The Synthesis and Gramine Alkylation of Some 3-Piperidones. A Synthetic Route to 2-(3-Indolylmethyl)-4-piperidineacetic Acid Derivatives

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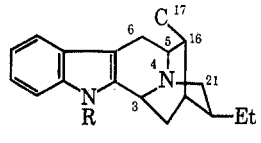
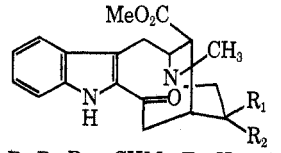
Syntheses of ethyl 1-benzoyl-3-oxo-4-piperidineacetate and methyl 1-benzoyl-5-ethyl-3-oxo-4-piperidineacetate starting with ethyl 1-benzoyl-1,2,3,6-tetrahydro-4-pyridineacetate and ethyl 1-benzoyl-3-ethyl-1,2,3,6-tetrahydro-4-pyridineacetate are described. Both of these 3-piperidones can be alkylated in fair yield by gramine *via* their pyrrolidine enamines to 2-(3-indolylmethyl)-3-piperidones. Stereochemical assignments for the 2-(3-indolylmethyl)-3-piperidones are made on the basis of stability relationships and analogy with prior stereochemical assignments to 2-substituted *N*-acylpiperidines. Two stereoisomeric ethyl 1-benzoyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetates, two stereoisomeric 1-benzoyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetic acid lactones, two stereoisomeric methyl 1-benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetates, and three stereoisomeric 1-benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetic acid lactones are described. Several other miscellaneous compounds are reported as a result of unsuccessful alternative approaches to these 3-piperidones.

The 2-(3-indolylmethyl)-4-piperidineacetic acid system constitutes a major portion of the skeleton of such indole alkaloids as the sarpagine–ajmaline group A[1] and the 2-acylindoles vobasine, dregamine, and tabernaemontanine (B).[2] The sarpagine–ajmaline skeleton



A



B, R_1, R_2 = CHMe; Et, H; H, Et

is not accessible by the Mannich-type cyclizations which have been so successful in the synthesis of other types of indole alkaloids, especially those containing the tetrahydro-β-carboline ring,[3] because of the prohibition against a bridgehead double bond. Successful syntheses of the ajmaline–sarpagine ring system and close structural relatives have therefore involved closure of the C-5–C-16[4] or C-21–N-4 bonds[5] for construction of the quinuclidine ring in the latter stages of the syntheses. It would appear that the sarpagine–ajmaline skeleton might also be approached *via* 2-acylindoles having the N_b-demethyl vobasine skeleton (B) by a transannular ring closure involving C-3 and N-4.[6] The closest approach to the vobasine skeleton is that of Yamada and Shioiri who have described the synthesis of 1-methyl-16-demethoxycarbonyl-20-deethylidene vobasine.[7] We record here our efforts to develop a synthesis of intermediates suitable for subsequent conversion to the vobasine and sarpagine type ring systems.

We decided to approach these systems by a gramine alkylation[8] of the pyrrolidine enamine of a 4-substituted 3-piperidone. Syntheses of the tetrahydropyridines **3b** and **3d** from 1-benzoyl-4-piperidones have been reported[9] and modifications described herein have made these compounds reasonably accessible. An initial approach commencing with hydroboration of the tetrahydropyridine ring failed for reasons discussed below. An alternative route outlined in Scheme I has provided the desired piperidones **9b** and **9c** in good overall yield from **3b** and **3d**.

The epoxidation can be carried out on pure **3** or **3** can be selectively epoxidized in the presence of the less reactive exocyclic esters **1** which are by-products in the synthesis of **3**.[9] Stereoisomers arbitrarily designated **4dA** and **4dB** are formed in the case of **4d** but separation is not required since the stereoisomers are equilibrated at a subsequent stage.

The epoxide ring in **4** is readily opened by bases *via* a β-elimination mechanism. For **4b** this reaction is most efficiently effected by adsorbing the epoxide on a column of basic alumina. Subsequent elution gives **5b** (60% yield) and **6a** (30% yield). Ring opening is rapid using potassium *tert*-butoxide at room temperature but total recovery of products is substantially lower (36% **5b**, 6% **6a**). For **4d** ring opening was effected using DABCO[10] in refluxing xylene or with alumina. A mixture containing **5d** and **6c** is generated. Separation of the various components (including stereoisomers) at this point is inefficient. Catalytic hydrogenation, hydrolysis, and diazomethane esterification provides **7c** in good overall yield.

Spectral data for the isolated intermediates in this scheme are reported in the Experimental Section. In general, the data are in accord with expectation and confirm each of the expected functional group changes. The nmr signals for the piperidine ring protons are diffuse multiplets which provide no direct insight into the stereochemistry of the various intermediates.

The piperidones **9a–d** were obtained by oxidation with Jones reagent of the corresponding hydroxy esters.

(1) W. I. Taylor in "The Alkaloids," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, pp 785–814; Vol. XI, 1968, pp 41–72.

(2) U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, **46**, 2186 (1963).

(3) For some typical examples, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 256–269.

(4) E. E. van Tamelen and L. K. Oliver, *J. Amer. Chem. Soc.*, **92**, 2136 (1970).

(5) S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar, and Y. Yasunari, *ibid.*, **89**, 2506 (1967); K. Mashimo and Y. Sato, *Tetrahedron Lett.*, 901, 905 (1969).

(6) G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **86**, 4631 (1964).

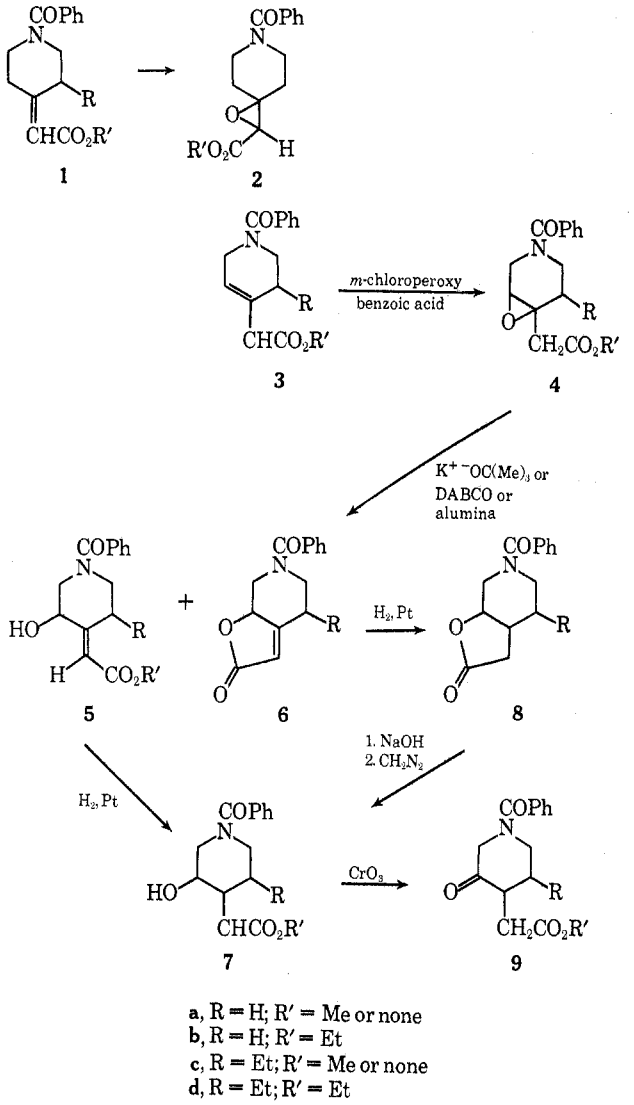
(7) T. Shioiri and S. Yamada, *Tetrahedron*, **24**, 4159 (1968).

(8) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 3240 (1965). A. A. Semenov and I. V. Terent'eva, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 235 (1965); *Chem. Abstr.*, **63**, 11478 (1965).

(9) R. J. Sundberg and F. O. Holcombe, Jr., *J. Org. Chem.*, **34**, 3273 (1969).

(10) 1,4-Diazabicyclooctane.

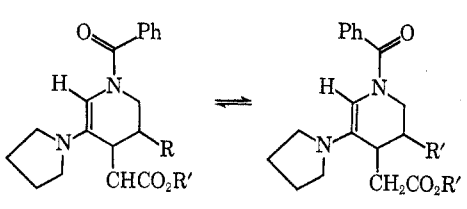
SCHEME I



a, R = H; R' = Me or none
b, R = H; R' = Et
c, R = Et; R' = Me or none
d, R = Et; R' = Et

These piperidones were not stable to extended storage and satisfactory analytical data were not obtained. Nevertheless, spectral data, including mass spectral data, left no doubt that the required piperidones were in hand.

When refluxed in benzene with pyrrolidine, enamine formation occurred as evidenced in particular by sharp nmr signals at 5.7 and 6.6 ppm in the case of **9b** and similar, slightly less well-defined signals for **9c**. These are assigned to the vinyl protons in the enamine. The occurrence of two singlets (total integration one

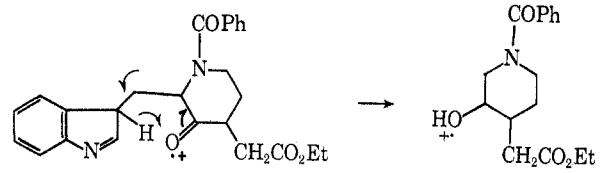


C

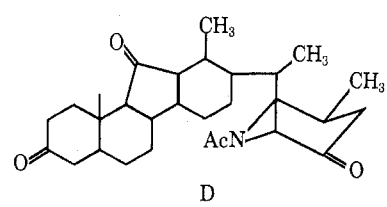
proton) is attributed to the presence of two conformational isomers resulting from slow (nmr time scale) rotation of the *N*-benzoyl group. Solutions of the enamines when refluxed with gramine and hydrolzyed gave product mixtures best processed by chromatography.

After alkylation of **9b**, chromatography gave diindolylmethane, cis and trans stereoisomers of the desired ketone **10b**, the pyrrolidine amide **10e**, and a byproduct assigned the structure **11b**.

