was collected, yield of **6a** 178 g (83% of theory), nmr ($CDCl_3$) δ 4.24 (q, 2, CH_2, J = 7 Hz).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.32; H, 8.37; N, 5.35.

The methyl ester **6b** was analogously prepared using the above procedure: yield 66.5% of theory; bp 142–145° (0.5 mm); nmr ($CDCl_3$) δ 3.76 (s, 3, $-COOCH_3$), 3.5–1.2 (m, 16-CH), 2.35 (s, 3, NCH_3), 2.13 (s, 3, $COCH_3$); ir ν_{max} (liquid) 1713, 1230, 745 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.90; H, 8.18; N, 5.87.

Monoketalization of 6a and 6b with Ethylene Glycol. 5a and 5b. An ethyl acetate solution of 165.2 g (0.685 mol) of methyl 1-methyl-4-oxo-3-(3-oxobutyl)nipecotate (**6b**) was treated with anhydrous HCl. The crude hydrochloride was filtered off and refluxed with 72.1 g (1.03 mol) of ethylene glycol in 1.3 l. of benzene for 12 hr using a water separator (15 ml of H_2O collected). After cooling, 500 ml of ether was added and the precipitated crude ketal hydrochloride was filtered off. It was converted to the free base and distilled *in vacuo*: yield 138.8 g; bp 156–158° (0.5 mm) (70.6% of theory); nmr ($CDCl_3$) δ 3.92 (s, 4, $-OCH_2CH_2O-$), 3.77 (s, 3, $OCOCH_3$), 3.5–1.4 (m, 13, $-CH-$), 2.37 (s, 3, NCH_3), 1.31 (s, 3, CH_3); ir ν_{max} (liquid) 1720 and 1230 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.05; H, 8.39; N, 4.82.

The ethyl ester **5a** was prepared analogously by the above procedure: nmr ($CDCl_3$) δ 4.5–1 (m, CH_x), 4.26 (t, J = 7 Hz, CH_2), 4.92 (s, 4, $-OCH_2CH_2O-$), 2.33 (s, 3, $-NCH_3$), 1.3 (s, 3, CH_3); ir ν_{max} (liquid) 1720, 1225 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.20; H, 8.34; N, 4.97.

The hydrochloride had mp 157° dec.

Anal. Calcd for $C_{15}H_{25}NO_5HCl$: C, 53.64; H, 7.80; N, 4.17. Found: C, 53.61; H, 7.93; N, 4.30.

Hydrolysis with KOH of Ethyl Ester 5a to 7 and 10. The reaction mixture, containing 17.2 g (0.057 mol) of the ethyl ester ketal **5a**, 3.23 g of KOH, and 75 ml of water, was refluxed for 2.5 hr. After cooling, 15 g of K_2CO_3 was added and the solution was extracted repeatedly with ether. The ether extracts were dried over K_2CO_3, filtered, and concentrated. The residue (7.4 g) was distilled *in vacuo* (0.2 mm). Two main fractions, 1.8 g (bp 115–125°) and 0.5 g (bp 126–134°), were obtained. The higher boiling fraction, **7**, was purified by preparative gas chromatography [Dexsil GS 300, 3% on Chromosorb G (acid washed and silanized) mesh 60/80 at 180°]: m/e 227 (M^+); nmr ($CDCl_3$) δ 3.92 (s, 4, OCH_2CH_2O), 2.38 (s, 3, NCH_3), 1.31 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.03; H, 9.58; N, 5.89.

The lower boiling material present was identified by mass spectrum, nmr, and analysis as ethyl 2-methyl-α-methylene-1,3-dioxolane-2-butyrate (**10**): nmr ($CDCl_3$) δ 6.17 (s, 1, CH_2=C), 5.57 (s, 1, CH_2=C), 4.24 (q, 2, CH_2, J = 7 Hz), 3.97 (s, 4, OCH_2CH_2O, 2.65–1.65 (m, 4, 2 CH_2), 1.37 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.53.

