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THE 3-ARYLPYRROLIDINE ALKALOID SYNTHON

A FORMAL TOTAL SYNTHESIS OF CEPHARAMINE UTILIZING AN ENDOCYCLIC ENAMINE*

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Abstract—A formal total synthesis of the hasubanonine alkaloid cepharamine (**3b**) from 7,8-dimethoxy-2-tetralone has been accomplished. A key intermediate in the synthesis was 3-methyl-1,2,4,5-tetrahydrobenz[*e*]indole **4a** which was prepared by a one step ring expansion reaction of cyclopropyl ketone **8b** effected by methylamine. The annelation of **4a** with methyl vinyl ketone yielded aminoketone **5a** which possesses the tetracyclic skeleton characteristic of the hasubanonine alkaloid group. The oxidation of **5a** to **5e**, which was reported to have been converted to cepharamine, completed the formal total synthesis of that alkaloid. The foregoing transformations and others related to them have also been carried out in the analogous desmethoxy series of compounds beginning with β-tetralone, **8d**.

APPLICATIONS of the chemistry of endocyclic enamines[2,3] in the form of their electrophilic iminium salts to the synthesis of various alkaloids has proven of considerable interest in recent years. Examples include the syntheses of *dl*-dihydrothebaine,[4] *dl*-lupinine,[5] *dl*-dehydrogambirtannine,[6] *dl*-corynantheidine,[7] *dl*-norcoralydine,[8] and other compounds[5–7,9] possessing the skeletons of (or related to) an assortment of alkaloid structural types.§ The nucleophilic reactivity of the endocyclic enamines themselves has also been applied to the same end although apparently less often. The total syntheses of *dl*-mesembrine[10] and of an erythrina alkaloid skeleton[11] are illustrative. In the case of mesembrine (**1**), the synthesis was planned about a key synthon,[12] 3-arylpyrrolidine unit **2** into which, for synthetic purposes, was incorporated the conjugated enamine double bond shown in that structure. The successful application of this latter approach to mesembrine[10] encouraged us to test further its utility in a synthesis of a more complex alkaloid which also incorporates a 3-arylpyrrolidine skeleton. For this purpose, members of the hasubanonine group (e.g., hasubanonine, **3a**) of the *Menispermaceae* alkaloids seemed attractive objectives, no work directed toward the synthesis of any one of them having been reported up to that time. In this paper we describe an investigation of a synthetic route to the hasubanonine group of alkaloids which has permitted a formal total synthesis of one of them, cepharamine (**3b**).[13]

* A portion of the work described herein has been the subject of an earlier communication.[1]

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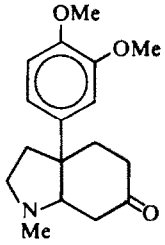
§ The use of iminium salt chemistry in alkaloid synthesis is, of course, not new. The well known Pictet–Spengler reaction proceeds by way of an iminium salt intermediate. The novelty of the more recent work lies in the way the chemistry of this class of compounds has been utilized in organic synthesis.



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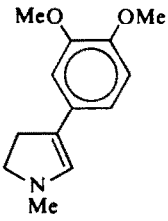

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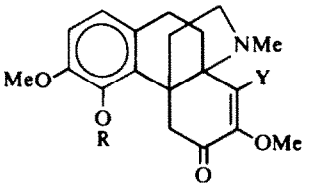
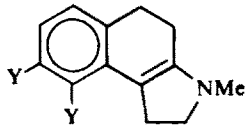
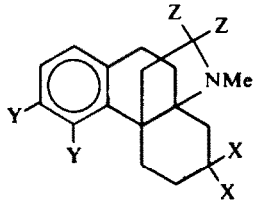


3a: R = Me, Y = OMe
b: R = Y = H

Our first goal was to develop a synthetic route to an intermediate having the tetracyclic hasubanan* skeleton characteristic of the hasubanonine alkaloids. Depending on the ease with which the rings of the intermediate could be functionalized, it subsequently would be converted to one or more of those alkaloids. By analogy with the mesembrine synthesis, such an intermediate would be assembled through the reaction of a modified 3-arylpyrroline synthon, tetrahydrobenz[*e*]indole **4a**. Reaction of **4a**, through its enamine system, with methyl vinyl ketone in a Stork-Robinson annelation reaction[15] should, ideally, lead to tetracyclic **5a**. A possible difficulty anticipated in this annelation step was that **4a** might exist in equilibrium with a small amount of its unconjugated tautomer, **6a**.† If the conjugated enamine proved the more reactive and if the two were in relatively mobile equilibrium, the major annelation product might be one or more of the stereoisomers of **7a**.‡ We

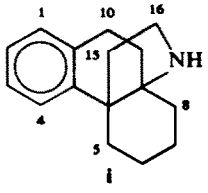


4a: Y = OMe
b: Y = H



5a: X + X = 0, Y = OMe, Z = H
b: X + X = 0, Y = Z = H
c: X + X = —OCH_2CH_2O—, Y = OMe, Z + Z = 0
d: X + X = —OCH_2CH_2O—, Y = OMe, Z = H
e: X + X = 0, Y = OMe, Z + Z = 0

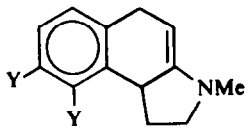
* The 10a,4a-iminoethanophenanthrene system **i** has been given the trivial name of hasubanan which will be used herein.[14]



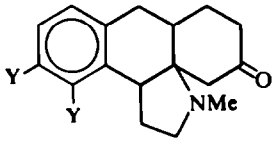
i

† That the equilibrium should lie largely in the direction of **4a** is owing to the conjugative stabilization of the enamine double bond in that tautomer as well as for steric reasons.[16]

‡ There are four stereoisomers corresponding to structure **7a** but those two having the two saturated six-membered rings *cis* fused are the most likely products.



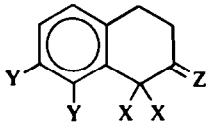
6a: Y = OMe
b: Y = H



7a: Y = OMe
b: Y = H

expected, nonetheless, that by selecting reaction conditions not favoring prototropic equilibria, that this problem could be overcome if it should arise at all.

