ture. The freeze–quench method made quantitative transfer of samples unnecessary, since the sample withdrawn could be measured directly in the 1-cm cell. Table IV gives the wavelengths and extinction coefficients used in analyzing the data.

Activation parameters were calculated from $\Delta H^{\ddagger} = \Delta E_a - RT$; $\Delta S^{\ddagger}/4.576 - \log k - 10.753 - \log T + E_a/4.576T$; $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

TABLE IV

ABSORPTION MAXIMA OF ACRYLANILIDES AND β-ETHOXYPROPIONANILIDES IN ETHANOL

p-X	Acrylanilide, λ_{max} (10^4 ε)	β-Ethoxypropionanilide, λ_{max} (10^4 ε)
$-OCH_3$	285 (1.32)	252.5 (1.64)
$-CH_3$	277.5 (1.20)	247.5 (1.60)
H	270 (1.08)	245.0 (1.49)
Br	275 (1.45)	252.5 (1.95)
$-CO_2C_2H_5$	290 (2.42)	272 (2.40)

Syntheses of β-Bromopropionanilides.—In a typical example 1 g of ethyl p-aminobenzoate was dissolved in 20 ml of anhydrous ether and mixed with 1 g of β-bromopropionyl chloride diluted with 10 ml of anhydrous ether. After filtering off the fluffy white precipitate of amine hydrochloride, the filtrate was washed with 5% hydrochloric acid and with water, and then evaporated on a rotary evaporator to yield yellow crystals. The yellow crystals were recrystallized from chloroform: p-H, mp 119–120° (lit. mp 119–120°); p-Br,[17] mp 135–136°; p-CH_3,[18] mp 137–138; p-OCH_3,[17] mp 111–112°; p-$CO_2C_2H_5$,[17] mp 119–120°.

Synthesis of Acrylanilides.—In a 50-ml pear-shaped flask equipped with a reflux condenser were placed 1 g of the bromopropionanilide, 20 ml of chloroform, and 1.5 ml of triethylamine. The solution was refluxed 1 hr and then cooled to room temperature. After washing three times each with 20 ml of water, 20 ml of 3 *M* hydrochloric acid, and water, the chloroform was dried with calcium chloride. After filtering the calcium chloride the chloroform was removed on a rotary evaporator, and the residue crystallized from chloroform–carbon tetrachloride. Most samples were then sublimed at reduced pressure: p-H, mp 93–95° (lit. mp 93–94°); p-Br,[17] mp 178–179°; p-CH_3,[17,19] mp 138–139°; p-OCH_3,[17,19] mp 91–92°; p-$CO_2C_2H_5$, mp 113–114° (lit. mp 110–112°).[18]

Synthesis of β-Ethoxypropionanilides.—These were prepared from the bromo compounds by the action of sodium hydroxide and ethanol. In a typical example 52 mg. of β-bromopropionanilide (2.3×10^{-4} mol) was dissolved in 200 ml of 0.030 *M* ethanolic potassium hydroxide and the solution was heated at 55° for 24 hr. After cooling, 0.5 *M* hydrochloric acid was added to an apparent pH of 6 (indicator paper). The solution was evaporated to 20 ml, and filtered with a Büchner funnel. The potassium chloride was washed with chloroform, and the combined filtrate and washings were evaporated on a rotary evaporator. The crude product was sublimed to yield 31 mg (80%) of product. Each preparation was repeated using 50 mg of the acrylanilide and 200 ml of approximately 0.015 *M* ethanolic potassium hydroxide; the work-up and yields were the same as for the bromo compounds. Two triplets were found for the methylene protons and the triplet–quartet pattern of the ethoxy group was easily identified in nmr spectra of the products: p-H,[17] mp 42–44°; p-Br,[17] mp 93–94°; p-CH_3, mp 63–64° (lit. mp 59–60°);[20] p-OCH_3,[17] mp 59–60°; p-$CO_2C_2H_5$,[17] mp 102–103°.

Registry No.—Ethanol, 64-17-5; 3,4′-dibromopropionanilide, 7661-10-1; 3-bromo-4′-methoxypropionanilide, 7661-14-5; 3-bromo-4′-ethoxycarbonylpropionanilide, 21690-53-9; acrylanilide, 2210-24-4; p-bromoacrylanilide, 13997-69-8; p-methylacrylanilide, 7766-36-1; p-methoxyacrylanide, 7766-37-2; p-ethoxycarbonylacrylanilide, 14745-58-5; β-ethoxypropionanilide, 21690-58-4; 4′-bromo-3-ethoxypropionanilide, 21690-59-5; 3-ethoxy-4′-methylpropionanilide, 21690-60-8; 3-ethoxy-4′-methoxypropionanilide, 21690-61-9; 3-ethoxy-4′-ethoxycarbonylpropionanilide, 21690-62-0.

(17) Satisfactory C, H, and N analyses (±0.3%) were obtained for this compound.

(18) R. Oda, S. Tokivra, A. Miyasu, and M. Okano, *Chem. High Polymers* (Tokyo), **16**, 260 (1959); C. K'ung, G. M. Chetrikina, T. A. Sokolva, and M. M. Koton, *Vysohomolekul. Soedin.*, **6** (1), 149 (1964).

(19) K. Yokota, T. Imamura, and Y. Ishii, *Kogyo Kaguku Zasshi*, **68** (11), 2280 (1965); *Chem. Abstr.*, **65**, 12085 (1966). The abstract gives no numerical data.

(20) H. H. Wasserman, B. Suryanarayana, and D. D. Gasetti, *J. Amer. Chem. Soc.*, **78**, 2808 (1956).

The Synthesis and Stereochemical Characterization of Derivatives of *cis*- and *trans*-3-Ethyl-4-piperidineacetic Acid[1a]

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Ethyl 1-benzoyl-3-ethyl-$\Delta^{4,\alpha}$-piperidineacetate (**4**) and ethyl 1-benzoyl-3-ethyl-1,2,3,6-tetrahydropyridine-4-acetate (**5**) have been prepared from 1-benzoyl-3-ethyl-4-piperidone by the phosphonate modification of the Wittig reaction. Compound **4** is partially isomerized into **5** in the presence of base. Catalytic reduction of **4** has been shown to give primarily ethyl *cis*-1-benzoyl-3-ethyl-4-piperidineacetate while **5** gives mainly ethyl *trans*-1-benzoyl-3-ethyl-4-piperidineacetate. The stereochemistry of these products has been established by interrelation with *cis*-1-benzoyl-3-ethyl-4-piperidineacetonitrile from cinchonine *via* trimethylsilyl derivatives of 3-ethyl-1-methyl-4-piperidineethanol. The literature assignments of stereochemistry to the *cis* and *trans* isomers of ethyl 5-ethyl-2-oxo-4-piperidineacetate are shown to be in error.