The stereoisomeric ketones **10b** can be separated by fractional crystallization. The higher melting isomer *t*-**10b**, mp 174–176°, is the major product, predominating over *c*-**10b**, mp 163–165°, by roughly 3:1 in most runs. The infrared and nmr spectral data confirm the presence of the expected functional groups in both *c*-**10b** and *t*-**10b** but fail to provide stereochemical information. The mass spectral data for *c*-**10b** and *t*-**10b** are virtually identical and confirm the expected molecular weight. Besides strong peaks at 105 and 130 corresponding to the benzoyl and indolylmethyl substituents, the mass spectra show prominent peaks at M, M − 129, and M − 175. The M − 129 peak indicates the loss of the indolylmethyl substituent with hydrogen atom transfer to the piperidine ring perhaps by a McLafferty rearrangement *via* the 3H tautomer.



Although spectral data provided no basis for a stereochemical assignment, demonstration that the isomer of mp 174–176° is stable relative to that of mp 163–165° permits stereochemical assignment by analogy with other *N*-acylpiperidines. Conventional alkoxide ion catalyzed equilibration led to substantial losses of material but equilibration could be effected by heating the ketones in ethanolic potassium fluoride.[11] Johnson and coworkers[11] have investigated the stereochemistry of the piperidone D derived from jervine and concluded that the more stable configuration is the cis isomer depicted in the formula. The large 2 substituent



D

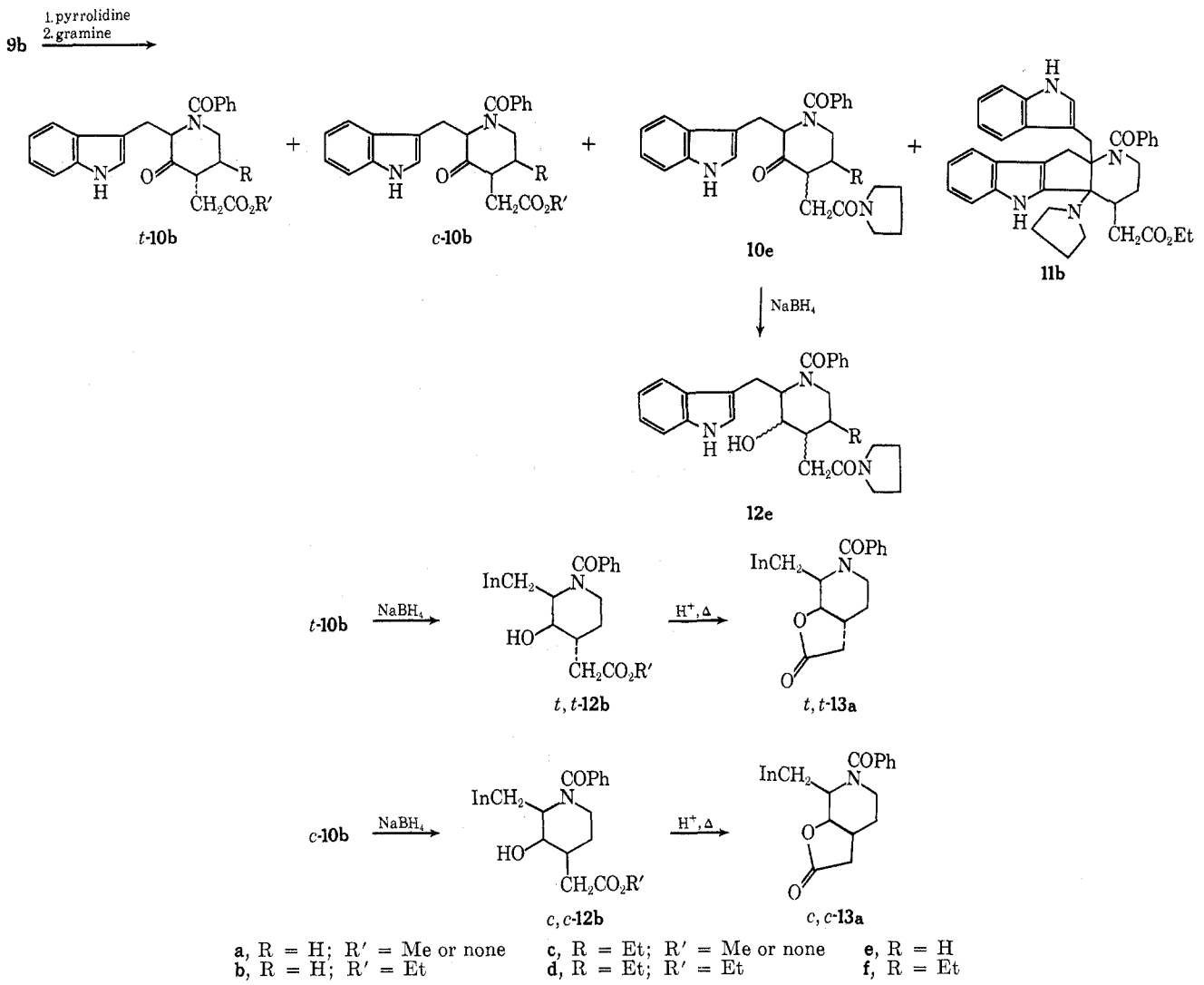
thus occupies an axial position in the preferred conformation. This stereochemistry is favored because of $A^{(1,3)}$ strain which develops between the amide group and a 2 substituent in the equatorial position.[12]

In the case of the stereoisomers of **10b**, the axial–equatorial isomer *t*-**10b** is therefore expected to be more stable than the cis isomer *c*-**10b** which must suffer either $A^{(1,3)}$ strain, a 1,3-diaxial interaction, or adopt a nonchair conformation. Equilibration of the ketones gave mixtures in which the ketone of mp, 174–176° now designated *t*-**10b**, dominates by roughly 4:1.

(11) J. W. Scott, L. J. Durham, H. A. P. de Jongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Lett.*, 2381 (1967).

(12) (a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); (b) H. Paulsen and K. Todt, *Angew. Chem., Int. Ed. Engl.*, **5**, 899 (1966); (c) H. Paulsen and F. Leupold, *Carbohyd. Res.*, **3**, 47 (1966); (d) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967); (e) G. Büchi, S. J. Gould, and F. Näf, *J. Amer. Chem. Soc.*, **93**, 2492 (1971).

SCHEME II[a]



a, R = H; R′ = Me or none c, R = Et; R′ = Me or none e, R = H
b, R = H; R′ = Et d, R = Et; R′ = Et f, R = Et

[a] Prefixes *c* and *t* designate stereochemistry of substituents relative to the 4-acetic acid residue.

By-product **10e** has not been isolated in crystalline form but it gives a crystalline dihydro derivative **12e** on sodium borohydride reduction. Spectral and analytical data are in accord with the structure assigned to **12e** in Scheme II. The structural assignment for **11b** is more tenuous. The mass spectrum shows an apparent parent ion at 600 corresponding to the molecular weight of a bisindolylmethyl derivative of the intermediate enamine. Analytical data are also consistent with this molecular composition. Ultraviolet data is in accord with structure **11b**. Structure **11b** could arise by dialkylation of enamine C followed by cyclization of the resulting iminium salt.[13]

The ketones *t*-**10b** and *c*-**10b** show divergent behavior on sodium borohydride reduction. *t*-**10b** gives a single alcohol in excellent yield. It is assigned the structure and stereochemistry *t,t*-**12b** (Scheme II) on the basis of the normal preference for formation of equatorial alcohols on reduction of six-membered cyclic ketones in the absence of strong steric effects. Neither an axial nor an equatorial substituent α to the carbonyl strongly perturb the axial–equatorial isomer ratio in hydride reductions.[14] Alcohol *t,t*-**12b** gives the corresponding lactone *t,t*-**13a** on heating with a trace of acid in toluene. In contrast, sodium borohydride reduction of *c*-**10b** gives approximately equal amounts of an alcohol and lactone assigned structures *c,c*-**12b** and *c,c*-**13a**, respectively. Lactonization of *c,c*-**12b** gives *c,c*-**13a**, demonstrating that the alcohol and lactone are of the same stereochemical family. The all cis configuration is assigned on the basis of the facile partial lactonization which accompanies reduction and the fact that *c,c*-**13a** has lower carbonyl frequency (1780 cm^{-1}) than the lactone *t,t*-**13a** (1810 cm^{-1}). The mass spectra of the stereoisomeric lactones are shown in Figure 1. The most significant difference in the spectra of the isomeric lactones is the strong M − 129 peak in *c,c*-**13a**. In addition, *t,t*-**13a** shows peaks at M − 105 and M − 121 which are not prominent in *c,c*-**13a**. A sample of *c,c*-**13a** deuterated (50%) at the indole nitrogen showed shift of the 374, 245, and 130 peaks to 375, 246, and 131, respectively, but the 186 peak was not shifted. This shows that the indole N–H hydrogen atom is transferred in formation of the M −

(13) The data in hand cannot rule out an alternative formulation of **11** in which the indolylmethyl substituent shown at the 2 position of the piperidine ring is placed on the 4 position.

(14) J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968); A. V. Kameritzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