Although neither **4a** nor any other 1,2,4,5-tetrahydro-3*H* benz[*e*]indole had previously been synthesized, its preparation seemed feasible by way of **8b** and **8c** through an extension of the cyclopropylaldimine-pyrroline ring expansion procedure developed by Stevens[10b,17] and ourselves.[10a] Unfortunately, the precursor (**8a**) required for this sequence is accessible only by way of a rather tedious preparative route*,[18] and, while accumulating a working quantity of this substance, we chose to examine the conversions to be effected upon it using its more readily available

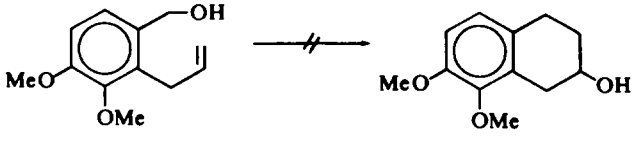


8a: Y = OMe, X = H, Z = 0
b: Y = OMe, X + X = —CH_2CH_2—, Z = 0
c: Y = OMe, X + X = —CH_2CH_2—, Z = NHMe
d: Y = X = H, Z = 0
e: Y = H, X + X = —CH_2CH_2—, Z = 0
f: Y = H, X + X = —CH_2CH_2—, Z = NHMe

desmethoxy analog, β-tetralone (**8d**).† From this study we hoped to be able to define optimal reaction conditions for each of the transformations and to gain some acquaintance with the properties of 1,2,4,5-tetrahydrobenz[*e*]indoles and the enamine system which they incorporate.

The alkylation of β-tetralone with 1,2-dibromoethane and potassium t-butoxide in DMSO gave the spiro compound **8e** in acceptable yield.[1] The NMR spectrum of

* Attempts to prepare this compound by a sequence involving the acid catalyzed cyclization of 2-allylveratryl alcohol, **i**, to β-tetralol **ii** were not successful, only a polymeric material or an ester of **i** being obtained.

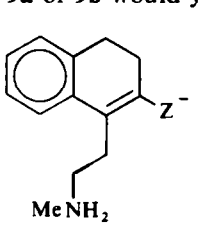


i **ii**

† β-Tetralone is commercially available and can also be easily prepared from β-methoxynaphthalene.[19]

8e showed a single aromatic proton as a multiplet centered 0·35 ppm upfield from the other aromatic protons. The upfield shift of this single aromatic proton signal[20] can be easily rationalized only in terms of diamagnetic anisotropic shielding by the adjacent cyclopropane ring. Such shielding would not be observed in the spectrum of any of the isomeric substances which might have been the product isolated in this alkylation.

Treatment of **8e** with methylamine under the forcing conditions required to cause the reaction to proceed at an appreciable rate yielded not the expected ketimine **8f** but, instead, the desired benz[*e*]indole, **4b**. Since the analogous cyclopropylaldimines are quite thermally stable in the absence of an acid catalyst,[10a,17] an observation in accord with the Woodward–Hoffmann rules,* the rearrangement must proceed by a mechanism different from that which applied in the cyclopropylaldimine series. A reasonable, though unproven, alternative mechanism would involve nucleophilic attack of methylamine upon a methylene carbon of the cyclopropane ring of **8e** and (or) **8f** with concurrent C–C bond cleavage and the formation of enolate anions **9a** and (or) **9b**, respectively.† Subsequent proton transfers and an intramolecular cyclization of either **9a** or **9b** would yield **4b**.



9a: Z = O
b: Z = NMe

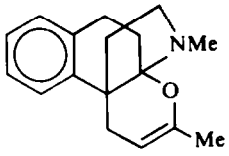
As had been anticipated, all spectral data obtained on **4b** gave no evidence for the presence of appreciable amounts of tautomeric **6b**. Trace quantities of the latter substance could, of course, be in equilibrium with **4b** and, conceivably, the product of the Stork–Robinson annelation might be **7b** rather than **5b**. The exothermic reaction which takes place between methyl vinyl ketone and **4b**, however, initially yields neither of those substances. Instead the spectral data on the reaction mixture indicate, in accord with earlier reports,[24] the formation of a dihydropyran, probably **10** and (or) **11**. When heated with a mole equivalent of glacial acetic acid, however, this material was converted into a carbocyclic annelation product, **5b** or **7b**.‡ Although thin layer chromatography indicated that this material was being formed in about

* If this thermally effected ring enlargement is to involve an allowed, hence facile, 1,3-sigmatropic migration, the rules[21] demand it be antarafacial, which is in this case sterically impossible. An alternative two-step radical process, by analogy with the vinylcyclopropane-cyclopentene rearrangement,[22] would occur only at temperatures well above those (110°) used in the preparation of **4b**, assuming the amino radical is as (or less) stable than an alkyl radical. We thank Dr. Michael Smith, Geigy Chemical Corporation, Ardsley, New York, for pointing out the Woodward-Hoffmann rules would have a bearing on this rearrangement.

† Similar nucleophilic cyclopropane ring cleavages have been observed by others.[23]

‡ These reaction conditions are not unlike those used by Curphey and Kim.[10c]

25% yield, the preparative TLC purification procedure used in its isolation reduced the yield to about 5%. After several attempts made to improve the purification process proved unrewarding, further work on that problem was discontinued in favor of other aspects of the synthesis.



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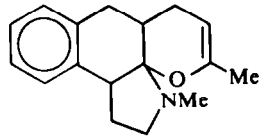

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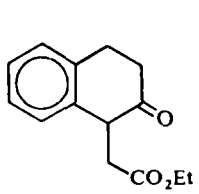
While spectral data obtained on the annelation product were entirely consistent with that obtained for **5b**, it did not preclude the possibility that this substance was, instead, one of the stereoisomers of **7b**.* Shortly before we had reached this point in our work, however, Ibuka *et al.*[26] reported the preparation by an independent route of **5c** whose structure they had unambiguously established. We obtained a specimen of **5c**† and converted it, by way of **5d**, to **5a** on which we obtained spectral data consistent with that structure. Our hope had been that the aliphatic proton region of the NMR spectrum of **5b** might bear a sufficient resemblance to that of the annelation product so as to provide convincing evidence that the two possessed identical skeletons. While there were certain resemblances between the two spectra, this was not the case. Nonetheless, the spectral data which had been obtained on **5a** remained of value as it would permit the identification of that material should it be obtained by way of the enamine route beginning with tetralone **8a**, a sequence we had well underway.

