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THE ABSOLUTE CONFIGURATION OF PHYSOSTIGMINE[1]

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Abstract—Physostigmine, the toxic alkaloid of the Calabar bean, has been degraded systematically to (+)-1,3-dimethyl-3-ethyloxindole (Chart 1), which contains only one of the original asymmetric centers. The enantiomorph of this oxindole was then synthesized from (*R*)-(−)-2-methyl-2-phenylbutyric acid, a substance of known configuration, allowing the assignment of the (3a*S*:8a*R*) configuration to physostigmine.

PHYSOSTIGMINE, the major alkaloid of the Calabar bean (*Physostigma venenosum*), has been of interest for more than a century, beginning with the intriguing history of the use of the beans by the natives of West Africa as an ordeal poison. As a stimulator of the parasympathetic nervous system it has widespread effects and has found medicinal application in the treatment of *Myasthenia gravis* and more commonly to induce miosis. Modern pharmacological interest centers about the efficacy of the alkaloid as an inhibitor of acetylcholinesterase.

The structure and reactions of physostigmine (I) have been thoroughly studied and a number of total syntheses recorded; several recent reviews summarize the chemistry.[2] The remaining feature of the alkaloid which still requires elucidation is the stereochemical configuration. With two asymmetric centers at the ring junction of the two 5-membered rings, physostigmine could in principle possess a *cis* or *trans* fusion. A number of experiments show that the alkaloid has the thermodynamically more stable *cis* ring fusion:[2d] all synthetic routes which would permit equilibration during construction of the ring junction afford only the natural isomer, and treatment of the "methine" (III) from Hofmann elimination with acid regenerates the original ring system of II.[3] With the relative configuration ascertained, determination of absolute configuration at either of the asymmetric centers would complete the configurational assignment, and it is this problem of absolute configuration which forms the subject of the present paper.

Degradation of physostigmine to 1,3-*dimethyl*-3-*ethyloxindole.*

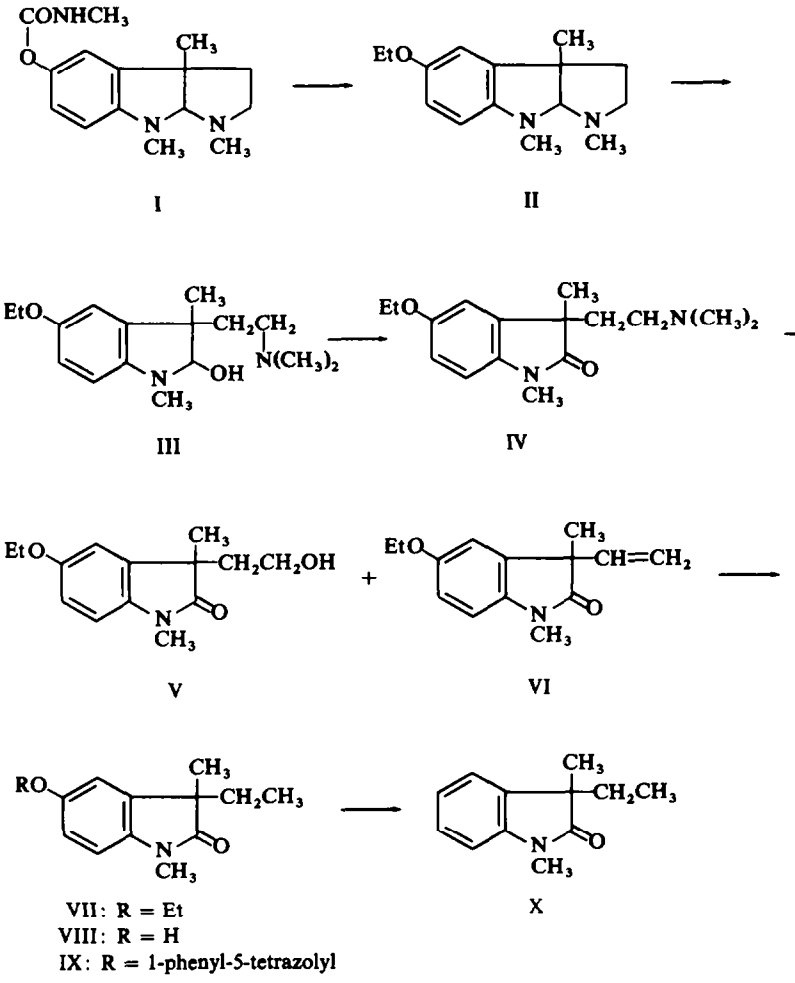
In order to correlate the configuration at one of the asymmetric centers of physostigmine with that of a compound of established configuration, it was necessary to degrade the alkaloid to a simpler molecule possessing only one center of asymmetry. Stedman and Barger[4] reported the degradation of physostigmine to the oxindole (VII), unfortunately without recording its optical rotation. We have accordingly repeated and extended their scheme as shown in Chart 1 to convert physostigmine to (+)-1,3-dimethyl-3-ethyloxindole (X).

Physostigmine was converted to eserethole (II) by ethanolysis followed by alkylation with ethyl *p*-toluenesulfonate. Hofmann elimination of II to eserethole methine (III) and ferricyanide oxidation to IV followed known procedures. Hofmann degrada-

tion of the methiodide of IV yielded, in addition to considerable amounts of recovered IV, the vinyl derivative (VI) as well as the previously unreported alcohol (V). The alcohol was characterized by IR absorption at 1715 and 3425 cm^{-1}, while VI had IR bands at 1690, 1625, 1600, and 925 cm^{-1} as well as the characteristic 3-proton vinyl NMR pattern at δ 5·0–6·4. Hydrogenation gave the saturated oxindole (VII), whose properties agreed with those reported by Stedman and Barger, and which was found to be levorotatory.

To facilitate direct optical comparison of a degradation product with a synthetic sample, the ethoxyl group was removed from VII. Ether cleavage with aluminium chloride gave phenol (VIII), from which the OH was smoothly removed by the elegant method of Musliner and Gates,[5] involving hydrogenolysis of the phenyltetrazolyl ether (IX). The resulting oxindole (X) was dextrorotatory, with increasing magnitude at lower wave lengths and the first peak of a Cotton effect at about 315 mμ.

CHART 1. Degradation of Physostigmine to 1,3-Dimethyl-3-ethyloxindole.