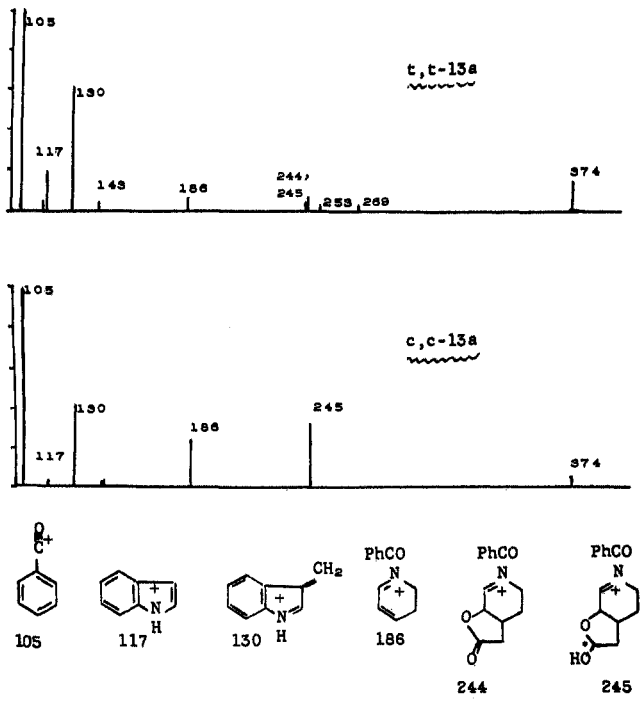
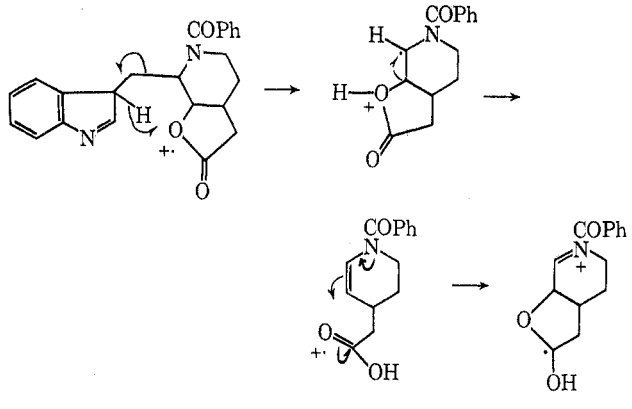
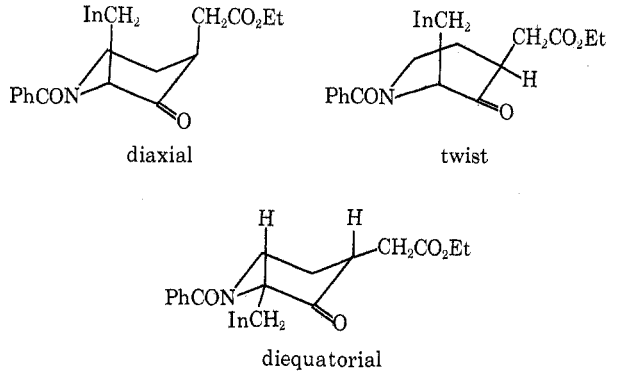


Figure 1.—Principal mass spectral fragments for *t,t*-**13a** and *c,c*-**13a**.

129 peak. A possible fragmentation mechanism is outlined below.



Of the conformations available to *c*-**10b**, the diaxial and twist conformations appear likely to give *c,c*-**12b** on reduction, but the diequatorial conformation would be expected to give the unobserved *c,t*-**12b**.

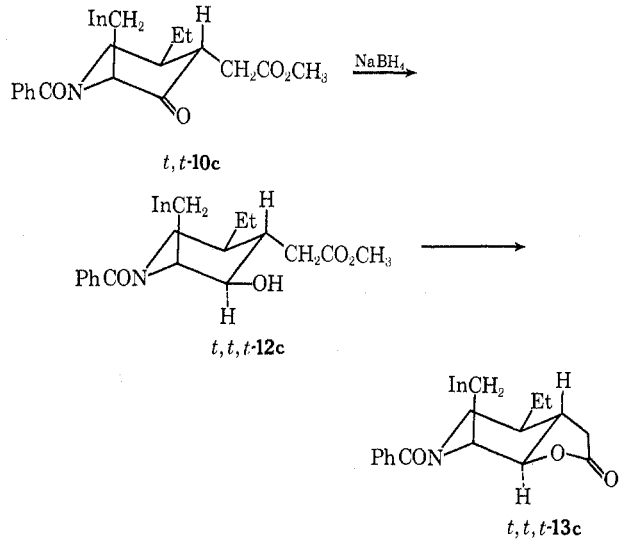


There is little quantitative information on the magnitude of the $A^{(1,3)}$ interaction in *N*-acylpiperidines.[12] However, it is known to be sufficiently large to cause 1-benzoyl-2,6-dimethylpiperidine to adopt the conformation with diaxial methyl groups.[15] It is known that cyclohexanone derivatives are more prone to adopt twist conformations than are cyclohexanes,[16] but the diaxial methyl interactions in 3,3,5,5-tetramethylcyclohexanone is apparently not sufficiently large to force this ketone to adopt a nonchair conformation.[17] It would appear therefore that *c*-**10b** probably exists predominantly in the diaxial conformation.

Independent evidence for the stereochemical assignments shown in Scheme II was obtained by examination of the nmr spectra of the lactones *t,t*-**13a** and *c,c*-**13a**. The nmr spectra in the region δ 3.5–5 are shown along with those of the 3-d_1 analogs in Figure 2.

These spectra permit identification of the 3 proton in *t,t*-**13a** as a doublet of doublets, J = 10, 5 Hz, whereas the corresponding signal in *c,c*-**13a** is a skewed triplet, J = 6.5 Hz. These coupling constants are consistent with the axial–axial and axial–equatorial couplings present in *t,t*-**13a** and the two axial–equatorial couplings present in *c,c*-**13a**.[12b-d,15]

Two ketones were also isolated by chromatography of the product mixture from gramine alkylation of **9c**. The major ketone gave a single alcohol on reduction which can be lactonized. These products are assigned structures *t,t,t*-**12c** and *t,t,t*-**13c** on arguments analogous to those in the desethyl series. The nmr spectrum of *t,t,t*-**13c** is reminiscent of *t,t*-**13a** in that it shows a doublet of doublets, J = 10, 5 Hz at δ 4.3. It is assumed that the C-5 ethyl group is in the more stable equatorial position. The major ketone is therefore assigned the stereochemistry *t,t*-**10c**. The mass spec-



trum of *t,t,t*-**13c** is analogous to that of *t,t*-**13a** and shows all of the expected shifts due to the added ethyl group.

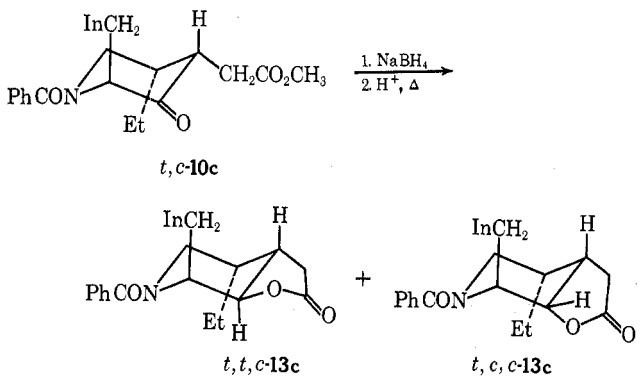
The minor ketone is converted largely to *t,t*-**10c** on refluxing in methanolic potassium fluoride. The minor ketone gives a stereoisomeric mixture of alcohols which can be converted to two lactones. The mass spectrum of one is similar to that of *c,c*-**13a** in showing no M − 130 peak; the second gives a mass spec-

(15) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); Y. L. Chow, C. J. Colón, and J. N. S. Tam, *Can. J. Chem.*, **46**, 2821 (1968).

(16) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 472–480.

(17) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

trum which is very similar to that of *t,t,t*-**13c**. The minor ketone, on the basis of this data, might be stereoisomeric with *t,t*-**13c** at C-3 or C-5. The latter possibility is favored by the nmr spectra of the derived lactones. The major lactone shows a doublet of doublets, J = 11, 5 Hz, indicating one axial–axial coupling of the C-3 proton. Only stereoisomer *t,t,c*-**13c** is consistent with this coupling pattern. The minor ketone is therefore apparently stereoisomeric with *t,t*-**10c** at C-5 and has structure *t,c*-**10c**. The second lactone derived from *t,c*-**10c** is assigned structure *t,c,c*-**13c**.



The nmr of the lactones *t,t*-**13a**, *t,t,t*-**13c**, *t,t,c*-**13c**, and *t,c,c*-**13c** are all temperature dependent because of the slow rotation of the benzoyl group.[15,18] The signals associated with piperidine ring protons are quite broad at room temperature but considerable fine structure is evident at 90–120° except for the 2 and 6 protons which remain broad even at this temperature. Similar broad signals are typical of the equatorial protons of simple *N*-benzoylpiperidines.[15,18] In contrast, *c,c*-**13a** shows fine structure in the signals near 5.0, even at room temperature. This observation suggests that *c,c*-**13a** is conformationally unique when compared with the other four lactones. The chair conformation of *c,c*-**13a** suffers from a diaxial interaction, as well as from the strain associated with fusion of the lactone ring. Both of these interactions can be relieved in a twist conformation without introducing $A^{(1,3)}$ strain. The combined energy of the 1,3-diaxial interaction (3–4 kcal) and the strain associated with the ring fusion (~4 kcal)[19] may be sufficient to cause adoption of a nonchair conformation.

Various modified conditions failed to increase the proportion of *c*-**10b** in the gramine alkylation product. Since a cis relationship is required for our ultimate synthetic goal, it is clear that a system in which the stereochemistry at C-2 is not governed by $A^{(1,3)}$ strain is needed. Nevertheless, the present work has established that gramine alkylation of 3-alkylamino-1,4,5,6-tetrahydropyridines is a feasible approach to the desired ring system.

Our initial efforts to obtain **7b** involved hydroboration of **3b**. Since reduction of tertiary amide groups by diborane is relatively rapid,[20] the benzoyl group in **3** was replaced by the less easily reduced carbobenzyloxy

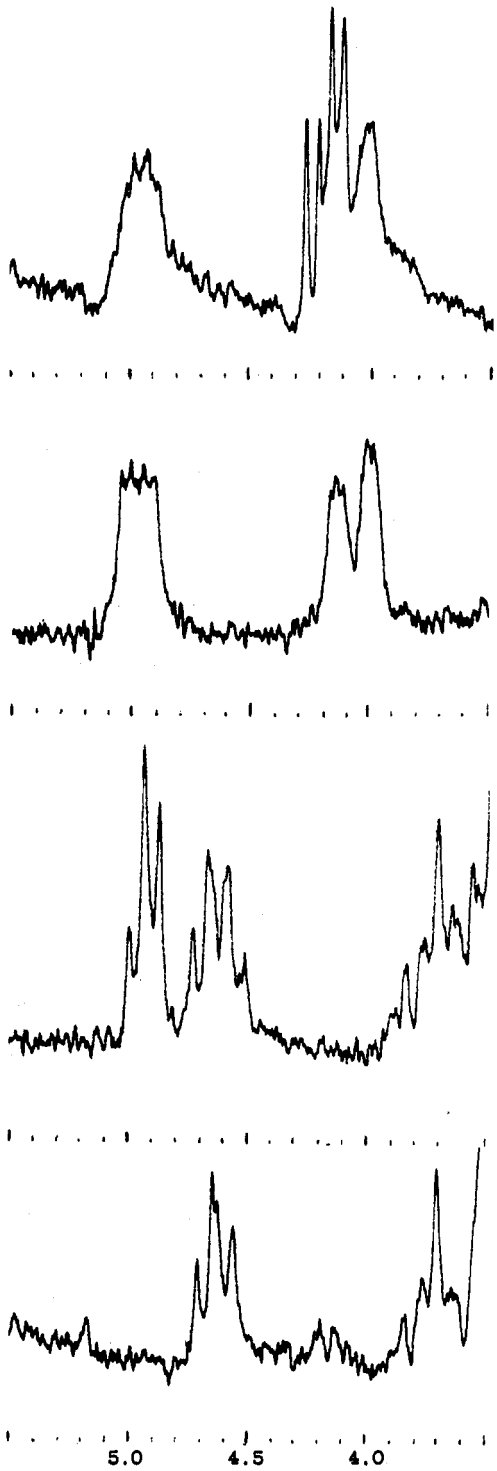
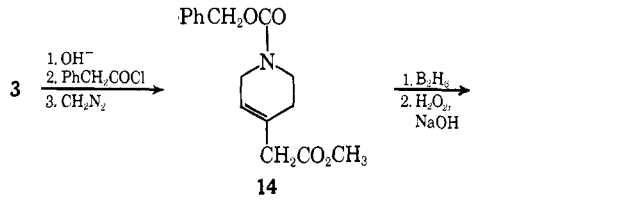
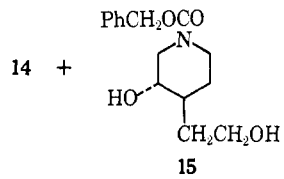