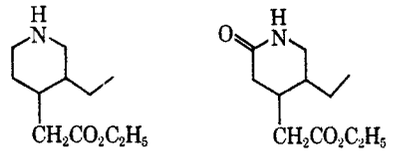
The 3-ethyl-4-piperidineacetic acid skeleton constitutes an important portion of the nonaromatic framework of a number of isoquinoline and indole alkaloids. In connection with synthetic work in the latter area we required a convenient source of 3-ethyl-4-piperidineacetic acid derivatives capable of functionalization at C-5 and having a known stereochemical relationship between the ethyl and acetic acid groups. Two compounds are of particular interest. Stork and McElvain[2] prepared ethyl 3-ethyl-4-piperidineacetate (**1**) but were able only to make a tentative (*cis*) stereochemical assignment. Evstigneeva and Preobrazhenskaya[3] have reported the preparation of crystalline (**2a**, mp 84–85°) and oily stereoisomers (**2b**) of ethyl 5-ethyl-2-oxo-4-piperidineacetate (**2**) and assigned *cis* stereochemistry to the crystalline isomer and *trans* configuration to

(1) (a) This work was supported by National Science Foundation Grant GP 5292; (b) National Defense Education Act Fellow, 1965–1968.

(2) G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).

(3) R. P. Evstigneeva, *J. Gen. Chem. USSR* (Engl. Transl.), **28**, 2494 (1958); R. P. Evstigneeva, Yu. F. Malina and N. A. Preobrazhenskaya, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, **5**, 46 (1958); *Chem. Abstr.*, **53**, 11369 (1959).

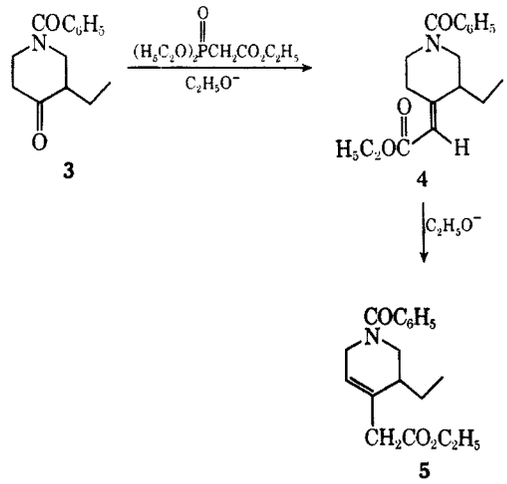
the oily isomer. The work described herein confirms the stereochemistry assigned to **1** but requires revision of the stereochemistry assigned to **2a** and **2b**.



1 **2**

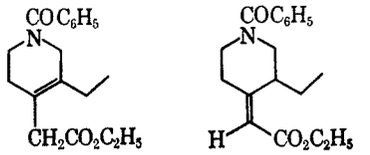
Stork and McElvain prepared **1** by condensing 1-benzoyl-3-ethyl-4-piperidone (**3**) with ethyl cyanoacetate. The condensation product was hydrogenated and then hydrolyzed, decarboxylated, and reesterified. In this work **3** was prepared as described by Stork and McElvain[2] or by a recent modification.[4] The piperidone was then elaborated into **4** by reaction with triethyl phosphonoacetate in ethanol containing sodium ethoxide.[5] The exocyclic ester **4** was partially isomerized into an isomer **5** by excess sodium ethoxide

SCHEME I



present during the Wittig reaction or by treatment with sodium ethoxide in ethanol after purification (Scheme I). The endocyclic isomer **5** was also formed along with **4** when the Wittig reaction was effected with sodium hydride in dimethoxyethane. The pure isomers **4** and **5** could be obtained by careful chromatography of the mixture on silicic acid.

The exocyclic isomer **4** is the expected principal product of the Wittig reaction.[5e] In addition to structure **5**, structures **A** and **B** must be considered as possible products of the base-catalyzed isomerization of **4**. Structure **A** is readily eliminated by the fact that the nmr spectrum of the isomer shows the presence of a vinyl proton as a broad singlet (peak width ~8 Hz at half-height) at δ 5.48 ppm. The ultraviolet spectrum of the isomer shows only end absorption in contrast to that of **4** which has a maximum at 230 mμ, indicating the absence of conjugation in the isomer and ruling out structure **B**. In further support of structure **5** is the presence in the nmr spectrum of a signal (two protons) at 2.93 ppm assigned to the methylene group α to the ester function.

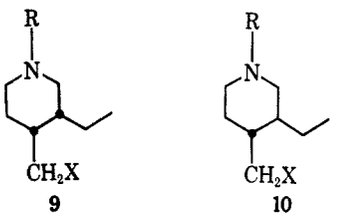


A **B**

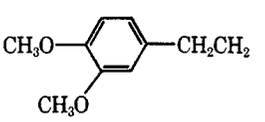
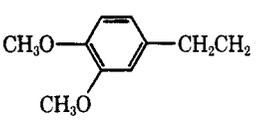
1-Benzoyl-4-piperidone also reacts with triethylphosphonoacetate to give a mixture of ethyl 1-benzoyl-$\Delta^{4,\alpha}$-piperidineacetate (**6**) and ethyl 1-benzoyl-1,2,3,6-tetrahydropyridine-4-acetate (**7**). Other examples of double-bond isomerizations during[5c,d] Wittig reactions involving 4-piperidones have been reported recently.

The exocyclic and endocyclic isomers **4** and **5** give substantially different proportions of the *cis*- and *trans*-3-ethylpiperidineacetic acid derivatives **9a** and **10a** on catalytic hydrogenation. See Chart I. It will

CHART I



9 **10**

Derivative	R	X
a	C_6H_5CO	$CO_2C_2H_5$
b	C_6H_5CO	CO_2H
c	H	CO_2H
d	CH_3	CO_2H
e	CH_3	$CO_2C_2H_5$
f	CH_3	CH_2OH
g	CH_3	$CH_2OSi(CH_3)_3$
h	H	$CO_2C_2H_5$
i		$CO_2C_2H_5$
j		CH_2OH

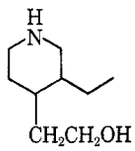
be shown below that the hydrogenation product from **4** consists of about 80% *cis* product **9a** and 20% **10a**, whereas, the ratio is reversed in the case of **5** with **10a** constituting about 80% hydrogenation product. Pure stereoisomeric crystalline acids **9b** and **10b** were readily obtained by saponification of ester samples which were predominantly **9a** and **10a**, respectively.

Since we eventually hoped to functionalize these compounds at C-5, it became necessary to establish the stereochemical relationship between the acetic acid and ethyl side chains. The previous assignment of *cis* stereochemistry to **2a** was made on the basis of in-

(4) J. D. Baty, G. Jones and C. Moore, *J. Chem. Soc., C*, 2645 (1967).

(5) (a) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1960); (b) R. J. Sundberg, P. A. Bukowick, and F. O. Holcombe, *J. Org. Chem.*, **32**, 2938 (1967); (c) C. Szantay, L. Töke, and P. Kolonits, *ibid.*, **31**, 1447 (1966); (d) N. Whittaker, *J. Chem. Soc., C*, 94 (1969); (e) D. H. Wadsworth, O. E. Schupp, III, E. J. Seus, J. A. Ford, Jr., *J. Org. Chem.*, **30**, 680 (1965).

frared comparison of samples of **11** obtained from crystalline **2a** and from quinine which is known to have *cis* stereochemistry.[3] We found that the differences in



11

the infrared spectra of noncrystalline stereoisomers in this series of compounds were usually minor and, therefore, of doubtful reliability for the assignment of stereochemistry.

