Tetrahedron. Vol. 24, pp. 6377 to 6386. Pergamon Press 1968. Printed in Great Britain

NEW REACTIONS OF 3-VINYLINDOLES*

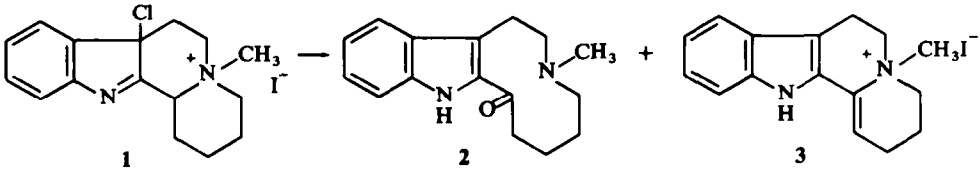
L. J. DOLBY† and G. W. GRIBBLE‡

Department of Chemistry, University of Oregon, Eugene, Oregon

(*Received in USA* 23 *January* 1968; *Received in the UK for publication* 27 *May* 1968)

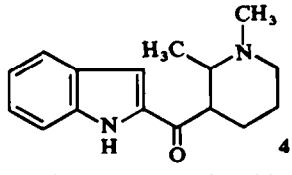
Abstract—The conversion of 5-methyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizinium iodide (**3**) into 1,2-dimethyl-3-(2-indolylcarbonyl) piperidine (**4**) is described along with subsequent transformations of **4** and related compounds. A reaction scheme is proposed for this transformation and is supported by a carbon-14 tracer experiment and model studies. Several transformations were encountered in which 3-vinylindoles undergo nucleophilic addition to the vinyl group to give products in which the nucleophile is attached to the C atom adjacent to the indole nucleus.

WE RECENTLY reported a study of the base-induced conversion of the chloroindolenine methiodide **1** to a mixture of the 2-acylindole **2** and the unsaturated quaternary ammonium salt **3**.[1] Further study of these compounds has revealed some new chemistry of 3-vinylindoles. The novel transformations encountered show that 3-vinylindoles undergo nucleophilic addition to give products in which the nucleophile is attached to the carbon adjacent to the indole ring. It was further found that the vinyl group of 3-vinylindoles is removed by treatment with aqueous base and it appears likely that this process involves anti-Markownikoff hydration of the vinyl group to give the 3-(1-hydroxyethyl) indole after which the side chain is lost as acetaldehyde.



1 **2** **3**

In the earlier study it was established that the quaternary ammonium salt **3** is not an intermediate in the conversion of the chloroindolenine **1** into the 2-acylindole **2**.[1] However, it appeared that more drastic conditions might effect the conversion of **3** into the desired 2-acylindole **2**. Accordingly the unsaturated quaternary ammonium salt **3** was refluxed with sodium hydroxide in aqueous ethanol. This treatment slowly converted **3** into a new 2-acylindole base for which we propose structure **4**.



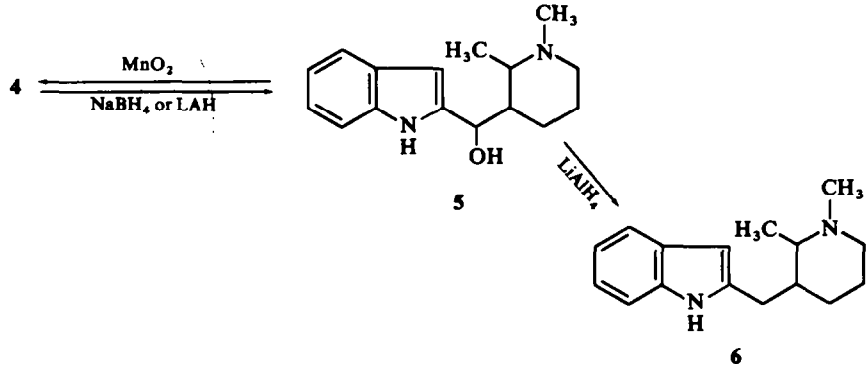
4

* This work was supported by the National Institutes of Health (Grant HE 09521) and a Public Health Service career program award 1-K3-NB-28,105 from the National Institute of Neurological Diseases and Blindness.

† Alfred P. Sloan Research Fellow.

‡ National Institutes of Health Predoctoral Fellow, 1965–67.