Figure 2.—100-MHz nmr spectra of *t,t*-**13a** and *t,t*-**13a**-3-d_1 at 120° (upper spectra) and *c,c*-**13a** and *c,c*-**13a**-3-d_1 at 35° (lower spectra) in DMSO-d_6.

group[21] by hydrolysis followed by acylation to give **14**. Starting material and the diol **15**, a reduction product, were the major products from several hydroboration attempts. Hydroboration must occur but is followed by intramolecular reduction of the ester group. There are prior examples of such intramolecular reductions in hydroboration and sodium borohydride reduction.[22]

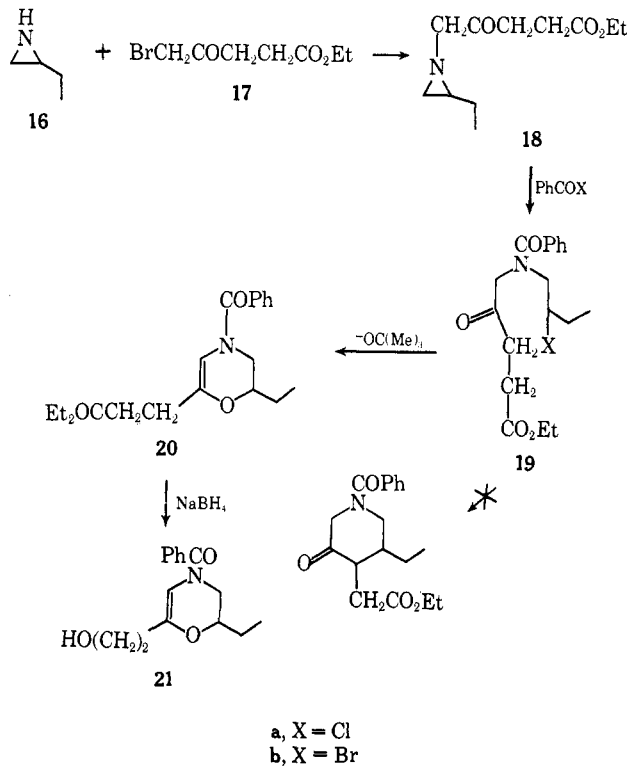
(18) H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966).
(19) W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.*, **83**, 1671 (1961); ref 16, p 230; W. Herz and L. A. Glick, *J. Org. Chem.*, **28**, 2970 (1963).
(20) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 1637 (1970).
(21) F. Irreverre, K. Morita, A. V. Robertson, and B. Witkop, *ibid.*, **85**, 2824 (1963); Y. Fujita, F. Irreverre, and B. Witkop, *ibid.*, **86**, 1844 (1964).
(22) H. C. Brown and K. A. Keblys, *ibid.*, **86**, 1795 (1964); U. T. Bhalerao, J. J. Plattner, and H. Rapoport, *ibid.*, **92**, 3429 (1970); J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).





This difficulty could probably be overcome by use of a dialkylborane but this possibility was not investigated in view of the general success encountered with the route described in Scheme I.

Although 1-benzoyl-3-ethyl-4-piperidone, the starting material required for **3d**, can be reliably prepared in 100-g quantities by the procedure of Stork and McElvain,[23] this preparation is sufficiently time consuming to make an alternative route to the 3-piperidone **9d** highly desirable. With this goal in mind we prepared the β-haloamide **19** from 2-ethylaziridine and ethyl 5-bromolevulinate.[24] Both the bromo and chloro compounds were easily prepared. Attempts to obtain **9d** by intramolecular C-alkylation following a route



utilized by Dolfini[25] for 3-acylpyrrolidines gave instead the O-alkylation product **20**. This structure is deduced from the slow reduction of **20** to the primary alcohol **21** and from spectral data. Both **20** and **21** show two sharp singlets in the vinyl proton region integrating for a total of one proton. The two singlets are ascribed to slowly interconverted conformers having the two possible orientations of the *N*-benzoyl group. The haloamides **19**, especially the bromide, are sensitive toward hydrolysis by mechanisms involving participation of the amide group.[26,27]

Experimental Section

Ethyl 1-Benzoyl-Δ$^{4,\alpha}$-piperidineacetate (1b) and Ethyl 1-Benzoyl-1,2,3,6-tetrahydropyridine-4-acetate (3b).—Sodium hydride (7.6 g of 50% mineral oil dispersion) was rinsed with hexane and covered with anhydrous ether (300 ml). A solution of triethyl phosphonoacetate (39.0 g, 0.182 mol) in ether (200 ml) was added slowly. When hydrogen evolution had ceased, a solution prepared from 1-benzoyl-4-piperidone (Aldrich, 30.0 g, 0.148 mol), dry benzene (200 ml), and ether (700 ml) was added in one portion. The resulting reaction mixture was refluxed under nitrogen for 20 hr. The organic solution was decanted and the gummy precipitate was washed with additional ether. The combined organic layers were filtered and washed successively with dilute hydrochloric acid, dilute sodium bicarbonate, and saturated sodium chloride. The solution was dried over magnesium sulfate. Evaporation of the solvent gave 35.5 g of a mixture of **1b** (8.9 g, 0.033 mol, 22%) and **3b** (26.6 g, 0.097 mol, 66%). Separation and characterization of **1b** and **3b** have been reported previously.[9]

Ethyl 1-Benzoyl-3-ethyl-Δ$^{4,\alpha}$-piperidineacetate (1d) and Ethyl 1-Benzoyl-3-ethyl-1,2,3,6-tetrahydropyridine-4-acetate (3d).—Sodium hydride (11 g of 50% dispersion in mineral oil) was washed with hexane and then covered with anhydrous ether (1300 ml). A solution of triethyl phosphonoacetate (52.0 g, 0.220 mol) in ether was added cautiously. When hydrogen evolution was complete, a solution prepared from crude 1-benzoyl-3-ethyl-4-piperidone[23] (40 g, ~0.16 mol) and ether (600 ml) was added. The resulting solution was refluxed under nitrogen for 20 hr. Work-up as described for **1b** and **3b** gave an oil (42.5 g, ~88%) containing **1d** and **3d** in the ratio 0.8:1.0. The pure components could be separated and characterized as described previously,[9] but normally the mixture was used directly in the epoxidation.

3-Benzoyl-6-carbethoxymethyl-7-oxa-3-azabicyclo[4.1.0]heptane (4b). A. From Pure 3b.—A solution of chromatographically purified **3b** (2.0 g, 7.3 mmol) and *m*-chloroperoxybenzoic acid (2.0 g, 85% peroxide content) in chloroform (50 ml) was stirred at room temperature for 5 hr. The resulting solution was washed successively with sodium sulfite and sodium carbonate solutions, dried over sodium sulfate, and evaporated. The residual oil (1.9 g, 6.6 mmol, 90%) was pure **4b** according to tlc. An analytical sample was prepared by chromatography on silicic acid using 1:4 ether–benzene for elution. Subsequent samples crystallized and could be recrystallized from ether–hexane: mp 79–80°; ν_{CO} 1725, 1620 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t) 2.05 (2 H, broad quartet), 2.35 (1 H, d, J = 16 Hz), 2.27 (1 H, d, J = 16 Hz), 3.0–3.9 (5 H, m), 4.15 (2 H, q), 7.35 (5 H, s); mass spectrum m/e (relative intensity), 289 (8), 271 (8), 202 (17), 105 (100), 77 (30).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.19; H, 6.85; N, 5.06.

B. From a 1b–3b Mixture.—A mixture of **1b** and **3b** (35.5 g, **1b**:**3b** ratio 1:3, 97 mmol of **3b**) was dissolved in chloroform (200 ml) and treated with a solution of *m*-chloroperoxybenzoic acid (21 g, 85% peroxide content) in chloroform (300 ml). The solution was stirred at room temperature for 5 hr and then washed successively with sodium sulfite, sodium bicarbonate, and sodium chloride solutions. The solution was dried and evaporated. Crystallization of the oily residue from ether (60 ml) by addition of hexane (40 ml) gave **4b** (15.8 g), mp 73–76°. Chromatography of the mother liquors on silicic acid using 30% ether in benzene as eluent afforded recovered **2b** (5.8 g), recovered **3b** (3.5 g), and additional **4b** (3.0 g, total yield 67%).