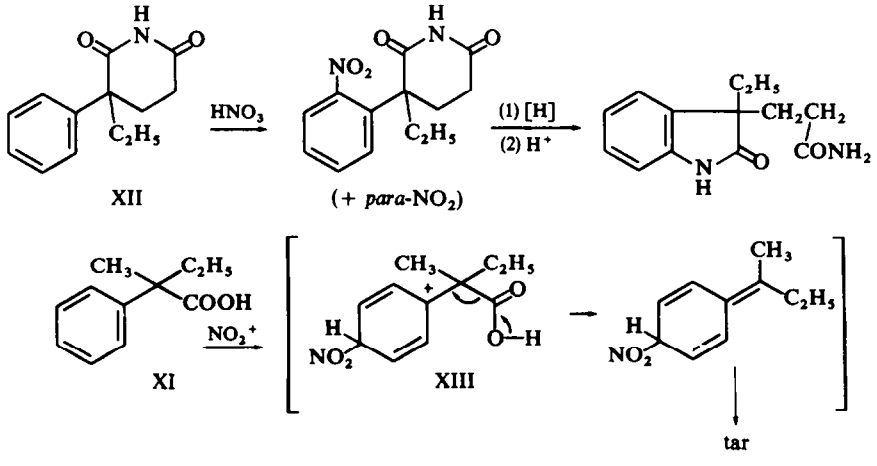
The roughly mirror image relationship between the ORD curves of oxindoles VII and X was unexpected, since a change of substituent does not ordinarily alter the shape of ORD curves of aromatic compounds,[6] an observation upon which frequent assignments of absolute configuration depend.[7] Earlier exceptions to this generalization have been noted,[8] however, and the present example serves as an additional warning that simple aromatic substituents can reverse the sign of rotation and plain ORD curves.

Synthesis of oxindole (X)

No simple optically active 3,3-disubstituted oxindole to which X might be related has been described; indeed, relatively few compounds containing a single quaternary asymmetric carbon of proven absolute configuration are known. Of those which have been reported, 2-methyl-2-phenylbutyric acid (XI) offered the clearest prospects for correlation with X. Both antipodes are available by resolution* and the absolute configuration has been established by correlation with atrolactic acid by a sequence of reactions carried out by two groups.[9,11] Attention was then directed toward the synthesis of the physostigmine degradation product (X) from (*S*)-(+)- or (*R*)-(−)-XI.

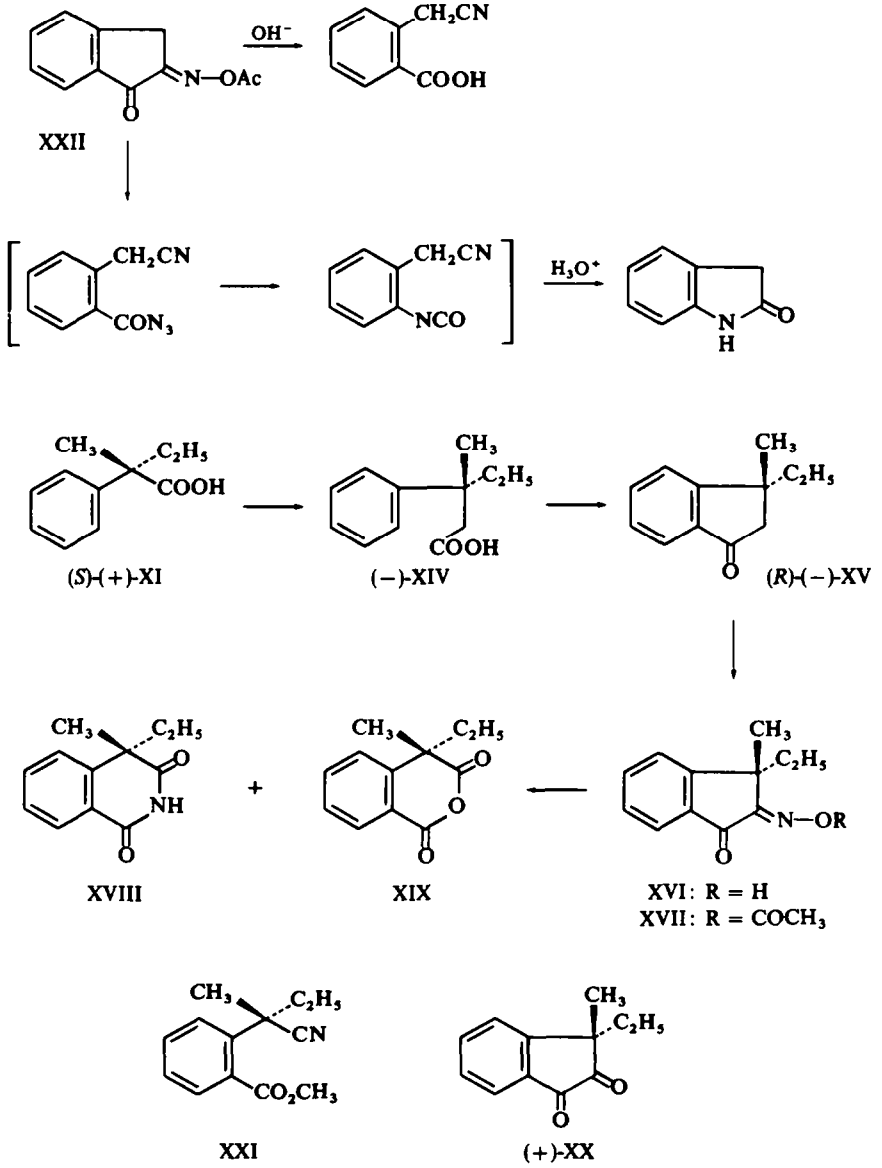
i. The problem of introducing a N atom *ortho* to the side chain in XI was first attacked by attempted nitration. Precedents for *ortho* nitration of an aromatic ring attached to a fully substituted carbon are found in the nitration of t-butylbenzene[12] and particularly in the nitration of the phenylglutarimide derivative (XII) which led,[13] after reduction, to an oxindole of type X. Nitration of XI, however, proved unsuccessful. A gas was evolved and a tarry polymer formed, probably as the result of decarboxylation of intermediate XIII. An attempt to circumvent decarboxylation by nitrating the corresponding nitrile gave evidence for *para* but no *ortho* nitro product.

ii. To ensure substitution at the *ortho* position, a more circuitous route involving intramolecular cyclization was chosen. Arndt-Eistert homologation of XI to acid (XIV) was followed by Friedel-Crafts cyclization of the acid chloride to give indanone