Mass spectral and combustion analyses of **4** establish that it is an isomer of the 2-acylindole **2**. The UV spectrum shows typical 2-acylindole absorption[2-4] λ_{max}^{EtOH} 235 mμ (ε 15,200) 310 mμ (26,500) which is unchanged by addition of acid. The lack of change upon addition of acid indicates that the basic nitrogen is not in a position to interact with the carbonyl group as in **2**[4] and certain other 2-acylindoles related to tetrahydro-β-carbolines.[5,6] The IR spectrum of **4** shows absorption at 3480 cm^{-1} (N—H) and carbonyl absorption at 1642 cm^{-1} which is normal for 2-acylindoles.[6,7] The NMR spectrum shows a sharp singlet at 2·35 ppm (3H) ascribed to an N-Me group and a three proton doublet (J = 6 cs) at 1·10 ppm which is attributed to a Me group on a carbon bearing a single proton. The fact that the indole of **4** is substituted only at the 2-position was established by examination of the reduction products of **4**. Treatment of **4** with sodium borohydride affords an alcohol **5**, which is converted back to **4** by the action of manganese dioxide. Vigorous LAH reduction of the 2-acylindole **4** yields the oxygen free base **6** along with the alcohol obtained by sodium borohydride reduction. These conditions slowly convert the alcohol **5** to the deoxygenated base **6**.



Such behaviour is expected for 2-acylindoles and 2-hydroxyalkylindoles.[8] The NMR spectra of both the alcohol and the oxygen free base show a signal at 6·22 ppm which is not present in the parent 2-acylindole. Such an absorption is most consistent with a proton at the β-position of the indole ring.[9] The absence of a peak in this area in the NMR of the 2-acylindole **4** is undoubtedly caused by the deshileding effect of the carbonyl group. This hypothesis is supported by the observation that the signal for the 3-proton of 2-carboethoxyindole is found with the protons of the benzene ring whereas the corresponding signal for 2-hydroxymethylindole and 2-methylindole is found near 6·22 ppm.[10]

The data presented thus far established that **4** is a 2-acylindole unsubstituted at the 3-position and bearing an N-Me group and a C-Me group attached to a methine C atom. That compound **4** is a tertiary amine is indicated by the observation that it is not acetylated upon treatment with acetyl chloride or acetic anhydride and it combines with one mole of methyl iodide to afford a quaternary ammonium salt (**7**). Evidence for the skeleton of **4** comes from its mass spectrum and degradation studies. The mass spectrum (Fig. 1) of the 2-acylindole **4** shows, in addition to the parent ion at *m/e* 256 and an M-15 peak corresponding to the loss of a Me group, an intense peak at *m/e* 144 which is attributed to cleavage along line a. Also seen are ions at *m/e* 112, 111, and 110 and their M-15 counterparts, which are ascribed to the piperidine

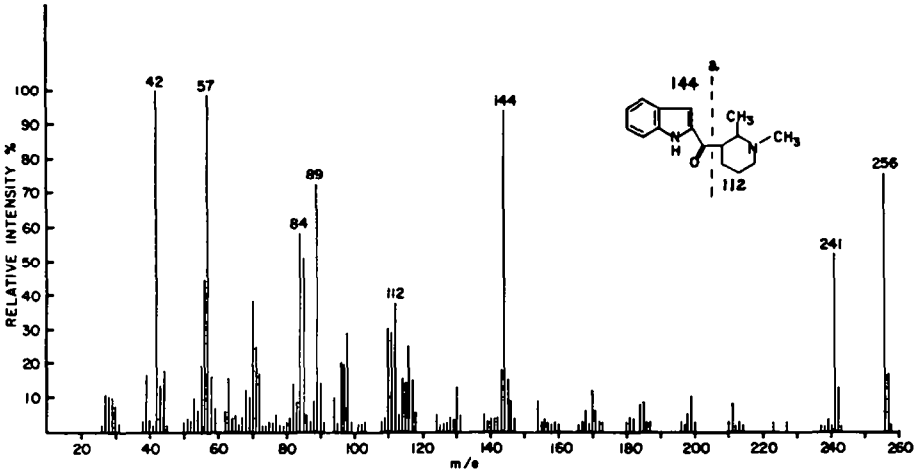


FIG. 1 Mass spectrum of 1,2-dimethyl-3-(2-indolyloxomethyl) piperidine.

half of the molecule. This α-cleavage of ketones and 2-acylindoles in particular is well documented.[5,6,11,12] Further cleavage of the piperidine ions leads to the intense peaks at *m/e* 42, 57, 70, and 84.

The mass spectrum of the oxygen free base **6** (Fig. 2) is readily rationalized. The two most intense peaks in the spectrum are at *m/e* 130 and 111 which are attributed to cleavage along line b.