3-Benzoyl-5-ethyl-6-carbethoxymethyl-7-oxa-3-azabicyclo-[4.1.0]heptane (4dA and 4dB).—A 1:1 mixture of crude **1d** and **3d** prepared as described above (45 g, 22.5 g of **3d**, 75 mmol) was dissolved in chloroform (300 ml) and a solution of *m*-chloroperoxybenzoic acid (25 g, 85% peroxide content) in chloroform (500 ml) was added. The solution was stirred at room temperature for 6 hr and then washed successively with sodium sulfite,

(23) G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).
(24) H. Dannenberg and S. Läufer, *Chem. Ber.*, **89**, 2242 (1956).
(25) J. E. Dolfini and D. M. Dolfini, *Tetrahedron Lett.*, 2053 (1965).
(26) W. C. J. Ross and J. G. Wilson, *J. Chem. Soc.*, 3616 (1959).
(27) Consult the Ph.D. Thesis of W. V. Ligon, Jr., University of Virginia, 1970, for characterization of some hydrolysis products.

sodium bicarbonate, and sodium chloride solutions. The solution was dried and evaporated. The residue was chromatographed on 1500 g of silicic acid using 20% ether in benzene as eluent. There was successively eluted **1d** (13.0 g), a mixture of **1d** and **3d** (3.2 g), a mixture of **3d** and **4dA** (3.8 g), **4dA** (4.0 g, 12 mmol, 17%), a mixture of **4dA** and **4dB** (10.2 g, 32 mmol), 43%) and **4dB** (1.9 g, 6 mmol, 8%). Analytical samples of the stereoisomeric epoxides were prepared by bulb-to-bulb distillation. The less polar stereoisomer **4dA** showed ν_{CO} 1740, 1640 cm^{-1} (CCl_4); nmr peaks ($CDCl_3$) at δ 1.30 (t) and 0.5–2.0 (m), total integration ~7 H, 2.22 (1 H, d, J = 16 Hz), 4.18 (q) and 3.2–4.5 (m), total integration ~6 H, 7.40 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11 H, 7.30. Found: C, 68.25; H, 7.35.

The more polar stereoisomer **4dB** showed ν_{CO} 1740, 1640 cm^{-1} (CCl_4); nmr peaks ($CDCl_3$) at δ 1.32 (t) and 0.5–2.3 (m), total integration ~7 H, 2.45 (1 H, d, J = 15 Hz), 2.95 (1 H, d, J = 15 Hz), 4.25 (q) and 3.0–4.7 (m), total integration ~6 H, 7.50 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30. Found: C, 68.19; H, 7.41.

4-Benzoyl-8-carbethoxy-7-oxa-4-azaspiro[5.2]octane (2b).—Crystalline **1b** (2.0 g, 7.3 mmol) was stirred with *m*-chloroperoxybenzoic acid (2.0 g, 85% peroxide content) in chloroform for 5 days. Tlc indicated quantitative conversion to **2b**. The chloroform solution was washed successively with sodium sulfite and sodium carbonate solutions, dried, and evaporated. The residue was crystallized from ether–hexane: mp 97–98°; ν_{CO} 1745, 1625 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.32 (3 H, t), 1.5–2 (3 H, m), 3.3–4.2 (~5 H, m with singlet at 3.5), 4.3 (2 H, q), 7.52 (5 H, s); mass spectrum m/e (rel intensity) 289 (30), 288 (28), 276–272 (each 1–2), 271 (3), 244 (2), 242 (1), 216 (20), 186 (8), 184 (4), 105 (100), 77 (60).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.33; H, 6.73; N, 4.94.

Ethyl 1-Benzoyl-3-hydroxy-$\Delta^{4,\alpha}$-piperidineacetate (5b) and 1-Benzoyl-3-hydroxy-$\Delta^{4,\alpha}$-piperidineacetate Acid Lactone (6a).

A. Ring Opening with Potassium *tert*-Butoxide.—To a solution of **4b** (14.5 g, 50 mmol) in dry *tert*-butyl alcohol (200 ml) was added a potassium *tert*-butoxide solution prepared by dissolving 0.5 g of potassium metal in 50 ml of dry *tert*-butyl alcohol. After addition of the base (5 min), the reaction solution was poured into a separatory funnel containing 500 ml of 5% hydrochloric acid and 500 ml of chloroform. The combined chloroform extracts were washed with aqueous sodium carbonate and sodium chloride. Drying and evaporation of the solvent gave 15 g of a viscous residue which was dissolved in hot benzene. Addition of ether caused the precipitation of a gum. The resulting solution was decanted and cooled, resulting in crystallization of **5b** (1.0 g). The mother liquors were chromatographed on 300 g of silicic acid using 30% ether in benzene as eluent. Additional **5b** (4.3 g, total yield 5.3 g, 18 mmol, 36%) and **6a** (0.7 g, 3 mmol, 6%) were obtained. Recrystallization of **5b** from chloroform–hexane gave crystalline material: mp 146–148°; ν_{OH} 3330 cm^{-1}; ν_{CO} 1720, 1625 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t), 1.50–4.0 (7 H, m), 4.15 (2 H, q), 6.10 (1 H, s), and 7.45 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.26; H, 6.64; N, 4.79.

Recrystallization of **6a** from hexane gave crystals: mp 160–165°; ν_{CO} 1745, 1630 cm^{-1}; nmr peaks ($CDCl_3$) at 2.4–3.1 (4 H, m), 4.0–5.0 (3 H, m), 5.85 (1 H, s), and 7.45 (5 H, s).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.39; H, 5.26; N, 5.70.

B. Ring Opening on Basic Alumina.—A solution of **4b** (4.8 g, 17 mmol) in benzene was run onto a column of Fisher Basic Alumina, Activity I, (125 g) packed in benzene. After standing for 3 hr the column was eluted with 40% ether in benzene. The lactone **6a** (1.3 g, 5.3 mmol, 31%) was eluted rapidly followed by **5b**. Elution of **5b** was slow and it proved to be convenient to remove the alumina from the column after removal of **6a**. The alumina was thoroughly washed with 1:1 ethanol–chloroform. Evaporation of the solvent gave **5b** (2.9 g, 10 mmol, 60%).

1-Benzoyl-3-hydroxy-4-piperidineacetic Acid Lactone (8a).—Hydrogenation of **6a** (0.60 g) over platinum oxide in ethanol effected quantitative conversion to a single new material. An analytical sample was prepared by eluting the compound through acidic alumina (activity II) with 1:1 ether–benzene. Compound **8a** was obtained as a very viscous oil: ν_{CO} 1790, 1640 cm^{-1} (CCl_4); nmr (DMSO-d_6) peaks at δ 1.0–4.4 (9 H, m), 4.55 (1 H, s, $W_{1/2}$ = 10 Hz), and 7.50 (5 H, s).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.49; H, 6.36; N, 5.67.

Methyl 1-Benzoyl-3-oxo-4-piperidineacetate (9a).—A solution of **8a** (4.0 g) in methanol (30 ml) was stirred 1 hr at room temperature with 10 ml of 10% sodium hydroxide solution. The solution was diluted with brine and extracted with ether. The aqueous phase was cooled, acidified, and rapidly extracted with chloroform. The chloroform solution was washed with brine, dried briefly over sodium sulfate, and treated with diazomethane to give 3.1 g of methyl 1-benzoyl-3-hydroxy-4-piperidineacetate (**7a**). Oxidation was carried out as for **9b**. The nmr spectrum closely resembled that of **9b** except for the expected differences in the signals of the alkoxy groups.

Ethyl 1-Benzoyl-3-oxo-4-piperidineacetate (9b).—A solution of **5b** (6.0 g, 21 mmol) in ethanol (150 ml) containing platinum oxide catalyst (300 mg) was hydrogenated at 30 psi for 40 min. The reaction mixture was filtered and concentrated at reduced pressure. Excessive heating was avoided to minimize lactonization. The alcohol was freed of residual ethanol using vacuum and then dissolved in acetone (150 ml). The resulting solution was treated with Jones reagent (11 ml)[28] and stirred for 20 min. The acetone layer was poured into a brine–chloroform mixture and the precipitate dissolved in water. The combined water layers were extracted with additional chloroform. The chloroform solution was washed with sodium chloride, dried, and evaporated leaving **9b** as an oil: ν_{CO} 1730, 1630 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.25 (3 H, t), 1.7–3.8 (series of multiplets), 4.15 (2 H, q), and 7.40 (5 H, s); mass spectrum m/e (rel intensity) 289 (12), 275 (15), 274 (18), 244 (6), 243 (6), 230 (4), 228 (2), 202 (12), 200 (3), 188 (2), 186 (6), 184 (4), 174 (10), 170 (14), 122 (6), 121 (2), 120 (1), 105 (100), 77 (60). The ketone was unstable to storage (color development, new tlc spots) and several attempts to prepare satisfactory analytical samples failed. Subsequently, the ketone was used directly in the next step.

Ethyl 1-Benzoyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (*c*-10b and *t*-10b).—A solution of **9b** (2.7 g, 9.3 mmol) in benzene (40 ml) was heated with pyrrolidine (1.6 ml) and *p*-toluenesulfonic acid (12 mg) for 18 hr. The reaction flask was equipped with a Dean-Stark trap partially filled with type 4A molecular sieve and a nitrogen atmosphere was maintained throughout the reflux period. The benzene was removed at reduced pressure and the residue was dissolved in dry toluene (40 ml). Gramine (2.5 g) was added and the solution was refluxed for 3 hr. The solution was cooled briefly and additional gramine (1.5 g) was added followed by 3-hr additional reflux. The toluene was removed at reduced pressure and the residue was dissolved in ethanol (30 ml). To the resulting solution there was added a solution prepared from ethanol (10 ml), water (2 ml), and concentrated hydrochloric acid (1 ml). This slightly acidic solution (pH 5–6) was stirred at room temperature for 20 min, poured into brine, and extracted thoroughly with chloroform. The chloroform solution was washed with sodium bicarbonate and sodium chloride solutions, dried, and evaporated. The residue was dissolved in benzene, treated with charcoal, and filtered and the filtrate evaporated. The residue was dissolved in ethanol (12 ml). On cooling it deposited a mixture (1.60 g) of *c*-**10b** and *t*-**10b** (mainly *t*-**10b**). The mother liquors were evaporated, dissolved in benzene, and chromatographed on silicic acid using 1:1.5:7.5 chloroform–ether–benzene as solvent. There was eluted diindolylmethane, the crystalline by-product **11b**, mp 151–155°, and then *t*-**10b** (0.15 g) and *c*-**10b** (0.18 g). Fractional crystallization of the original crystalline product using ethanol gave 1.0 g of pure *t*-**10b**, mp 173–175° (total yield 1.15 g, 2.7 mmol, 30%), and 0.35 g of *c*-**10b**, mp 163–165° (total yield 0.53 g, 1.2 mmol, 14%).