It remained of interest, however, to establish conclusively the structure of the product obtained in the annelation of **4b**. If it proved to be **7b**, then new reaction conditions favoring the formation of **5b** would need to be established. The classical approach, that of synthesizing **5b** by an unambiguous route, was chosen as the way to solve this problem. The general route to the hasubanan alkaloid skeleton that had been reported by Ibuka[26] seemed well suited to this purpose. Beginning with **8d**, the first three steps of the synthesis proceeded as expected and, as was subsequently proven, by way of intermediates **12**, **13a** and **13b**. From **13b** on, however, the synthesis was completed by a sequence different from that reported by Ibuka. Treatment of **13b** with a large excess of methylamine gave **14a** which was reduced with an excess of lithium aluminum hydride to gummy amino alcohol **14b**. The latter compound was not purified but was converted by aqueous acid directly to tetracyclic aminoketone **5b** identical to that obtained from the enamine route.

* The use of ^{13}C high resolution NMR spectroscopy in conjunction with the noise off-resonance decoupling technique[25] would almost certainly have permitted the establishment of the structure of the annelation product. Since this method was not available to us, we had to rely upon more conventional methods.

† We thank Professor Ibuka for generously providing us with a sample of **5c**.



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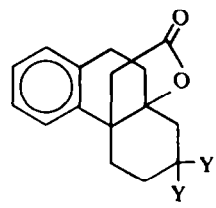
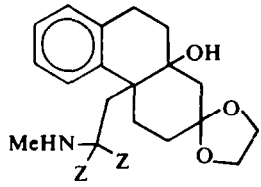


13a: Y + Y = O
b: Y + Y = —OCH_2CH_2O—



14a: Z + Z = O
b: Z = H

Proof of the structure of the tetracyclic framework of **5b**, which provides additional evidence as to the structures of all substances previously described, was obtained by a Pd-C dehydrogenation of **13a**.* The products from the dehydrogenation, although not isolated in pure form, were shown to include phenanthrene, 4-methylphenanthrene, a phenanthrol and a methylphenanthrol (combined thin layer chromatographic and spectral data). No anthracene could be detected in the reaction mixture. Since the structure of the cyclopropyl ketone intermediate (**8e**) in the enamine route to **5b** was unquestionably that depicted in **8e**, the former must also incorporate a benz[*e*]-indole skeleton. Together, these two pieces of structural data establish the structure of the tetracyclic product as **5b**. Not long before our own work on this substance was complete, there appeared a report by Evans[27] of its synthesis following a route quite similar to our own. A comparison of the products obtained from each route showed them to be identical.†

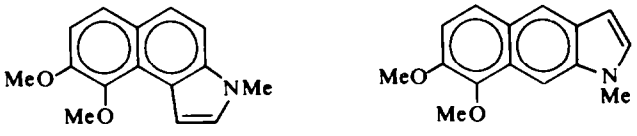
Following the reaction sequence used to prepare **4b**, we succeeded in obtaining its analog **4a** from tetralone **8a**. The only notable point of difference between the two conversions occurred in the tetralone alkylation reaction which gave considerably better yields of product in the case of **8e** than were observed in that of **8b**. The lower yields in the latter alkylation may be owing to steric hindrance at the site of alkylation in **8a** caused by the adjacent methoxyl substituents.‡ Although we were able,

* A catalytic dehydrogenation was not carried out on the annelation product itself as the limited quantities of that material which were available were reserved for exploration of the ring functionalization reactions we planned to use in its conversion to a hasubanonine alkaloid.

† We wish to thank Professor Evans for generously providing comparison spectra and for having carried out the direct comparison cited. The results of his own investigations related to the work described here are to be the subject of a forthcoming paper.

‡ The hindrance to alkylation in this case, however, seems substantially less than that observed in a similarily substituted suberone system used in a colchicine synthesis.[28]

after several attempts, to acquire a satisfactory elemental analysis on **4a**, mass spectral evidence clearly demonstrated that even the purified material was contaminated with a small amount of a substance of mass 243, probably 3-methyl-8,9-dimethoxy-1,2-dihydrobenz[*e*]indole, and traces of other materials. While the small amount of proton absorption in the τ 6·0–6·7 ppm region of the NMR spectrum of **4a** not due to the OMe group protons could be, at least in part, due to the vinyl proton of the unconjugated enamine **6a**, it more likely has its source in the trace impurities in the former. A Pd-C dehydrogenation of **4a** yielded a tetradehydro product whose spectra were in accord with **15** rather than **16**.



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The Stork–Robinson annelation of **4a** was carried out as it had been for **4b** but with the use of slightly modified reaction conditions. A single addition product was isolated by preparative TLC. As in the annelation of **4b**, while TLC analysis of the reaction mixture indicated this product was formed in about 20% yield, the yield of purified product isolated was less than half that figure. The IR and NMR spectra of **5a** were, in every significant respect, identical to those obtained previously on this material prepared from **5c**. TLC comparisons of the two in a variety of solvent systems also confirmed their identity.

At the time we were investigating the later stages of the synthesis of **5a**, a total synthesis of *dl*-cepharamine was reported by Ibuka *et al.*[29] by a route different from our own. The preparation of one intermediate in that synthesis, **5c**, had also been achieved earlier by that group through another reaction sequence[26] in which **5e** was an immediate precursor of that substance. Since the ethanamine bridge of certain hasubanonine alkaloids had been oxidized by neutral permanganate to the corresponding lactam,[30] the one-step conversion of **5a** to **5e** seemed feasible and was, in fact, accomplished without difficulty. This conversion, along with the others preceeding it, constitute a formal total synthesis of cepharamine. At present, we are studying alternative routes whereby the synthesis of cepharamine from **5a** may be more expeditiously achieved.

The advantages and disadvantages of the endocyclic enamine approach in alkaloid synthesis deserve brief comment. The main advantage is that it permits the three-step conversion of a methylenecarbonyl moiety to a 6-oxoperhydroindole system. The principal disadvantage is the low yield of product formed in the Stork–Robinson annelation step of the sequence. Our own results have suggested, however, that our purification procedure partly accounts for the unsatisfactory yields we have obtained. Further, the fact that others[10b,c] have fared better than ourselves in applying the annelation reaction in closely related systems, leads us to expect that, despite our failure in defining them at this time, superior reaction conditions and isolation procedures may yet be found. If this is the case, then the endocyclic enamine route to polycyclic alkaloids and allied heterocycles should prove a valuable synthetic approach rather than a passing curiosity of limited application.