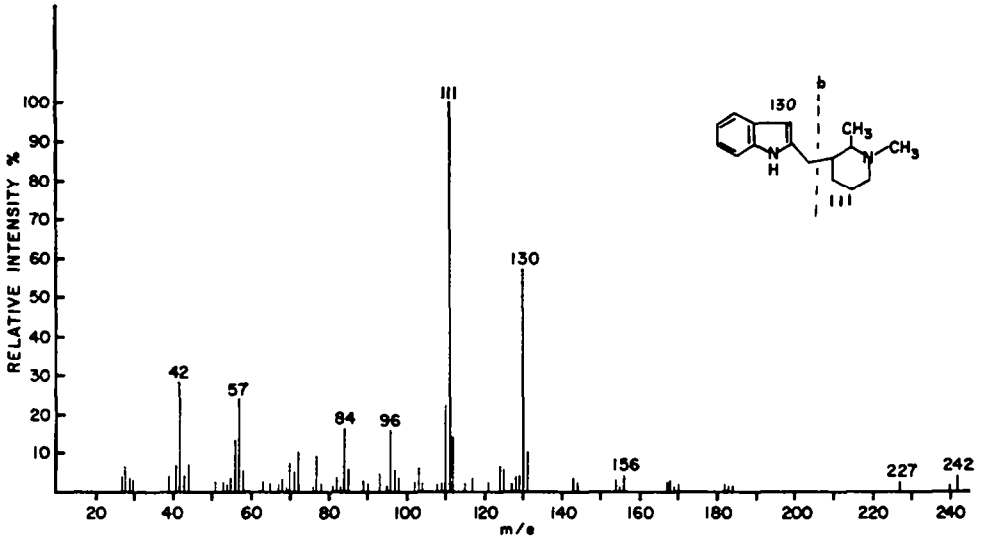
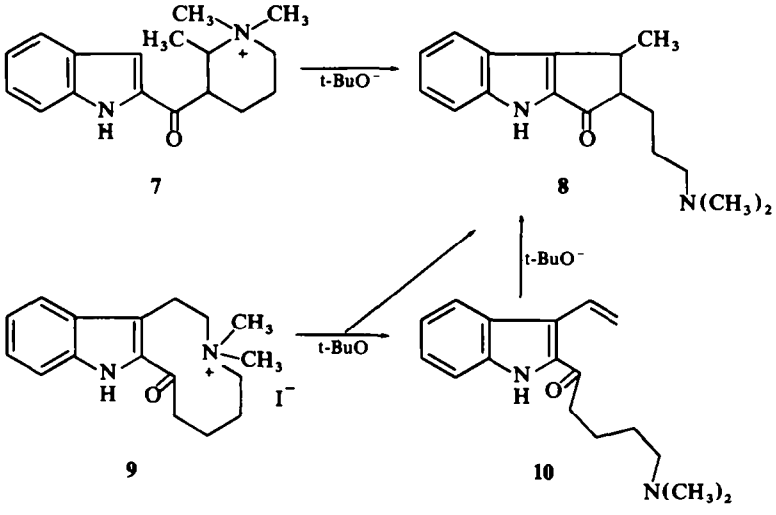


FIG. 2 Mass spectrum of 1,2-dimethyl-3-(2-indolylmethyl) piperidine.

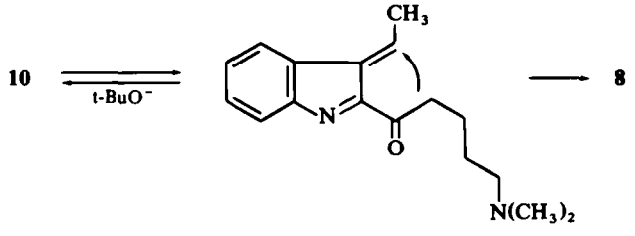
Degradation studies were carried out on the methiodide of **4**. Treatment of the methiodide with potassium t-butoxide in t-butanol afforded a new 2-acylindole for which we propose structure **8**. Similar degradation of the methiodide **9** from the tricyclic 2-acylindole **2** yields the expected 3-vinyl-2-acylindole **10** confirmed by spectral

data and further transformations. The UV spectrum of **10** shows λ_{max}^{EtOH} 248 mμ (ε 22,600), 318 mμ (19,200) which is in good agreement with that of the 3-vinyl-2-acylindole derived from vobasine.[13] The NMR spectrum of 10 shows a sharp singlet (6 protons) at 2·23 ppm assigned to the N-Me groups and a typical 3-vinylindole ABC pattern[14] for the three vinyl protons. Hydrogenation of the 3-vinyl-2-acylindole **10** afforded the corresponding 3-ethyl-2-acylindole **11** which showed the presence of an Et group in its NMR spectrum (Experimental). Prolonged exposure to potassium t-butoxide of the methiodide **9** or the derived 3-vinyl-2-acylindole **10** yielded only the same 2-acylindole **8** that was obtained by the degradation of the methiodide of **4**. These transformations are summarized in Scheme I.