The mixtures of esters **9a** and **10a** were hydrolyzed by hydrochloric acid into the amino acids **9c** and **10c** which were, without purification, N methylated by formaldehyde–formic acid into **9d** and **10d**. The mixtures of acids **9d** and **10d** were converted into ethyl esters **9e** and **10e**. Lithium aluminum hydride reduction of mixtures of **9e** and **10e** gave the amino alcohols **9f** and **10f**. Finally, these mixtures were converted into the trimethylsilyl ethers **9g** and **10g**. The two isomers were readily separated by gas–liquid chromatography on Carbowax 20M columns. The mixture of **9g** and **10g** derived from **4** was found to consist of 82% **9g** and 18% **10g**. The mixture derived from hydrogenation of **5** was about 79% **10g** and about 21% **9g**.

The same silyl derivatives were prepared from crystalline (**2a**) and oily (**2b**) stereoisomers of **2**. The synthetic sequence being lithium aluminum hydride reduction, methylation with formaldehyde–formic acid and trimethylsilylation. The trimethylsilyl ether derived from **2a** was found to have a retention time identical with that of the principal component (**10g**) of the mixture derived from **5**. The trimethylsilyl ether obtained from **2b** was a mixture of both **9g** and **10g** but it was primarily **9g**. Thus, **2a** and **10a** have identical stereochemistry as do **2b** and **9a**. Unfortunately, if Evstigneeva's assignments[3] are not definitive, this information alone does not establish the stereochemistry of **9a** and **10a**.

To interrelate the trimethylsilyl ethers obtained from **2a**, **2b**, **9a**, and **10a** with a substance of known stereochemistry cinchonine was degraded following the classical scheme[6] into optically active *cis*-1-benzoyl-3-ethyl-4-piperidineacetonitrile (N-benzoylcincholoiponitrile). This material of known *cis* stereochemistry was then hydrolyzed, N methylated with formaldehyde–formic acid, esterified, reduced, and silylated as with **9a** and **10a** to give the trimethylsilyl derivative of *cis*-1-methyl-3-ethyl-4-piperidineethanol (**9g**). Comparison of the retention time of this sample of **9g** with those of samples derived from **4**, **5**, **2a**, and **2b** permitted the following stereochemical conclusions. The exocyclic isomer **4** is hydrogenated primarily into the *cis* product **9a**, whereas **5** gives mainly **10a**. The retention time of the trimethylsilyl derivative from (**2a**) is different from that of **9g** but identical with that of **10g**. Compound **2a** must, therefore, be ethyl *trans*-2-oxo-5-ethyl-4-piperidineacetate. The **9g**–**10g** mixture derived from the oily stereoisomer **2b** is primarily **9g**.

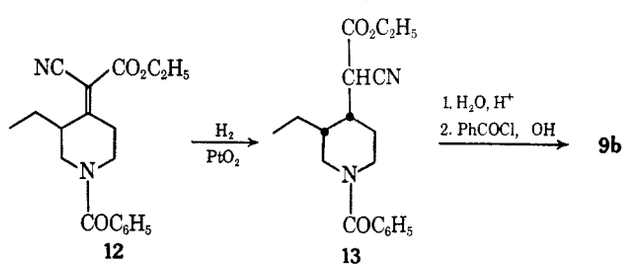
(6) A. Kauffmann, E. Rothlin, and P. Brunnschweiler, *Ber.*, **49**, 2299 (1916).

Fujii[7] has prepared the stereoisomers (**2c**, mp 147–149°, **2d**, mp 205–207°) of 2-oxo-5-ethyl-4-piperidineacetic acid. On the basis of his interrelation of these compounds with **2a** and **2b** the stereoisomer **2c** can be assigned the *trans* configuration and **2d** the *cis* configuration.

Prior to completion of the interrelation of the various products with cinchonine an alternative approach had given reasonably conclusive evidence that the reduction product of **4** was primarily **9a**. The crystalline acid **9b** obtained by saponification was hydrolyzed to **9c** and then esterified with ethanol to give an amino ester **9h**. Compound **9h** was alkylated with 2-(3,4-dimethoxyphenyl)ethyl iodide giving **9i** which was not characterized but was reduced to **9j** with lithium aluminum hydride. This crystalline compound, mp 71.5–72.5°, had an infrared spectrum identical with that of a sample[8] of **9j** kindly supplied by Dr. J. M. Osbond (lit.[8] mp 76.5–79.5°). The infrared spectrum was distinctly different from that of a sample[8] of **10j** supplied by Dr. Osbond (lit.[8] mp 64.5–65.5°).

The preparation of ethyl 1-benzoyl-α-cyano-3-ethyl-4-piperidineacetate (**12**) was repeated as described by Stork and McElvain.[2] Hydrolysis, decarboxylation, and benzoylation afforded **9b**, confirming the original stereochemical assignment.[2] The nmr spectrum of the intermediate ethyl 1-benzoyl-α-cyano-3-ethyl-$\Delta^{4,\alpha}$-piperidineacetate (**13**) indicated that this compound was uncontaminated with any endocyclic isomer. This result is in accord with recent studies on alicyclic ketones.[9] Both **4** and **13**, thus, show a strong preference for reduction by addition of hydrogen from the equatorial side of the exocyclic double bond (Scheme II).

SCHEME II



12 **13**

The stereochemistry of an alternative synthetic route to the systems of interest was also investigated. The piperidineacetic acid skeleton was generated *via* a Mannich reaction of benzylamine or methylamine with the keto triesters **14** and **15**, respectively. Two stereoisomeric piperidones **16a** and **16b** were isolated from the former reaction in approximately equal amount (Scheme III). The stereochemistry of the isomers was not further investigated.

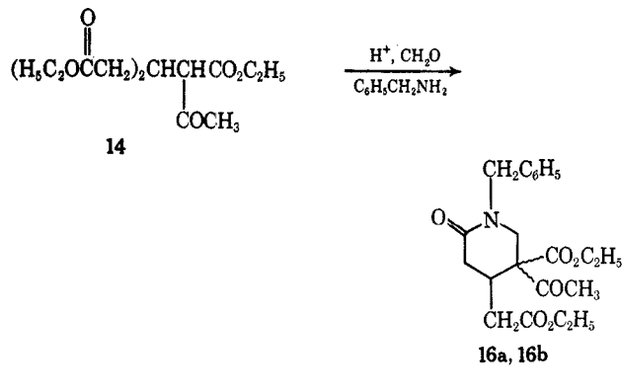
Methylamine condensed with formaldehyde and the ester **15** to give **17**. Pyrolytic distillation removes the carbo-*t*-butoxy group, giving **18** (Scheme IV). The acetyl group was reduced *via* the thioketal. The nmr spectra of **17** and **18** suggested that the compounds were mixtures of stereoisomers. This was confirmed

(7) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

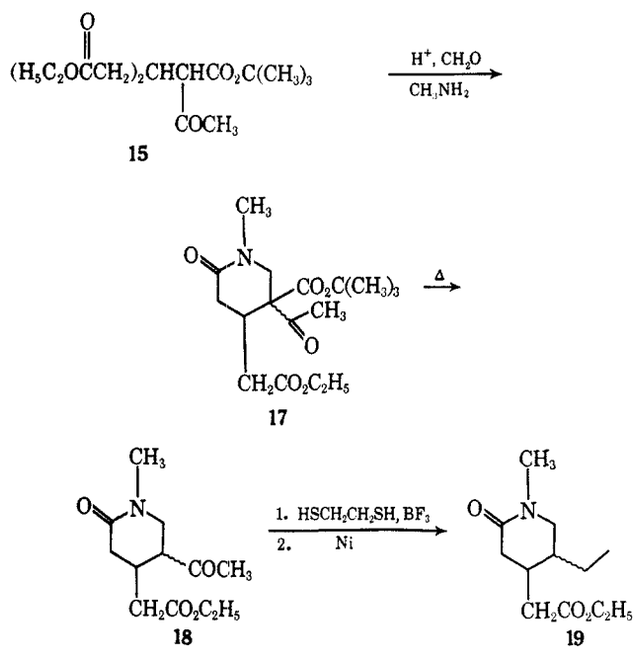
(8) A. Brossi, A. Cohen, J. M. Osbond, P. A. Plattner, O. Schnider, and J. Wickens, *Chem. Ind.* (London), 491 (1958).

