Simplified Analogs of Lysergic Acid. V. Derivatives of *N,N*-Diethyl-1-methyl-9*H*-indeno-1,2,3,9a-tetrahydro[2,1-*b*]pyridine-3-carboxamide

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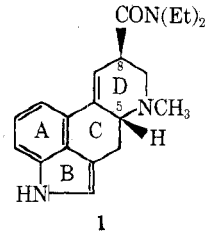
The synthesis of the simplified analog of lysergic acid diethylamide, *N,N*-diethyl-1-methyl-9*H*-indeno-1,2,3-9a-tetrahydro[2,1-*b*]pyridine-3-carboxamide (**6b**), in which the β-arylethylamine moiety exists twice with reference to one benzene nucleus, is described. The starting material (indene) was converted to the tricyclic intermediate ethyl 4a-hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (**28a**) *via* a six-step sequence and thence to the title compound **6b** in four steps. The stereochemistry of some of the key intermediates and of the final product is discussed.

Widespread interest in the synthesis of lysergic acid analogs has been stimulated by the remarkable pharmacological properties of lysergic acid diethylamide (LSD, **1**[1a]), which exhibits a plethora of pharmacological effects including peripheral serotonin antagonism, vasoconstrictor activity, and sympathomimetic activity.[1b] However, its psychotropic and oxytocic[1c] (uterine contractile) activities are of primary interest.

The presence of the indole moiety in other compounds showing hallucinogenic activity (*e.g.*, bufotenine, *N,N*-dimethyltryptamine, psilocin)[2b] and the presence of the β-arylethylamine moiety coupled with the absence of the indole nucleus in compounds exhibiting oxytocic activity (**2**,[2a] **3**,[3] **4**[4]) suggests that different parts of the molecule may be responsible for the various pharmacological activities. The synthesis of ethyl 4-methyl-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (**5**) and the demonstration of its marked oxytocic activity[5] has led to our further interest in synthesizing the title compound **6b.** In the parent compound, **1**, the β-arylethylamine moiety exists twice, once with reference to each half (rings A and B) of the indole nucleus. Compound **5** does not possess this feature, whereas **6b** possesses this dual β-arylethylamine function and hence may exhibit the powerful pharmacological activity of the parent compound.



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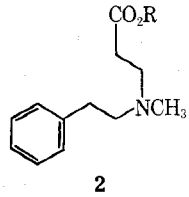

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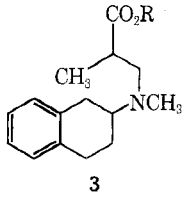

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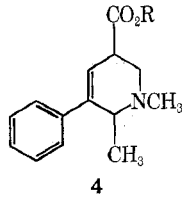

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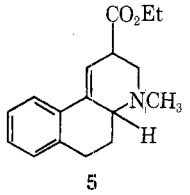

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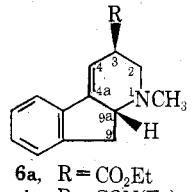
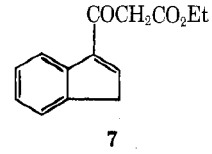


6a, R = CO_2Et
b, R = $CON(Et)_2$

Attempts to synthesize **6** through intermediates **10a**, **7**,[5] and **8**[6] were unsuccessful. By analogy, compound **7** should be obtainable from 1-acetylindene and diethyl carbonate.[5] Reaction of 1-indenecarboxylic acid chloride[7] with dimethylcadmium[8] gave complex mixtures, while indenyllithium[9] and acetyl bromide produced **10a** (9%) along with 3,3-diacetylindene **9** and the isomeric **10b** (15%) formed by further acetylation of **10a.** The low yield of **10a** coupled with the unstable nature of the compound led to investigations of other methods of synthesizing **7.** Treatment of indenyllithium with monoethylmalonyl chloride[10] in order to prepare **7** directly resulted in complex mixtures. Indenecarboxylic acid chloride on treatment with the magnesium salt of ethyl *tert*-butyl malonate[11] gave ethyl *tert*-butyl 1-indenoylmalonate (**11**, 66%). Heating **11** with *p*-toluenesulfonic acid formed the desired **7** (84%) as an unstable oil, but the Mannich[6] reaction of **7** and **11** failed. The lack of success in this reaction may be attributed to the high reactivity of the allylic protons in the indene nucleus and the resulting side reactions.



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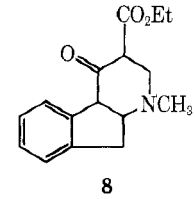

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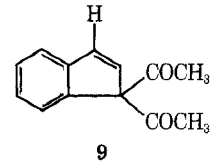

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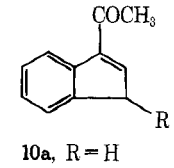
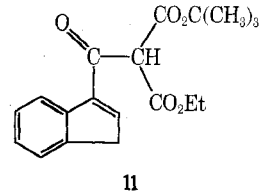


10a, R = H
b, R = $COCH_3$



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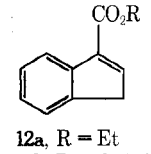
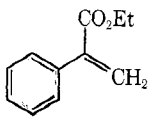


12a, R = Et
b, R = $C(CH_3)_3$

Our next attempts to synthesize **6** were aimed at the introduction of nitrogen at C_2 in indene. Direct reaction of ethyl 1-indenecarboxylate (**12a**)[12] with ethyl β-*N*-methylaminopropionate[17] yielded only the starting material, in marked contrast to the ready addition of **13** to the same reagent.[13] Condensation of 2-indanone[14] with ethyl β-*N*-methylaminopropionate yielded the enamine[15] **15** but attempts to obtain product **16** for subsequent hydrogenation and cyclization were unsuccessful.

Our further efforts were directed at the reaction of amines with the epoxide **17a** prepared from **12a** with *m*-

chloroperbenzoic acid in quantitative yield. The interaction of β-methylaminopropionitrile[16,17] with **17a** yielded a mixture (45%) of the two possible amino esters **18a** and **19a** in the ratio of 2:1 as shown by gas chromatography. The isomers were separated by elution chromatography on silica gel. The preferential attack on the epoxide rather than on the ester may be due to the hindered approach of the nucleophile to the carbonyl of the ester group. Since **19a** was the unwanted side product, its chemistry was not further investigated. By decreasing the temperature and increasing the time of this reaction **19a** became the major product and is thus probably the thermodynamically controlled product, while the desired **18a** is the kinetically controlled product of the reaction. The isolation of the two isomeric amines is in marked contrast to the reaction of amines with compounds of type **20**, which yielded only one isomer in high yield.[18] An attempted Thorpe–Ziegler[19] cyclization of **18a** failed to produce usable amounts of the cyclic amine.



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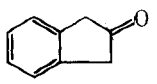

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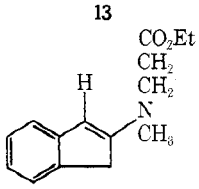

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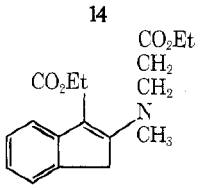

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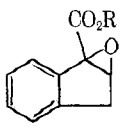
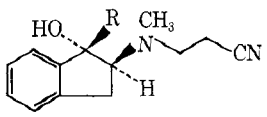
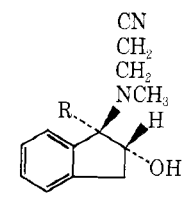


17a, R = Et
b, R = Me
c, R = $C(CH_3)_3$

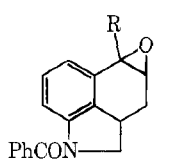


18a, R = CO_2Et
b, R = $CO_2C(CH_3)_3$

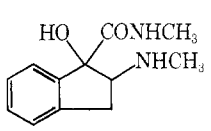
In order to improve the yield of the desired amino ester **18**, two changes were explored: the size of the ester function in **17** and the size of the attacking nucleophile. An investigation of the ring opening of the epoxide **17a** with the small nucleophile methylamine at 100° revealed that the amino amide **21** was formed in quantitative yield. No trace of isomeric **22** could be found. The structure of **21**, which was characterized as the hydrochloride, was deduced from the infrared and nmr spectra. The methyl ester epoxide **17b** also yielded the same product **21** on reaction with methylamine. Numerous attempts to hydrolyze the amide function in **21** were unsuccessful under both acidic and basic conditions. The reaction of epoxide **17c**, prepared from *tert*-butyl indene-1-carboxylate (**12b**) and *m*-chloroperbenzoic acid in benzene, with methylamine at room temperature in methanol led to the two isomeric amines **23a** and **24** in a 1:10 ratio. The isomers were readily separated by fractional crystallization and could be distinguished by their nmr spectra. Compound **23a** could be converted *via* a Michael reaction[20] to **18b** or transesterified to the methyl ester **23b**, whereas **24** was unreactive in both instances, presumably owing to steric problems. Efforts to improve the yield of **23a** by carrying out the reaction in a bomb at 100° were hampered by the formation of a significant amount of **21**.