EXPERIMENTAL

M.ps (oil bath) are uncorrected and those taken in an evacuated capillary are designated by "(vac)". Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or by Galbraith Laboratories, Inc., Knoxville, Tenn. NMR spectra were obtained on a Varian A-60 spectrometer with (unless otherwise noted) $CDCl_3$ the solvent and TMS the internal standard. IR spectra were obtained on Perkin–Elmer 21 and 337 spectrometers. Mass spectra were obtained on an AEI MS12 spectrometer except in the case of high resolution spectra which were obtained on an AEI MS9 spectrometer (Battelle Memorial Institute Mass Spectrometry Center). Unless otherwise indicated, TLC separations were effected using glass backed precoated silica gel plates with fluorescent indicator obtained from Brinkmann Instruments, Westbury, N.Y. For preparative TLC 2·0 mm layers and for analytical work 0·5 or 0·25 mm layers were used.

3-*Methyl*-8,9-*dimethoxy*-1,2,4,5-*tetrahydro*-3H-*benz*[e]*indole* (**4a**)

A mixture of 0·84 g (15·0 mmole) CaO, 1·18 g (5·08 mmole) of **8b**, approximately 3·1 g (0·1 mole) $MeNH_2$ and 10 ml benzene were heated in a stainless steel bomb at 100–110° for 7 days. The mixture was then diluted with about 50 ml benzene, filtered under dry N_2 cover, and the solvent removed by distillation *in vacuo* leaving 2·3 g of an oil. Molecular distillation of the oil (0·25 mm, 108–110°) yielded 0·86 g (69%) 3-methyl-8,9-dimethoxy-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole as a viscous oil. Of this material, 0·234 g were dissolved in 1·5 ml 2N HCl, the soln diluted with 1·0 ml H_2O, washed with three 2·0 ml portions CH_2Cl_2, basified with 4·0 ml 1N NaOH and extracted with three 3·0 ml portions CH_2Cl_2. The combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered, and the solvent removed by distillation *in vacuo*. Molecular distillation of the oil (0·30 mm, 105°) gave an analytical sample. (Found: C, 73·16; H, 7·89; N, 5·65. $C_{15}H_{19}NO_2$ requires: C, 73·44; H, 7·81; N, 5·71%); NMR: τ 3·39 (2H, q, J_{AB} = 8·0 c/s), 6·19 and 6·27 (6H, 2 identical s's), 6·63–7·97 ppm (11H, overlapping m's—NCH_3 singlet at τ 7·38 ppm). A small amount of proton absorption (several small signals) present in the τ 6·20 ppm region of the spectrum was probably owing to the presence of a minor contaminant as was a weak broad singlet (*ca* 0·3H) at τ 8·56 ppm; IR: ν_{max} ($CHCl_3$) 1619 and 1597 cm^{-1}; UV: λ_{max} (cyclohexane) 230 (11800), 251 (8830), 327 mμ (ε 12600); Mass spectrum (70 ev, source temp 175°): *m/e* 245 (M^+), 230, 215, 185, 184, 183, 182, 115 (+2 ion?), 86, 84, 53, 49.

The material was subsequently obtained in crystalline form but, in part owing to the small quantity available and its air sensitivity, recrystallization from n-heptane failed to raise its m.p. above the 34–38° range. Low ionization potential (8 ev) mass spectra also indicated that even the purest samples of it obtained contained small amounts of a dihydrobenz[*e*]indole analog (*m/e* 243).

3-*Methyl*-1,2,4,5-*tetrahydro*-3H-*benz*[e]*indole* (**4b**)

In a stainless steel bomb was placed 10 g (0·058 mole) of **8e**, 10 g (0·178 mole CaO, and 200 ml benzene containing approximately 20 g (0·65 mole) $MeNH_2$. The sealed bomb was heated at 110 ± 10° and rocked for 7 days. The bomb was then opened and the mixture filtered under dry N_2 cover. The solvent and excess $MeNH_2$ were removed by distillation *in vacuo* and the residual oil vacuum distilled yielding 7·8 g (72·5%) 3-methyl-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole, b.p. 131–135° at 1·1 mm. (Found: C, 84·54; H, 8·35; N, 7·48. $C_{13}H_{15}N$ requires: C, 84·28; H, 8·16; N, 7·56%); NMR: τ 2·61–3·33 (4H, m), 6·58–7·99 ppm (11H, overlappings m's—NCH_3 singlet at τ 7·41 ppm); IR: ν_{max} (CH_2Cl_2) 1632 cm^{-1}; UV: λ_{max} (cyclohexane) 218 sh (7100); 233 (9340); 322 mμ (ε 12800).

N-*methyl*-3,4-*dimethoxy*-7-*oxohasubanan* (**5a**)

Method A. To 13·2 mg (0·0354 mmole) N-methyl-3,4-dimethoxy-7,16-dioxohasubanan ethylene ketal in 1·0 ml dry THF was added 10·5 mg (0·276 mmole) LAH and an additional 1·5 ml THF. The mixture was gently refluxed under a dry N_2 atmosphere for 14 hr at which time was added 10 μl H_2O in 60 μl THF and reflux continued for 10 min. The reaction mixture was cooled to room temp, diluted with 3·0 ml Et_2O, filtered, and the residue washed with 5·0 ml Et_2O. The filtrate and washings were combined, the solvent removed by distillation *in vacuo*, the residual glassy solid dissolved in 3·0 ml 22% H_2SO_4aq and the soln kept a day at room temp. The pale yellow soln was basified to pH 10–12 by the addition of 30% K_2CO_3aq, the resulting emulsion diluted with 5·0 ml H_2O, extracted with four 3·0 ml portions CH_2Cl_2, and the combined organic layers dried over Na_2SO_4. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* yielded as a colorless glass 9·3 mg (83%) N-methyl-3,4-dimethoxy-7-oxohasubanan. Although the material prepared in this manner was not obtained crystalline, TLC indicated that, except for minor impurities, it was homogeneous. Spectral data obtained on it, moreover, were in good agreement

with the assigned structure and were, in all significant respects, identical to those obtained on the crystalline product prepared by Method B (see spectral data cited therein). The specimen of **5a** prepared above decomposed on storage (possibly owing to acidic contaminants) but its preparation on a tenth the scale used in that preparation was successfully accomplished. TLC on material from this second preparation again established aside from minor impurities, that the substance was homogeneous and identical (comparison of R_f values with 6 different solvent developing systems) to the material prepared by Method B. (TLC R_f values on silica gel plates; (v:v solvent composition, R_f): —$CHCl_3$, 0·08; 1:5:5 *t*-BuOH:$CHCl_3$:C_6H_6, 0·39; 1:1 EtOAc:$CHCl_3$, 0·28; 3:1 C_6H_6: i-PrOH, 0·60, 1:1 C_6H_6: EtOAc, 0·28).