(9) N. Itoh, K. Yonezawa, K. Abe, and M. Ohda, *Chem. Pharm. Bull.* (Tokyo), **17**, 206 (1969).

SCHEME III



SCHEME IV



by reducing **19** with lithium aluminum hydride to a mixture of **9f** and **10f**. Analysis of the trimethylsilyl derivative indicated that the *cis* isomer **9g** predominated only slightly, the ratio of **9g** to **10g** being 55:45.

Convenient synthetic routes to both the *cis*- and *trans*-3-ethylpiperidineacetic acid systems are now available. The compound **9b** represents the most conveniently available *cis* derivative of high stereochemical purity, whereas **2a** provides an entry into the *trans* system.

Experimental Section

Reaction of 1-Benzoyl-3-ethyl-4-piperidone with Triethyl Phosphonacetate. A. With Nearly Stoichiometric Amount of Sodium Ethoxide.—The ketone **3** (22.1 g, 0.096 mol) was dissolved in absolute ethanol (20 ml). The resulting solution was added to a solution of the phosphonate anion which had been prepared by adding triethyl phosphonoacetate (23.5 g, 0.105 mol) to a solution of sodium ethoxide prepared from sodium metal (2.5 g, 0.10 g-atom) and absolute ethanol (100 ml). After 45 min, the reaction mixture was poured into brine and extracted with ether. Evaporation of the ether left an oil (29.7 g) shown by thin layer chromatography to contain mainly **4** but also **5**, **3**, and a fourth unidentified contaminant. Chromatography on alumina using 10% ether in benzene as solvent gave pure **4** (16.25 g, 0.0541 mol, 56%) and a fraction containing a mixture of **4** and **5** (4.3 g, 0.014 mol, 14%). An analytical sample of **4** was prepared by short-path distillation: bp 167–170° (0.05 mm); $\nu_{C=O}$ 1710, 1640 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 230 mμ (log ε 4.23); nmr peaks (CCl_4) at δ 7.32 (singlet, 5 H), 5.63 (singlet, 1 H), 3.6–4.1 (multiplet under quartet at 4.08, 4 H), 2.4–3.6 (multiplet, 4 H), 1.8–2.3 (multiplet, 1 H), 1.0–1.7 (multiplet under a triplet at 1.22, 5 H), and 0.85 (distorted triplet, 3 H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.90; H, 7.50.

B. With Subsequent Treatment with Excess Sodium Ethoxide.—The reaction flask was charged as described under A above but after the 45-min reaction period a solution of sodium ethoxide (from 0.8 g of sodium metal and 25 ml of ethanol) was added; the resulting solution was kept at room temperature for 2 hr prior to work-up. The product was separated into fractions rich in **4** and **5** by a preliminary chromatography on silicic acid. Rechromatography of these fractions on silicic acid using 7–10% ether in benzene as the solvent gave pure **4** (8.61 g, 0.0287 mol, 30%), pure **5** (6.6 g, 0.022 mol, 23%) and a mixed fraction (1.45 g, 0.0048 mol, 5%). An analytical sample of **5** was prepared by short-path distillation: bp 173–178° (0.05 mm); $\nu_{C=O}$ 1730, 1630 cm^{-1}, no $\lambda_{max}^{95\%\ EtOH}$ 290–220 mμ; nmr peaks (CCl_4) at δ 7.29 (singlet, 5 H), 5.48 (broad singlet, 1 H), 3.7–4.5 (multiplet under a quartet at 4.07, 4 H), 3.0–3.7 (multiplet, 2 H), 2.93 (broad singlet, 2 H), 1.8–2.4 (multiplet, 2 H), 1.0–1.7 (multiplet under a triplet at 1.22, 5 H) and 0.7–1.0 (multiplet, 3 H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.74; H, 7.60.

Isomerization of Ethyl 3-Ethyl-$\Delta^{4,\alpha}$-piperidineacetate (4).—Chromatographically pure **4** (9.0 g, 0.030 mol) was dissolved in ethanol (50 ml) and treated with a solution of sodium ethoxide prepared from sodium metal (0.15 g, 0.007 g-atom) and ethanol (10 ml). The reaction mixture was stirred at room temperature for 3 hr and then poured into brine. The mixture was extracted with ether and the ether was dried over magnesium sulfate and concentrated to dryness giving 7.3 g (81%) of an approximately 1:1 mixture of **4** and **5** as indicated by infrared absorptions of equal intensity at 1710 and 1735 cm^{-1}. Chromatography on silicic acid using 10% ether in benzene as the eluent separated the mixture to give pure **4** (3.2 g) and **5** (3.0 g).

Ethyl 1-Benzoyl-$\Delta^{4,\alpha}$-piperidineacetate (6) and Ethyl 1-Benzoyl-1,2,3,6-tetrahydropyridine-4-acetate (7).—1-Benzoyl-4-piperidone[4] (3.2 g, 0.016 mol) was dissolved in dry dimethoxyethane (15 ml). This solution was added to solution in dimethoxyethane (50 ml) prepared from triethylphosphonoacetate (4.5 g, 0.020 mol) and sodium hydride (0.6 g, 0.025 mol) which had been washed free of mineral oil. The solution was stirred at room temperature for 1 hr and then poured into brine. The solution was extracted with ether. After the solution was dried and distilled, a mixture of **6** and **7** (1.8 g, 0.007 mol, 43%) was obtained: bp 150–170° (0.05 mm). Judging from the nmr spectrum of the mixture **6** predominated by a ratio of 1.3:1.

Separation of **6** and **7** was effected by chromatography on silicic acid using 20% ether in benzene as solvent. The exocyclic isomer **6** was eluted first. It solidified and was recrystallized from ether–hexane: mp 104–106°; nmr peaks ($CDCl_3$) at δ 1.27 (triplet, 3 H), 2.35 (broad triplet, 2 H), 3.00 (broad triplet, 2 H), 3.70 (multiplet, 4 H), 4.18 (quartet, 2 H), 5.85 (singlet, 1 H) and 7.45 (singlet, 5 H).

Anal. Calcd for $C_{16}N_{19}NO_3$: C, 70.31; N, 7.01; N, 5.13. Found: C, 70.43; N, 7.15; N, 5.07.

The endocyclic isomer was an oil: nmr peaks ($CDCl_3$) at 1.25 (triplet, 3 H,), 2.2 (broad signal, 2 H), 3.03 (singlet, 2 H), 3.6 (broad signal, 2 H), 4.13 (quartet superimposed on broad signal, 4 H), 5.45 (broad singlet, 1 H), 7.40 (singlet, 5 H).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.17; H, 7.01; N, 5.05.