19a, R = CO_2Et
b, R = $CO_2C(CH_3)_3$



20, R = $CONH_2$



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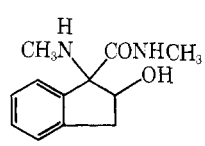

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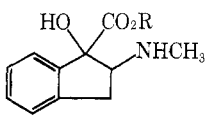
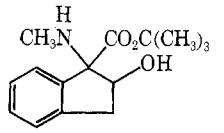


23a, R = $C(CH_3)_3$
b, R = Me



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The reaction of the methyl ester epoxide **17b** with amines would be expected to favor the undesirable thermodynamic product relative to **17a**, since there would be less of a steric problem. In fact the ring opening of **17b** with β-methylaminopropionitrile yielded only a basic amide [as shown by infrared absorption at λ_{max} (neat) 1660 cm^{-1}] which was not further investigated. The reaction of the bulky *tert*-butyl ester epoxide **17c** with β-methylaminopropionitrile gave the two expected amino alcohols **18b** and **19b** in a 3:1 ratio. However, the desired product **18b** was a solid whereas the undesirable isomer **19b** was a liquid; the troublesome chromatographic separation could thus be avoided. Small amounts of **23a** and **24** were also isolated from the reaction mixture, presumably arising from either a reverse Michael reaction[21] of **18b** and **19b** or from the addition of methylamine (decomposed β-methylaminopropionitrile) to **17c**. A separate experiment revealed that heating **18b** to 180° did give a small amount of **23b**; so both routes to the minor products are feasible.

The three nitriles **18a**, **18b**, and **19b** could be smoothly converted to the diesters **25a** and **26** with HCl gas in ethanol. Nmr, infrared, and gas chromatographic studies revealed that the nitrile function of **18b** hydrolyzed more rapidly than the *tert*-butyl ester function and an intermediate diester **25b** was formed which was then slowly hydrolyzed to the desired diethyl ester **25a**. It was also possible to prepare **25a** by the direct reaction of the epoxide **17a** with ethyl β-methylaminopropionate,[17] but the overall yield was lower and the mixture of isomers (**26** was also found) was difficult to separate.

The diester **25a** could be easily dehydrated in concentrated sulfuric acid to yield the unstable enamine **16**. All attempts to utilize this sensitive intermediate for the formation of the desired tricyclic system proved fruitless. Attempted cyclization or hydrogenation led to no recognizable products, distillation caused decomposition, and chromatography resulted in hydrolysis to the enol **27**, mp 66–67° (lit. mp 68–69°).[22]

The third ring was finally introduced *via* a Dieckmann cyclization[23,24] of **25a**. Sodium hydride in benzene afforded the tricyclic ester **28a** (66%) whereas dry potassium *tert*-butoxide in benzene resulted in an 82% yield. The structure of **28a** was in accord with its spectral and analytical data. Two distinct routes starting with **28a** were employed for the syntheses of the desired unsaturated ester **6a** and amide **6b**.

Hydrogenolysis of the ester **28a** over 10% Pd on charcoal in glacial acetic acid containing perchloric acid[25a] led to a mixture of three products. Similar results were obtained when the methyl ester **28b** prepared from precursor **25c** was hydrogenated under identical conditions.[25b] The

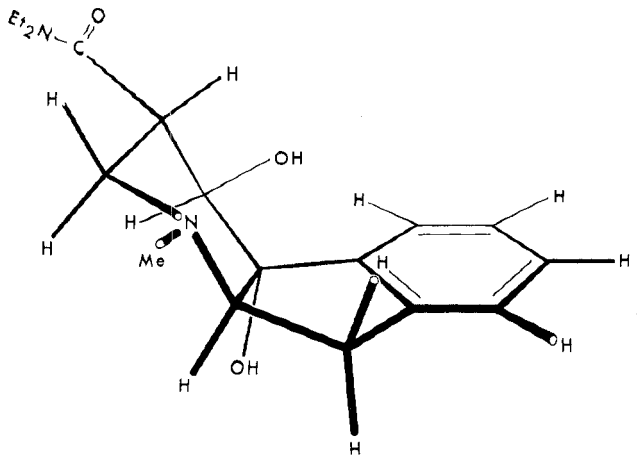


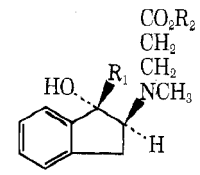
Figure 1. A drawing of the trans diol **33a** showing the proximity of the C_4 equatorial OH and the C_5 aromatic proton.

equatorial hydroxy isomer **29** (20%) was isolated by crystallization from ether. The residue was chromatographed on silica gel to give the ketone **8** (27%, characterized as the picrate) and the axial alcohol **30** (21%). The identity of the three compounds was established from the following evidence: the infrared spectrum of **8** showed absorption characteristics for a highly enolic β-keto ester,[26] its nmr spectrum showed no absorption for a proton α to a hydroxyl group, and its mass spectrum showed a parent peak in accord with its calculated molecular weight; the hydroxy esters were tentatively distinguished by noting that their nmr spectra were significantly different in the aromatic regions. The axial alcohol **30** had four equivalent aromatic protons while its epimer **29** showed one aromatic proton clearly deshielded from the other three. Inspection of Dreiding models revealed that in the three-ring indeno-[2,1-*b*]pyridine system whenever a substituent at C_4 is equatorial it is in a position very close to the aromatic proton at C_5 (see Figure 1). Nagata[27] and Horii[28] have noted that strong deshielding of the aromatic C_5 proton in systems **31a** and **31b** is caused by the steric effect of the equatorial C_4 proton and the degree of this deshielding is closely related to the interatomic distance between the two protons. In the conformation of **29** depicted in Figure 1, the distance (as measured from Dreiding models) between the hydrogen atom at C_5 and the center of the oxygen atom at C_4 is 1.8 Å, well within the range shown to cause a strong deshielding effect.[27] Further evidence supporting these stereochemical assignments comes from the expected observation that sodium borohydride reduces ketone **8** only to the equatorial isomer **29**.[18]

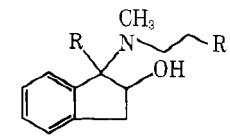
Dehydration of either of the hydroxy esters **29** and **30** with phosphorus oxychloride in pyridine[29] containing a trace of H_3PO_4 gave the same mixture of the two expected double-bond isomers **32a** and **6a**,[30a] as evidenced by their mass spectra and nmr and ir spectra.

Synthesis of the amide **6b** was carried out in the following manner. Ester **28a** was smoothly converted to amide **28c** by heating with diethylamine and xylene,[30b] followed by reduction with sodium borohydride in methanol to give diol **33a**.