Hydrolysis with K_2CO_3 of Ethyl Ester 5a to 7. A mixture of 9.0 g (0.03 mol) of ethyl ester ketal **5a**, 12.4 g (0.09 mol) of K_2CO_3, 75 ml of water, and 30 ml of ethanol was refluxed gently for 14 hr. The solution was cooled, 20 g of K_2CO_3 was added, and the solution was extracted three times with ether. The combined ether extracts were dried and concentrated. The residue was distilled *in vacuo*, yield 1.4 g, bp 126–128° (0.5 mm). Gas chromatography indicated that the product was essentially pure and identical with the material obtained by KOH hydrolysis and purified by gas chromatography [glc Dexsil GC 300, 3% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 1.8 min at 210°]. This was identical with the minor product **7** obtained from **5a** and KOH.

4-Hydroxy-1-methyl-3-(3-oxobutyl)-4-phenylpiperidine (8a). A solution of phenyllithium was prepared from 0.625 g (0.09 mol) of Li wire and 6.92 g (0.044 mol) of bromobenzene in 30 ml of ether. With stirring and cooling, a solution of 9.2 g (0.04 mol) of oxo ketal **7** in 25 ml of ether was added dropwise. The reaction mixture was stirred for 4 hr at 25°. After an additional 48 hr at room temperature, water was added dropwise with cooling. The ether layer was separated, dried, and concentrated. The residue was redissolved in ether and extracted with 2 *N* HCl. After addition of Na_2CO_3 solution the aqueous extracts were extracted with ether. The ether extracts were dried and concentrated and the residue, 6.5 g, was distilled *in vacuo*. The main fraction boiled at 175–182° (0.7 mm): yield 4.2 g (40.2% of theory), 97% by glc, of compound **8a** [DC 530, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 5.5 min at 270°]; nmr ($CDCl_3$) δ 7.7–7.2 (m, 5, ArH), 2.28 (s, 3, NCH_3), 1.87 (s, 3, CH_3); ir ν_{max} (liquid) 3440, 1710, 855, 700 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87; N, 5.36. Found: C, 73.59; H, 8.82; N, 5.36.

4-Hydroxy-1-methyl-3-(3-oxobutyl)-4-phenylpiperidine Ketal (8b). To a stirred, cooled solution of phenyllithium prepared from 1.4 g (0.2 mol) of Li wire and 15.7 g (0.1 mol) of bromobenzene in 75 ml of anhydrous ether, a solution of 14.6 g (0.0643 mol) of **7** in 50 ml of anhydrous ether was added dropwise. The reaction mixture was stirred for 4 hr at 25°. After an additional 48 hours at room temperature, water was added dropwise with cooling, and the ether layer was separated, dried, and concentrated, yielding an oil that was distilled at 170–181° (0.3 mm), yield 12.8 g (65.9% of theory) of compound **8b**: nmr ($CDCl_3$) δ 7.7–7 (m, 5, ArH), 3.72 (s, 4, OCH_2CH_2O), 3.1–0.7 (m, 18, CH), 2.24 (s, NCH_3), 1.08 (s, 3, CH_3); glc DC 500, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 6.0 min at 265°. The deketalized material **8a** had a retention time of 4 min under these conditions.

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.78; H, 8.91; N, 4.59. Found: C, 70.60; H, 8.71; N, 4.56.

4a,5,7,8-Tetrahydro-2,6-dimethyl-8a-phenyl-4*H*-pyrano[3,2-c]pyridine (12). A solution of 4.3 g of ketal **8b** and 3.42 g of $TsOH \cdot H_2O$ in 400 ml of benzene was refluxed for 12 hr. After 6 hr at room temperature the reaction mixture was poured into aqueous Na_2CO_3. After mixing well, the layers were separated. The aqueous layer was extracted once with $CHCl_3$. The combined organic fractions were dried and concentrated. The residue was distilled in a Kugelrohr apparatus at 150° (0.4 mm), yield 1.7 g of compound **12**: m/e 243 (M^+); nmr ($CDCl_3$) δ 7.32 (s, 5, ArH), 4.38 (d, 1, J = 4 Hz, C=CH), 2.32 (s, 3, NCH_3), 1.86 (s, 3, CCH_3); ir ν_{max} (liquid) 1684, 756, 697 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.51; H, 8.74; N, 5.97.