Ethyl *cis*-1-Benzoyl-3-ethyl-4-piperidineacetate (9a).—A solution of **4** (0.39 g, 1.3 mmol) in ethanol (20 ml) was hydrogenated at 30 psi over 10% palladium on carbon for 45 min. Filtration, evaporation and bulb to bulb distillation gave a mixture of **9a** and **10a** in quantitative yield: $\nu_{C=O}$ 1720, 1630 cm^{-1}; nmr peaks at δ 7.31 (singlet, 5 H), 4.0 (quartet, 2 H), 3.5–4.0 (multiplet, 2 H), 2.7–3.4 (multiplet, 2 H), 2.2 (singlet, 2 H), 1.0–1.7 (multiplet under a triplet at 1.12, 8 H) and 0.8–1.0 (multiplet, 3 H).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31. Found: C, 71.41; H, 8.50.

Subsequent experiments (see text) indicate about 20% contamination by the *trans* isomer **10a**. The nmr and infrared spectra of the product prepared by reduction over platinum were identical with that of the product described above.

cis-**1-Benzoyl-3-ethyl-4-piperidineacetic Acid (9b).**—The **9a–10a** mixture from hydrogenation of **4** (2.4 g, 0.008 mol) was dissolved in 95% ethanol (15 ml) and treated with a solution of sodium hydroxide (0.35 g) in water (15 ml). The reaction mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with cold alkaline brine, extracted with ether, and then acidified with dilute hydrochloric acid. The acidic product was isolated by extraction with ether. The dried, concentrated extract crystallized on standing giving **9b** (1.6 g, 0.006 mol, 74%), mp 125–133°. The analytical sample was prepared by several recrystallizations from benzene: mp 136–137°; ν_{OH} 2500–3300; $\nu_{C=O}$ 1595, 1730 cm^{-1}; nmr peaks ($CDCl_3$) at δ 10.9 (singlet, 1 H), 7.4 (singlet, 5 H), 2.6–5.0 (multiplet, ~5 H), 2.35 (singlet, 2 H) and 0.6–2.0 (multiplet, ~9 H).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.90; H, 7.80; N, 5.19.

Ethyl *trans*-**1-Benzoyl-3-ethyl-4-piperidineacetate (10a).**—Chromatographically pure endocyclic isomer **5** was hydrogenated over 10% palladium on charcoal as described above. Distillation gave a mixture of **9b** and **10b** as an oil: bp 165–175° (0.05 mm); $\nu_{C=O}$ 1740, 1645 cm^{-1}; nmr peaks ($CDCl_3$) at δ 7.30 (singlet, 5 H), 4.1 (quartet on a multiplet, 4 H), 2.0–3.3 (multiplets, 5 H), 1.0–2.0 (multiplet under a triplet at 1.22, 8 H) and 0.9 (multiplet, 3 H).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.40; H, 8.16; N, 4.63.

Subsequent experiments suggest ~20% contamination by the *cis* isomer in product isolated in this manner. Use of platinum oxide catalyst gave a reduction product having nmr and infrared spectra identical with those of the above product.

trans-**1-Benzoyl-3-ethyl-4-piperidineacetic Acid (10b).**—Saponification as described for the *cis* isomer **9b** gave **10b** (86% yield), mp 133–142°. The analytical sample was obtained by recrystallization from benzene: mp 141–143°, ν_{OH} 2300–3300, $\nu_{C=O}$ 1595, 1720 cm^{-1}; nmr peaks ($CDCl_3$) at δ 10.9 (singlet, 1 H), 7.5 (singlet, 5 H), 0.6–5.0 (multiplet, ~16 H).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.89; H, 7.58; N, 5.14.

Ethyl *cis*-**1-Methyl-3-ethyl-4-piperidineacetate (9e).**—Compound **4** (2.0 g, 7.0 mmol) in absolute ethanol was hydrogenated at 30 psi over 10% palladium-on-carbon catalyst (0.4 g). After 3–4 hr, the solution was filtered and concentrated to give **9b** (containing ~20% **10b**) as a clear oil. The oil was refluxed with 40 ml of concentrated HCl overnight (N_2 atmosphere). The resulting solution was cooled and filtered to remove the precipitated benzoic acid and was then evaporated to dryness on a rotary evaporator. To the residue there was added 0.5 ml of concentrated ammonium hydroxide, 30 ml of 90% formic acid and 15 ml of 37% aqueous formaldehyde. The resulting solution was refluxed for 18 hr, concentrated hydrochloric acid (5 ml) was added and the solution was then evaporated to a viscous oil. This residue was thoroughly dried using a vacuum pump and then dissolved in absolute ethanol (60 ml). Concentrated sulfuric acid (0.15 ml) was added and the solution was refluxed for 48 hr. The solution was cooled and poured into cold alkaline water. The solution was extracted with ether. The ether was extracted with dilute hydrochloric acid. The aqueous layer was made alkaline and extracted with ether. The extract was dried and concentrated. Distillation of the residue gave **9e** as a mobile colorless liquid, bp 78° (0.1 mm), containing ~20% *trans* isomer: $\nu_{C=O}$ 1730 cm^{-1}; nmr peaks at δ 4.10 (quartet, 2 H), 2.0–3.0 (multiplet under singlet at 2.15, ~8 H) and 0.8–2.0 (multiplet under triplet at 1.22, ~12 H).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87. Found: C, 67.61; H, 10.89.

Ethyl *trans*-**1-Methyl-3-ethyl-4-piperidineacetate (10e).**—The sequence of reactions described for the preparation of the *cis* isomer was applied to the endocyclic ester **5**. Compound **10e** (containing ~20% **9e**) was obtained as a mobile liquid: bp 73° (0.08 mm); $\nu_{C=O}$ 1740 cm^{-1}; nmr peaks (CCl_4) at δ 4.08 (quartet, 2 H), 2.2–3.0 (multiplet, 4 H), 2.12 (singlet, 3 H), 1.1–2.0 (multiplet under a triplet at 1.22, 10 H) and 0.8–1.0 (multiplet, 3 H).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.31; H, 10.69; N, 6.83.

1-Methyl-3-ethyl-4-piperidineethanol. A. *cis* **Isomer 9f.**—Compound **9e** (0.050 g, 2.3 mmol) in ether (8 ml) was slowly added to a suspension of $LiAlH_4$ (0.057 g, 1.5 mmol) in dry ether (10 ml). The reaction mixture was stirred at room temperature for 1 hr and then refluxed 0.5 hr. The standard hydrolysis technique for basic products[10] was employed. Evaporation of the ether and tetrahydrofuran gave a colorless oil. The basic product was isolated by a standard extraction sequence and distilled giving **9f** (0.31 g, 1.8 mmol, 79%): bp 75° (0.03 mm); ν_{OH} 3100–3400 cm^{-1} (very broad); nmr peaks at δ 3.72 (singlet, 1 H), 3.50 (triplet, 2 H), 2.15 (singlet, 3 H) and 2.0–3.0 (multiplet, 3 H), 1.1–1.8 (multiplet, 7 H) and 0.8–1.0 (multiplet, 3 H).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.08; H, 12.50; N, 8.30.

A trimethylsilyl derivative was prepared by refluxing a solution of **9f** (0.040 g) in hexamethyldisilazane (0.8 ml) overnight (nitrogen atmosphere). Analysis of a hexane solution of the derivative indicated that the *cis* isomer **9g** predominated over the *trans* isomer (**10g**) by a ratio of 82:18.