An analytical sample of *t*-**10b** was prepared by recrystallization from ethanol: mp 174–176°; ν_{NH} 3450, 3220 cm^{-1}; ν_{CO} 1740, 1610 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 70°) at δ 1.1 (3 H, t), 1.3–2.0 (~2 H, broad) 2.2 (d, portion of d of d partially obscured by DMSO-d_5), 2.6 (1 H, d of d, J = 16, 6 Hz), 3.3 (~2 H broad d), 3.5 (broad d, J = 10 Hz), 4.0 (~3 H, q superimposed on broad signal), 4.8 (1 H, broad); mass spectrum m/e (rel intensity) 418 (3), 373 (1), 372 (1), 289 (27), 243 (18), 170 (2), 144 (2), 143 (3), 130 (100), 117 (2), 115 (2), 105 (53).

(28) Prepared as described by A. C. Cope and W. D. Burrows, *J. Org. Chem.*, **31**, 3099 (1966).

Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.64; H, 6.28; N, 6.60.

An analytical sample of *c*-**10b** was prepared by recrystallization from ethanol: mp 163–165°; ν_{NH} 3250 cm^{-1}; ν_{CO} 1745, 1740, 1620 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 70°) at δ 1.1 (3 H, t), 1.3–2.0 (~2 H, broad), 2.3 (d, portion of d of d partially obscured by DMSO-d_5), 2.6 (1 H, d of d, J = 16, 6 Hz), 3.2 (~2 H, broad d), 3.6 (1 H, broad d, J = 10 Hz), 4.0 (2 H, q), 4.1 (1 H, broad); mass spectrum *m/e* (rel intensity) 418 (3), 373 (1), 372 (1), 289 (17), 243 (13), 144 (2), (143) (2), 130 (100), 117 (1), 115 (1), 105 (57).

Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.83; H, 6.43; N, 6.65.

The crude reaction mixture also contained several components more polar than *c*-**10b** and *t*-**10b**. These could be eluted from silicic acid with 5:10:30:55 ethanol–chloroform–ether–benzene. Attempts to crystallize these materials failed but reduction with sodium borohydride gave **10e**, mp 243–248°. An analytical sample was prepared by recrystallization from ethanol–benzene: mp 255–257°; $\nu_{OH,NH}$ 3450, 3250 cm^{-1}; ν_{CO} 1635, 1620 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 72.78; H, 7.01; N, 9.43. Found: C, 72.49; H, 7.28; N, 9.37.

An analytical sample of **11b** was prepared by recrystallization from ethanol: mp 227–228°; ν_{NH} 3470, 3270 cm^{-1}; ν_{CO} 1740, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 601 (6), 600 (10), 471 (21), 470 (32), 342 (21), 341 (27), 131 (22), 130 (61), 129 (41), 105 (100), 102 (27), 77 (45), 69 (20); $\lambda^{max}_{95\%\ EtOH}$ (log ϵ) 223 (5.02), 277 (4.34), 283 (4.35), 292 (4.30).

Anal. Calcd for $C_{38}H_{40}N_4O_3$: C, 75.97; H, 6.71; N, 9.33. Found: C, 76.28; H, 6.98; N, 8.91.

Equilibration of *c*-10b and *t*-10b.—Identical experiments were carried out with each ketone. A solution of the ketone (100 mg) and potassium fluoride (300 mg) in ethanol (20 ml) was refluxed for 31 hr. The ethanol was removed at reduced pressure and the residue was dissolved in chloroform and washed with water. Tlc on silica gel (three elutions using 1:1:0.3:0.7 methylene chloride–ether–hexane–benzene) indicated that the product from both *c*-**10b** and *t*-**10b** had identical composition favoring *t*-**10b** by ~4:1. The chloroform was evaporated and the residue was crystallized from ethanol. *t*-**10b** gave 69.6 mg of crystalline product having an infrared identical with pure *t*-**10b**. *c*-**10b** gave 63.1 mg of crystalline product, having an infrared spectrum identical with that of pure *t*-**10b**.

Methyl 1-Benzoyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (10a).—The ketone **9d** (3.0 g, 11 mmol) was converted to the enamine and alkylated by a procedure analogous to that used for **10b**. The crude product was hydrolyzed as for **10b** except that methanol was used instead of ethanol. Chromatography of the product gave **10a** (0.365 g, 0.95 mmol, 8%): mp 114–116° after recrystallization from methanol; ν_{NH} 3300 cm^{-1}; ν_{CO} 1720, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 404 (5), 373 (2), 372 (3), 355 (1), 276 (5), 275 (33), 243 (18), 174 (1), 170 (2), 144 (1), 143 (2), 142 (1), 130 (100), 105 (64).

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; 5.98; N, 6.93. Found: C, 71.34; H, 6.14; N, 7.01.

Ethyl 1-Benzoyl-3-hydroxy-2-(3-indolylmethyl)piperidine-4-acetate (*t,t*-12b).—A solution of *t*-**10b** (0.120 g, 0.29 mmol) in ethanol (20 ml) was stirred for 0.5 hr with sodium borohydride (50 mg). Acetone (2 ml) was added and after 5 min the solution was poured into dilute hydrochloric acid and extracted thoroughly with chloroform. The chloroform was washed with sodium bicarbonate solution, dried, and evaporated. The residue was dissolved in chloroform. Addition of a small amount of hexane induced crystallization of **12b**, (0.108 g, 0.26 mmol, 90%), mp 165°. Recrystallization from chloroform–hexane gave the analytical sample: mp 167–168°; $\nu_{OH,NH}$ 3340 cm^{-1}; ν_{CO} 1745, 1620 cm^{-1}; nmr peaks ($CDCl_3$–DMSO-d_6) at δ 1.22 (3 H, t), 1.5–3.5 (m), 4.1 (2 H, q), 5.2 (d, 1 H exchanged by D_2O), 6.2 (d, 1 H), and 6.5–7.8 (9 H, m); mass spectrum *m/e* (rel intensity) 420 (2), 375 (2), 374 (6), 290 (13), 269 (2), 245 (3), 244 (5), 186 (3), 168 (2), 144 (2), 143 (3), 130 (35), 117 (8), 105 (100).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.40; H, 6.69; N, 6.73.

The 3-d_1 analog was prepared similarly using sodium borodeuteride: mass spectrum *m/e* (rel intensity) 421 (8), 376 (6), 375 (12), 291 (40), 246 (8), 245 (12), 187 (5), 130 (36), 117 (8), 105 (100).

1-Benzoyl-3-hydroxy-2-(3-indolylmethyl)piperidine-4-acetic Acid Lactone (*t,t*-13a).—A mixture of *t,t*-**12b** (1.20 g, 2.9 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (50 ml) was refluxed for 12 hr. The toluene was removed by distillation at reduced pressure and the residue was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried, and evaporated. The residue crystallized from chloroform–hexane to give *t,t*-**13a** (0.65 g, 1.7 mmol, 60%), mp 193–198°. Recrystallization from chloroform–hexane gave the analytical sample: mp 202–204°; ν_{NH} 3250 cm^{-1}; ν_{CO} 1810, 1620 cm^{-1}; nonaromatic nmr signals (DMSO-d_6, 90°) at 1.2–2.0 (~3 H, m), 2.8–3.4 (~3 H, m), 4.2 (2 H, d of d, J = 10, 5 Hz superimposed on broad singlet), 4.9 (1 H, broad); mass spectrum *m/e* (rel intensity) 374 (15), 269 (4), 253 (4), 245 (7), 244 (6), 240 (2), 230 (2), 226 (2), 186 (7), 172 (2), 171 (2), 170 (2), 169 (2), 168 (2), 167 (2), 157 (2), 156 (2), 155 (2), 143 (7), 144 (2), 142 (2), 141 (2), 130 (62), 117 (20), 115 (4), 105 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.58; H, 5.92; N, 7.46.

The 3-d_1 analog was prepared similarly from *t,t*-**12b**-d_1: nmr spectrum identical with *t,t*-**13a**'s except lacking d of d at δ 4.2; mass spectrum *m/e* (rel intensity) 375 (75), 270 (7), 253 (8), 246 (15), 245 (11), 187 (14), 170 (4), 169 (6), 168 (10), 167 (6), 165 (6), 130 (60), 117 (18), 105 (100).

Reduction of *c*-10b.—A solution of *c*-**10b** (200 mg, 0.48 mmol) was reduced with sodium borohydride (100 mg) in ethanol and the product mixture obtained as described for *t*-**10b**. Tlc showed two major components which were isolated by preparative tlc. The more readily eluted component was an alcohol, *c,c*-**12b**: mp 217–218° (95 mg, 47%); $\nu_{NH,OH}$ 3360, 3250 cm^{-1}; ν_{CO} 1730, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 420 (1), 374 (3), 290 (4), 245 (18), 186 (11), 144 (1), 143 (1), 130 (31), 117 (2), 105 (100).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 72.14; H, 6.87; N, 6.42.

The less readily eluted component (85 mg, 47%) was recrystallized from methylene chloride–ether–hexane to give *c,c*-**13a**: mp 154–156°; ν_{NH} 3410, 3270 cm^{-1}; ν_{CO} 1780, 1605 cm^{-1}; nmr (DMSO-d_6, 35°) δ 1.9 (2 H, broad q), 2.8 (2 H, d), 3.2 (? H, m), 3.7 (2 H, q), 4.5–5 (2 H, 6 line m), 7.0–7.5 (10 H, m); (DMSO-d_6, 90°) δ 1.8 (2 H, septet), 2.5–2.8 (2 H, m), 3.1 (2 H, unsym q), 3.2–3.8 (2 H, 12 line m), 4.6 (1 H, q), 4.8 (1 H, t); mass spectrum *m/e* (rel intensity) 374 (5), 245 (32), 186 (24), 181 (3), 169 (5), 168 (3), 155 (3), 144 (3), 143 (5), 130 (42), 119 (3), 117 (3), 115 (3), 105 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.53; H, 6.00; N, 7.49.

Lactonization of the alcohol *c,c*-**12b** as described for *t,t*-**12b** gave only *c,c*-**13a**. Reduction of *c*-**10b** with sodium borodeuteride gave *c,c*-**13a**-3-d_1, having an nmr identical with *c,c*-**13a**'s except that the t at 4.8 is missing and the signal at 4.6 is a t: mass spectrum *m/e* (rel intensity) 375 (19), 246 (75), 187 (35), 169 (5), 168 (7), 130 (45), 117 (3), 115 (3), 105 (100).