SCHEME I

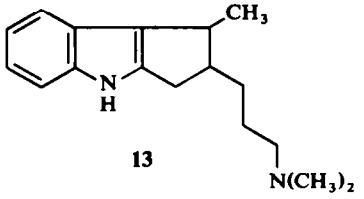


We would propose that the 3-vinyl-2-acylindole **10** is converted to **8** by an internal Michael condensation proceeding from the tautomeric 3-alkylideneindolenine.



Structure **8** is supported by its UV spectrum which shows λ_{max}^{EtOH} 233 mμ (ε 23,000) and 302 mμ (22,300). This unusually short wavelength absorption indicates that the 2-acylindole grouping is part of a 5-membered ring fused to the indole nucleus. The UV spectrum of **8** is virtually superimposable on that of an authentic sample of 1-keto-,2,3,8-tetrahydrocyclopent[b]indole **12**.[15,16] The IR spectrum of **8** shows carbonyl absorption at 1670 cm^{-1} while that for **12** is found at 1675 cm^{-1} (chloroform solution). The NMR spectrum of **8** furnishes further support for structure **8** (Experimental).

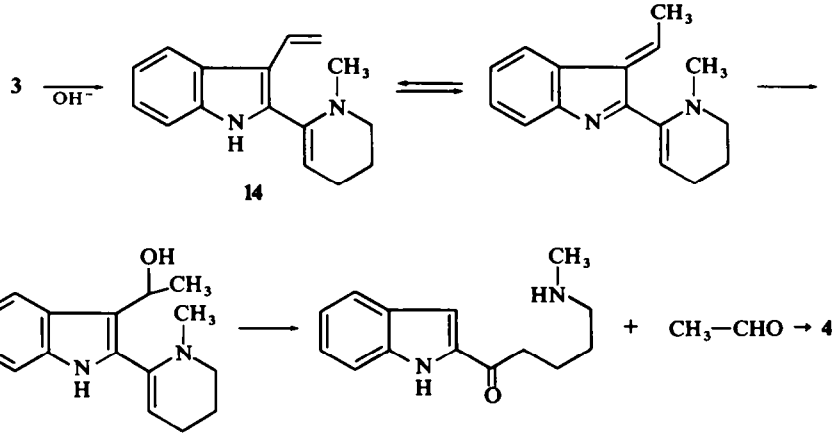
Vigorous LAH reduction of **8** affords an oxygen free base **13**. The UV spectrum of **13** shows λ_{max}^{EtOH} 228 mμ (ε 17,400), 280 (3600) which again shows the effect of a 5-membered ring fused to the indole nucleus. This spectrum is identical to that of an authentic sample of 1,2,3,8-tetrahydrocyclopent[b]indole prepared by a Fischer indole synthesis.



13

Having secured the structure of **4** from the accumulated spectral and chemical data, it is of interest to consider how it is derived from the quaternary ammonium salt **3**. We would propose the sequence of transformation shown in Scheme II.

SCHEME II

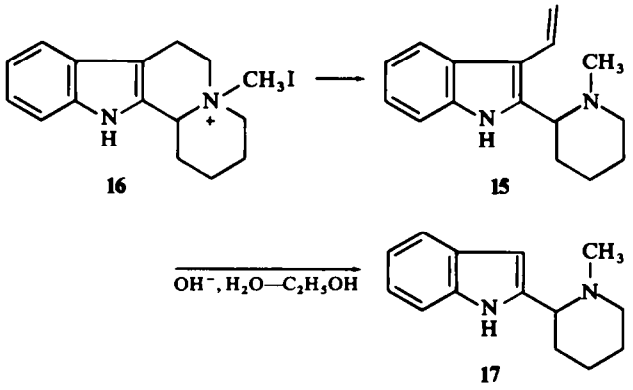


The formation of the 2,3-divinyl indole **14** from **3** is reasonable in view of the similar elimination observed with the quaternary ammonium salt **16** (*vide infra*). It is not possible to determine the order of the following steps, but the important transformations are the loss of the 3-vinyl group as acetaldehyde and a subsequent Mannich condensation between acetaldehyde and the amino ketone derived from the enamine portion of **14**. Firm chemical evidence has been adduced to support this reaction scheme. Firstly, the reaction conditions used in the conversion of the salt **3** to **4** serve to efficiently cleave the vinyl group from the 3-vinyl indole **15**, which was obtained by the action of potassium t-butoxide on the known tetracyclic quaternary ammonium salt **16**.[4]