A hydrochloride was prepared by dissolving 1.5 g of **12** in ethyl acetate and adding anhydrous HCl. After recrystallization from isopropyl alcohol it melted at 255° dec, nmr ($CDCl_3$) δ 7.37 (s, 5, ArH), 4.41 (d, 1, J = 4 Hz, C=CH).

Anal. Calcd for $C_{16}H_{21}NO \cdot HCl$: C, 68.65; H, 7.92; N, 5.00. Found: C, 68.77; H, 8.12; N, 4.90.

1-Methyl-3-(3-oxobutyl)-4-phenyltetrahydropyridine (9). Polyphosphoric acid (25 g) was liquified by heating to 95°, 1 g of ketal **8b** was added with stirring, and the temperature was maintained for 10 min. The reaction mixture was cooled by adding ice and made basic by addition of NH_4OH. Repeated extraction with $CHCl_3$ yielded an oil which was distilled *in vacuo*: bp 170–180° (0.5 mm); m/e 243 (M^+); nmr ($CDCl_3$) δ 7–7.6 (m, 5, aromatic), 5.92 (t, 2, J = 3.5 Hz, CH=CH), 2.4 (s, 3, NCH_3), 1.97 (s, 3, $COCH_3$); ir ν_{max} (liquid) 1710, 1660, 760, 700 cm^{-1}; glc DC 530, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 6.8 (69.5%), 7.6 min (30.5%) at 230°. Spectral data suggested that the major product was the $\Delta^{3,4}$ isomer and the minor product was the $\Delta^{4,5}$ isomer.

The same product was obtained when 1 g of ketal **8b** was refluxed for 3 hr in a mixture of 20 ml of trifluoroacetic acid and 2 ml of trifluoroacetic anhydride. It was identified by glc and nmr.

Reaction of the Ketal 8b with PPA to give 11. To 26 g of polyphosphoric acid heated to 95°, 1 g of ketal **8b** was added with stirring. After heating for 3 hr, ice and water were added, and the solution was made basic by adding NH_4OH. Repeated extraction of the aqueous solution with $CHCl_3$ yielded 0.5 g of an oil which was subjected to preparative glc. One fraction was identified by nmr and mass spectrum [m/e 243 (M^+)] as the dehydration products **9**, retention times 3.5 and 4.3 min [DC 550, 5% on Chromosorb G (acid washed and silanized) mesh 60/80 at 235°]. The second fraction, retention time 7.5 min, had a molecular ion of m/e 225 corresponding to compound **11**: nmr ($CDCl_3$) δ 8.2–7.3 (m, 5, ArH), 7.0 (s, 1, ArH), 3.67 (s, 2, $-CH_2-$), 3.3–2.6 (m, 6, 3 CH_2), 2.49 (s, 3, NCH_3), 1.33 (t, 3, J = 7 Hz, $-CH_3$); ir ν_{max} (CS_2) 1655, 750 cm^{-1}; uv λ_{max} (MeOH) 231 nm (ϵ 48,600), 286 (5790), 323 (680).

Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.19; H, 8.65; N, 5.90.

1,3,4,7,8,8a-Hexahydro-2-methylisoquinolin-6-one (17). To a solution of 185 g (0.77 mol) of diketo ester **6b** in 1800 ml of water was added 428 g (3.1 mol) of K_2CO_3 and the reaction mixture was refluxed under N_2 for 2 hr, then stirred for an additional 1 hr at room temperature. Following addition of 400 g of K_2CO_3, the solution was cooled in an ice bath and extracted four times with a total of 1.6 l. of ether. The ether extracts were combined, dried over K_2CO_3, and concentrated. The residue was distilled *in vacuo*, yield 74 g (58.2% of theory) of **17**:[5] bp 103–111° (0.2–0.3 mm); 98–99% pure by glc [VC-W98, 3% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 3.6 min, 180°]; nmr ($CDCl_3$) δ 5.81 (s, 1, CH=C), 2.3 (s, 3, NCH_3); ir ν_{max} (liquid) 1670, 1626 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.23; H, 9.85; N, 8.67.