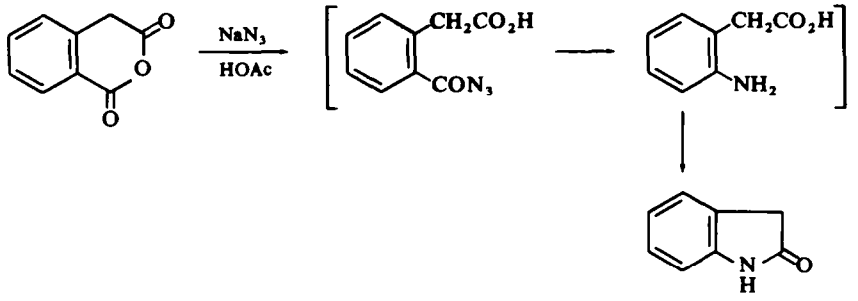
* The authors[9] used a combination of quinine and brucine for the resolution. In the present study partial resolution to 81% optical purity was easily accomplished with the more readily available and inexpensive resolving agent, dehydroabietylamine.[10]

(XV) in good yield. Our initial plan for converting XV to an oxindole involved first cleaving the 5-membered ring by Beckmann fragmentation of an α-keto oxime.[14] A close model for this cleavage was realized in the conversion of 2-oximinoindanone-1 acetate (XXII) by aqueous base at room temperature to 2-carboxyphenylacetonitrile. However, though indanone (XV) could be readily converted to the α-keto oxime (XVI) and its acetate (XVII), reaction of the latter with base could not be stopped at the cyano acid stage but led instead to a mixture of imide (XVIII) and anhydride (XIX). The structure of anhydride (XIX) was shown by independent synthesis; oxime (XVI) was hydrolyzed by dilute acid in the presence of formaldehyde to diketone



(XX) and this was oxidized by alkaline hydrogen peroxide to XIX. Aqueous workup of the reaction mixture resulting from fragmentation of oxime (XVI) with phosphorus pentachloride also afforded anhydride (XIX). Treatment of oxime acetate (XVII) with sodium methoxide did provide a low yield of cyanoester (XXI).

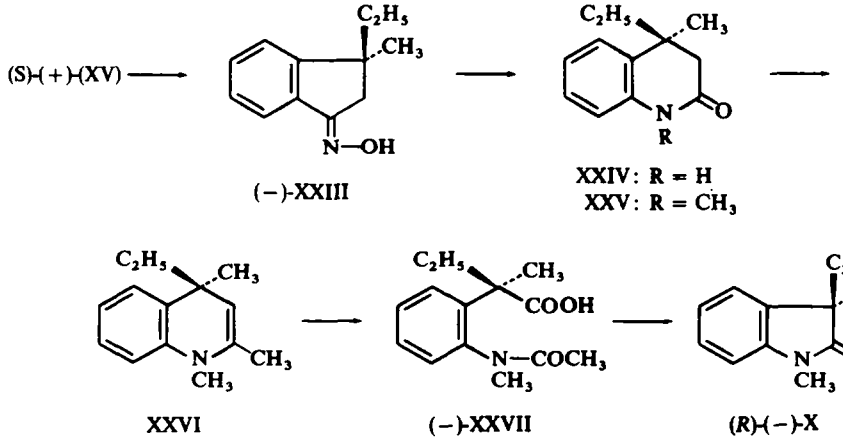
The availability of anhydride (XIX) led to an attempt to prepare the desired oxindole by the Schmidt reaction. Maffei and Bettinetti[15] have reported that homophthalic anhydride is converted directly to oxindole by hydrazoic acid:



We were able to confirm this interesting reaction, isolating oxindole in over 80% yield. The substituted anhydride (XIX), however, was recovered unchanged from similar treatment, and more stringent conditions failed to yield any oxindoles.

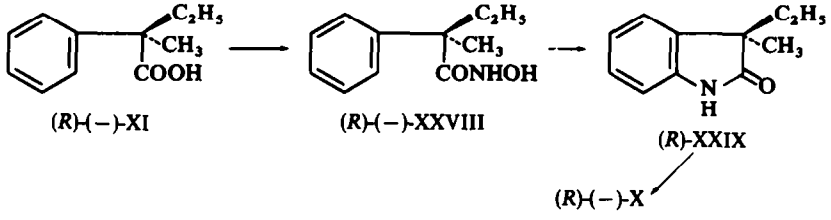
An attempt to use azide ion as the nucleophile in fragmentation of oxime acetate (XVII), which might have led to an oxindole, was also unsuccessful. The model oxime acetate (XXII) gave a low yield of impure oxindole by this method, but no oxindoles were isolated from treatment of XVII with sodium azide, even though IR bands consistent with a cyano isocyanate were observed in the reaction mixture before hydrolysis.

iii. The approach which finally proved successful was to introduce the necessary ring nitrogen by Beckmann rearrangement of the oxime of the (*S*)-(+) indanone (XV). The resulting levorotatory dihydrocarbostyril (XXIV) was methylated, then treated with methyl lithium,[16] and the dihydroquinoline (XXVI) immediately ozonized. Oxidative hydrolysis of the ozonide gave a mixture of oxindole (X) and the

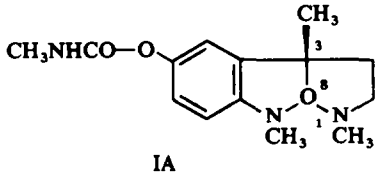


N-acetyl acid (XXVII); hydrolysis of XXVII gave more of the oxindole. This sample of (*R*)-(−)-X obtained by synthesis had IR and NMR spectra identical with those of the physostigmine degradation product, though the ORD curves of the two samples were enantiomorphic.

iv. Following the recent report of the polyphosphoric acid catalyzed amidation of aromatic rings by hydroxamic acids,[17] we were able to use this method in an independent, and more direct, synthesis of oxindole (X) from 2-methyl-2-phenylbutyric acid (XI). The hydroxamic acid (XXVIII) prepared from (*R*)-(−)-XI was heated in polyphosphoric acid at 160° for 30 minutes. Chromatography of the mixture of products formed in this reaction led to isolation of the crystalline oxindole (XXIX) in 2–3% yield. N-Methylation gave (*R*)-(−)-X, identical with the sample obtained in part (iii).



This unambiguous correlation permits the configurational assignment (3a*S*:8a*R*) shown in IA to physostigmine. Geneserine, the naturally occurring 1-N-oxide, has been converted to physostigmine and so has the same absolute configuration at the asymmetric carbons.