Method B. To 122·5 mg (0·500 mmole) 3-methyl-8,9-dimethoxy-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole in an ampoule and under dry N_2 was added 38·5 mg (0·550 mmole) methyl vinyl ketone after which the ampoule was immediately stoppered. A mild exothermic reaction of a few min duration took place at once. During this reaction period, the ampoule contents were swirled to ensure thorough mixing. 10 min after the reagents had been mixed, the ampoule was heated briefly on a 40° oil bath and the contents again swirled. After the mixture had remained 1·0 hr at room temp, 30·0 mg (0·500 mmole) glacial HOAc was added to the mixture which was again momentarily heated to 40° and swirled in the ampoule. The ampoule was then cooled to −78°, evacuated to about 125 mm, sealed, and then heated at 70° for 5·0 hr. The ampoule was then opened, the mixture diluted with 2·0 ml benzene and shaken with 2·0 ml 4% NH_4OH aq. The benzene layer was separated, dried over Na_2SO_4, filtered, and the solvent removed by distillation *in vacuo*. Of the remaining 216·2 mg clear viscous oil, all but 62·2 mg was chromatographed on two 20 × 20 cm preparative TLC plates using 2:2:1 (v:v) $CHCl_3$:EtOAc:MeOH as the developing solvent. The band between R_f 0·61 and 0·74 was removed from the plates, powdered, and extracted with 50 ml of 0·2N HCl and with 15 ml H_2O. The combined extracts were basified with 10 ml 7% NH_4OH aq, the resulting emulsion extracted with three 25 ml portions CH_2Cl_2, and the combined organic layers dried over Na_2SO_4. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left 42 mg pale yellow viscous oil which was crystallized from n-heptane yielding 20·4 mg crystalline material, m.p. (vac) 109–112·5°. Of this material, 10·0 mg were recrystallized from n-heptane to give 5·7 mg (10·4% yield corrected for partitioning of material described above) N-methyl-3,4-dimethoxy-7-oxohasubanan, m.p. (vac) 112–114·3°. TLC on this material showed it to be homogeneous, except for two very minor impurities, and identical to that prepared by Method A; NMR: τ 3·23 (2H, s), 6·11 and 6·17 (6H, two identical s's), 6·94–8·61 ppm (17H, overlapping m's—NCH_3 singlet at τ 7·77 ppm); IR: λ_{max} ($CDCl_2$) 1709 cm^{-1}; Mass spectrum (70 ev, source temp 200°): *m/e* 315·1823 (M^+, $C_{19}H_{25}NO_3$ requires 315·1843), 245 (base peak), 244, 243, 230, 229, 213.

TLC comparisons (2:5 abs EtOH: light petroleum (30–60°) developer, I_2 visualization) of known amounts of crude **5a**, prepared as described above and prior to the preparative TLC purification, with known amounts of the pure product (comparisons of intensity of coloration and size of the spots at R_f 0·40) indicated the material was being produced in approximately 20% yield.

N-*Methyl-7-oxohasubanan* (**5b**)

Method A. A soln of 3·0 g (9·05 mmole) of **14a** and 0·684 g (1·80 mmole) LAH in 200 ml glyme was stirred and refluxed 21 hr under dry N_2. The mixture was cooled to room temp and 0·324 ml H_2O added. Removal of a ppt by filtration and the solvent by distillation *in vacuo* left a residue which was taken up in ether, the resulting soln filtered, and the solvent removed by distillation *in vacuo* leaving 2·0 g clear viscous oil. A 1·0 g sample of this liquid was dissolved in 40 ml H_2O containing 6·0 ml conc H_2SO_4 and the soln allowed to remain at room temp overnight. The resulting light yellow soln was washed with CH_2Cl_2, basified with K_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and the solvent removed by distillation *in vacuo* leaving 0·60 g yellow oil. Molecular distillation of the oil (0·34 mm, 100–127°) yielded 88 mg yellow oil which spontaneously crystallized. A single recrystallization of this material from n-hexane gave 35 mg (3·0% yield corrected for partitioning of material described above) N-methyl-7-oxohasubanan, m.p. (vac) 68·5–70·0°. (Found: C, 79·95; H, 8·44; N, 5·47. $C_{17}H_{21}NO$ requires: C, 79·96; H, 8·29; N, 5·49%); NMR: τ 2·55–3·08 (4H, m), 7·02–8·60 ppm (17H, overlapping m's—NCH_3 singlet at τ 7·77 ppm); IR: ν_{max} (film) 1711 cm^{-1}.

Method B. (Preliminary spectroscopic studies were carried out on the reaction between mole equivs 3-methyl-1,2,4,5-tetrahydrobenz[*e*]indole and methyl vinyl ketone (MVK) in sufficient benzene-d_6 to give a solution *ca* 2M in each reagent. On mixture, the two underwent a rapid mildly exothermic addition reaction (disappearance of the MVK vinyl proton signals in the NMR and of the enamine C=C bond absorption in the IR spectra taken on the reaction mixture) to form, as judged by the appearance of a strong IR absorption at *ca* 1680 cm^{-1}, a dihydropyran.[24] Although this reaction mixture then undergoes

a subsequent much slower reaction to form ketonic material (attenuation of the 1680 cm^{-1} absorption and appearance of a strong absorption at *ca* 1710 cm^{-1}), and while TLC evidence suggests at least some of the material is the desired annelation product, **5b**, other reaction conditions, those described here, appeared to provide a more satisfactory way of preparing that substance.)

To a soln of 0·925 g (5·00 mmole) of **5b** in 4·0 ml benzene in an ampoule was added 0·390 g (5·58 mmole) MVK (containing 1% hydroquinone as a stabilizer). The ampoule was briefly flushed with dry N_2, sealed, kept 3 hr at room temp and 18 hr at 58°. After being kept a final 2 hr at room temp, the ampoule was opened and to the mixture was added 0·334 g (5·57 mmole) glacial HOAc. The ampoule was resealed as before and heated 15 hr at 58°. The ampoule was opened, the contents dissolved in 50 ml CH_2Cl_2, the CH_2Cl_2 layer shaken with 25 ml 4% K_2CO_3aq and dried over Na_2SO_4. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left 1·21 g viscous brown oil. Of this material, 500 mg was chromatographed on six 20 × 20 cm thin layer plates coated with *ca* 0·4 mm layers Mallinckrodt TLC-4G SilicAR with fluorescent indicator. The plates were developed using 2:2:1 (v:v) $CHCl_3$:EtOAc:MeOH as the developing solvent. The zone between R_f 0·65 and 0·80 was removed from the developed plates and extracted with 20 ml 1N HCl and 10 ml H_2O. The combined extracts were washed with 25 ml CH_2Cl_2, basified with 10 ml 12% NH_4OHaq, and the resulting emulsion promptly extracted with three 25 ml portions CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, the drying agent removed by filtration and the solvent by distillation *in vacuo*. The partly crystalline residue was recrystallized from n-heptane to yield 26·4 mg (5·0%, yield corrected for partitioning of material described above) N-methyl-7-oxohasubanan, m.p. (vac) 67·0–69·0°. A mixture m.p. taken with this material and that prepared by Method A was undepressed. All spectral data obtained on both these substances were, in every significant respect, identical and are reported in Method A.