1,3,4,7,8,8a-Hexahydro-2-methyl-4a-phenylisoquinolin-6(8*H*)-one (18). To a stirred suspension of 38 g of cuprous iodide (previously washed with anhydrous ether) in 150 ml of anhydrous ether under nitrogen and cooled to 0–5° was added over a period of 20 min a solution of phenyllithium freshly prepared by allowing 69 g of bromobenzene and 6.1 g of lithium wire to react in 375 ml of anhydrous ether. The mixture was stirred for 30 min at 0°; then a solution of 16.5 g of **17** in 100 ml of anhydrous ether was added dropwise over a 30-min period. After stirring for 30 min at 0–5° and 1.5 hr at room temperature the reaction mixture was poured into a stirred mixture of 75 g of ammonium chloride in 200 ml of water and ice. The mixture was well shaken and filtered and the layers were separated. The aqueous layer was extracted with ether, and the combined ether extracts were washed with

water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, leaving an oil that was distilled, bp 145–155° (0.3 mm), yield 18.2 g (75%). The oil was crystallized from 50 ml of hexane, yield 13.8 g (57%) of the ketone **18**: mp 72–74°; *m/e* 243 (M^+); nmr ($CDCl_3$) δ 7.6–7.1 (m, 5, ArH), 2.34 (s, 3, NCH_3); ir ν_{max} (liquid) 1703, 754, 695 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.91; H, 8.41; N, 5.40.

This was further characterized as the methobromide, mp 300°.

Anal. Calcd for $C_{17}H_{24}BrNO$: C, 60.39; H, 7.15; N, 4.14. Found: C, 60.31; H, 7.16; N, 4.20.

This methobromide was crystallized from methanol to obtain a crystal for X-ray crystallographic analysis.

1,3,4,7,8,8a-Hexahydro-6-hydroxy-6-(*m*-methoxyphenyl)-2-methylisoquinoline. A 15-g portion of *m*-bromoanisole was treated with 2 g of magnesium turnings in 50 ml of anhydrous THF. Reagent was added to a stirred suspension of CuI in 40 ml of THF under N_2 and cooled in an ice bath. After stirring for 45 min at 5° a solution of 6.6 g of the hexahydroisoquinolone **17** in 20 ml of THF was added dropwise over a 20-min period. The reaction mixture was stirred for 1 hr at 5° and 2.5 hr at room temperature, and then was poured into a stirred solution of 20 g of ammonium chloride in 150 ml of ice water. Ether was added, the mixture was well shaken and filtered, and the layers were separated. The aqueous layer was extracted once more with ether, and the combined ether extracts were washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*, leaving a dark brown oil which was purified by preparative tlc. The only pure identifiable product was the 1,2-addition product: mp 109–111°; nmr ($CDCl_3$) δ 7.8–6.6 (m, 4, ArH), 5.51 (s, 1, C=CH), 3.82 (s, 3, OCH_3), 2.22 (s, 3, NCH_3); ir ν_{max} (Nujol) 3115, 1666, 1253 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 75.01; H, 8.54; N, 5.06.

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ol (19). A mixture of 2.4 g of **18** and 1 g of 10% Pd/C in 25 ml of glacial acetic acid was hydrogenated at 60° (1000 psi) for 6 hr. The mixture was filtered and concentrated *in vacuo*, and the residue was dissolved in water, basified with 10% Na_2CO_3, and extracted three times with ether. The combined ether extracts were washed with water, dried over K_2CO_3, filtered, and concentrated *in vacuo*, yielding 2.1 g (86% of theory) of an oil, the alcohol **19**, nmr ($CDCl_3$) δ 7.7–7.0 (m, 5, ArH), 4.0–3.2 (m, 1, CHOH), 2.3 (s, 3, NCH_3).

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ols (19 and 20). To a stirred solution of 2.4 g of **18** in 50 ml of anhydrous ethanol, 1.13 g of sodium borohydride was added in several portions. After stirring for 75 min at room temperature the solution was concentrated *in vacuo*, water and ether were added, and the layers were separated. The aqueous layer was extracted once with ether, and the combined ether extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, leaving 2.3 g (94% of theory) of an oil that was an isomeric mixture of compounds **20** and **19**: nmr ($CDCl_3$) δ 7.71–7.1 (m, 5, ArH), 4.17–3.0 (m, 1, CHOH), 2.31 (s, 3, NCH_3); ir ν_{max} ($CHCl_3$) 3610 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.53; H, 9.91; N, 5.71.