IA

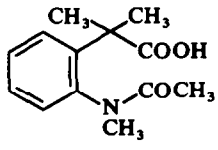
NMR spectra

Several aspects of the NMR spectra of the intermediates reported here deserve comment.

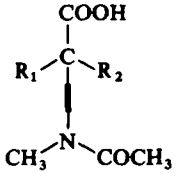
(a) In all the compounds studied which have an Et group attached to an asymmetric quaternary carbon, the methylene protons of the Et group are magnetically nonequivalent and consequently[18] generally appear as a pair of quartets. The chemical shift difference between the two quartets is usually small (2–5 cycles) but in compounds XVI and XVII reaches 35–50 cycles.

(b) Amide acid XXVII showed an additional interesting feature: the quaternary Me appeared as a pair of singlets, δ 1·41 and 1·65, and the Me of the Et group as a pair of triplets, centered at δ 0·88 and 1·02, in each case of unequal intensity. This doubling is unrelated to the magnetic nonequivalence which splits the ethyl methylene protons, and is attributed instead to restricted rotation about the aryl C—N bond. To examine this phenomenon in a somewhat simpler molecule we prepared the

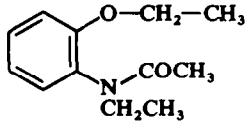
corresponding amide acid (XXX) with *gem*-dimethyl groups and lacking the asymmetric carbon. Its NMR spectrum showed the *gem*-dimethyls as *two* singlets, at δ 1·48 and 1·71. The appearance of two singlets requires that the nitrogen substituents not lie coplanar with the aromatic ring and that rotation around the aryl C—N bond be slow on the NMR time scale. In a resulting conformer such as XXXI, when R_1 and $R_2 = CH_3$ the two Me's will experience different chemical shifts, and when R_1 and R_2 are Me and Et, two conformers (of unequal energy) related to XXXI are possible with different chemical shifts for both substituents. A closely analogous case is XXXII,[19] in which the ethoxy methylene protons give rise to two sets of signals. Discussion of this and related hindered amides[20] has focused on restricted rotation about the bond joining nitrogen to the aromatic ring as the source of chemical shift nonequivalence.



XXX



XXXI



XXXII

EXPERIMENTAL SECTION

M.ps were taken in open capillaries on a Thomas-Hoover m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 237-B spectrophotometer. NMR spectra were obtained on a Varian Associates A-60-A spectrometer; TMS was used as an internal standard. Coupling constants for Me and methylene protons of Et and OEt groups in all compounds were 7 Hz. ORD curves were recorded on a Cary model 60 spectropolarimeter; we thank Drs. O. J. Jacobus and G. Krow for obtaining these spectra. Mass spectra were run on an A.E.I. MS-9 high resolution mass spectrometer; funds from the National Science Foundation, Grant GP-5200, which contributed toward the purchase of this instrument are gratefully acknowledged. Microanalyses were carried out by Spang Microanalytic Laboratory, Ann Arbor, Mich.

Physostigmine, m.p. 104–105°, $[\alpha]_D^{21}$ −87·2° (*c*, 5·24 in MeOH), was obtained as the sulfate from Fluka AG.

Eserethole (II) was prepared in 67% yield by treatment of physostigmine with ethanolic NaOEt and ethyl *p*-toluenesulfonate according to the procedure of Polonovski;[21] b.p. 128–130° (0·5 mm), lit.[21] b.p. 308–310°. The colorless methiodide was formed in quantitative yield, m.p. 168–169°, lit.[21] m.p. 171°.

Eserethole methine (III), m.p. 82°, lit.[22] m.p. 80°, was formed in 92% yield by treatment of eserethole methiodide with 6N NaOH according to the published procedure.[22]

Dehydroeserethole methine (IV) was obtained from III by oxidation with alkaline $K_3Fe(CN)_6$ according to Stedman and Barger,[4] and purified as the picrate, m.p. 195–197°, lit.[4] m.p. 199°. The free base was regenerated from the picrate by chromatography over alumina in $CHCl_3$ and converted to the *methiodide*, m.p. 127–129° d., lit.[4] m.p. about 131°, in 51% overall yield from III; NMR (in D_2O): δ 1·35 (t, ethyl Me), 1·42 (s, tert Me), 2·3–2·8 (m, —CH_2CH_2—), 3·04 (s, NMe_3), 3·20 (s, N—Me), 4·07 (q, ethyl CH_2), 7·0 (m, aromatic).

1,3-*Dimethyl*-3-(2-*hydroxyethyl*)5-*ethoxyoxindole* (V). An aqueous soln of 3·9 g dehydroeserethole methine methiodide was stirred for 5 hr with AgO, freshly precipitated from 5 g $AgNO_3$. After filtration the water was removed *in vacuo* and the residual oil distilled at 5 mm. The orange-yellow distillate was taken up in ether, washed with 0·5N HCl, dried and concentrated. Crystallization of the residue from CCl_4–pet. ether (b.p. 30–60°) gave V, 580 mg, m.p. 67–73°, $[\alpha]_D^{22}$ −32·5° (*c*, 3·2 in MeOH), mol. wt. (mass spec) 249·136932; calc. for $C_{14}H_{19}NO_3$, 249·136485. The IR spectrum showed a broad band at 3425 as well as bands at 1715 and 1600 cm^{-1}; NMR ($CDCl_3$): δ 1·32 (s, tert Me), 1·38 (t, ethyl Me), 2·00 (q, J = 6·5

Hz, —CH_2—), 2·71 (s, OH), 3·12 (s, N—Me), 3·4 (broad, —$\underline{CH_2}$OH), 3·95 (q, ethyl CH_2), 6·6–6·8 (m, aromatic). Found: C, 67·72; H, 7·90; N, 5·42. $C_{14}H_{19}NO_3$ requires: C, 67·45; H, 7·68; N, 5·62%.

1,3-*Dimethyl*-3-*vinyl*-5-*ethoxyoxindole* (VI). The mother liquors from the crystallization of V were combined, concentrated, and the residue recrystallized to give 480 mg of VI, m.p. 58–60° (lit.[4] m.p. 62°), $[\alpha]_D^{22}$ −73·9° (*c*, 1·0 in MeOH). The IR spectrum showed characteristic absorption at 1690, 1625, 1600, and 925 cm^{-1}; NMR ($CDCl_3$): δ 1·25 (t, ethyl Me), 1·33 (s, tert Me), 3·00 (s, N—Me), 3·87 (q, ethyl CH_2), 5·0–6·4 (vinyl, 3H), 6·8–7·0 (m, aromatic).