TLC comparisons (2:5 abs EtOH:light petroleum (30–60°) developer, I_2 visualization) of known amounts of crude **5b**, prepared as described above and prior to the preparative TLC purification, with known amounts of the pure product (comparisons of intensity of coloration and size of the spots at R_f 0·40) indicated the material was being produced in approximately 20–25% yield.

N-*methyl*-3,4-*dimethoxy*-7,16-*dioxohasubanan* (**5e**)

To a stirred mixture of 25·0 mg (0·0793 mmole) N-methyl-3,4-dimethoxy-7-oxohasubanan, 19·1 mg (0·159 mmole) $MgSO_4$, 1·0 ml H_2O and 3·0 ml Me_2CO kept at 15° on a H_2O bath was added 22·0 mg (0·139 mmole) $KMnO_4$ in 1·0 ml H_2O. The mixture was stirred 1·0 hr, extracted with three 3·0 ml portions benzene, and the combined organic layers diluted with 3·0 ml CH_2Cl_2 and dried over Na_2SO_4. The drying agent was removed by filtration and the solvent by distillation *in vacuo* leaving 26·5 mg green gum. The gum was taken up in 2·0 ml benzene, the soln washed with 2·0 ml 0·4N HCl, 2·0 ml 0·4M K_2CO_3, and then dried over Na_2SO_4. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* yielded 17·7 mg gum which was dissolved in $CDCl_3$ and an NMR spectrum obtained. This spectrum, but for some minor impurities, proved to be identical to that of **5e** (see spectral data below) but also showed the presence of a considerable amount of benzene (benzene: **5e** mole ratio of *ca* 1:3). Removal of the $CDCl_3$ by distillation *in vacuo* and crystallization of the residue from benzene yielded, after vacuum drying at 80°, 9·34 mg crystalline solid. An NMR spectrum of this material in $CDCl_3$ soln was virtually identical to **5e** but still showed the presence of benzene (benzene: **5e** mole ratio of *ca* 1:2) suggesting **5e** formed a benzene solvate. Removal of the $CDCl_3$ by distillation *in vacuo* and recrystallization of the residue from i-PrOH gave 5·6 mg (21·4%) of **5e**, m.p. (vac) 176·5–177·8° (lit.[26] 170–172°); NMR τ 3·19 (3H, s), 6·11 and 6·15 (6H, two identical s's), 6·93–8·78 ppm (17H, overlapping m's-- NCH_3 singlet at τ 7·22 (lit.[26] 7·20) ppm); IR: ν_{max} ($CDCl_3$) 1678 and 1719 cm^{-1} (lit.[26] 1675 and 1718 cm^{-1} in $CHCl_3$); Mass spectrum (70 ev, source temp. 170°): *m/e* 329·1638 (M^+, $C_{19}H_{23}NO_4$ requires 329·1627), 259, 258 (base peak), 227. The mass spectrum also indicates the presence of a minor impurity (relative abundance 1·43%) at *m/e* 345·1572 ($C_{19}H_{23}NO_5$).

Spiro[*cyclopropane*-1,1'-(7',8'-*dimethoxy*-1',2',3',4'-*tetrahydro*-2'-*oxonaphthalene*)] (**8b**)

To half the volume of t-BuOK (12·3 g, 0·110 mole) soln in 75 ml dry DMSO stirred under dry N_2 was added dropwise 10·3 g (0·050 mole) 7,8-dimethoxy-2-tetralone[18] in 50 ml of the same solvent. To this soln was promptly added in one portion half the volume of 10·9 g (0·058 mole) $BrCH_2CH_2Br$ and the mixture stirred 0·5 hr at 55–60°. The mixture was then cooled to room temp and half of the remaining t-BuOK soln and half the remaining $BrCH_2CH_2Br$ (in that order) were quickly added. The mixture was again stirred 0·5 hr at 55–60° and then cooled to room temp. The remaining portions of the t-BuOK soln and the dibromoethane were added, the mixture heated to 55–60° for 0·5 hr, 5·47 g (0·029 mole) additional

$BrCH_2CH_2Br$ was added, and heating continued for another 0·5 hr. The mixture was diluted with 1·0 l H_2O containing 20 ml conc HCl, extracted with three 300 ml portions CH_2Cl_2, and the combined organic layers dried over Na_2SO_4. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left 13·3 g oil. The oil was vigorously stirred 1 hr with 375 ml $NaHSO_3$ aq (a sat soln at 65°), the resulting paste filtered, and the filtrate and filter cake being thoroughly washed with a total of 350 ml ether. The dried (Na_2SO_4) then filtered ether layers were freed of solvent by distillation *in vacuo* leaving an orange oil which crystallized when seeded with crystals of the desired product. Recrystallization of this material gave 1·79 g (15·4%) of **8b**, m.p. (vac) 59·1–61·3°. An additional 1·13 g (9·7%) of this material, m.p. (vac) 60·5–61·7°, was recovered from the mother liquor. A single recrystallization of this substance from i-PrOH was carried out to obtain an analytical sample, m.p. (vac) 61·3–62·4°. (Found: C, 72·21; H, 6·98. $C_{14}H_{16}O_3$ requires: C, 72·39; H, 6·94%); NMR: τ 3·16 (2H, q), 6·16 and 6·26 (6H, two identical s's), 6·82–7·53 (4H, m), 8·00–8·47 ppm (4H, m); IR: ν_{max} ($CHCl_3$) 1691 cm^{-1}.

Decomposition of the bisulfite adduct with HCl aq and recrystallization of the crude product gave 1·84 g (17·9%) recovered 7,8-dimethoxy-2-tetralone, m.p. (vac) 72·5–74·5° (lit.[18] m.p. 76°). An inadvertent mechanical loss of the bisulfite adduct occurred during the recovery described here and so better than 20% recoveries of the starting material can be expected.