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ol Propionates (21 and 22). A solution of 4.8 g of a mixture of the octahydroquinolinols **20** and **19** in 3.75 ml of propionic anhydride and 6 ml of pyridine was allowed to stand at room temperature for 4 days. The solution was diluted with toluene and concentrated *in vacuo*. The residue was dissolved in ether, treated with ice and 10% aqueous Na_2CO_3, filtered, and concentrated *in vacuo*, leaving 4.4 g (74.5%) of an oil. This oil was dissolved in acetone and the solution was acidified by addition of HCl–EtOAc solution. Two isomers were obtained by fractional crystallization from acetone–ether. The major isomer **22** (1.7 g, 25.7% had mp 247–248° dec; nmr ($CDCl_3$) δ 7.9–7.1 (m, 5, ArH), 5.2–4.7 (m, 1 -CHO–), 2.96 (d, 3, J = 4.5 Hz, NCH_3), 1.13 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{19}H_{27}NO_2 \cdot HCl$: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.20; H, 8.14; N, 4.30.

The minor isomer **21** (0.45 g, 6.8%) had mp 233° dec; nmr ($CDCl_3$) δ 7.43 (s, 5, ArH), 5.33–4.77 (m, 1, -CHO–), 2.68 (d, 3, NCH_3), 1.06 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{19}H_{27}NO_2 \cdot HCl$: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.45; H, 8.46; N, 3.96.

The alcohol **19** obtained from catalytic reduction was acylated under the same conditions. Only a single propionate hydrochloride could be obtained identical (melting point, mixture melting point, nmr, ir) with **22**.

1,3,4,5,6,7,8,8a-Octahydro-2,6-dimethyl-4a-phenylisoquinolin-6-ol (23 and 24). A stirred solution of methyllithium (prepared from 17 g of methyl iodide and 1.7 g of lithium in 200 ml of anhydrous ether) under nitrogen was cooled to −70° and a solution of 9.6 g of **18** in 50 ml of anhydrous ether was added dropwise over a 30-min period. The reaction mixture was stirred for 15 min at −70° and then allowed to warm to room temperature overnight. The mixture was cautiously poured into a stirred solution of 50 g of ammonium chloride in 150 ml of ice water. The mixture was shaken in a separating funnel and the layers were separated. The aqueous layer was extracted twice with methylene chloride, the combined organic layers were dried, filtered and concentrated *in vacuo*, and the residue was triturated with ether, leaving a mixture of two solid isomers which were separated by fractional crystallization from acetone–ether. The major isomer **24** (28%) had mp 177–181°; nmr ($CDCl_3$) δ 7.3 (broad s, 5, ArH), 2.10 (s, 3, NCH_3), 1.04 (s, 3, CCH_3); ir ν_{max} (Nujol) 3190, 765, 693 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.40. Found: C, 79.07; H, 9.26; N, 5.50.

The minor isomer **23** (5.7%) had mp 91–93°; nmr ($CDCl_3$) δ 7.6–7.0 (m, 5, ArH), 2.28 (s, 3, NCH_3), 1.18 (s, 3, CCH_3). As a satisfactory elemental analysis could not be obtained on this material, it was characterized as the maleate, mp 175–176°.

Anal. Calcd for $C_{17}H_{25}NO \cdot C_4H_4O_4$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.40; H, 7.91; N, 3.61.

The major isomer **24** was also converted to a maleate, mp 198–203° dec, for comparison purposes.

Anal. Calcd for $C_{17}H_{25}NO \cdot C_4H_4O_4$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.40; H, 7.53; N, 3.87.