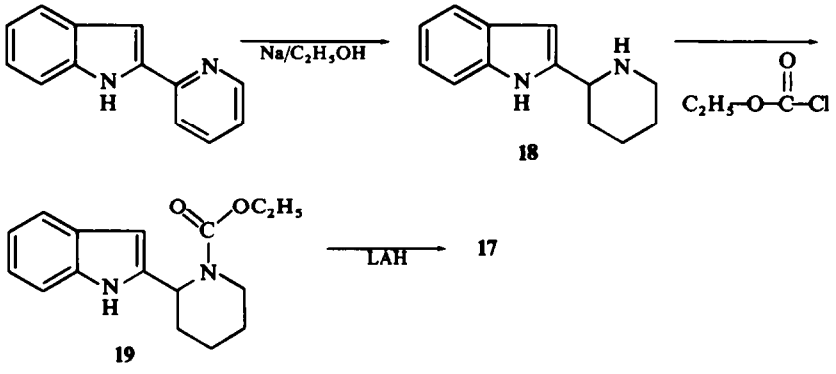
The structure of the 3-vinylindole **15** follows from its UV and NMR spectra (Experimental) which compare favourably with those of 3-vinylindole.[17] Hydrogenation of **15** affords 2-(N-methyl-2-piperidyl)-3-ethylindole which showed an easily recognized ethyl group in its NMR spectrum. The structure of the 2-piperidylindole **17** was confirmed by an independent synthesis, as shown in Scheme IV.

The synthesis proceeds in straightforward fashion from the known 2-[2-pyridyl]

SCHEME III



SCHEME IV



indole and affords **17** identical to that obtained from the cleavage of **15**. In addition, 3-vinylindole itself yields indole upon treatment with sodium hydroxide in aqueous ethanol. The details of the devinylation reaction have not been secured, but it seems quite likely that the vinyl group is lost as acetaldehyde and that the corresponding hydroxyethylindole is an intermediate. It is well known that 3-hydroxyalkylindoles and their derivatives are readily cleaved to indole and a carbonyl compound in basic media.[17,18] Further evidence for the intermediacy of free acetaldehyde and the overall sequence involving loss of a two carbon fragment and subsequent condensation with a two carbon fragment was obtained by carrying out the rearrangement of **3** in aqueous ethanol-1-^{14}C. The specific activity of the 2-acylindole **4** from this experiment was 95% of that of the labeled ethanol indicating virtually complete incorporation of the ethanol solvent into the product. This result is completely consistent with the loss of the vinyl group as acetaldehyde, which would rapidly undergo oxidation-reduction with the solvent ethanol under the alkaline reaction conditions.

The important finding of this study is that 3-vinylindoles are susceptible to nucleophilic addition to give products in which the nucleophile is attached to the carbon adjacent to the indole ring. This is completely the reverse of the situation encountered with vinylpyridines for example. That nucleophilic addition to 3-vinylindoles is a

fairly general process is shown by the observation that treatment of 3-vinylindole with aqueous ethanolic sodium cyanide affords 3-(1-cyanoethyl) indole in good yield. The 3-(1-cyanoethyl) indole was identified from its spectral properties and it was synsized by another route.

EXPERIMENTAL

General. M.ps and b.ps are uncorrected. Anhydrous K_2CO_3 was used to dry solns unless otherwise specified. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Woelm alumina was used for column chromatography unless otherwise specified and Silica gel G (according to Stahl) was used for TLC. R_f values and spot colors reported herein usually refer to a 98% EtOAc-2% Et_3N solvent system using a 3% $CeSO_4$-10%H_2SO_4 soln and heat to develop the spots. IR spectra were measured in $CHCl_3$ soln with a Beckman IR-5A infrared spectrophotometer and UV spectra were recorded on a Cary Model 15 spectrophotometer. A Varian Associates A-60 instrument was used to record the NMR spectra. $CDCl_3$ and formamide (for the organic salts) were used as solvents and TMS was the internal standard. The mass spectra were determined by the Morgan–Schaffer Corporation, Montreal, Quebec, Canada.

1,2-Dimethyl-3-(2-indolylcarbonyl)piperidine (**4**). A soln of 177 mg (0·483 mmole) of **3** obtained previously,[1] 10 ml 10% NaOH aq, and 20 ml 50% aqueous EtOH was refluxed under N_2 for 6 days. The soln was extracted with benzene and the benzene extract washed well with water. After drying, concentration gave 124 mg of an amber semi-solid. Chromatography over activity III neutral alumina gave, with benzene elution, 51 mg (41%) of off-white solid. Crystallization from ether gave pure material as prism clusters, m.p. 167–168°. The UV spectrum (EtOH) showed 235 mμ (ε 15,200) and 310 mμ (26,500). The IR spectrum showed 3490 cm^{-1} (N—H) and 1645 cm^{-1} (C═O). The NMR spectrum showed a sharp signal at 2·35 ppm (N-Me) and a doublet at 1·10 ppm (J = 6 cs) attributed to the C-Me group. The mass spectrum is shown in Fig. 1. (Found: C, 75·23; H, 8·09; N, 10·79. $C_{16}H_{20}N_2O$ requires: C, 74·97; H, 7·86; N, 10·93%). In another experiment, 980 mg of the salt **3**, 25 ml water, 25 ml 92% EtOH-1-^{14}C (specific activity 18,600 counts/min/mmole) water, and 25 ml 10% NaOH aq were refluxed for 6 days and processed as just described. The benzene eluates afforded 0·113 g of pure **4** which crystallized immediately. The material obtained in this manner was sublimed and found to have a specific activity of 17,600 counts/min/mmole.