B. *trans* **Isomer 10f.**—Compound **10e** was reduced as described above for **9e** to give **10f** as a colorless oil (0.34 g, 2.0 mmol, 87%): bp ~80° (0.05 mm); ν_{OH} 3100–3400 cm^{-1} (very broad); nmr peaks (CCl_4) at δ 4.05 (singlet, 1 H), 3.50 (triplet, 2 H), 2.5–3.0 (multiplet, 2 H), 2.17 (singlet, 3 H), 1.1–2.0 (multiplet, 10 H), 0.8–1.0 (multiplet, 3 H).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.21; H, 12.36; N, 8.18. Found: C, 69.92; H, 12.36; N, 8.23.

Analysis of the trimethylsilyl derivative of this product as described for the *cis* isomer indicated a **9g**:**10g** ratio of 21:79.

Ethyl *cis*- **and** *trans*-**5-Acetyl-1-benzyl-5-carboethoxy-2-oxo-4-piperidineacetate.**—The triethyl ester **14**[11] (6.1 g, 19 mmol) was dissolved in absolute ethanol (10 ml). Benzylamine (2.3 ml) and 37% aqueous formaldehyde (2.2 ml) were added and the resulting solution was kept slightly warm for 4 days. The reaction mixture was concentrated to a viscous oil on a rotary evaporator and the residue was dissolved in ether. The ether solution was washed with dilute hydrochloric acid, dried, and concentrated giving a golden oil (6.42 g, 16.5 mmol, 87%) consisting of roughly equal amounts of **16a** and **16b**. Chromatography on alumina gave partial separation of the two components. Rechromatography of the partially separated fractions gave the pure stereoisomers **16a** and **16b**. The most readily eluted component **16a** showed $\nu_{C=O}$ 1730, 1710, and 1650 cm^{-1}. The nmr spectrum ($CDCl_3$) showed peaks at δ 1.11 and 1.24 (triplets, both $OCH_2\mathbf{CH_3}$), 2.03 (singlet, $COCH_3$), 2.23 (nearly symmetrical doublet, $CH_2CO_2C_2H_5$), 2.5–3.4 (multiplet, ring CH_2CN), 3.62 (unsymmetrical doublet, ring CH_2N), 4.12 (quartet, both OCH_2CH_3) superimposed on weak unassigned signals, 4.53 (singlet, $NCH_2C_6H_5$) and 7.24 (singlet, C_6H_5).

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.57; H, 7.10; N, 3.81.

The less readily eluted **16b** showed $\nu_{C=O}$ 1735, 1715, and 1650 cm^{-1}. The nmr spectrum ($DCCl_3$) showed signals at δ 1.18 and 1.25 (triplets, both $CO_2CH_2\mathbf{CH_3}$), 2.03 (singlet, $COCH_3$), 2.1–2.78 (multiplet, ring CH_2CN and $CH_2CO_2C_2H_5$), 3.68 (singlet, $NCH_2C_6H_5$), 4.13 (quartet, both OCH_2CH_3), 4.60 (unsymmetrical doublet, ring CH_2N), and 7.27 (singlet, C_6H_5).

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.79; H, 7.10; N, 3.50.

Ethyl 4-(*t***-Butoxycarbonyl)-2-(ethoxycarbonylmethyl)-5-oxohexanoate (15).**—Diethyl glutaconate (44.3 g, 0.238 mol) and *t*-butyl acetoacetate (38.0 g, 0.240 mol) were mixed in *t*-butyl alcohol (50 ml). The solution was maintained at 90–100° and kept alkaline (pH 8) by occasional addition of a solution of potassium *t*-butoxide in *t*-butyl alcohol for a period of 16 hr. The yellow solution was then poured into a mixture of ice-cold dilute sulfuric acid and ether. The ether layer was separated and the acidic aqueous solution was extracted with additional ether. The combined ether solutions were washed with aqueous sodium chloride, dried over magnesium sulfate, and concentrated on a rotary evaporator. Distillation of the residue gave **15** suitable for further preparative use (36.0 g, 0.105 mol, 44%), bp 170–180 (1–3 mm, some decomposition, as evidenced by gas evolution, occurs during distillation). An analytical sample was collected by redistillation: bp 162° (1 mm); $\nu_{C=O}$ 1725 cm^{-1} nmr peaks at (CCl_4) δ 4.10 (quartet, 4 H), 3.71 (doublet, 1 H), 2.40 (doublet, 4 H), 2.2 (singlet, 3 H), 1.43 (singlet, 9 H), and 1.25 (triplet, 6 H).

(10) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 27.

(11) R. Lukes and J. Palecek, *Collect. Czech. Chem. Commun.*, **29**, 1073 (1964); *Chem. Abstr.*, **60**, 13136 (1964).

Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.28; H, 8.19. Found: C, 59.42; H, 8.17.

Ethyl 5-Acetyl-5-(*t*-butoxycarbonyl)-1-methyl-2-oxo-4-piperidineacetate (17).—The *t*-butyl ester **15** (3.0 g, 9 mmol) was dissolved in *t*-butyl alcohol (4 ml). Aqueous methylamine (40%, 0.8 ml) and formaldehyde solution (37%, 1.2 ml) were added and the mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with ether and extracted with dilute hydrochloric acid. The ether layer was dried over magnesium sulfate and concentrated. The residual oil showed a strong amide carbonyl absorption. Chromatography on silicic acid gave some recovered ketoester (eluted with 10% anhydrous ether in benzene). Moist ether eluted **17** as a clear oil which was distilled in a shortpath apparatus at 0.05 mm to give pure **17** (0.43 g, 1.2 mmol, 14%): $\nu_{C=O}$ 1725, 1650 cm^{-1}; nmr peaks (CCl_4) at δ 4.13 (quartet, 2 H), 3.60 (singlet, 2 H), 2.88 (singlet, 3 H), 2.0–2.5 (multiplet, ~6 H), 1.48 (singlet, 9 H), and 1.28 (singlet, 3 H).

Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.80; H, 7.97; N, 4.10. Found: C, 60.01; H, 8.16; N, 4.35.

Ethyl 5-Acetyl-1-methyl-2-oxo-4-piperidineacetate (18).—The *t*-butyl ester **15** (36.0 g, 0.105 mol) was dissolved in *t*-butyl alcohol (48 ml). Formaldehyde (37% solution, 14 ml) and aqueous methylamine (40% solution, 10 ml) were added. The resulting solution was stirred for 1 week with slight warming from a magnetic stirrer. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ether. The ether extract was washed with dilute hydrochloric acid and then with sodium chloride solution. The ether solution was dried and concentrated to a viscous oil. Distillation resulted in the vigorous evolution of a gas at 190–215° (1 mm) and in the distillation of **18** as a yellow oil (5.9 g, 0.024 mol, 23%): bp 158–163° (0.07 mm) after redistillation; $\nu_{C=O}$ 1730, 1715, 1650 cm^{-1}; nmr peaks at δ 4.1 (quartet, 2 H), 3.3 (doublet, 2 H), 2.83 (singlet, 3 H), 2.1–2.4 (singlet superimposed on a multiplet, ~7 H) and 1.22 (triplet, 3 H).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94. Found: C, 59.45; H, 7.98.