Spiro[cyclopropane-1,1'-(1',2',3',4'-tetrahydro-2'-oxo-naphthalene)] (**8e**)

To half the volume of a soln of 9·0 g (0·080 mole) t-BuOK in 125 ml dry DMSO stirred under dry N_2 was added dropwise 5·0 g (0·034 mole) β-tetralone. The stirred mixture was warmed to 50° on a H_2O bath and, after 10 min, half of 7·5 g (0·040 mole) $BrCH_2CH_2Br$ was added. After 1·0 hr, half the remaining base and $BrCH_2CH_2Br$ was added to the mixture which was again stirred 1·0 hr. Again half the remaining base soln and $BrCH_2CH_2Br$ was added, the mixture stirred 1·0 hr, and then all remaining base solution and $BrCH_2CH_2Br$, plus 7·5 g (0·040 mole) additional of the latter reagent, were added. The mixture was stirred 3·0 hr, cooled to room temp, diluted with 500 ml 2N HCl, and extracted with three 200 ml portions CH_2Cl_2. The combined organic layers were washed with two 500 ml portions H_2O and dried over $MgSO_4$. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* yielded an oil which was converted to a bisulfite adduct by stirring with 250 ml sat $NaHSO_3$ aq and allowing the mixture to stand overnight. The adduct was removed from soln by filtration and washed with CH_2Cl_2. The filtrate was extracted with two 250 ml portions CH_2Cl_2, all CH_2Cl_2 layers were combined and washed with 200 ml H_2O and dried over $MgSO_4$. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left an oil which was vacuum distilled to yield 3·0 g distillate (b.p. 97–101° at 0·7 mm) which subsequently crystallized, m.p. 41–49°. The crystals were dissolved in benzene and passed through a short column containing Woelm activity grade I neutral alumina, elution being effected with benzene. Removal of the solvent by distillation *in vacuo* yielded 2·8 g (63% yield corrected for 1·2 g recovered β-tetralone obtained by decomposing the bisulfite adduct) of **8e**, m.p. 45–49°. Recrystallization of this material from 95% EtOH gave 1·5 g of **8e**, m.p. 50–51°. Two additional amounts, 0·5 g (m.p. 49–51°) and 0·3 g (m.p. 48–50°), of **8e** were recovered from the mother liquor. (Found: C, 83·94; H, 6·85. $C_{12}H_{12}O$ requires: C, 83·69; H, 7·02%); NMR: τ 2·75–3·09 (3H, two envelopes, 2·91 and 2·95, and a possible underlying m), 3·15–3·49 (1H, m), 6·78–7·61 (4H, m), and 8·15–8·98 ppm (4H, m); IR: ν_{max} ($CHCl_3$) 1692 cm^{-1}.

1-Carbethoxymethyl-1,2,3,4-tetrahydro-2-oxonaphthalene (**12**)

A soln of 10·0 g (0·068 mole) β-tetralone and 9·8 g (0·138 mole) pyrrolidine in 100 ml dry benzene was refluxed in a dry N_2 atmosphere under a Dean–Stark trap for 20 hr. The benzene and excess pyrrolidine were removed by distillation *in vacuo*, the light brown residue remaining dissolved in 45 ml dry benzene and to this soln, stirred under dry N_2, was added over a 20 min period 11·4 g (0·068 mole) ethyl bromoacetate in 23 ml benzene. The resulting mixture was refluxed 2·5 hr, diluted with 20 ml H_2O and refluxed an additional 2·5 hr. The benzene layer was separated from the cooled reaction mixture, the aqueous phase extracted with two 10 ml portions benzene, and the combined organic layers dried over $MgSO_4$. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left 17 g dark brown oil which was vacuum distilled to give 12·8 g (81%) 1-carbethoxymethyl-1,2,3,4-tetrahydro-2-oxonaphthalene, b.p. 148–150° at 1·2 mm. (Found: C, 72·23; H, 6·84. $C_{14}H_{16}O_3$ requires: C, 72·39; H, 6·94%); NMR: τ 2·69–3·04 (4H, mainly as an envelope at 2·81), 5·88 (2H, q, J = 7 c/s), 5·96–6·18 (1H, broadened t or a m-a singlet at 6·34 may be due to a minor impurity), 6·72–7·14 (4H, m), 7·28–7·65 (2H, m), and 8·79 ppm (3H, q, J = 7 c/s); IR: ν_{max} (CCl_4) 1721 and 1735 cm^{-1}.

1,2,3,4,4a,9,10,10a-*Octahydro*-2,12-*dioxo*-10a,4a-*epoxyethanophenanthrene* (**13a**)

To 11·2 g (0·0783 mole) 1-diethylamino-3-butanone, stirred under dry N_2 at 0°, was added dropwise 11·2 g (0·0789 mole) MeI over a period of 0·5 hr. The resulting semisolid was mechanically stirred at 0° an additional 0·5 hr, brought to room temp, and stirred another 45 min. While stirring continued, 20 g (0·0861 mole) 1-carbethoxymethyl-1,2,3,4-tetrahydro-2-oxonaphthalene was added in 100 ml dry benzene, the resulting mixture cooled to 0°, and to it was added dropwise over a 10 min period 80 ml ethanolic KOEt (prepared by dissolving 4·90 g (0·126 mole) K in abs EtOH). After all solid material had dissolved, the mixture was refluxed 0·5 hr, cooled to room temp, diluted with 200 ml 2N H_2SO_4, and the benzene layer separated. The aqueous layer was extracted with two 75 ml portions benzene and the 3 benzene layers combined and dried over $MgSO_4$. Removal of the drying agent by filtration and the solvent by distillation *in vacuo* left a solid residue which was washed with ether to give 13·7 g (62%) of **13a**, m.p. 167–168°. (Found: C, 75·03; H, 6·19. $C_{16}H_{16}O_3$ requires: C, 74·98; H, 6·29%); NMR: τ 2·61–3·05 (4H, m), 6·91–8·26 ppm (12H, m). IR: ν_{max} (KBr) 1708 and 1770 cm^{-1}.