1,2-Dimethyl-3-(2-indolylmethyl)piperidine (**6**). A mixture of 400 mg of **4** and 900 mg LAH in 100 ml dry N-methylmorpholine was refluxed under N_2 for 4·5 days, after being stirred for 30 min at 25°. The excess hydride was destroyed by the careful addition of water to the ice-cold mixture. After the addition of NaOH, $CHCl_3$ extraction gave an orange syrup, after concentration of the dried extract. This oil crystallized on standing. TLC revealed two new compounds and the absence of starting material. The smaller slower-moving spot corresponded to alcohol **5**, the sole product of sodium borohydride reduction of **4**. These two compounds could be separated by chromatography on activity III neutral alumina. Benzene elution gave 260 mg (69%) of the oxygen-free base **6**. Further elution with benzene gave mixtures of this compound and alcohol **5**, which could be retreated with LAH to give additional material. Crystallization from hexane several times gave pure **6** as clumps of colorless crystals; m.p. 128–129°. The UV spectrum (EtOH) showed 221 mμ (ε 31,900), 275 mμ (7000) and 287 mμ (5500); the IR spectrum exhibited absorption at 3500 cm^{-1} (N—H). The NMR spectrum had a doublet (J = 6 cs) at 1·17 ppm (C-Me), a singlet at 2·27 ppm (N-Me) and absorption at 6·22 ppm (3-indole proton). (Found: C, 79·35; H, 9·05; N, 11·49. $C_{16}H_{22}N_2$ requires: C, 79·29; H, 9·15; N, 11·56%).

Manganese dioxide oxidation of **5**. A mixture of **5**, which could not be obtained in crystalline form, 500 mg freshly prepared MNO_2,[19] and 20 ml CH_2Cl_2 was stirred at 25° for 14 hr. Filtration and concentration of the filtrate afforded ketone **4**.

1,1,2-Trimethyl-3-(2-indolylcarbonyl)piperidinium iodide (**7**). A soln of 100 mg of **4** and 1 ml MeI in 10 ml benzene was stored at 25° for 2 days. The resulting ppt was collected and crystallized from MeOH–ether to give clumps of white crystals, m.p. 225–226°.

1-Keto-3-methyl-3-(3-dimethylaminopropyl)-1,2,3,8-tetrahydrocyclopent[b]indole (**8**) *from methiodide* **7**. A soln of 200 mg (0·5 mmole) of **7** and 10 ml 0·5 M t-BuOK was refluxed under N_2 for 10 hr. The usual workup gave 134 mg of a semi-solid which was filtered through activity II neutral alumina with benzene to yield 86 mg (64%) of **8** which was identical with the material prepared from the methiodide **9** as described below.

5,5-*Dimethyl*-12b-*keto*-5,12b-*seco*-1,2,3,4,6,7,12,12b-*octa-hydroindolo*[2,3-a]*quinolizinium iodide* (**9**). A soln of 400 mg of **2**[1] and 5 ml MeI in 50 ml benzene was allowed to stand at 25° for 12 hr. The resulting solid was collected and crystallized from MeOH–ether to give 570 mg (92%) of tiny prisms, m.p. 244–246°. The UV spectrum shows typical 2-acylindole adsorption but, as expected, shows no shift with acid because the lone pair of electrons on N_b is no longer available for this interaction. (Found: C, 50·53; H, 5·77; N, 6·95. $C_{17}H_{23}N_2OI$ requires: C, 51·26; H, 5·82; N, 7·03%).

2-(1-*Keto*-5-*dimethylaminopentyl*)-3-*vinylindole*(**10**)*and* 1-*keto*-3-*methyl*-2-(3-*dimethylaminopropyl*-1,2,3,8-*tetrahydrocyclopent*[b]*indole* (**8**). A soln of 475 mg (1·2 mmole) of **9** and 15 ml 1 M t-BuOK soln in t-BuOH and 15 ml of additional t-BuOH was refluxed under N_2 for 20 hr. The cooled reaction mixture was poured into water and extracted with benzene. The benzene extract was washed, dried and concentrated to give 380 mg of an amber green syrup. Chromatography over activity III neutral alumina gave, with benzene elution, 213 mg of white solid (fraction A). $CHCl_3$ elution gave 115 mg of a yellow oil (fraction B). It is interesting to note that B had a higher R_f value than A when examined by TLC.