The acidic washings of the crude Hofmann product were basified with 6N NaOH, extracted with ether, and the extracts dried and concentrated. The residual oil (1·24 g) furnished a picrate, m.p. 198–199° d. which did not depress the m.p. of the picrate of IV.

1,3-*Dimethyl*-3-*ethyl*-5-*ethoxyoxindole* VII. A soln of 480 mg of VI in 10 ml of EtOH was hydrogenated at atm press over 10% Pd–C to afford a quantitative yield of VII, m.p. 68° (lit.[4] m.p. 68°), $[\alpha]_D^{24}$ −46° (*c*, 0·025 in MeOH); NMR ($CDCl_3$): δ 0·57 (t, ethyl Me), 1·28 (s, tert Me), 1·31 (t, ethoxy Me), 1·78 and 1·88 (pair of quartets, ethyl CH_2), 3·17 (s, N—CH_3), 4·01 (q, ethoxy CH_2), 6·7–6·9 (m, aromatic).

1,3-*Dimethyl*-3-*ethyloxindole* (X). A suspension of 100 mg of VII and 100 mg anhyd $AlCl_3$ in 20 ml pet. ether (b.p. 60–70°) was refluxed with stirring under N_2 for 10 hr. Cold water (10 ml) was added cautiously to the cooled mixture, followed by an equal volume of $CHCl_3$. After stirring 30 min and separating the layers, the aqueous layer was extracted with $CHCl_3$ and the combined organic layers dried and concentrated *in vacuo*, leaving 60 mg of VIII, m.p. 202–204°.

A mixture of crude VIII (42·5 mg), 5-chloro-1-phenyltetrazole (41·4 mg), and anhyd K_2CO_3 (100 mg) in 10 ml acetone was refluxed for 10 hr. The mixture was cooled and filtered; evaporation of the filtrate left the colorless IX, 72 mg, m.p. 187–189°.

A soln of 70 mg of IX in 20 ml EtOH was stirred with 10% Pd–C (100 mg) under 1 atm H_2 for 30 hr. After filtration of the catalyst the soln was concentrated. The residue was taken up in ether and washed with 1N NaOH, 1N HCl, and water, then dried and concentrated to afford 35 mg of X. A sample was purified for analysis and spectra by VPC, and had $[\alpha]_D^{23}$ +5·6° (*c*, 0·3 in MeOH), mol. wt. 189·115399 ($C_{12}H_{15}NO$ requires 189·115358). The IR spectrum showed a strong CO peak at 1715 cm^{-1}; NMR (CCl_4): δ 0·57 (t, ethyl Me), 1·28 (s, tert Me), 1·78 and 1·82 (pair of quartets, ethyl CH_2), 3·15 (s, N—Me), 6·6–7·35 (m, aromatic).

Resolution of 2-*methyl*-2-*phenylbutyric acid.* To a hot soln of 235 g dehydroabietylamine[10] in 750 ml abs EtOH was added 135 g 2-methyl-2-phenylbutyric acid[9] in 750 ml EtOH. The ppt which formed immediately was kept at 0° for 24 hr before filtering; the crude salt had m.p. 165–175°. Four recrystallizations from 3:1 EtOH–acetone gave 72 g of the salt, m.p. 190–194°. The salt was shaken vigorously with a mixture of dil KOH and ether until all of the solid dissolved, the layers separated, the aqueous layer washed with ether and acidified with conc HCl. Extraction with ether gave 39 g of the (+)-acid, m.p. 78–82°. Recrystallization from pet. ether (b.p. 60–70°) raised the m.p. to 81–82°, $[\alpha]_D^{23}$ +24·5° (*c*, 4.1 in benzene). Recovery of the antipode from the mother liquors of the resolution in the same way gave 85 g of the (−) acid, m.p. 65–68°, $[\alpha]_D$ −9·5° (*c*, 1 in benzene). The optically pure acid is reported[23] to have m.p. 86–87°, $[\alpha]_D^{22}$ 30·2° (*c*, 4·5 in benzene).

(*R*)-(−)-3-*Methyl*-3-*phenylvaleric acid* (XIV). Arndt-Eistert homologation of (*S*)-(+)-XI was accomplished in 55% yield by the procedure of Cram *et al.*[24] Recrystallization from pentane gave (*R*)-(−)-XIV, m.p. 39–40°, $[\alpha]_D^{22}$ −15·2° (*c*, 3·7 in $CHCl_3$); lit.[24] m.p. 43–44°, $[\alpha]_D^{22}$ +14·6° (*c*, 3·8 in $CHCl_3$) for the acid prepared from optically pure (*R*)-(−)-XI.

(*R*)-(−)-3-*Methyl*-3-*ethyl*-1-*indanone* (XV). (*R*)-(−)-XVI, 25·5 g, was warmed with excess $SOCl_2$ at 50° for 3 hr. The excess $SOCl_2$ was removed at reduced press and the residue distilled, yielding 27 g of the acid chloride, b.p. 75–78° (0·5 mm).

The acid chloride was added dropwise to a stirred suspension of 40 g anhyd $AlCl_3$ in 925 g benzene (distilled from CaH_2), maintaining the temp below 10°. After 2 hr additional stirring 50 ml ether and 250 ml 5% HCl were added slowly. The aqueous layer was extracted with ether (3 × 50 ml) and the combined organic solns washed with 5% $NaHCO_3$, 5% KOH, and water, then dried and concentrated. Distillation gave XV, 20·8 g, b.p. 58–60° (0·05 mm), n_D^{22} 1·5411, $[\alpha]_D^{22}$ −10·1° (*c*, 3·4 in benzene). The IR spectrum had bands at 1710, 1610, and 770 cm^{-1}; NMR (CCl_4): δ 0·70 (t, ethyl Me), 1·35 (s, tert Me), 1·69 (q, ethyl CH_2), 2·42 (q, ring CH_2), and 6·9–7·8 (m, aromatic). Found: C, 82·61; H, 7·95. $C_{12}H_{14}O$ requires: C, 82·71; H, 8·09%.