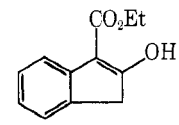
The stereochemistry of the diol may be deduced from the following evidence. Since the ring opening of a cycloalkane epoxide is known to yield the trans diaxial compound,[31,32] the hydroxy and amino functions in **18a** should have the trans di-quasi-axial conformation. It is reasonable to assume that this configuration will not change during the hydrolysis to diester **25a** and similarly it would be expected that this relationship (responsible for a cis B–C ring junction) would be retained in **28a**, since



25a, $R_1 = CO_2Et$; $R_2 = Et$
b, $R_1 = CO_2$-*t*-Bu; $R_2 = Et$
c, $R_1 = CO_2Me$; $R_2 = Me$



26, $R = CO_2Et$



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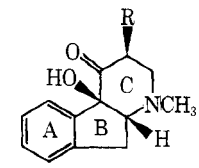
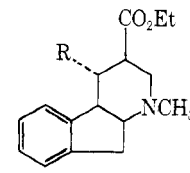
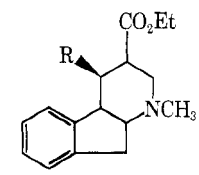


28a, $R = CO_2Et$
b, $R = CO_2Me$
c, $R = CON(Et)_2$



29
R = equatorial OH

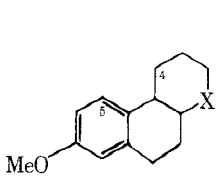


30
R = axial OH

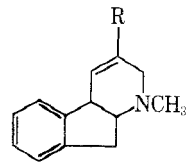
any change in stereochemistry at C_{9a} would necessitate the unlikely formation of a trianion. Dreiding models also reveal that with a quasi-equatorial (with respect to the five-membered ring) C–N bond in **28a**, which would have to arise from a conformational change during the formation of either **25a** or **28a**, there is severe crowding between the C_2 axial proton and the quasi-axial proton at C_9. This crowding is not manifested in conformations with a quasi-axial C–N bond (see Figure 1). Furthermore, a quasi-equatorial C–N bond would give rise to a conformer of **33a** in which the distance between the C_4 equatorial OH and the C_5 proton is over 3 Å, too far to cause the observed downfield shift of the aromatic proton[27] in **33a**. The carboethoxy function at C_3 in **28a** would be expected to be in the more stable equatorial position, since an opportunity for base-catalyzed equilibration has been provided by the proximity of the carbonyl function at C_4. Neither the formation of the keto amide **28c** nor its sodium borohydride treatment would be expected to alter the stereochemistry of the ring junction, and, since borohydride reduction is known to favor the formation of the equatorial isomer,[18] the stereochemistry of diol **33a** may be regarded as shown.

Other evidence favoring the stereochemistry depicted in **33a** comes from the observation that the nmr spectrum shows one deshielded proton in the aromatic region, indicative of an equatorial C_4 substituent (*vide supra*). A very small quantity (4%) of the isomeric diol **34a** was also obtained from the reduction of **28c**; its nmr spectrum revealed that all the aromatic protons were equivalent. It was also noted that borohydride reduction of the keto ester **28a** afforded two isomeric diols in the ratio 7:1. According to evidence already presented, the major product should have been the diequatorial diol **33b** and the minor product diol **34b**. This expectation was confirmed by the nmr spectra; the aromatic protons were nonequivalent in **33b** (equatorial OH at C_4) and equivalent in the minor diol **34b**.

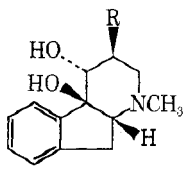
Hydrogenolysis of diol **33a** with 10% palladium on charcoal in glacial acetic acid containing perchloric acid[25] resulted in the unexpected loss of the nonbenzylic hydroxyl group,[33] affording the benzylic alcohol **35**. The absence of any proton α to an hydroxyl group as well as the equiva-



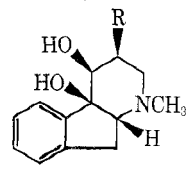
31a, X = CH_2
b, X = NCH_3



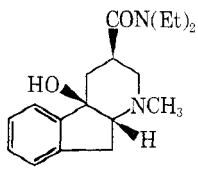
32a, R = CO_2Et
b, R = $CON(Et)_2$



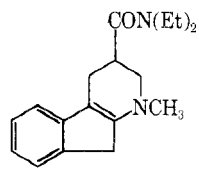
33a, R = $CON(Et)_2$
b, R = CO_2Et



34a, R = $CON(Et)_2$
b, R = CO_2Et



35



36

lence of all the aromatic protons in the nmr, the observation that the alcohol could not be oxidized with Jones[34] reagent, and the analytical and mass spectral data, all pointed to the tertiary benzylic alcohol **35** as the sole product. Alcohol **35** could be dehydrated to the desired target compound **6b** with thionyl chloride in pyridine,[35] and no undesired isomer **36** was formed; the nmr spectrum of **6b** exhibited one olefinic proton and the uv maxima revealed that the product [λ_{max} 224 (sh), 254, and 273 nm (sh)] closely resembled **5**[5] [λ_{max} 225 (sh) and 255 nm] with similar absorption coefficients of *ca.* 10,000 to those of indene (249 nm) and 3,4-dihydronaphthalene (262 nm).[36] Isomeric **36** would be expected to show a uv absorption band of similar intensity at *ca.* 300 nm due to the $C_6H_5C{=}CNR_2$ chromophore[37] which should change hypsochromically upon addition of acid. No shift in the uv maxima of the product was observed upon acidification. All other analytical data were in accord with structure **6b**.[38] From the earlier discussion on stereochemistry one may conclude that the bridgehead proton at C_{9a} (quasi-equatorial with respect to ring B) and the amide function at C_3 (equatorial) are syn as in LSD rather than anti as in the biologically uninteresting[41] isolysergic acid molecule.

A preliminary evaluation of the pharmacological activity of **6b** has revealed that the compound is highly effective in reversing the ileal contractions induced by the standard oxytocic ergonovine maleate.

Experimental Section

Melting points are uncorrected and were determined on a Mel-Temp apparatus. Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer and uv spectra were measured on a Cary Model 15 spectrophotometer. Nmr spectra were recorded on a Varian A-60A spectrometer. Absorptions are quoted in δ values using TMS as internal standard (abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). High-resolution mass spectra were obtained on an AEI-MS9 spectrometer. The purity of all compounds was checked by glc and tlc analyses. Glc data were obtained using a Varian Aerograph series 2100 chromatograph equipped with all-glass U-tube columns packed with 1 or 3% SE-30 and 1.5% OV-17 stationary phases coated on Gas-Chrom Q (100–120 mesh). All gc was carried out at column temperatures of 165–185°. Tlc analyses were performed on silica gel G with one of the following solvent systems: $CHCl_3$, 15% ethyl acetate in $CHCl_3$, 5% EtOH in PhH, and 10% EtOH in Et_2O. Microanalyses were performed by Mr. V. Tashinian of the University of California at Berkeley. Petroleum ether refers to that fraction of bp 30–60°.

1-Acetylindene (10a), 1,3-Diacetylindene (10b), and 3,3-Diacetylindene (9). Acetyl bromide (12.3 g, 0.1 *M*) was added slowly to indenyllithium, prepared from indene (12.5 g, 0.1075 mol) and *n*-butyllithium (62.5 ml, 1.6 *M*, 0.1 mol) in hexane (62.5 ml) and ether (75 ml). The reaction mixture was refluxed for 30 min, cooled, and diluted with water. The ethereal layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield an oil. Chromatography on silicic acid gave three compounds. On elution with 2% ethanol in pentane, 1,3-diacetylindene (**10b**, 2.5 g, 15%) was obtained as an oil: ir (neat) 1750 (saturated ester C=O), 1680 cm^{-1} (conjugated ester C=O); nmr ($CDCl_3$) δ 7.5 (m, 1 H, aromatic), 7.1 (m, 3 H, aromatic), 6.7–6.4 (m, 2 H), 2.3 (s, 3 H, $COCH_3$), 2.1 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.51, H, 6.35.

Elution with 3% ethanol in pentane gave 1-acetylindene, mp 52–54° (1.3 g, 9%). Recrystallization from pentane gave a sample: mp 67–68°; ir ($CHCl_3$) 1675 cm^{-1} (conjugated C=O); nmr ($CDCl_3$) δ 8.1 (m, 1 H, aromatic H), 7.15 (m, 4 H, three aromatic and one olefinic H), 3.23 (m, 2 H, allylic methylene protons), 2.25 (s, 3 H, CH_3).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; ; H, 6.43. Found: C, 83.65; ; H, 6.66.

Further elution with 5% ethanol in pentane yielded 3,3-diacetylindene (200 mg, 1%). Recrystallization from ether–pentane gave a sample: mp 90–90.5°; ir (Nujol) 1725 and 1700 cm^{-1} (saturated C=O); nmr ($CDCl_3$) δ 7.52 (m, 1 H, aromatic H), 7.38 (m, 3 H, aromatic H), 6.77 (dd, 2 H, olefinic H), and 1.96 (s, 6 H, methyl H).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.15; H, 5.91.