Fraction A purified by several crystallizations from hexane to give tiny needles, m.p. 70–71°, or from ether-petroleum ether (30–60°), m.p. 103–104°. The UV spectrum (EtOH) showed 248 mμ (ε 22,600) and 318 mμ (19,200). The IR spectrum had absorption at 3490 cm^{-1} (N—H) and 1648 cm^{-1} (N-Me) and the NMR spectrum had a typical 3-vinylindole-type ABC pattern for the three vinyl protons. The mass spectrum showed the expected parent ion at 270 and was consistent with structure 10 for Fraction A. (Found: C, 75·83; H, 8·30; N, 10·63. $C_{17}H_{22}N_2O$ requires: C, 75·52; H, 8·20, N, 10·36%).

Fraction B crystallized very slowly over a period of months. Crystallization from ether–hexane gave colorless crystal clumps, m.p. 124–125°. The UV spectrum (EtOH) showed absorption at 233 mμ (ε 23,000) and 302 mμ (22,300) in excellent agreement with that of the model compound **12**. The IR spectrum showed 1670 cm^{-1} (C=O) which is the location of the carbonyl band in model compound **12** (see separate entry). The NMR spectrum showed a singlet at 2·27 ppm (N-Me) and a doublet at 1·47 ppm (J = 7 cs; C-Me). The mass spectrum also showed a parent ion peak at 270 These data are in accord with structure **8** for Fraction B. (Found: C, 75·41; H, 8·24; N, 10·41. $C_{17}H_{22}N_2O$ requires: C, 75·52; H, 8·20; N, 10·36%).

Shorter reaction periods (3 hr) led only to the production of **10**. When pure **10** was treated with t-BuOK under the above conditions, it was converted slowly to **8**. This reaction was complete in 4 days and could be easily followed by TLC.

1-*Keto*-1,2,3,8-*tetrahydrocyclopent*[b]*indole* (**12**) was prepared according to the procedure of Jennings.[18] The UV spectrum (EtOH) showed 233 mμ (ε 20,000) and 301 mμ (ε 24,200) [lit.[8] λ_{max}^{MeOH} 234 mμ (ε 20,870) and 300 mμ (ε 28,170)]. The carbonyl absorption in the IR spectrum appeared at 1669 cm^{-1} (lit.[8] 1661 cm^{-1}).

3-*Methyl*-2-(3-*dimethylaminopropyl*)-1,2,3,8-*tetrahydrocyclopent*[b]*indole* (**13**). A mixture of 75 mg of **8**, 400 mg LAH and 25 ml dry N-methylmorpholine was refluxed under N_2 for 3 days after an initial period of stirring for 30 min at 25°. The usual addition of water and NaOH, followed by extraction with $CHCl_3$, gave a nearly quantitative yield of light amber solid. Crystallization from ether-pet ether (30–60°) gave colorless prisms, m.p. 147–148° (another preparation had m.p. 121–122° but showed identical spectra). The UV spectrum (EtOH) has 228 mμ (ε 17,400) and 280 mμ (3600). The NMR spectrum showed a sharp absorption at 2·28 ppm (N-Me's) and a doublet (J = 6·5 cs) at 1·38 ppm (C-Me). The mass spectrum showed the expected parent ion peak at 256 and was fully consistent with the assigned structure. (Found: C, 79·83; H, 9·58; N, 10·69. $C_{17}H_{24}N_2$ requires: C, 79·64; H, 9·44; N, 10·92%).

1,2,3,8-*Tetrahydrocyclopent*[b]*indole* was prepared by the procedure of Perkin and Plant.[20] Crystallization from ether-pet ether (30–60°) gave pure material, m.p. 106–107° (lit.[20] m.p. 108°) and UV (EtOH) 229 mμ (ε 34,000) and 280 mμ (ε 8200) [lit.[21] 229 mμ (ε 26,750) and 280 mμ (ε 5070)].