(*S*)-(+)-2-*Oximino*-3-*methyl*-3-*ethyl*-1-*indanone* (XVI). A soln of 2·0 g of (−)-XV in 20 ml MeOH and 0·5 ml conc HCl was stirred at 40–50° while 3 ml of n-butyl nitrite was added dropwise. After stirring 20 hr the soln was concentrated and the residual oil taken up in ether and extracted with 0·5N NaOH

until the remaining ether soln was colorless. The aqueous extracts were acidified with HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated, and the residual solid recrystallized from benzene–pet. ether (b.p. 60–70°) to afford 1·70 g of colorless XVI, m.p. 136–137°, $[\alpha]_D^{24}$ +46·3° (*c*, 5·9 in benzene). The IR spectrum showed bands at 3550, 3240, 1720, and 1635 cm^{-1}; NMR ($CDCl_3$): δ 0·55 (t, ethyl Me), 1·69 (s, tert Me), 1·88 and 2·72 (pair of quartets, ethyl CH_2), 7·3–8·1 (m, aromatic), and 9·5 (broad singlet, NOH). Found: C, 71·02; H, 6·39; N, 6·90. $C_{12}H_{13}NO_2$ requires: C, 70·91; H, 6·45; N, 6·89%.

(S)-(+)-2-*Acetoximino*-3-*methyl*-3-*ethyl*-1-*indanone* (XVII). A soln of 1·3 g of (+)-XVI in 5 ml pyridine and 5 ml Ac_2O was kept at room temp for 12 hr. The mixture was poured into ice water and the solid filtered, dried, and recrystallized from ether–pet. ether (b.p. 30–60°) to give 1·35 g of XVII, m.p. 137–138°, $[\alpha]_D^{22}$ +44·6° (*c*, 1·3 in benzene). Characteristic IR absorption was observed at 1785, 1730, 1630, and 1605 cm^{-1}; NMR ($CDCl_3$): δ 0·55 (t, ethyl Me), 1·66 (s, tert Me), 2·05 and 2·55 (two quartets, ethyl CH_2), 2·47 (s, acetate Me), and 7·3–8·1 (m, aromatic). Found: C, 68·44; H, 6·13; N, 5·78. $C_{14}H_{15}NO_3$ requires: C, 68·55; H, 6·16; N, 5·71%.

(S)-(+)-3-*Methyl*-3-*ethyl*-*indandione* (XX). A mixture of (+)-XVI (1·0 g), 2·4 ml 40% aqueous formaldehyde, and 0·4 ml conc HCl was heated with stirring on a steam bath for 30 min. Stirring was continued for 40 hr with occasional additions of formaldehyde and HCl. The soln was poured into water and extracted with ether. Distillation of the dried extracts gave the orange-red XX, 840 mg, b.p. 104–106° (0·25 mm), $[\alpha]_D^{22}$ +87·3° (*c*, 3·1 in MeOH). The IR spectrum showed absorption at 1765 and 1725 cm^{-1}; NMR ($CDCl_3$): δ 0·62 (t, ethyl Me), 1·39 (s, tert Me), 1·88 and 1·96 (two quartets, ethyl CH_2), and 7–8 (m, aromatic). Found: C, 76·37; H, 6·44. $C_{12}H_{12}O_2$ requires: C, 76·57; H, 6·43%.

(S)-(+)-α-*Methyl*-α-*ethylhomophthalimide* (XVIII). A mixture of 1·8 g of XVII and 10 ml 6N NaOH was stirred at 10° until it became homogeneous. The soln was acidified with 6N HCl and extracted with $CHCl_3$. Concentration of the extracts gave a pale yellow oil, which crystallized from pet. ether (b.p. 30–60°) with 5% benzene to afford 500 mg of XVIII, m.p. 110–113°. Recrystallization from CCl_4–pet. ether (b.p. 30–60°) gave material of m.p. 113–114°, $[\alpha]_D^{21}$ +23·7° (*c*, 4·8 in benzene). The IR spectrum showed bands at 3350, 3170, 1710, 1690, and 1605 cm^{-1}; NMR ($CDCl_3$): δ 0·61 (t, ethyl Me), 1·63 (s, tert Me), 1·7 and 2·5 (two quartets, ethyl CH_2), 7·2–7·7 (m, aromatic, 3H), 8·25 (d, 1H, aromatic H ortho to CO), and 8·75 (broad, NH). Found: C, 70·92; H, 6·39; N, 6·88. $C_{12}H_{13}NO_2$ requires: C, 70·91; H, 6·45; N, 6·89%.

(S)-(+)-α-*Methyl*-α-*ethylhomophthalic anhydride* (XIX). (a) From the mother liquor of crystallization of XVIII was isolated by distillation 500 mg of XIX, b.p. 120–122° (0·2 mm), $[\alpha]_D^{23}$ +41·2° (c, 9·2 in MeOH). The IR spectrum displayed bands at 1800, 1755, 1605, 1290, 1040, and 1020 cm^{-1}; NMR ($CDCl_3$): δ 0·74 (t, ethyl Me), 1·71 (s, tert Me), 2·04 and 2·11 (two quartets, ethyl CH_2), 7·3–7·8 (m, aromatic, 3H) and 8·18 (d, 1H, aromatic H *ortho* to CO). Found: C, 70·56; H, 6·07. $C_{12}H_{12}O_3$ requires: C, 70·58; H, 5·92%.

(b) A soln of 500 mg of (+)-dione XX in 30 ml MeOH was stirred in an ice bath while 10 ml of 30% H_2O_2 was added followed by a soln of 4 g K_2CO_3 in 10 ml H_2O. Stirring was continued for 3 hr and the soln kept overnight, then concentrated *in vacuo*. The solid residue was dissolved in water, washed with ether, acidified with HCl, and extracted with $CHCl_3$. Distillation of the $CHCl_3$ extracts gave 475 mg of (+)-XIX, b.p. 115–120° (0·15 mm), identical with the sample prepared in part (a).

(c) A suspension of 1 g of XVI and 3 g of PCl_5 in 10 ml ether was stirred for 45 min, then poured into ice water and stirred 30 min. The mixture was extracted with ether and the extracts washed with dil KOH aq, dried, and distilled, affording 500 mg of the crude anhydride, b.p. 115–120° (0·2 mm). The oil was refluxed with 50% KOH aq for 2 hr, acidified and extracted with ether. Distillation gave XIX as a pale yellow oil, b.p. 120–125° (0·25 mm), with an IR spectrum identical with that of the anhydride from (b).