Ethyl *tert*-Butyl 1-Indenoylmalonate (11). 1-Indeneacetyl chloride,[4] from indeneacetic acid (16.0 g, 0.1 mol) in ether (30 ml), was added to a solution of the magnesium salt of ethyl *tert*-butyl malonate[8] (16.0 g, 0.1 mol) in ether (20 ml) and ethanol (11 ml). The reaction mixture was refluxed for 30 min, cooled, and acidified with dilute sulfuric acid. The ether layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to yield **11** (22 g, 66%, based on 80% yield of acid chloride).[4] Recrystallization from ethanol gave a sample: mp 103.5–104.5°; ir (Nujol) 1750, 1745 (ester C=O), and 1695 cm^{-1} (conjugated C=O); nmr ($CDCl_3$) δ 8.05 (m, 1 H, aromatic H), 7.2 (m, 4 H, three aromatic and one olefinic H), 4.81 (s, 1 H, methylene H α to esters), 3.45 (d, 2 H, allylic methylene H), 1.4 (s, 9 H, *tert*-butyl ester H), 1.25 (t, 3 H, CH_3CH_2).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.01; H, 6.86.

Ethyl 3-Oxo-3-inden-1-ylpropionate (7). *p*-Toluenesulfonic acid (1 g) was added to ethyl *tert*-butyl 1-indenoylmalonate (9.78 g, 0.03 mol) in benzene (100 ml). The reaction mixture was refluxed for 45 min, neutralized ($NaHCO_3$), filtered, and evaporated under reduced pressure to yield **7** (8.0 g) as an oil. Chromatography on silica gel using benzene as eluent gave a sample (5.8 g, 84%): ir (neat) 1750 (saturated ester), 1680 (conjugated ester), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 8.05 (m, 1 H, aromatic H), 7.17 (m, 4 H, three aromatic H and one olefinic H), 4.05 (q, 2 H, CH_3CH_2–), 3.65 (s, 2 H, methylene H α to the ester), 3.37 (d, 2 H, allylic methylene H), and 1.2 (t, 3 H, CH_3CH_2–).

***tert*-Butyl Indene-1-carboxylate (12b).** A mixture of 100 g (0.625 mol) of indene-1-carboxylic acid, 160 ml of $SOCl_2$, and 800 ml of dry benzene was stirred at 50° until solution had occurred (*ca.* 16 hr). The liquid was then evaporated under reduced pressure and the remaining crude acid chloride was dissolved in 300 ml of anhydrous Et_2O. This mixture was slowly added to a solution of 50 g (0.68 mol) of t-BuOH and 90 g (0.74 mol) of *N,N*-dimethylaniline in 450 ml of Et_2O. After the mixture had stood for 12 hr, 300 ml of H_2O was added to the mixture to dissolve the separated amine hydrochloride and the mixture was transferred to a separatory funnel. The mixture was washed with H_2O (2 × 100 ml), 10% H_2SO_4 (until acidic), saturated $NaHCO_3$ (until basic), and finally salt water. The solution was dried ($MgSO_4$) and evaporated, and the residue was distilled (100°, 0.016 Torr) to give 100 g (76%) of a light yellow oil which crystallized upon standing (mp 48–49°): ir (KBr) 1700 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 8.0 (m, 1, aromatic), 7.4–7.1 (m, 4, olefin and aromatic), 3.3 (d, 2, methylene), 1.6 (s, 9, methyls).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.77; H, 7.41. Found: C, 77.53; H, 7.43.

Ethyl 1,2-Epoxyindane-1-carboxylate (17a). *m*-Chloroperbenzoic acid (1.98 g, 85%, 0.01 mol) was added to a cooled solution of

1-carboethoxyindene (1.88 g, 0.01 mol) in chloroform (50 ml) and the reaction mixture was left at room temperature for 48 hr. The chloroform solution was extracted with saturated sodium bicarbonate solution (3 × 100 ml) and water (100 ml), dried ($MgSO_4$), filtered, and evaporated to yield an oil (2.0 g, 98%). Crystallization from pentane gave a sample: mp 42–43°; ir (CCl_4) 1730 cm^{-1} (ester); nmr ($CDCl_3$) δ 7.75 (m, 1 H, aromatic H), 7.12 (m, 3 H, aromatic H), 4.15 (m, 3 H, one H α to an oxide ring and two ester H), 2.95 (s, 2 H, allylic methylene H), and 1.25 (t, 3 H, CH_3CH_2–).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.83. Found: C, 70.73; H, 6.09.

Ethyl 1-Hydroxy-2-(methyl-β-cyanoethylamino)indan-1-carboxylate (18a) and Ethyl 2-Hydroxy-1-(methyl-β-cyanoethylamino)indan-1-carboxylate (19a). Ethyl 1,2-epoxyindan-1-carboxylate (100 g, 0.499 mol) was added under nitrogen to β-methylaminopropionitrile[13] (300 ml) at 125°. The reaction mixture was stirred at 125° for 35 min and cooled, and the excess β-methylaminopropionitrile was distilled. The residual brown oil was chromatographed on silica gel to yield **18a** and **19a** (63 g, 45%) in the ratio 2:1 (see discussion). Further chromatography of an aliquot on silica gel gave **18a** on elution with 1% ethanol in benzene. Distillation at 140° (0.010 Torr) gave a sample: ir (neat) 3450 (OH, broad), 2250 (C≡N), and 1720 cm^{-1} (ester); nmr ($CDCl_3$) δ 7.15 (s, 4 H, aromatic H), 4.32 (m, 1 H, –OH), 4.1 (m, 2 H, CH_3CH_2–), 3.0 (m, 8 H), 2.4 (s, 3 H, *N*-methyl H), 2.4 (m, 1 H, proton α to N, and 1.15 (t, 3 H, CH_3CH_2–); mass spectrum peaks at *m/e* 288, exact mass 288.1496 (calcd for $C_{16}H_{20}N_2O_3$, 288.1473).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.49; H, 6.76; N, 9.75.

Further elution with 2% ethanol in benzene gave **19a.** Distillation at 150° (0.010 Torr) gave a sample: ir (neat) 3450 (OH, broad), 2265 (C≡N), 1725 cm^{-1} (ester); nmr ($CDCl_3$) δ 7.20 (m, 4 H, aromatic H), 5.0 (t or dd, 1 H, proton α to –OH) 4.2 (q, 2 H, CH_3CH_2–), 3.6 (broad s, 1 H, OH), 3.1 (m, 5 H, methylene protons), 2.6 (s, 3 H, *N*-methyl H), 2.4 (m, 1 H, H α to nitrogen), and 1.25 (t, 3 H, CH_3CH_2–); mass spectrum *m/e* 246 ($M^+ - C_2H_4N$).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.61; H, 6.67; N, 9.76.

1-(*N*-Methylcarbamoyl)-1-hydroxy-2-methylaminoindan (21). Ethyl 1,2-epoxyindan-1-carboxylate (5.5 g, 0.0269 mol) was dissolved in methylamine (100 ml) and heated at 100° for 24 hr. The reaction mixture was cooled and excess methylamine was evaporated to yield **21** (5.9 g, 100%); ir ($CHCl_3$) 3420, 3310 (hydroxyl, amine, and amide) 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.3 (broad s, 1 H, replaceable H), 7.2 (s, 4 H, aromatic H), 4.1 (broad s, 2 H, replaceable H), 2.8–3.5 (m, 3 H, methylene H), 3.7 (d, 3 H, methyl amide H, on addition of D_2O d becomes s at 3.67), and 2.33 (s, 3 H, *N*-methyl H). The hydrochloride was recrystallized from ethanol to give a sample: mp 266–267°; ir (Nujol) 3345 (OH, NH, CNH), 2445 (HCl), 1655 cm^{-1} (amide C=O).

Anal. Calcd for $C_{12}H_{17}O_2N_2Cl$: C, 56.14; H, 6.80; N, 10.92; Cl, 13.84. Found: C, 55.98; H, 6.66; N, 11.01; Cl, 13.75.