Ethyl 5-Ethyl-1-methyl-2-oxo-4-piperidineacetate (19).—Compound **18** (2.0 g, 8 mmol) was treated with 2.5 ml of ethanedithiol and then with 2.2 ml of boron trifluoride etherate. The resulting solution was kept at room temperature for 15 min then cooled to 0° and treated with 1.0 *N* NaOH (4 ml) followed by ether (20 ml). The ether layer was separated and washed three times with 0.1 *N* NaOH. The crude thioketal was isolated by drying the ether over magnesium sulfate and evaporating the volatile solvent. The residue was refluxed for 20 hr with prereduced Raney nickel in absolute ethanol. The nickel was removed by filtration and thoroughly washed with hot ethanol. Concentration and distillation gave **19** as a colorless oil (0.68 g, 3.0 mmol, 36%): bp 122–130° (0.05 mm, short path): $\nu_{C=O}$ 1740, 1600 cm^{-1}; nmr peaks at δ 4.10 (quartet, 2 H), 3.0–3.3 (multiplet, 2 H), 2.83 (singlet, 3 H), 1.5–2.5 (multiplet with broad singlet at 2.2, ~7 H), 1.3 (triplet, 3 H), and 0.8–1.1 (multiplet, 3 H).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.15; H, 9.55; N, 6.09.

A solution of **19** (0.40 g, 1.8 mmol) in tetrahydrofuran was added slowly to a suspension of lithium aluminum hydride (0.100 g) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 0.5 hr and then refluxed for 1.5 hr. The usual work-up procedure gave the basic product as an oil which was subjected to short-path distillation to give a mixture of **9f** and **10f** (0.20 g, 1.2 mmol, 65%), bp 85° (0.05 mm).

The O-trimethylsilyl derivative was prepared and analyzed by glpc. Peaks having retention times identical with those of **9g** and **10g** were observed in the ratio 55:45.

***cis*- and *trans*-Ethyl Esters of 5-Ethyl-2-oxo-4-piperidineacetic Acid (2a and 2b).**—Diethyl 3-(1-cyanopropyl)glutaconate[12] (7 g, 0.02 mol) was dissolved in absolute ethanol (50 ml) and hydrogenated over Raney nickel (W-7) for 2 hr at 100° at a pressure of 1400 psi. The reaction mixture was cooled, filtered and evaporated to an oil which partially solidified. The mixture was washed with ether leaving the crystalline isomer **2a**, mp 83–85° (lit.[3] mp 84–85°). The ether washings were concentrated and chromatographed on silicic acid. A total of 3.2 g (0.015 mol, 68%) of **2a** and 0.85 g (0.004 mol, 18%) of **2b** were obtained.

Reduction, Methylation, and Trimethylsilylation of 2a and 2b.

A. Isomer 2a.—The crystalline **2a** (1 g, 5 mmol) in tetrahydrofuran (10 ml) was added to a suspension of lithium aluminum hydride (0.72 g) in tetrahydrofuran (20 ml). The mixture was stirred at 25° for 0.5 hr and then refluxed for 1 hr. Standard work-up gave 0.58 g (74%) of 3-ethyl-4-piperidineethanol. A portion of the product (0.58 g, 3.7 mmol) was refluxed in a mixture of formic acid (6.2 g) and 37% formaldehyde solution (2.6 g) for 4 hr. Concentrated hydrochloric acid was added until the solution was strongly acidic. The mixture was concentrated, made alkaline with 40% sodium hydroxide, diluted with water, and extracted with ether. The ether was evaporated and the residue was subjected to bulb-to-bulb distillation and then refluxed overnight with hexamethyldisilazane (6 ml). Distillation gave 0.118 g of the trimethylsilyl derivative **10g**. No trace of **9g** was detected by glpc analysis.

B. Isomer 2b.—A sample of **2b** was subjected to the same sequence of reactions. The trimethylsilyl derivative was predominantly **9g**.

Optically Active 9g from Cinchonine.—N-Benzoylcincholoiponitrile from cinchonine[6] was refluxed for 48 hr in 6 *N* hydrochloric acid. The solution was cooled, filtered, extracted with ether, and evaporated to dryness. Methylation and esterification were carried out as for **9e** from **4**. The infrared spectrum of this sample was identical with that of **9e** from **4** but different from that of **10e**. A solution of 1 g of **9e** prepared in this manner was reduced in ether (20 ml) with lithium aluminum hydride (1.1 g). The basic product was isolated in the usual manner to give **9f** (70% yield). The infrared spectrum matched that of **9f** and differed from that of **10f**. The trimethylsilyl derivative **9g** was prepared by refluxing for 12 hr with hexamethyldisilazane (8 ml).

Gas–Liquid Phase Chromatography.—A 0.125 in. × 10 ft column of Carbowax 20M (15% on Chromosorb W) was used at 180–182°. The carrier gas was nitrogen and the flow rate was 35 ml/min. A Wilkens Aerograph HY-FI instrument with flame detector was used. The relative retention times of **9g** to **10g** was 0.92–1.00.

***cis*-3-Ethyl-1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidineethanol (9j).**—A solution of **9b** (0.7 g, 2.5 mmol) was refluxed in 50 ml of 11 *N* hydrochloric acid for 8 hr and then evaporated to dryness at reduced pressure. The residue was washed with chloroform and the residue was refluxed for 40 hr in ethanol (15 ml) containing concentrated sulfuric acid (5 ml). The reaction solution was diluted with water, extracted with ether, brought to pH 11 with sodium carbonate, and extracted with ether. After drying over magnesium sulfate the solution was evaporated. Distillation of the residue gave **9h** (130 mg). Without further characterization the amino ester **9h** was refluxed for 23 hr in dry acetone (10 ml) with 0.2 g of 2-(3,4-dimethoxyphenyl)ethyl iodide and 0.1 g sodium carbonate. The reaction solution was diluted with water, extracted with ether, and concentrated giving 250 mg of a light oil, presumably **9i**, which was dissolved in tetrahydrofuran and refluxed for 2.5 hr with lithium aluminum hydride (0.08 g). The basic product was isolated as an oil which had mp 71.5–72.5° after recrystallization from petroleum ether. The infrared spectrum was identical with that of a sample of authentic **9j**, mp 78.5–79.5°, kindly supplied by Dr. J. M. Osbond.

Stereochemistry of Hydrogenation of Ethyl 1-Benzoyl-α-cyano-3-ethyl-$\Delta^{4,\alpha}$-piperidineacetate (13).—A sample of **13** (9.1 g, 0.028 mol) was prepared as described by Stork and McElvain[2] and reduced over platinum oxide. The product was refluxed for 24 hr with concentrated hydrochloric acid (100 ml) and cooled. The solution was filtered and extracted with ether to remove benzoic acid and then evaporated to a light brownish yellow residue. The residue was dissolved in water (60 ml), sodium bicarbonate (41 g) was added, and benzoyl chloride (9 ml) was added over 15 min. The solution was stirred vigorously for 1.5 hr, filtered and extracted with chloroform. The solution was acidified, giving an oil. The oil was stirred for 2 hr with 10% sodium hydroxide, and the solution was washed with ether. Acidification followed by extraction with ether gave a solid which was recrystallized from hexane–benzene (1.9 g, 0.0076 mol, 27%), mp 131–136°. The infrared spectrum was identical with that of **9b**.

(12) R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskaya, *Zh. Obshch. Khim.*, **22** 1467 (1952); *Chem. Abstr.*, **47**, 5949 (1953).