(R)-(+)-3-*Methyl*-3-*ethyl*-1-*indanone oxime* (XXIII). A mixture of 2·0 g of XV, 2 g hydroxylamine hydrochloride, 2 g KOH, and 40 ml 95% EtOH was refluxed for 8 hr. The soln was poured into water, washed with ether, and acidified with HCl to precipitate the oxime. Recrystallization from benzene–pet. ether (b.p. 60–70°) gave the (+)-oxime, 1·3 g, m.p. 105–106°, $[\alpha]_D^{22}$ +8·3° (*c*, 3·0 in benzene). The IR spectrum had bands at 3560, 3200, 1650, and 1600 cm^{-1}; NMR ($CDCl_3$): δ 0·78 (t, ethyl Me), 1·33 (s, tert Me), 1·71 (q, ethyl CH_2), 2·87 (q, ring CH_2), 7·1–7·9 (m, aromatic), and 9·55 (broad, NOH). Found: C, 76·21; H, 7·91; N, 7·34. $C_{12}G_{15}NO$ requires: C, 76·13; H, 7·99; N, 7·40%.

The (*S*)-(−)-oxime XXIII, m.p. 105–106°, $[\alpha]_D^{22}$ −3·8° (*c*, 8·5 in benzene), was prepared in 86% yield in the same way from the (+)-ketone XV, derived in turn from (*R*)-(−)-XI, $[\alpha]_D$ −9·5°.

(S)-(−)-4-*Methyl*-4-*ethyl*-3,4-*dihydrocarbostyril* (XXIV). The (−) oxime XXIII was slowly added with manual stirring to polyphosphoric acid (20 g per g of oxime), preheated to 160°. After addition was complete, the reaction mixture was allowed to cool slowly to 100° and crushed ice (10 times the weight of acid) was added. The mixture was extracted with $CHCl_3$ and the extracts dried and concentrated. The orange oily

residue crystallized from ether or benzene–pet. ether (b.p. 30–60°) to yield colorless XXIV, m.p. 96–97°, $[\alpha]_D^{21}$ −7·1° (*c*, 4·6 in benzene), in 50–70% yield. The IR spectrum showed absorption at 3390, 3175, and 1690 cm^{-1}; NMR ($CDCl_3$): δ 0·80 (t, ethyl Me), 1·28 s, (tert Me), 1·65 (q, ethyl CH_2), 2·50 (s, ring CH_2), 6·8–7·4 (m, aromatic), and 9·38 broad, NH). Found: C, 76·08; H, 7·90; N, 7·38. $C_{12}H_{15}NO$ requires: C, 76·15; H, 7·99; N, 7·40%.

(S)-(−)-*1,4-Dimethyl-4-ethyl-3,4-dihydrocarbostyril* (XXV). A suspension of NaH (809 mg) in 20 ml dimethylformamide was rapidly stirred at 55–60° while a soln of 5·8 g of (−)-XXIV and 3·0 g MeI in 25 ml dimethylformamide was added dropwise. The mixture was heated for 6 hr at 60° and concentrated *in vacuo* The residue was distributed between water and CH_2Cl_2 and the organic layer dried and distilled, affording 3·5 g of colorless XXV, b.p. 103–105° (0·075 mm), $[\alpha]_D^{22}$ −5·8° (*c*, 5·6 in benzene). The IR spectrum showed bands at 2830, 1675, and 1600 cm^{-1}; NMR (CCl_4): δ 0·88 (t, ethyl Me), 1·21 (s, tert. Me), 1·55 (q, ethyl CH_2), 2·39 (s, ring CH_2), 3·29 (s, N–Me), and 6·75–7·35 (m, aromatic). Found: C, 76·52; H, 8·76; N, 6·90. $C_{13}H_{17}NO$ requires: C, 76·80; H, 8·43; N, 6·89%.

(R)-(−)-*α,N-Dimethyl-α-ethyl-N-acetyl-o-aminophenylacetic acid* (XXVII). An ethereal soln of MeLi (708 mg) was stirred at 0° under N_2 while a soln of 3·5 g of (−) lactam XXV in 10 ml ether was added dropwise. After 4 hr additional stirring the soln was poured over 10 g dry ice and allowed to stand until the dry ice evaporated, then washed with 0·5 N NaOH and water, dried over $MgSO_4$ and concentrated *in vacuo* The residual oil (XXVI) decomposes quickly at room temp, and consequently was immediately taken up in anhyd EtOAc, cooled to −10°, and ozonized. The O_3 stream was continued until the soln became colorless (about 30 min), the solvent evaporated in a stream of N_2, and the oily residue refluxed in 10 ml of glacial AcOH and 2 ml 30% H_2O_2 for 6 hr. The soln was made alkaline and extracted with $CHCl_3$ (5 × 25 ml). The extracts were dried over $MgSO_4$ and distilled, affording 200 mg of X, b.p. 93–96° (0·2 mm), identical with the sample described below.

The aqueous alkaline soln was acidified with HCl and extracted with $CHCl_3$. Concentration of the extracts gave a brown solid, which was washed with cold ether to give 147 mg of XXVII, m.p. 180–182°, $[\alpha]_D^{26}$ −1·54° (*c*, 0·32 in MeOH). The IR spectrum showed bands at 1725, 1620, and 1595 cm^{-1}; NMR ($CDCl_3$); δ 0·88 and 1·02, (two triplets, ethyl Me), 1·41 and 1·65 (two singlets, tert Me), 1·94 (s, acetyl Me), 2·2 (m, ethyl CH_2), 3·15 (s, N–Me), 6·85–7·7 (m, aromatic), and 10·25 (s, COOH). Found: C, 67·60; H, 7·72; N, 5·66. $C_{14}H_{19}NO_3$ requires: C, 67·45; H, 7·68; N, 5·62%.

(R)-(−)-*1,3-Dimethyl-3-ethyloxindole* (X). A mixture of 146 mg of XXVII and 10 ml conc HCl was refluxed for 8 hr, made basic, and extracted with $CHCl_3$. Concentration of the extracts gave 15 mg of (−)-X, purified by gas chromatography, $[\alpha]_D^{21}$ −2·4° (*c*, 0·092 in MeOH). The sample had IR and NMR spectra and VPC retention times identical with those of the sample of X prepared by degradation of physostigmine, but the ORD spectra were mirror images. Found: C, 76·10; H, 7·87; N, 7·47. $C_{12}H_{15}NO$ requires: C, 76·15; H, 7·99; N, 7·40%.

Acidification of the aqueous alkaline soln gave 63 mg of recovered XXVII.