Methyl 1,2-Epoxyindan-1-carboxylate (17b). This compound was prepared in the same manner as **17a** in 100% yield, mp 72–74°. Recrystallization from ether–pentane gave a sample: mp 74–75°; ir (Nujol) 1750 cm^{-1} (ester); nmr ($CDCl_3$) δ 7.7 (m, 1 H, aromatic H), 7.18 (m, 3 H, aromatic H), 4.3 (m, 1 H, proton α to epoxide ring), 3.78 (s, 3 H, CH_3O–), and 3.3 (deformed d, 2 H, allylic methylene H).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.27; H, 5.30.

Ethyl 1-Hydroxy-2-(methyl-β-carboethoxyethylamino)-indan-1-carboxylate (25a) and Ethyl 2-Hydroxy-1-(methyl-β-carboethoxyethylamino)indan-1-carboxylate (26). A. 25a from 18a. Ethyl 1-hydroxy-2-(methyl-β-cyanoethylamino)indan-1-carboxylate (3.3 g, 0.0115 mol) was dissolved in ethanol (50 ml) saturated with HCl. The reaction mixture was allowed to stand overnight and the solvent was evaporated under reduced pressure. The resultant oil was dissolved in water (20 ml) and extracted with ether (25 ml). The aqueous layer was basified (NH_4OH) and the precipitated oil was extracted with ether. The ethereal layer was washed (H_2O), dried ($MgSO_4$), filtered, and evaporated to yield **25a** (3.2 g, 84%). Distillation at 140° (0.010 Torr) gave a sample: ir (neat) 3500 (OH), 1740, 1730 cm^{-1} (esters); nmr ($CDCl_3$) δ 7.2 (m, 4 H, aromatic H), 4.1 (m, 5 H, four ester H, –OH), 3.1 (m, 6 H, methylene H), 2.5 (m, 1 H, proton α to nitrogen), 2.3 (s, 3 H, *N*-methyl), and 1.1 (m, 6 H, ester H).

Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.46; N, 4.18. Found: C, 64.29; H, 7.42; N, 4.38.

B. 25a from 18b. *tert*-Butyl 1-hydroxy-2-(methyl-β-cyanoethylamino)indan-1-carboxylate (30 g, 0.095 mol) was dissolved in 500 ml of absolute EtOH saturated with dry HCl at −10°, and allowed to stand for 2 days. The presence of an intermediate diester **25b** (first noted from glc data) was shown by nmr analysis. Most of the EtOH was then removed under reduced pressure and the resulting oil was diluted with cold NH_4OH and extracted with ether. The Et_2O was washed (salt water), dried ($MgSO_4$), and evaporated to give an oil (29 g, 92%) which was shown to be identical (ir, glc) with that produced from A above.

C. 26 from a Mixture of 18a and 19a. Treatment of a 2:1 mixture of **18a** and **19a** in the same manner as in A leads to a mixture of **25a** and **26,** in the ratio of 2:1, respectively, separable by chromatography on silica gel. Elution with 1% ether in pentane gave **25a.** Elution with 2% ether in pentane gave **26.** Distillation at 135° (0.010 Torr) gave a sample: ir (neat) 3510 (OH), 1735 cm^{-1} (esters); nmr ($CDCl_3$) δ 7.3 (m, 1 H, aromatic H), 7.1 (m, 3 H, aromatic H), 4.65 (m, 1 H, proton α to OH), 4.05 (m, 4 H, ester H), 2.3–3.2 (m, 6 H, methylene H), 2.25 (m, 3 H, *N*-methyl), and 1.2 (m, 6 H, ester H); mass spectrum *m/e* 335, exact mass 335.1737 (calcd for $C_{18}H_{25}NO_5$, 335.1735).

Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.45; N, 4.18. Found: C, 64.25; H, 7.45; N, 4.36.

D. 25a from 17a. Ethyl 1,2-epoxyindan-1-carboxylate was added under N_2 to ethyl β-*N*-methylaminopropionate at 125°. After work-up and isolation (similar to the preparation of **18a** and **19a** from **17a**) a low yield of **25a** was obtained, identical in tlc, glc, and ir with the material obtained in procedure A above.

Methyl 1-Hydroxy-2-methylaminoindan-1-carboxylate (23b). This ester was obtained from **23a,** methanol, and dry HCl in a manner similar to the preparation of **25a** from **18b** (*vide supra*) in near-quantitative yield as white needles: mp 135–136° (from benzene); nmr ($CDCl_3$) δ 7.5 (s, 4 H, aromatic), 4.0 (s, 3 H, OCH_3), 4.0–3.0 (m, 5 H), 2.6 (s, 3 H, NCH_3).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.15; H, 6.79; N, 6.33. Found: C, 64.91; H, 6.69; N, 6.31.

Ethyl 2-(Methyl-β-carboethoxyethylamino)indene-1-carboxylate (16). Ethyl 1-hydroxy-2-(methyl-β-carboethoxyethylamino)indan-1-carboxylate (7.0 g, 0.0209 mol) was slowly dissolved in concentrated sulfuric acid (20 ml) at 0–10° over 90min. The reaction mixture was basified with ammonium hydroxide and the resultant oil was extracted with ether. The ethereal layer was washed (H_2O), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield **16** as an unstable oil (5.6 g, 74%): ir (neat) 1730 (saturated ester), 1680 (conjugated ester), 1600 cm^{-1} (C=C); ir (perchlorate, neat) 1750, 1740 (saturated esters), 1700 cm^{-1} ($C=N^+$). Attempted chromatography of **16** yielded **27,** mp 66–67° (lit.[16] mp 68–69°).

Methyl 4a-Hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,-3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (28b). This compound was obtained in 73% yield from **25c** in a manner similar to the preparation of **28a** with KO-*t*-Bu as white cubes (from Et_2O): mp 164–165°; ir (KBr) 1650 cm^{-1} (enolized β-keto ester); nmr ($CDCl_3$) δ 7.8 (m, 1 H, aromatic), 7.4 (m, 3 H, aromatic), 3.8 (m, 4 H, OCH_3 and bridgehead H), 3.58 and 3.22 (AB doublet, 1 H each, J = 16 Hz, methylene), 3.1–2.4 (m, 5 H, NCH_3 and benzylic H).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.30;H, 6.17; N, 5.03.

Ethyl 4a-Hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (28a). A. From NaH. Ethyl 1-hydroxy-2-(methyl-β-carboethoxyethylamino)indan-1-carboxylate (31.0 g, 0.0925 mol) in benzene (300 ml) was added under nitrogen to a suspension of sodium hydride (7.5 g, 53.5%, 0.167 mol) in benzene (600 ml). The reaction mixture was refluxed for 90 min, cooled, and extracted with 10% HCl (2 × 200 ml). The aqueous layer was washed (C_6H_6) and basified (NH_4OH) to yield **28a,** mp 133–135° (16.8 g, 66%). Recrystallization from ether gave 14.1 g: mp 145–146°; ir (Nujol) 3110 (OH, broad), 1665, and 1620 cm^{-1} (β-keto ester); nmr ($CDCl_3$) δ 7.55 (m, 1 H, aromatic), 7.2 (m, 3 H, aromatics), 6.0 (broad s, 1H, OH), 4.15 (q, 2 H, ester protons), 3.74 (t, 1 H, J = 8 Hz, bridgehead H), 3.46 and 3.19 (AB d, 1 H each, J = 15 Hz, methylene), 2.95 and 2.79 (two d each, 1 H each, J = 15 and 8 Hz, nonequivalent benzylic further split by bridgehead H), 2.5 (s, 3 H, NCH_3) 1.25 (t, 3 H, CH_3CH_2); mass spectrum exact mass 289.1317 (calcd for $C_{16}H_{19}NO_4$, 289.1314).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.25; H, 6.54; N, 4.87.

B. From KO-*t*-Bu. Into a flask containing *ca.* 20 g (0.158 mol) of freshly prepared potassium *tert*-butoxide was distilled 500 ml of dry benzene. The suspension was flushed with N_2 gas and 26.5 g (0.08 mol) of **25a** in 25 ml of dry benzene was added all at once. The mixture was allowed to stand overnight and was worked up in a manner similar to that in procedure A to give 18.5 g (81%) of desired **28a**, identical in tlc, ir, and nmr with the material prepared in A.