1,3,4,5,6,8a-Octahydro-2,6-dimethyl-4a-phenylisoquinolin-6-ol Propionate (25). A solution of 4 g of **24** in 6 g of propionic anhydride and 20 ml of pyridine was refluxed for 8 hr and then allowed to stand at room temperature for 16 hr. The solution was concentrated *in vacuo*, and the residue was dissolved in methylene chloride, washed with cold 10% sodium carbonate solution and water, and dried over sodium sulfate. Filtration and concentration *in vacuo* left an oil that was triturated with ether–hexane (1:1) and the insoluble solid was filtered off and identified as starting material. The filtrate was concentrated and the maleate salt was prepared from the oil, yield 3.3 g (68%) of oil, 3.6 g (53%) of the maleate: mp 185–186°; nmr ($CDCl_3$) δ 7.38 (s, 5, ArH), 6.27 (s, 2, maleate), 2.66 (s, 3, NCH_3), 1.42 (s, 3, CCH_3), 1.12 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 66.80; H, 7.71; N, 3.35. Found: C, 66.81; H, 7.55; N, 3.46.

Wolff–Kishner Reduction of 18. A mixture of 2.4 g of **18**, 2 g of hydrazine hydrate (99–100%), 2 g of KOH, and 30 ml of diethylene glycol was heated to 100° until the KOH dissolved. The solution was heated to reflux (200° oil bath) for 1 hr, then material was distilled until the temperature of distillate rose to 175° (internal) and the solution was refluxed for 1.5 hr. After cooling to room temperature the solution was diluted with water and extracted four times with ether. Combined extracts were washed with water, dried over K_2CO_3, filtered, and concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate and acidified with HCl–EtAc solution. The precipitate was recrystallized from acetone–isopropyl alcohol to yield 1.15 g (43.3%), mp 222–224°, of compound **26**: nmr ($CDCl_3$), δ 7.7–7.0 (m, 5, ArH); ir ν_{max} (Nujol) 761, 698 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}N \cdot HCl$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.49; H, 9.02; N, 5.52.

The hydrochloride was converted to the free base and a picrate formed, mp 144–146°.

Anal. Calcd for $C_{16}H_{23}N \cdot C_6H_3N_3O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.51; H, 5.76; N, 12.26.

The picrate, mp 212–213°, obtained from Professor Boekelheide[8] was reanalyzed in view of its age.

Anal. Calcd for $C_{16}H_{23}N \cdot C_6H_3N_3O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.62; H, 5.41; N, 12.26.

The two picrates were not identical by melting point and the depression of melting point on admixture. Tlc was carried out on the two picrates (Al_2O_3 GF254 Merck, $CHCl_3$; detection Dragendorff reagent): R_f 0 (picric acid), 0.3 (major), 0.53 (trace) (Boekelheide sample); R_f 0 (picric acid), 0.53 (major) (picrate of **26**).

Wittig Reaction of 18 to 27. To a stirred solution of the triphenylmethylenephosphorane under N_2 (prepared by treating 17.4 g of triphenylmethylphosphonium bromide with 32 ml of 1.6 *M* *n*-butyllithium) in 150 ml of anhydrous ether a solution of **18** (9.6 g) in 50 ml of anhydrous ether was added dropwise. A pale yellow solid precipitated. After stirring for 20 hr at room temperature the solids were filtered off and washed with ether. The combined

ether fractions were washed with water until the water filtrate was neutral and then dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure left 6.5 g of an oil that was distilled, bp 120–135° (0.3 mm), to give **27**: 4.3 g (43%); nmr ($CDCl_3$) δ 7.6–7.0 (m, 5, ArH), 4.67 (d, 2, J = 4 Hz, $=CH_2$), 2.16 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.24; H, 9.33; N, 5.73.

This oil **27** was further characterized as the hydrochloride, mp 208–209° dec.

Anal. Calcd for $C_{17}H_{23}N \cdot HCl$: C, 73.49; H, 8.71; N, 5.04. Found: C, 73.12; H, 8.98; N, 5.06.