Methyl 1-Benzoyl-5-ethyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (*t,t*-10c and *t,c*-10c).—A mixture of **4dA** and **4dB** (8.0 g, 2.5 mmol) was dissolved in xylene (300 ml) and refluxed for 4 hr with diazabicyclooctane (8.0 g). The xylene was removed by distillation at reduced pressure and the residue was dissolved in chloroform and washed with dilute hydrochloric acid solution and brine. The chloroform was dried, leaving a mixture of the stereoisomers of **5d** and **6c**. The mixture was dissolved in ethanol (200 ml) and hydrogenated over platinum oxide (250 mg) for 2 hr at 35 psi. The solution was filtered and evaporated leaving 7 g of an oil. This was dissolved in ethanol (60 ml) and stirred at room temperature for 45 min with 20 ml of 10% aqueous sodium hydroxide solution. The reaction mixture was poured into brine and extracted with ether which removed 0.5 g of unhydrolyzed material. The aqueous layer was cooled and carefully acidified to pH 2–3 with cold hydrochloric acid. The acidic aqueous solution was extracted with chloroform. The chloroform was washed with brine, dried briefly over sodium sulfate, and then treated with excess diazomethane. The acidification, extraction, and methylation were carried out as quickly as possible to minimize relactonization of the hydroxy acid. The methyl ester was isolated after excess diazomethane was destroyed with acetic acid by washing the chloroform solution with sodium bicarbonate solution and brine. Evaporation of the dried chloroform solution gave 7.5 g of hydroxy ester. Oxidation with Jones reagent was carried out as for **9b**. The resulting ketone **9c** (7.0 g) was dissolved in benzene (100 ml) and refluxed for 30 hr with pyrrolidine (5 cc) and *p*-toluenesulfonic acid (40 mg) using a Dean-Stark water separator filled with molecular

sieve. After removal of the benzene, alkylation with gramine was accomplished as for **10b**. Hydrolysis of the reaction product was carried out using methanol. Chromatography of the product on silicic acid (200 g) using 1:1.5:7.5 chloroform–ether–benzene gave *t,t*-**10c** (1.01 g, 0.23 mmol, 9%), mp 173–175° after crystallization from benzene–hexane, and *t,c*-**10c** (0.433 g, 0.10 mmol, 4%), mp 203–205° after crystallization from ethanol.

An analytical sample of *t,t*-**10c** was prepared by recrystallization from ethanol–hexane: mp 174–175°; ν_{NH} 3200 cm^{-1}; ν_{CO} 1730, 1720, 1620 cm^{-1}; nonaromatic nmr peaks at δ (DMSO-d_6, 70°), 1.8 (3 H, t), 1.0–2.0 (~4 H, very broad), 2.6 (2 H, d), 2.7–3.0 (2 H, m), 3.3 (~3 H, broad doublet), 3.55 (3 H, s), 4.0 (1 H, very broad), 4.8 (1 H, very broad); mass spectrum *m/e* (rel intensity) 432 (3), 400 (1), 303 (25), 271 (17), 198 (1), 171 (1), 170 (1), 144 (2), 143 (3), 130 (100), 117 (2), 115 (2), 105 (67).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.01; H, 6.58; N, 6.60.

An analytical sample of *t,c*-**10c** was prepared by recrystallization from ethanol: mp 210–212°; ν_{NH} 3280 cm^{-1}; ν_{CO} 1740, 1720, 1610 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 70°) at δ 0.7–1.8 (~6 H, very broad), 2.3 (1 H, d of d, J = 17, 8 Hz), 3.4 (2 H, broad d), 3.6 (3 H, s), 3.6–3.8 (~2 H, broad); mass spectrum *m/e* (rel intensity) 432 (3), 401 (0.5), 400 (1), 303 (25), 271 (17), 244 (1.5), 243 (2), 231 (1), 230 (1), 219 (1), 198 (1), 181 (2), 171 (1), 170 (1), 169 (1), 167 (1), 166 (1), 157 (1), 156 (1), 155 (1), 144 (2), 143 (2), 130 (100), 119 (2), 117 (2), 115 (2), 105 (83).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.22; H, 6.70; N, 6.61.

Elution of the column with 5:10:30:55 methanol–chloroform–ether–benzene gave several more polar fractions containing pyrrolidine amides **10f**. Two of the fractions gave crystalline sodium borohydride reduction products **12f** which could be recrystallized from ethanol–hexane. One fraction gave an amide: mp 175–177°; ν_{NH} 3400 cm^{-1}; ν_{CO} 1630 cm^{-1}; mass spectrum *m/e* (rel intensity) 473 (6), 454 (2), 402 (6), 343 (58), 272 (11), 221 (6), 214 (3), 130 (26), 117 (4), 105 (100).

Anal. Calcd for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87. Found: C, 73.71; H, 7.57; N, 8.97.

A second fraction gave a second amide as a solvate: mp (with desolvation) 147–152°; ν_{NH} 3400 cm^{-1}; ν_{CO} 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 473 (4), 402 (7), 343 (34), 273 (5), 272 (9), 221 (4), 214 (5), 130 (29), 117 (7), 105 (100).

Anal. Calcd for $C_{29}H_{35}N_3O_3$: C, 73.54; H, 7.45; N, 8.87. Found (after drying at 150°): C, 73.64; H, 7.59; N, 8.94.

The **4dA–4dB** mixture could also be converted to *t,c*-**10c** and *t,t*-**10c** after ring opening on basic alumina. A mixture of 9.5 g of the epoxides was absorbed onto 200 g of basic alumina and kept for 3 hr. Elution with 20% ether–benzene eluted a mixture containing mainly unsaturated lactone (4.0 g). Ether–benzene–ethanol (30:65:5) eluted a readily crystallized alcohol **5d** (2.4 g): mp 135–136° after recrystallization from methylene chloride–hexane; ν_{OH} 3300 cm^{-1}; ν_{CO} 1700, 1600 cm^{-1}; $\nu_{C=C}$ 1650 cm^{-1}; nmr peaks ($CDCl_3$) at δ 0.6–1.8 (8 H, m and t at 1.25), 2.2–3.4 (m, ~1 H), 3.5–5.1 (7 H, very broad with q at δ 4.15), 6.2 (1 H, s), 7.4 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11, H, 7.30; N, 4.41. Found: C, 68.21; H, 7.35; N, 4.49.

Combination of the alcohol and lactone fractions followed by the same reaction sequence described for the DABCO ring opening product gave *t,c*-**10c** and *t,t*-**10c** in yields similar to those described above.

Ethyl 1-Benzoyl-5-ethyl-2-(3-indolylmethyl)-3-oxo-4-piperidineacetate (10d).—The alcohol **5d** (0.70 g, 2.2 mmol) was hydrogenated and oxidized as in the preparation of **9b**. The spectral properties of the resulting ketone were in accord with expectation. The ketone was dissolved in benzene (40 ml) and refluxed 18 hr with pyrrolidine (1 ml) and a trace of *p*-toluenesulfonic acid. The benzene was removed and alkylation with gramine was carried out in toluene as described for **10b**. The crude product was chromatographed on silicic acid to give **10d** (0.053 g, 0.012 mmol, 5%): mp 174–176° after recrystallization from ethanol; ν_{NH} 3300 cm^{-1}; ν_{CO} 1745, 1735, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 446 (4), 401 (1), 400 (3), 317 (54), 295 (1), 271 (35), 244 (1), 243 (1), 144 (1), 143 (1), 130 (100), 105 (88).

Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.47; H, 6.83; N, 6.24.

Methyl 1-Benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetate (*t,t,t*-12c).—Reduction of *t,t*-**10c** (200 mg) with sodium borohydride in methanol as described for *t*-**10b** gave *t,t,t*-**12c** (180 mg, 90%): mp 215–217° after recrystallization from chloroform–hexane; $\nu_{NH,OH}$ 3400, 3280 cm^{-1}; ν_{CO} 1740, 1600 cm^{-1}; mass spectrum *m/e* (rel intensity) 434 (2), 402 (6), 304 (5), 297 (2), 285 (1), 281 (2), 273 (3), 272 (5), 252 (1), 231 (1), 219 (1), 214 (4), 181 (2), 169 (2), 168 (1), 157 (1), 156 (1), 155 (1), 154 (1), 144 (2), 143 (2), 130 (33), 119 (3), 117 (10), 115 (1), 105 (100).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.60; H, 7.12; N, 6.34.

Lactone of 1-Benzoyl-5-ethyl-3-hydroxy-2-(3-indolylmethyl)-4-piperidineacetate Acid (*t,t,t*-13c).—A solution of *t,t,t*-**12c** was lactonized as described for *t,t*-**12b** giving *t,t,t*-**13c** in 78% yield. An analytical sample was prepared by recrystallization from benzene: mp 220–221°; ν_{NH} 3310 cm^{-1}; ν_{CO} 1795, 1635 cm^{-1}; nmr peaks ($CDCl_3$) at 1.0–4.0 (~11 H, diffuse multiplets), 4.15 (1 H, d of d, J = 9, 5 Hz) 4.45 (1 H, m), 4.95 (1 H, d, 14 Hz), 6.3 (1 H, d, 7 Hz), 6.6–7.7 (9 H, m), 8.5 (1 H, s); nonaromatic nmr peaks (DMSO-d_6, 90°) at 1.9 (3 H, t), 1.0–2.0 (~4 H, broad), 2.5–3.4 (? H, m), 4.2 (2 H, d of d, J = 11, 5 Hz on broad signal), 4.8 (1 H, broad); mass spectrum *m/e* (rel intensity) 402 (9), 297 (1), 285 (1), 281 (3), 273 (4), 272 (5), 258 (3), 252 (1), 226 (1), 214 (5), 186 (1), 180 (1), 172 (1), 171 (1), 169 (1), 168 (3), 167 (1), 154 (3), 144 (3), 143 (4), 130 (37), 117 (9), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.88; H, 6.62; N, 6.94.

Reduction of *t,c*-10c.—A solution of *t,c*-**10c** (94 mg) was reduced in the standard manner with sodium borohydride. Tlc indicated a major and a minor product. Some of the major product *t,t,c*-**12c** crystallized from benzene (30 mg, 32%): mp 200–201° after recrystallization from methylene chloride–benzene; $\nu_{NH,OH}$ 3450, 3300 cm^{-1}; ν_{CO} 1740, 1610 cm^{-1}; mass spectrum *m/e* (rel intensity) 434 (1), 402 (8), 304 (10), 297 (2), 281 (1), 273 (5), 272 (7), 226 (1), 214 (5), 154 (2), 144 (2), 143 (2), 130 (37), 117 (8), 105 (100).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.66; H, 7.01; N, 6.53.