***N,N*-Diethyl-4a-hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxamide (28c).** Ethyl 4a-hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (1.0 g, 0.00346 mol) was heated at 110° in xylene (25 ml) and diethylamine (3 ml) for 12 hr. The solution was cooled and extracted with 10% HCl (100 ml). The aqueous layer was washed (Et_2O), basified (NH_4OH), and reextracted with ether (100 ml) and chloroform (100 ml). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated to yield an oil (1.07 g). Chromatography on silica gel yielded **28c** (750 mg, 68%) on elution with 5% ether in pentane. Removal of solvent gave a crystalline sample which was recrystallized from ether: mp 126–127°; ir (KBr) 3300 (OH), 1690, and 1620 cm^{-1} (β-keto amide); nmr ($CDCl_3$) δ 7.9 (m, 1 H, aromatic), 7.23 (m, 3 H, aromatics), 5.5 (broad s, 1 H, replaceable by D_2O, -OH), 3.9–2.8 (m, 10 H, six methylene and four ethyl amide H), 2.17 (s, 3 H, *N*-methyl H), and 1.13 (m, 6 H, ethylamide H); mass spectrum exact mass 316.17833 (calcd for $C_{18}H_{24}N_2O_3$, 316.17868).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.08; H, 7.61; N, 8.59.

Ethyl *cis*-4,4a-Dihydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (34b) and Ethyl *trans*-4,4a-Dihydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro-[2,1-*b*]pyridine-3-carboxylate (33b). $NaBH_4$ (60 mg, 0.001446 mol) was added slowly to a cooled solution (−5°) of ethyl 4a-hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]-pyridine-3-carboxylate (**28a**, 1.5 g, 0.00519 mol) in ethanol (200 ml). The reaction mixture was left at room temperature overnight and evaporated under reduced pressure. The resultant solid was boiled with ether and filtered. The ether solution was boiled to small volume and cooled to give **33b**: mp 157.5–158.5° (565 mg, 37%); ir (Nujol) 3545 (OH), 3145 (OH), 1735 cm^{-1} (saturated ester); nmr ($CDCl_3$) δ 7.7 (m, 1 H, aromatic), 7.3 (m, 3 H, aromatics), 4.2 (m, 1 H, proton α to hydroxyl group), 4.15 (q, 2 H, ester protons), 3.45 (broad s, 2 H, replaceable -OH), 3.2–2.35 (m, 6 H, methylene H), 2.26 (s, 3 H, *N*-methyl), and 1.25 (t, 3 H, ester H).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.21; N, 4.81. Found: C, 65.68; H, 7.35; N, 4.70.

The mother liquors were evaporated to dryness to yield an oil, which was chromatographed on silica gel to give **33b**, 150 mg (total 46%). Further elution afforded **34b**, mp 173–174° (115 mg, 7%). Recrystallization from ether gave a sample: ir (KBr) 3480 (OH), 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.28 (m, 4, aromatics), 4.18 (m, 3, two ester and one proton α to hydroxyl group), 3.54 (broad, 1, replaceable OH), 3.3–2.4 (m, 6, methylenes), 2.3 (s, 3, NCH_3), 1.22 (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.21; N, 4.81. Found: C, 65.91; H, 7.35; N, 4.99.

Ethyl 4-Keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro-[2,1-*b*]pyridine-3-carboxylate (8). Ethyl 4α-Hydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (29) and Ethyl 4β-Hydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (30). Ethyl 4a-hydroxy-4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (2.5 g, 0.00865 mol) in acetic acid (25 ml) containing perchloric acid (1 ml) was hydrogenated over palladium on carbon (10%, 700 mg) for 48 hr. The reaction mixture was filtered, evaporated under reduced pressure, and basified (NH_4OH) and the resultant precipitate was extracted with ether. The ethereal layer was dried ($MgSO_4$), filtered, and evaporated to small volume to yield **29**, mp 142–145°, the equatorial alcohol (500 mg, 20%). Recrystallization from ether gave a sample: mp 145.5–146°; ir (KBr) 3550 (OH), 1705 cm^{-1} (saturated ester); ir (CCl_4) 3550 (OH), 1720 cm^{-1} (saturated ester); nmr ($CDCl_3$) δ 7.55 (m, 1 H, aromatic), 7.15 (m, 3 H, aromatic), 4.32 (m, 1 H, proton α to hydroxyl group), 4.17 (q, 2 H, ester H), 3.4 (s, 1 H, replaceable OH), 3.45 (m, 2 H, methylene H), 2.95 (m, 5 H, methylene H), 2.4 (m, 1 H, methylene H), 2.28 (s, 3 H, *N*-methyl), and 1.25 (t, 3 H, ester H); mass spectrum peak at *m/e* 275 (M^+, 50%), exact mass 275.151642 (calcd for $C_{16}H_{21}NO_3$, 275.152134).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.63; N, 5.09. Found: C, 70.08; H, 7.43; N, 5.28.

The mother liquors were evaporated under reduced pressure and the resultant oil (1.4 g) was chromatographed on silica gel (100 g). Elution with 1% ethanol in benzene gave **8** as an oil (680 mg, 27%): ir (neat) 3380, 1730, 1655, and 1625 cm^{-1} (β-keto ester); nmr ($CDCl_3$) δ 7.5 (m, 1 H, aromatic), 7.1 (m, 3 H, aromatic H), 4.19 (q, 2 H, ester H), 1.8–3.9 (m, 6 H, methylene H), 2.46 (s, 3 H, *N*-methyl), and 1.26 (t, 4 H, three ester and one methylene H); mass spectrum exact mass 273.13610 (calcd for $C_{16}H_{19}NO_2$, 273.1365). The picrate was recrystallized from ethanol–ethyl acetate to give a sample, mp 158–159°.

Anal. Calcd for $C_{22}H_{22}N_4O_{10}$: C, 52.58; H, 4.38; N, 11.15. Found: C, 52.48; H, 4.63; N, 10.96.

Elution with 2% ethanol in benzene gave **30**, the axial alcohol (505 mg 21%). Recrystallization from ether gave a sample: mp 132°; ir (KBr) 3510 (OH), 1725 cm^{-1} (saturated ester); nmr ($CDCl_3$) δ 7.25 (s, 4 H, aromatic), 4.45 (m, 1 H, proton α to hydroxyl group), 4.25 (q, 2 H, ester H), 3.0 (m, 7 H, methylene H), 2.82 (s, 1 H, -OH, replaceable by D_2O), 2.45 (s, 3 H, *N*-methyl), and 1.3 (t, 3 H, ester H); mass spectrum exact mass 275.1519 (calcd for $C_{16}H_{21}NO_3$, 275.1521).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.63; N, 5.09. Found: C, 69.80; H, 7.82; N, 5.01.

Hydrogenation of the methyl ester **28b** under identical conditions gave a similar mixture (not further investigated) of the corresponding methyl ester analogs of **8**, **29**, and **30**, as shown by tlc, glc, and ir analyses.

$NaBH_4$ Reduction of 8. $NaBH_4$ (50 mg, 0.001315 mol) was added in portions to a cooled solution of ethyl 4-keto-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxylate (1.0 g, 0.00366 mol) in ethanol (25 ml). The reaction mixture was allowed to stand at room temperature overnight and was evaporated under reduced pressure. The resultant solid was dissolved in dilute HCl and the aqueous layer was extracted with ether, basified with ammonium hydroxide, and reextracted with ether. The ethereal extracts were washed (H_2O), dried, ($MgSO_4$), filtered, and evaporated to yield white crystals (570 mg, 57%), mp 146–147°. A mixture melting point with **29a** showed no depression.

***tert*-Butyl 1,2-Epoxyindan-1-carboxylate (17c).** This compound was prepared in the same manner as **17a** in 95% yield using benzene as the solvent. Recrystallization from petroleum ether gave a sample as white cubes: mp 74–75°; nmr ($CDCl_3$) δ 7.7 (m, 1 H, aromatic), 7.1 (m, 3 H, aromatics), 4.2 (m, 1 H, proton α to epoxide ring), 3.0 (m, 2 H, allylic methylene H), 1.5 (s, 1 H, *tert*-butyl protons).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.44; H, 7.07.