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Registry No.—**3a**, 25012-72-0; **3b**, 13221-89-1; **5a**, 50640-99-8; **5a** hydrochloride, 50641-00-4; **5b**, 50641-01-5; **6a**, 50641-02-6; **6b**, 50641-03-7; **7**, 50641-04-8; **8a**, 50641-05-9; **8b**, 50641-06-0; **9**, 50640-72-7; **10**, 50640-73-8; **11**, 50641-07-1; **12**, 50641-08-2; **12** hydrochloride, 50641-09-3; **17**, 19608-59-4; **18**, 50640-74-9; **18** methobromide, 50640-75-0; **19**, 50640-76-1; **20**, 50640-77-2; **21** hydrochloride, 50640-78-3; **22** hydrochloride, 50640-79-4; **23**, 50640-80-7; **23** maleate, 50640-81-8; **24**, 50640-82-9; **24** maleate, 50640-83-0; **25** maleate, 50640-85-2; **26** hydrochloride, 50640-86-3; **26** picrate, 50790-98-2; **27**, 50640-87-4; **27** hydrochloride, 50640-88-5; 1,3,4,7,8,8a-hexahydro-6-hydroxy-6-(*m*-methoxyphenyl)-2-methylisoquinoline, 50790-99-3.

Supplementary Material Available. A table with the final atomic positional and thermal parameters and a figure with bond angles and bond lengths will appear following these pages in the microfilm edition of this volume of the journal. The standard deviations and observed structure factors are no longer available. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1118.

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(9) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 87.
(10) As was pointed out by a referee, **18** is probably a mixture of both conformers. An approximate calculation suggests a 2:1 mixture of **18a** and **18b**.
(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained with Perkin-Elmer spectrophotometers, Models 21 and 521. Nmr spectra were obtained with a Varian A-60 nmr instrument. Mass spectra were obtained with an AEI MS 902 mass spectrometer at 70 eV.

Reaction of Acetylenes with Hydrogen Chloride in Acetic Acid. Effect of Structure upon AdE2 and Ad3 Reaction Rates

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Studies of the initial reaction rate and product composition for the reaction of phenylacetylene, 1-phenylpropyne, 1-hexyne, and *tert*-butylacetylene with HCl in HOAc at 25° are reported. The stereochemistry of HCl addition to 1-hexyne-*1-d* at 50° was also examined. The results are found to be consistent with reaction *via* competing AdE2 and anti Ad3 reaction mechanisms. The results show that the AdE2 and Ad3 mechanisms involve different regiospecificity, as well as stereospecificity. The effect of structure upon reaction rate is found to be quite different in the two mechanisms, implicating significantly different transition-state structures.

In previous papers[1-6] we have presented evidence for two distinct mechanisms for addition of HCl to olefins and acetylenes in acetic acid. Reaction *via* the AdE2 mechanism[1-3] occurs by slow protonation of the unsaturated compound to form a carbonium chloride ion pair in-

olefin (acetylene) + HCl ⟶ $[R^+Cl^-]$ ⟶

RCl + ROAc ⟶ (ketone)

termediate which collapses to a mixture composed mainly of chloride and some acetate, the vinyl acetates formed from acetylenes undergoing a rapid subsequent reaction to form a ketone. The rate of reaction depends upon unsaturated reactant and HCl concentrations, but the ratio of the RCl to ROAc is not influenced by the HCl concentration. Moreover, the presence of chloride salt does not increase the percentage of RCl formed and, at 0.2 *M*, causes a less than threefold rate increase. This shows that, once formed, the ion-pair intermediate collapses rapidly to a product mixture determined solely by the structure of the ion pair and not significantly influenced by the composition of the external reaction solution. The effect of salt upon the rate results from a salt effect upon the rate of formation of the carbonium ion pair. Styrene and *tert*-butylethylene react exclusively *via* this mechanism.[3]

Other olefins and acetylenes exhibit different behavior under the same reaction conditions. Thus, the ratio of RCl to ROAc obtained from 3-hexyne[2] and also from cyclohexene[4,5] varies with the HCl concentration. The presence of chloride salt not only markedly increases the ratio of RCl to ROAc but gives rise to a rate increase indicative of catalysis by chloride ion. Under these conditions addition occurs with anti stereochemistry. The observations imply that an Ad3 addition, formally the reverse of E2 elimination, is involved.

The reaction of 1,2-dimethylcyclohexene has been found to involve AdE2 addition, giving largely syn HCl adduct, at low HCl concentration, but in the presence of chloride salt a more rapid anti Ad3 addition of HCl dominates.[6]

An understanding of how structure influences reactivity in each of these mechanisms is important in designing synthetic procedures and also in understanding the electronic structure of the transition states. We report here