2-Carboxyphenylacetonitrile. A soln of 2-oximino-1-indanone[25] (1·5 g) in 15 ml pyridine and 5 ml Ac_2O was kept overnight at room temp and poured into ice water. The ppt was filtered off and dried, giving a quantitative yield of XXII, m.p. 150–154°. Recrystallization from benzene–ether gave pale yellow crystals, m.p. 159–161° dec. The IR spectrum showed characteristic absorption at 1785, 1735, and 1645 cm^{-1}, while the NMR spectrum showed the acetate methyl at δ 2·40.

On stirring 800 mg of the solid oxime acetate in 6N NaOH, the solid dissolved completely with evolution of heat. Cooling and acidification with 6N HCl gave a ppt which was filtered off, dried, and recrystallized from benzene–pet. ether (b.p. 60–70°), affording 600 mg of colorless 2-carboxyphenylacetonitrile, m.p. 126–127°, lit.[26] m.p. 126°. The IR spectrum ($CHCl_3$) showed bands at 2240, 1695, and 1730 cm^{-1}, and was identical with the spectrum of authentic material (Sadtler Standard Spectrum 19497).

α,α,N,-Trimethyl-N-acetyl-o-aminophenylacetic acid (XXX). A mixture of 10 g 4,4-dimethyl-3,4-dihydrocarbostyril,[27] 1·65 g NaH, and 14·8 g MeI in 100 ml dimethylformamide was stirred and heated at 50–55° for 2 hr. Evaporation of the solvent left a brown residue, which was taken up in CH_2Cl_2, washed with water, dried, and distilled. The methylation product, 1,4,4-trimethyl-3,4-dihydrocarbostyril (8·5 g), was collected at 94–95° (0·1 mm). Its IR spectrum showed lactam absorption at 1675 cm^{-1}; Mol. wt. 189·11594 (mass spec); $C_{12}H_{15}NO$ requires 189·11536.

A soln of the lactam in 20 ml ether was added dropwise to a stirred soln of MeLi, prepared from 12·6 g MeI and 2·48 g Li in 100 ml ether. After stirring 1 hr the soln was poured over dry ice and kept until the dry ice evaporated. After washing with 0·5N NaOH and drying over $MgSO_4$, the ethereal soln was concentrated and distilled, affording 7·5 g 1,2,4,4-tetramethyl-1,4-dihydroquinoline, b.p. 78–80° (0·1 mm).

The IR spectrum (neat) showed enamine absorption at 1670 cm^{-1} but no bands in the CO or OH regions. The dihydroquinoline turns red rapidly on standing, and was therefore ozonized at once.

A slow stream of O_3 (4% in O_2) was bubbled through an EtOAc soln of 4·0 g of the dihydroquinoline, rapidly stirred at 0°, for 2 hr. The solvent was removed in a stream of N_2 and the residue heated under reflux with a mixture of 10 ml 30% H_2O_2 and 25 ml glacial AcOH for 10 hr. After diluting with 200 ml water, the soln was made alkaline with NaOH and washed with $CHCl_3$, then acidified with conc HCl and extracted with $CHCl_3$. Concentration of the extracts left a brown residue which solidified on standing and which was triturated with cold ether. The ether extracts furnished 400 mg of XXX, m.p. 191–193°. The IR spectrum showed CO absorption at 1725 and 1620 cm^{-1}, along with broad absorption at 3200–2500 cm^{-1}; NMR ($CDCl_3$): δ 1·48 (s, tert Me); 1·71 (s, tert Me); 1·91 (s, COMe); 3·13 (s, N-Me); 7·4 (m, aromatic protons); 11·4 (broad, CO_2H). Found: C, 66·16; H, 7·20; N, 5·85. $C_{13}H_{17}NO_3$ requires: C, 66·36; H, 7·28; N, 5·96%.

(R)-(−)-2-*Methyl*-2-*phenylbutyrohydroxamic acid* (XXVIII). (*R*)-(−)-2-Methyl-2-phenylbutyric acid (4 g), $[\alpha]_D^{21}$ −9·5°, was converted to the acid chloride with $SOCl_2$. A soln of the acid chloride in 10 ml ether was added dropwise to a stirred suspension of 1·6 g NH_2OH–HCl and 6 g Na_2CO_3 in 100 ml ether, and the mixture stirred for 3 hr. The mixture was warmed and filtered, and concentration of the filtrate left the crude hydroxamic acid, m.p. 112–116°. Recrystallization from benzene–pet. ether (b.p. 60–70°) afforded the colorless XXVIII; 3·58 g, m.p. 122–123°, $[\alpha]_D^{23}$ −3·5° (c = 4·0 in $CHCl_3$); NMR ($CDCl_3$): δ 0·77 (t, ethyl Me); 1·53 (s, tert Me); 2·08 (q, ethyl CH_2); 7·35 (broad s, aromatic protons); 8·2 (broad, OH and NH). Found: C, 68·42; H, 7·85; N, 7·25. $C_{11}H_{15}NO_2$ requires: C, 68·37; H, 7·82; N, 7·25.

3-*Ethyl*-3-*methyloxindole* (XXIX). To 50 g stirred polyphosphoric acid, preheated to 160°, was added 1·0 g of solid XXVIII, and stirring was continued for 30 min. After cooling, the mixture was stirred into ice water and extracted several times with $CHCl_3$. The extracts were dried and concentrated at reduced press, and the solid residue chromatographed over Florisil. Elution with ether gave an oily fraction which crystallized from pet. ether (b.p. 30–60°), affording 19·4 mg of colorless XXIX, m.p. 138–139°. The IR spectrum showed absorption at 3420, 3150, 1705, and 1620 cm^{-1}; NMR ($CDCl_3$): δ 0·68 (t, ethyl Me); 1·35 (s, tert Me); 1·88 (two quartets, ethyl CH_2); 7·1 (m, aromatic protons); 0·8 (broad s, NH); Mol. wt. 175·099709 (mass spec); $C_{11}H_{13}NO$ requires 175·099708.

(R)-(−)-1,3-*Dimethyl*-3-*ethyloxindole* (X). A suspension of NaH (2 mg) in dimethylformamide (1 ml) was stirred at 60° while a soln of 19·4 mg of XXIX and 25 mg MeI in 1 ml dimethylformamide was added dropwise. After stirring at 60° for 4 hr the solvent was removed at reduced press and the residue partitioned between water and CH_2Cl_2. The organic layer was dried and distilled, affording 10 mg of (*R*)-(−)-X, b.p. (bath temp) 120° (1 mm). The oxindole was levorotatory; its NMR, IR, and ORD spectra were identical with those of the sample prepared from (−)-XXVII.

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