Catalytic dehydrogenation of 1,2,3,4,4a,9,10,10a-*octahydro*-2,12-*dioxo*-10a,4a-*epoxyethanophenanthrene* (**13a**)

A mixture of 0·196 g (0·765 mmole) of **13a** and 0·063 g 5% Pd/C was heated in a flask equipped with a N_2 inlet and a reflux condenser. The mixture was kept at 200° for 25 hr while a gentle stream of N_2 was passed through the vessel. At the end of the heating period, a dark brown tar remained in the reaction flask and a pale yellow viscous liquid in the condenser. The reaction flask and condenser were each separately washed with CH_2Cl_2 and each soln filtered. Removal of the solvent by distillation *in vacuo* yielded the material from the condenser, A, 50·9 mg, and that from the reaction flask, B, 79·7 mg. Each of these materials was thin layer chromatographed on 0·25 mm silica gel plates with benzene the developing solvent and were both found to contain the same major components although in somewhat different relative amounts. Significantly, while both mixtures contained a component with an R_f value of about 0·60–0·65, it did not exhibit under UV light the strong green fluorescence characteristic of anthracene which also has the same R_f value. Two major components of A and B were isolated by removal of the silica gel containing them from the developed TLC plates, extraction of the silica gel with 95% EtOH, and removal of solvent from the filtered extracts by distillation *in vacuo* yielding (R_f, weight) from A, 0·14 (8·0 mg), 0·60 (13·8 mg); B, 0·15 (11·7 mg), 0·65 (10·0 mg).

The high R_f value materials from A and B were found to be mixtures essentially identical in composition (TLC and UV comparisons). The two major components of the mixture were phenanthrene and 4-methylphenanthrene as was established by the following data. In addition to lesser amounts of unidentified materials (none of which show the spectral characteristics expected for anthracene or an alkyl anthracene) the NMR spectrum shows aromatic proton signals characteristic of phenanthrene and 4-methylphenanthrene as well as a singlet at τ 6·90 ppm (lit.[31] τ 6·87 ppm) for the Me protons of the latter substance. A low ionization potential (8 ev) mass spectrum showed as the two major peaks those at *m/e* 178 and 192, the latter of twice the abundance of the former. While phenanthrene, anthracene, and their simple alkyl derivatives have quite similar UV spectra, they are distinguishable by an absorption (λ_{max} between 290 and 310 mμ (ε of about 10,000)), which is present in the phenanthrene but not in the anthracene series. The UV spectrum on the high R_f material, with respect to the more intense maxima in terms of frequency and relative intensity, was in good agreement with those reported for phenanthrene and the alkylphenanthrenes.

The low R_f value material was similarly investigated. A low ionization potential (8 ev) mass spectrum showed the two most abundant ions at *m/e* 194 and 208, the former twice as intense as the latter, suggesting the presence of phenanthrol and a methylphenanthrol in the mixture. The UV spectrum of the material, with respect to the more intense maxima in terms of frequency and relative intensity, was in reasonable agreement with those reported for 2-phenanthrol.

Although spectra on both of the mixtures showed the presence of substances other than phenanthrene derivatives, there was no evidence for the presence of significant amounts of anthracene or its alkyl derivatives in either.

Spiro[(1,2,3,4,4a,9,10,10a-*octahydro*-12-*oxo*-10a,4a-*epoxyethanophenanthrene*)-2,2'-(1',3')*dioxolane*] (**13b**)

A soln of 10·0 g (0·039 mole) of **13a**, 2·4 g (0·039 mole) ethylene glycol and a crystal of *p*-TsOH in 75 ml dry benzene was refluxed under a Dean–Stark trap in a dry N_2 atmosphere for 20 hr. The mixture was cooled to room temp and the white crystalline ppt which formed isolated by filtration. Removal of the solvent by distillation *in vacuo* yielded an additional quantity of crystals which were combined with those

isolated before. The crystals were washed with ether and dried leaving 10·8 g (92%) **13b**, m.p. 155–156°. (Found: C, 72·05; H, 6·82. $C_{18}H_{20}O_4$ requires: C, 71·98; H, 6·71%); NMR: τ 2·66–2·96 (4H, m), 6·09 (4H, s), 6·68–8·54 ppm (12H, overlapping m's); IR: λ_{max} (KBr) 1773 cm^{-1}.

N-*Methyl*-1,2,3,4,5a,9,10,10a-*octahydro*-10aα-*hydroxy*-2-*oxophenanthrene*-4aα-*acetamide ethylene ketal* (**14a**)

A soln of 1·0 g (3·3 mmole) **13b**, 0·24 g (3·5 mmol) $MeNH_2 \cdot HCl$, and 10 ml $MeNH_2$ in 20 ml dioxan was sealed at −80° into a stainless steel bomb. The bomb was heated at 100° for 48 hr, cooled to *ca* 25°, vented, opened, and the volatile materials removed by distillation *in vacuo*. The residual crystalline solid was washed with H_2O and ether (in that order) and dried leaving 0·76 (69%) of **14a**, m.p. 170–172°. (Found: C, 68·85; H, 7·69; N, 4·20. $C_{19}H_{25}NO_4$ requires: C, 68·86; H, 7·60; N, 4·23%); IR: ν_{max} (KBr) 3260, 1627 and 1584 cm^{-1}.

3-*Methyl*-8,9-*dimethoxy*-3H-*benz*[e]*indole* (**15**)

A soln of 71·3 mg (0·291 mmole) 3-methyl-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole in 1·5 ml mesitylene was gently refluxed 7·5 hr under N_2 with 25·9 mg 5% Pd/C. The mixture was then diluted with several milliliters benzene, centrifuged, and the supernatant separated. The residue was mixed with another small portion benzene, the mixture centrifuged, and the supernatant added to the one previously separated. Removal of the solvent by distillation *in vacuo* left 71·4 mg solid which, on recrystallization from benzene yielded 47·6 mg (68%) 3-methyl-8,9-dimethoxy-3*H*-*benz*[*e*]indole, m.p. 126·5–128·0°. An additional 12·1 mg (17%) cruder material, m.p. 114–123°, was recovered from the mother liquors. Recrystallization of the former material yielded an analytical sample, m.p. 128·8–129·4°. (Found: C, 74·91; H, 6·22; N, 5·76. $C_{15}H_{15}NO_2$ requires: C, 74·67; H, 6·27; N, 5·80%); NMR τ 2·24–2·94 (6H, overlapping q's), 5·89 and 6·01 (6H, two identical s's), and 6·16 ppm (3H, s); IR: ν_{max} (film on ATR crystal) 1624, 1581, 1553 cm^{-1}; UV: λ_{max} (cyclohexane) 238 sh (71,100), 249 (89,900), 268 (46,700), 312 (24,000), *ca* 323 mμ (ε 20,700).

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