The mother liquors from which *t,t,c*-**12c** crystallized contained additional *t,t,c*-**12c** and the minor reduction product. Concentration and lactonization of the residue gave two lactones which were separated by tlc. The more mobile lactone, *t,t,c*-**13c** (23 mg, 26%), was recrystallized from benzene, mp 203–204°, also isolated as a benzene solvate, mp 110–120°, with desolvation: ν_{NH} 3430, 3300 cm^{-1}; ν_{CO} 1780, 1630 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 120°) at 1.8 (3 H, t), 1.0–1.6 (2 H, m), 1.9 (1 H, broad s), 2.5–2.9 (?, obscured by DMSO-d_5, H_2O), 3.0–3.5 (3 H, m), 4.1 (1 H, broad d), 4.4 (1 H, d of d, J = 11, 5 Hz), 4.9 (1 H, broad s); mass spectrum *m/e* (rel intensity) 402 (10), 297 (2), 285 (1), 281 (2), 273 (5), 272 (6), 226 (2), 214 (6), 186 (1), 180 (1), 170 (1), 169 (1), 168 (2), 167 (1), 154 (2), 144 (2), 143 (3), 130 (43), 117 (11), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.74; H, 6.56; N, 6.75.

The less mobile lactone, *t,c,c*-**13c** (21 mg, 24%), was recrystallized from ethanol–hexane: mp 235–236°; ν_{NH} 3420, 3220 cm^{-1}; ν_{CO} 1775, 1620 cm^{-1}; nonaromatic nmr peaks (DMSO-d_6, 90°) at δ 0.9 (3 H, t), 1.3 (~2 H, q) 2.0–3.0 (? H, obscured by DMSO-d_5, H_2O), 3.5 (2 H, m), 4.0–5.0 (~3 H, very broad with d of d, J = 8, 1 Hz at 4.6); mass spectrum *m/e* (rel intensity) 402 (5), 273 (19), 262 (1), 244 (1), 228 (1), 223 (1), 214 (12), 186 (2), 181 (2), 169 (2), 168 (3), 144 (2), 143 (2), 130 (25), 119 (2), 117 (2), 115 (2), 105 (100).

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.63; H, 6.66; N, 6.95.

Separate lactonization of *t,t,c*-**12c** gave *t,t,c*-**13c**.

Methyl 1-Benzyloxycarbonyl-1,2,3,6-tetrahydropyridine-4-acetate (14).—A mixture of **1b** and **3b** (2.3 g, 8.5 mmol) was stirred at room temperature for 5 hr with a solution of 10% aqueous sodium hydroxide (10 ml) in ethanol (20 ml). The solution was then diluted with water and extracted with ether. The aqueous layer was added to 20 ml of 10% sodium hydroxide solution and refluxed for 24 hr. After extraction with ether the reaction mixture was acidified and extracted with chloroform. It was then brought to neutrality and concentrated until precipitation began. Aqueous 15% sodium hydroxide (30 ml) was added and the solution was cooled in an ice bath. Portions (~0.5 ml) of benzyl chloroformate (total 4 ml) were added with shaking and cooling over a period of 20 min. The solution was extracted with ether, acidified, and extracted with chloroform to give 2.2 g of a mix-

ture of the exocyclic and endocyclic acids. The nmr spectrum indicated that the endocyclic isomer predominated over the exocyclic by about 7:1. Esterification of the acid mixture with diazomethane gave **14**: bp 170–185° (0.5 mm); ν_{CO} 1760, 1730 cm^{-1}; nmr peaks ($CDCl_3$) at δ 2.2 (2 H, m), 3.04 (2 H, s), 3.65 (5 H, s superimposed on m), 4.0 (2 H, m), 5.15 (2 H, s), 5.5 (1 H, m), 7.30 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.60; H, 6.72; N, 4.67.

Hydroboration of 14. 1-Benzyloxycarbonyl-3-hydroxy-4-piperidineethanol (15).—A solution of **14** (1.8 g, 6.3 mmol) in glyme (10 ml) at 0° was treated with 1.0 *M* diborane solution in tetrahydrofuran (3 ml, 3 mmol). After 0.5 hr, water (4 ml), 30% hydrogen peroxide (10 ml) and potassium carbonate (10 g) were carefully added, and the solution was stirred at room temperature for 3 days. The reaction mixture was poured into water and extracted with ether. Chromatography of the crude product (1.6 g) on silicic acid using 30% ether–benzene gave recovered **14** (0.8 g, 44%) and **15** (0.45 g, 16 mmol, 45%): nmr peaks ($CDCl_3$) at δ 1.0–2.0 (5 H, m), 2.0–5.0 (7 H, m), 5.1 (2 H, s), and 7.35 (5 H, s).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58. Found: C, 64.77; H, 7.80.

***N*-(2-Oxo-4-carbethoxybutyl)-2-ethylaziridine (18).**—2-Ethylaziridine (1.77 g, 0.025 mol) was dissolved in triethylamine (10 ml) and added dropwise during 10 min to a solution of ethyl 5-bromolevulinate[24] (5.56 g, 0.025 mol) in benzene (50 ml) at 0°. After stirring 2 hr at 0° triethylamine hydrobromide was removed by filtration and the solvent was removed using a rotary evaporator at room temperature. The product, obtained as a clear pale yellow oil (5.0 g, 94%), was used in subsequent experiments within 0.5 hr.

Ethyl *N*-Benzoyl-*N*-(2-chlorobutyl)-5-aminolevulinate (19).—A solution of **18** (5.56 g, 0.025 mol) in benzene (50 ml) was added dropwise to benzoyl chloride (3.5 g, 0.025 mol) in benzene (50 ml) at 0°. After stirring for 20 min the solvent was removed using a rotary evaporation, and the residue was dissolved in chloroform and washed with dilute potassium carbonate, dilute hydrochloric acid, and water. Evaporation of the chloroform gave the crude haloamide: ν_{CO} 1735, 1640 cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.23 (3 H, s), 0.6–2.0 (5 H, unresolved m), 2.9–2.3 (4 H, d), 4.1 (2 H, q), 4.38 (2 H, s), 7.39 (5 H, broad s). Attempts to effect complete purification by distillation or silicic acid chromatography failed.

***N*-Benzoyl-6-(2-carbethoxyethyl)-2-ethyl-3,4-dihydro-2*H*-1,4-oxazine (20).**—A solution of **19** (1.0 g, 2.8 mmol) in dry tetrahydrofuran (10 ml) was treated with potassium *tert*-butoxide (0.317 g, 2.8 mmol) and stirred at room temperature for 3 hr. Gaseous hydrochloric acid was passed through the solution. The solvent was removed and the residue was dissolved in a small amount of chloroform and eluted through Florisil with chloroform giving **20** (0.4 g, 1.2 mmol, 44%). Rechromatography gave the analytical sample: ν_{CO} 1740, 1640 cm^{-1}; $\nu_{C=C}$ 1690 cm^{-1}; nmr signals ($CDCl_3$) at 1.21 (3 H, t), 0.7–2.0 (5 H, complex m), 2.2–2.7 (2 H, m), 4.1 (2 H, q), 2.9–4.5 (3 H, unresolved m), 6.6, 5.8, (1 H, singlets in 1:2 ratio), 7.47 (5 H, s).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.13; H, 7.25; N, 4.42. Found: C, 67.86; H, 6.98; N, 4.41.

Reduction of this material by $NaBH_4$ slowly (overnight) gave *N*-benzoyl-2-ethyl-6-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,4-oxazine (**21**) as indicated by mass spectral parent ion 275 and infrared absorption data: ν_{OH} 3440 cm^{-1}; ν_{CO} 1640 cm^{-1}; no ester carbonyl; nmr peaks ($CDCl_3$) at δ 0.7–2.5 (9 H, complex m), 2.32 (1 H, s, exchanged by D_2O), 3.9–4.5 (5 H, complex unresolved signal), 6.65, 5.8 (1 H, singlets in 1:2 ratio), 7.52 (5 H, s).

Registry No.—**2b**, 30338-60-4; **4b**, 30338-61-5; **4d**, 30338-62-6; **5b**, 30338-63-7; **5d**, 30338-64-8; **6a**, 30338-65-9; **8a**, 30338-66-0; **9b**, 30338-67-1; **10a**, 30338-68-2; *t*-**10b**, 30338-69-3; *c*-**10b**, 30338-70-6; *t,t*-**10c**, 30338-71-7; *t,c*-**10c**, 30338-72-8; **10d**, 30338-73-9; **10e**, 30338-74-0; **11b**, 30338-75-1; *t,t*-**12b**, 30338-76-2; *c,c*-**12b**, 30338-77-3; *t,t,t*-**12c**, 30409-18-8; *t,t,c*-**12c**, 30338-78-4; **12f**, 30338-79-5; *t,t*-**13a**, 30338-80-8; *c,c*-**13a**, 30338-81-9; *t,t,t*-**13c**, 30338-82-0; *t,t,c*-**13c**, 30338-83-1; *t,c,c*-**13c**, 30338-84-2; **14**, 30338-85-3; **15**, 30338-86-4; **19**, 30338-87-5; **20**, 30409-19-9; **21**, 30344-94-6.

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The Synthesis of Polyalkyl-1-tetralones and the Corresponding Naphthalenes[1]

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The stepwise synthesis of specifically substituted trialkyl-3,4-dihydro-1(2*H*)-naphthalenones (1-tetralones), the corresponding naphthalenes, and partially hydrogenated derivatives, several having the cadalene-type 1,4,6 substitution, has been reexamined. Individual steps have been improved and new approaches with *fewer* steps and higher overall yields have been devised. Syntheses utilizing lactones in Friedel–Crafts reactions were also carried out. These latter Friedel–Crafts reactions are responsible for rearrangements during tetralone syntheses which were previously attributed to polyphosphoric acid during cyclization.

The synthesis of cadalene (**1**) became important to us as a route to pure polyalkylnaphthalenes and as a model to develop new and improved hydrocarbon syntheses.[3,4]

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(3) (a) S. Dev and P. C. Guha, *J. Indian Chem. Soc.*, **25**, 13 (1948); (b) B. A. Nagasampagi, S. Dev, and (in part) C. Rai and K. L. Murthy, *Tetrahedron*, **22**, 1949 (1966); (c) L. Ruzicka and L. Ehmann, *Helv. Chim. Acta*, **15**, 140 (1932).

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