Registry No.—**2a**, 21372-26-9; **4**, 21363-68-8; **5**, 21389-71-9; **6**, 21363-69-9; **7**, 21363-70-2; **9a**, 21372-27-0; **9b**, 21372-28-1; **9c**, 21372-29-2; **9e**, 21372-30-5;

9f, 21372-31-6; **9**, 21372-61-2; **10a**, 21372-32-7; **10b**, 21372-33-8; **10c**, 21372-34-9; **10e**, 21372-35-0; **10f**, 21372-36-1; **15**, 21363-71-3; **16a**, 21372-37-2; **16b**, 21389-72-0; **17** (*cis*), 21372-38-3; **17** (*trans*), 21372-62-3; **18** (*cis*), 21372-39-4; **18** (*trans*), 21372-63-4; **19** (*cis*), 21372-40-7; **19** (*trans*), 21372-64-5.

The Nitro Enol, 3-Hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one, and Its Reactive Methyl Ether[1]

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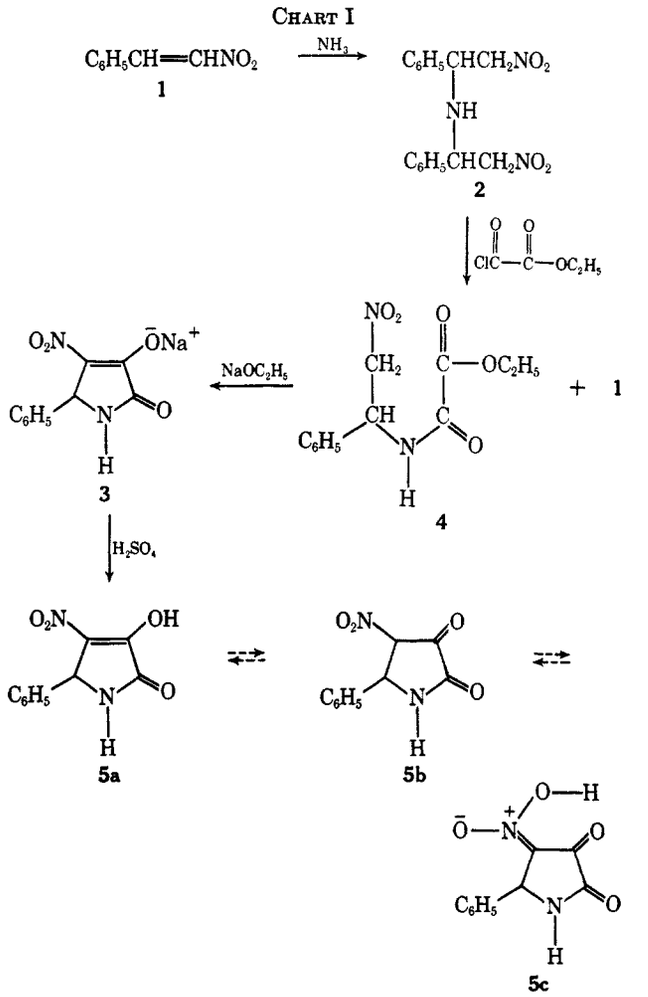
A completely enolized cyclic α-nitro ketone, 3-hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one (**5a**), was prepared by means of the base-catalyzed cyclization of ethyl N-(1-phenyl-2-nitroethyl)oxamate (**4**). The nitro enol, a very strong acid, was the only tautomer which could be detected. The enol underwent facile ring cleavage as a result of nucleophilic attack by water or amines at the 3 position. Methylation of the nitro enol with diazomethane yielded the methyl enol ether, 3-methoxy-4-nitro-5-phenyl-3-pyrrolin-2-one (**8**). The product was shown to be the enol ether rather than the isomeric keto nitronic ester by sodium borohydride reduction to 3-methoxy-4-nitro-5-phenylpyrrolidin-2-one (**10**) followed by stannous chloride reduction to 4-amino-3-methoxy-5-phenylpyrrolidin-2-one (**13**). The nitro enol ether (**8**) reacted rapidly with ammonia and with primary or secondary amines to yield 3-amino-4-nitro-5-phenyl-3-pyrrolin-2-ones (**9**, **11**, or **12**).

As has been shown in previous work,[2] 2,3-dioxopyrrolidines having a substituent in the 4 position are acidic, fully enolized compounds, and those having an electron-withdrawing carbethoxy or carbomethoxy group at the 4 position are similar in acid strength to carboxylic acids. It became of interest, therefore, to prepare and examine the properties of a 4-nitro-2,3-dioxopyrrolidine, wherein the strong electron-withdrawing effect of the nitro group might be expected to produce a still greater increase in the acidity of the enolic tautomer. Other α-nitro ketones give rise to rather acidic tautomers,[3] but all previously studied compounds of this type appear to have existed at least in part in the keto form, whereas it could be anticipated that 4-nitro-2,3-dioxopyrrolidines would be entirely enolic, *i.e.*, that they would in fact exist entirely as 4-nitro-3-hydroxy-3-pyrrolin-2-ones, and provide an opportunity to examine the chemistry of compounds having a vinylogous relationship to nitric acid. It was also felt that the chemistry of such derivatives of these nitro compounds as O-alkylation products (vinylogs of alkyl nitrates) would be of interest, and that these compounds might serve as useful intermediates in the synthesis of other pyrrolidines.

The synthesis of 4-nitro-5-phenyl-2,3-dioxopyrrolidine (**5**) was achieved by use of the sequence of reactions shown in Chart I. Addition of ammonia to β-nitrostyrene (**1**) in dry benzene yielded a bis adduct (**2**) incorporating two molecules of β-nitrostyrene and one of ammonia.[4] (No useful procedure was found for ob-

CHART I



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(2) (a) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. Herbert Carlson, *J. Org. Chem.*, **21**, 1087 (1956); (b) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98, 1554, 1560 (1957); (c) W. R. Vaughan and I. S. Covey, *J. Amer. Chem. Soc.*, **80**, 2197 (1958); (d) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962); (e) P. L. Southwick and J. A. Vida, *ibid.*, **27**, 3075 (1962).

(3) See, for example, (a) R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, **20**, 373 (1964); (b) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **31**, 3152 (1966); (c) T. Simmons, R. F. Love, and K. L. Freuz, *ibid.*, **31**, 2400 (1966); (d) A. A. Griswald and P. S. Starcher, *ibid.*, **30**, 1687 (1965); (e) K. H. Meyer and P. Wertheimer, *Ber.*, **47**, 2374 (1914); (f) G. Vanags and J. Bungs, *ibid.*, **75B**, 987 (1942); (g) O. Neilands, J. Stradins, and G. Vanags, *Dokl. Akad. Nauk. SSSR*, **131**, 1084 (1960); *Chem. Abstr.*, **54**, 20911 (1960). In ref 3f and 3g and references cited therein, Vanags and his associates have described spectroscopic and chemical evidence of tautomerism in a number of 2-nitro-1,3 diketones. Some of these 1,3-diketone derivatives are probably completely enolic under appropriate conditions. 2-Nitrodimedone, for example, was regarded as highly enolized in the solid state, but in aqueous solution showed only relatively weak acidity (comparable with formic acid). 2-Nitro-1,3-indandione was found to be a very strong acid, but was considered to exist either as the nitro diketone or the nitronic acid tautomer, not as the nitro enol.

(4) This compound was first described by D. E. Worrall, *J. Amer. Chem. Soc.*, **49**, 1598 (1927). Difficulty was experienced with Worrall's preparative procedure, however, particularly in purification of the product.