Methyl 1-Hydroxy-2-(methyl-β-carbomethoxyethylamino)-indan-1-carboxylate (25c). *Ca.* 250 ml of anhydrous methanol at −10° containing 11 g (0.035 mol) of **18b** was saturated with dry HCl gas and N_2 by bubbling through the solution for 20 min. The reaction mixture was allowed to stand at −10° for 3 days and was worked up in a manner similar to the preparation of **25a** from **18b** to give 10.5 g (98%) of a viscous oil which slowly solidified. Recrystallization from petroleum ether–cyclohexane (1:1) gave a sample as white crystals: mp 59–60°; ir (KBr) 3400 (OH), 1740 and 1700 cm^{-1} (ester carbonyls); nmr ($CDCl_3$) δ 7.2 (s, 4 H, aromatics), 4.2 (s, 1 H, replaceable OH), 3.65, 3.60 (s, 3 H each, CO_2CH_3), 3.4–2.4 (m, 7 H, methylenes), 2.3 (s, 3 H, NCH_3).

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.41; H, 6.83; N, 4.73.

***tert*-Butyl 1-Hydroxy-2-(methyl-β-cyanoethylamino)indan-1-carboxylate (18b).** *tert*-Butyl 1,2-epoxyindan-1-carboxylate (70 g, 0.3 mol) was added under nitrogen to a refluxing solution of 220 ml of β-methylaminopropionitrile. The reaction mixture was stirred for 15 min, poured onto crushed ice, and diluted with 5% HCl solution. The aqueous acid was washed (ether) and basified (NH_4OH). The basic fraction was extracted with ether and the ether was washed with salt water to remove the excess of β-methylaminopropionitrile. Evaporation of the ether after drying ($MgSO_4$) gave a viscous oil which contained two main components in a 3:1 ratio according to vpc. Crystallization of the oil by dissolving it in a 5:1 mixture of petroleum ether–ether afforded a ready separation of the two compounds **18b** and **19b**. The undesired **19b** remained in solution while 18b crystallized as a white solid: mp 94–95°; nmr (CCl_4) δ 7.13 (s, 4 H, aromatics), 4.0 (broad s, 1 H, OH), 3.3–2.2 (m, 7 H), 2.38 (s, 3 H, NCH_3), 1.33 (s, 9 H, ester H).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.65; N, 8.86. Found: C, 68.11; H, 7.75; N, 9.02.

Small amounts of **23a** and **24** were also isolated from the reaction mixture and identified by ir, glc, and comparison with authentic material (see below).

***tert*-Butyl 1-Hydroxy-2-methylaminoindan-1-carboxylate (23a) and *tert*-Butyl 2-Hydroxy-1-methylaminoindan-1-carboxylate (24).** A solution of 100 g of **17c**, 50 ml of anhydrous methylamine, and 200 ml of anhydrous methanol was allowed to stand at 20° for 36 hr. Evaporation of the excess methylamine and methanol afforded two products in a 9:1 ratio (from vpc). Fractional crystallization from petroleum ether afforded a convenient method of separation and purification. The less soluble isomer, the major product **24**, had mp 112–113°; ir (KBr) 3300–2800 (broad, NH and OH) 1720 cm^{-1} (ester carbonyl); nmr (DMSO-d_6) δ 7.2 (s, 4 H, aromatics), 5.15 (d, 1 H, J = 10 Hz, hydroxyl proton coupled to α H, this disappears upon shaking with D_2O), 4.38 (q, 1 H, J = 10 Hz, proton α to OH, this becomes a triplet upon shaking with D_2O), 3.4–2.3 (m, 3 H, benzylic and NH), 2.2 (s, 3 H, NCH_3), 1.3 (s, 9 H, t-Bu).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.44; H, 8.00; N, 5.36. Found: C, 68.25; H, 7.82; N, 5.56.

The more soluble isomer, the minor product **23a**, had mp 105–106°; ir (KBr) 3300–2800 (broad NH and OH), 1705 cm^{-1} (ester carbonyl); nmr (DMSO-d_6) δ 7.2 (s, 4 H, aromatics), 5.8–5.0 (broad, 1 H, NH or OH, disappears upon shaking with D_2O), 3.5–2.5 (m, 4 H, methylenes and NH or OH, one proton lost after shaking with D_2O), 2.4 (s, 3 H, NCH_3), 1.3 (s, 9 H, ester H).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.44; H, 8.00; N, 5.36. Found: C, 68.33; H, 8.06; N, 5.17.

***N,N*-Diethyl-*trans*-4,4a-dihydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxamide (33a) and *N,N*-Diethyl-*cis*-4,4a-dihydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxamide (34a).** A mixture of 1.5 g (4.75 mmol) of **28c** and 0.105 g (4.05 mmol) of $NaBH_4$ in 200 ml of absolute EtOH was allowed to stir under N_2 at room temperature for 12 hr. The solution was evaporated to a small volume, diluted with 150 ml of 10% HCl solution, and washed with Et_2O. The solution was then made basic (NH_4OH) and extracted with Et_2O and $CHCl_3$. The extracts were washed ($NaCl$-H_2O), dried ($MgSO_4$), and evaporated to give a white solid, 1.6 g. Recrystallization from Et_2O–petroleum ether afforded white cubes of **33a** (96%): mp 121–122°; ir (KBr) 3450 (OH), 1620 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.96 (s, 1, replaceable OH), 7.7–7.5 (m, 1, aromatic), 7.3–7.1 (m, 3, aromatics), 4.7 (s, 1, proton α to OH), 3.5–2.5 (m, 11), 2.4 (s, 3, NCH_3), 1.3–0.9 (m, 6, CH_3CH_2).

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.71; H, 8.26; N, 8.98.

The mother liquors from the crystallization of **33a** were evaporated and the residue was chromatographed on silica gel with 10:1 Et_2O–EtOH as the eluent. A small amount of **33a** was recovered followed by *ca.* 70 mg (4%) of **34a**. Purification *via* sublimation (95°, 0.02 Torr) afforded white crystals: mp 99–100°; ir ($CHCl_3$) 3520, 3200 (OH), 1610 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.4–7.1 (m, 4, aromatics), 4.4 (m, 1, proton α to OH), 3.6–2.6 (m, 12), 2.4 (s, 3, NCH_3), 1.3–0.9 (t, 6, CH_3CH_2–); mass spectrum exact mass 318.2032 (calcd for $C_{18}H_{26}N_2O_3$, 318.2021).

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.01; H, 8.19; N, 8.79.

***N,N*-Diethyl-4a-hydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxamide (35).** *N,N*-Diethyl-*trans*-4,4a-dihydroxy-1-methyl-9*H*-indeno-1,2,3,4,4a,9a-hexahydro[2,1-*b*]pyridine-3-carboxamide (1.0 g, 3.15 mmol) in acetic acid (50 ml) containing $HClO_4$ (1 ml) was hydrogenated over 10% Pd/C for 4 days. The reaction mixture was worked up in a manner similar to the preparation of **29a** to give *ca.* 1.0 g (100%) of a pale yellow oil. The oil was purified by chromatography on silica gel using Et_2O as the eluent (a small amount of unreacted **33a** eluted first): ir (CCl_4) 3300 (OH), 1620 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.14 (s, 4, aromatics), 6.9 (s, 1, replaceable OH), 3.5–2.6 (m, 12), 2.5 (s, 3, NCH_3), 1.3–0.9 (q, 6, CH_3CH_2); chemical ionization mass spectrum mol wt 318 (calcd for $C_{18}H_{26}N_2O_2$, 318).

The picrate was made in the usual manner and recrystallized (EtOH) to give yellow needles, mp 203–204°.

Anal. Calcd for $C_{24}H_{29}N_5O_9$: C, 54.23; H, 5.50; N, 13.18. Found: C, 54.52; H, 5.77; N, 13.32.

***N,N*-Diethyl-1-methyl-9*H*-indeno-1,2,3,9a-tetrahydro[2,1-*b*]pyridine-3-carboxamide (6b).** A solution of **35** (100 mg), $SOCl_2$ (4 ml), anhydrous pyridine (4 ml), and CH_2Cl_2 (4 ml) was kept at −50° for 30 min and was then allowed to warm to room temperature. After an additional 60 min the solution was diluted with Et_2O and extracted with 10% cold HCl. The aqueous extract was washed with Et_2O, made basic with cold NH_4OH, and evaporated under reduced pressure to give 55 mg of a yellow oil. Chromatography over silica gel using 4% EtOH in benzene as eluent gave *ca.* 35 mg of **6b** as the major fraction: ir (liquid film) 1650 cm^{-1} (amide C=O), no OH; nmr ($CDCl_3$) δ 7.0–7.2 (m, 4, aromatics), 6.2 (m, 1, olefinic), 4.0–2.6 (m, 10), 2.2 (s, 3, NCH_3), 1.3–0.7 (m, 6, CH_3CH_2); uv (absolute EtOH) λ_{max} (log ϵ), 224 (sh, 3.93), 254 (3.925), 273 nm (sh, 3.66); mass spectrum exact mass 284.1966 (calcd for $C_{18}H_{24}N_2O$, 284.1967). The picrate, made in the usual manner, was obtained as yellow crystals, mp (sealed tube) 163–164°.

Anal. Calcd for $C_{24}H_{27}N_5O_8$: C, 56.13; H, 5.30; N, 13.64. Found: C, 56.31; H, 5.28; N, 13.84.

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Registry No.—6b, 51056-30-5; **6b** picrate, 51056-31-6; **7,** 51056-32-7; **8,** 51056-33-8; **8** picrate, 51153-00-5; **9,** 51056-34-9; **10a,** 28529-48-8; **10b,** 51056-35-0; **11,** 51056-36-1; **12a,** 51056-37-2; **12b,** 51056-38-3; **16,** 51108-12-4; **17a,** 51056-39-4; **17b,** 51056-40-7; **17c,** 51056-41-8; **18a,** 51056-42-9; **18b,** 51056-43-0; **19a,** 51056-44-1; **21,** 51056-45-2; **21** hydrochloride, 51056-46-3; **23a,** 51056-47-4; **23b,** 51056-48-5; **24,** 51056-49-6; **25a,** 51056-50-9; **25c,** 51108-13-5; **26,** 51056-51-0; **28a,** 51056-52-1; **28b,** 51056-53-2; **28c,** 51056-54-3; **29,** 51056-55-4; **30,** 51153-01-6; **33a,** 51056-56-5; **33b,** 51056-57-6; **34a,** 51153-02-7; **34b,** 51153-03-8; **35,** 51056-58-7; **35** picrate, 51153-04-9; acetyl bromide, 506-96-7; indenyllithium, 51056-59-8; 1-indeneacetyl chloride, 51056-60-1; ethyl *tert*-butyl malonate magnesium salt, 51056-61-2; indene-1-carboxylic acid, 14209-41-7.

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(38) It is unlikely that the product is the conjugated amide **32b** which theoretically can arise from a rearrangement of **6b**, since **5** cannot be rearranged to its conjugated ester isomer[39] and 6-methyl-$\Delta^{8,9}$-ergoline-8-carboxylic acid rearranges quite easily to lysergic acid.[40] Furthermore, the uv spectrum of **32b** would be expected to show only low-intensity (ϵ less than 300) *o*-xylene-like absorption in the 255-nm region.
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Carboxylation of γ-Butyrolactones with Methyl Methoxymagnesium Carbonate. A New Synthesis of *dl*-Protolichesterinic Acid

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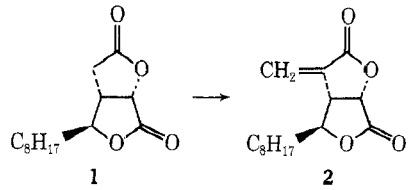
The carboxylation of γ-lactones at the α position is, in most cases, easily accomplished by means of Stiles' reagent (methyl methoxymagnesium carbonate). This combined with a simplified decarboxylative methylenation procedure, namely treatment of the α-carboxylactones with a mixture of formaldehyde and diethylamine, usually in a buffered acidic medium, affords a relatively simple method of synthesizing α-methylenelactones. These methods have been used in a new synthesis of *dl*-protolichesterinic acid. Free-radical addition of tetradecanal to dimethyl maleate led to methyl 3-methoxycarbonyl-4-oxoheptadecanoate, which was reduced by borohydride and cyclized to a 50:50 mixture of the methyl esters of *cis*- and *trans*-3-carboxy-4-*n*-tridecylbutyrolactones, **20b** (R = CH_3) and **20a** (R = CH_3), respectively. Carbonylation of the acid from the latter isomer afforded 2,3-dicarboxy-4-*n*-tridecylbutyrolactone, which when treated with formaldehyde and diethylamine at room temperature afforded *dl*-protolichesterinic acid. Acylative decarboxylation of tricarballylic acid by tetradecanoic anhydride gives the di-γ-lactone of 3-(1,1-dihydroxytetradecyl)glutaric acid. The action of alkaline borohydride on the latter leads to *trans*-3-carboxymethyl-4-*n*-tridecylbutyrolactone (**24**, R = H). The methyl ester of this acid is also obtained almost exclusively when **20a** (R = H) is subjected to an Arndt-Eistert homologation sequence. The cis acid **20b** (R = H) on homologation gives varying mixtures containing both **24** (R = CH_3) and its cis isomer. The latter results together with other evidence allow the tentative assignment of stereochemistry to the carboxylactones **20a** and **20b** (R = H), the former being trans and the latter cis.

In a pair of communications[1,2] in 1969 we reported briefly a new method for the preparation of α-methylenebutyrolactones. This paper describes that work in detail and reports its application to a new synthesis of protolichesterinic acid.

The origins of our research lay in our need to methylenate the bislactone **1** in order to obtain avenaciolide (**2**),

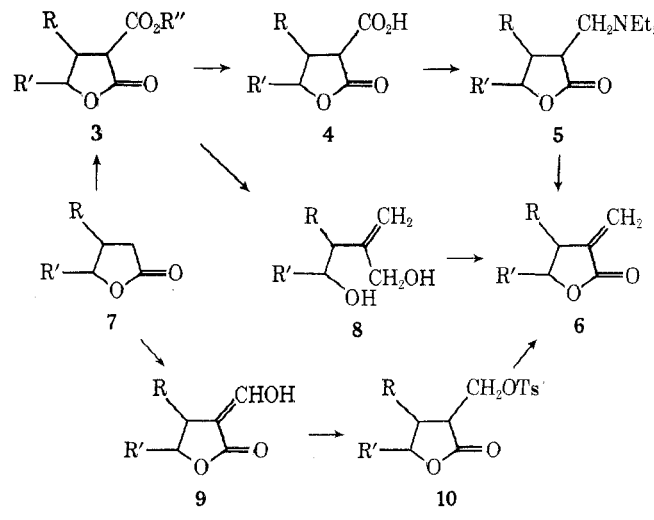


1 **2**

the object of an earlier synthetic program.[2] The methods available to us at that time left much to be desired. The early procedure due to van Tamelen and Bach[3a,b] demanded the construction of a butyrolactone such as **3**, already provided with an alkoxycarbonyl group at the α position. Subsequent steps involved hydrolysis and relactonization of **3** to give **4**, which when subjected to a Mannich reaction led to **5**. Quaterization of **5** followed by heating with base gave the desired **6** (Chart I).

Two quite different methods began with a butyrolactone of structure **7**. In the first, due to Marshall and Cohen,[4] the sodium salt of **3**, derived directly from the alkoxycarbonylation of **7**, was reduced mainly to **8** with lithium aluminum hydride. Manganese dioxide oxidation of

Chart I



3 **4** **5** **6** **7** **8** **9** **10**

8 gave **6** directly. The second procedure, reported by Minato and Horibe,[5] involved formylation of **7** give **9**, which was reduced and tosylated, affording **10**. Refluxing pyridine converted **10** to **6**.

Subsequent to our initial reports, Behare and Miller[6] reported that α-methylene lactones could be synthesized by first treating lactones such as **3** (R, R′ = $-(CH_2)_4-$; R″ = Et) with formaldehyde and diethylamine to give **11**, followed by heating the methiodide of the latter in dimethylformamide. An entirely different approach has been taken

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