2-(N-*Methyl*-2-*piperidyl*)-3-*vinylindole* (**15**). A soln of 3·6 g (9·78 mmole) of previously[4] obtained methoidide **16** in 100 ml t-BuOH and 100 ml 1 M t-BuOK in t-BuOH was refluxed under N_2 for 45 hr. The mixture was poured into water and extracted with benzene. The washed and dried benzene extract was concentrated to give 2·7 g of foamy material. TLC showed two compounds. Chromatography over activity III neutral alumina gave, with benzene elution, 1·g (64 ≈) of a light yellow syrup which corresponded to the faster-moving compound on TLC (blue-black major spot). Further benzene elution gave foamy material which corresponded to the slower-moving compound on TLC (dark-brown minor spot). The structure of this minor compound remains unknown but it is likely a degradation product of the major compound since shorter reaction times (1·7 hr; 45% of 15 isolated) showed none of this compound on TLC. Spectral data readily established the structure of the faster-moving compound. The UV spectrum showed typical 3-vinylindole absorption at 228, 261, 283 and 291 mμ. The IR spectrum showed peaks at 3495 cm^{-1}

(N—H) and 1625 cm^{-1} (C=C). The NMR spectrum possessed a typical 3-vinylindole-type ABC pattern at 5·18, 5·65 and 6·93 ppm. The N-Me signal appears at 1·92 ppm.

The reported UV spectrum (EtOH) of 3-vinylindole[14] is 225 mμ (ε 27,500), 253 mμ (ε 13,500), 208 mμ (ε 16,200), 278 mμ (ε 8700), 282 mμ (ε 8900), 289 mμ (ε 7800) and 297 mμ (ε 6300).[17] The vinyl double bond stretching frequency is reported to appear at 1630 cm^{-1} and appears to be characteristic of 3-vinylindoles.[17]

N,N-*Dimethyl*-2-[2-(3-*vinyl*)*indolyl*]*piperidinium iodide*. A soln of 105 mg of **15** and 5 ml MeI in 20 ml benzene was allowed to stand at 25° for 20 hr. The crude solid was purified by several crystallizations from MeOH–ether to afford colorless needles, m.p. 200° dec. The UV spectrum (EtOH) showed 224 mμ (ε 42,900), 250 mμ (ε 12,500), 258 mμ (ε 13,500) and 285 mμ (ε 12,900). (Found: C, 53·66; H, 6·31; N, 7·44. $C_{17}H_{23}N_2I$ requires: C, 53·41; H, 6·06; N, 7·33%).

2-(N-*Methyl*-2-*piperidyl*)-3-*ethylindole*. A mixture of 1·5 g olefin and 0·5 g 5% Pd-$BaSO_4$ in 50 ml EtOH–benzene (1 : 1) was hydrogenated at 25° and 1 atm for 18 hr. Filtration and concentration gave 1·57 g of a light yellow viscous syrup. TLC showed no remaining starting material. The material did not crystallize but spectral data are in accord with the assigned structure. The UV spectrum showed absorption at 232, 274, 282 and 290 mμ. The IR spectrum showed absorption at 2·87 μ (N—H). The NMR spectrum had peaks at 2·23 ppm (N-Me) as a singlet, a triplet at 1·23 ppm (C-Me; J = 7·5 cs) and a quartet at 2·77 ppm (methylene group). This oily material[22] could be characterized as its methiodide prepared below.

The NMR spectrum of 3-ethylindole is given as comparison: A triplet at 1·20 ppm (J = 7·5 cs) (C-Me) and a quartet at 2·63 ppm (J = 7·5 cs) methylene group).

N,N-*Dimethyl*-2-[3-*ethylindol*-2-*yl*]*piperidinium iodide*. A soln of 1·33 g of 76 and 10 ml MeI in 50 ml benzene was allowed to stand at 25° for 2·5 days. The crude yellow powder (1·88 g) was crystallized from MeOH–ether to give 1·71 g of tiny crystals in two crops, m.p. 189–190°. (Found: C, 52·92; H, 6·60; N, 7·40. $C_{17}H_{25}N_2I$ requires: C, 53·13; H, 6.56; N, 7·29%).

2-[2-(N-*methylpiperidyl*)]*indole* (**17**). A soln of 300 mg of **15** and 20 ml 5% NaOH aq in 20 ml 50% aqueous EtOH was refluxed for 3·5 days under N_2. The amber soln was extracted with benzene. After washing and drying, concentration gave 200 mg of a dark semi-solid residue. Filtration through activity III neutral alumina, with benzene elution, gave 105 mg (39%) of a light amber syrup. TLC showed a single light brown spot. The material crystallized on standing and could be purified by crystallization from hexane, m.p. 75–76°. The NMR spectrum showed a sharp singlet at 2·03 ppm (N-Me) and a doublet (J = 2 cs) at 6·33 ppm (3-indole proton).

This material was identical to authentic material (TLC and IR) prepared via amine **18**.

2-(2-*Pyridyl*)*indole* was prepared according to the procedure of Sugasawa, *et al.*[23]

2-(2-*Piperidyl*)*indole* (**18**). To a soln of 4·47 g 2-(2-pyridyl)indole and 250 ml dry EtOH (fresh bottle of commercial anhyd EtOH was satisfactory) was added about 25 g Na sodium (pellets) in portions so as to keep the soln at reflux. The addition took about 1–2 hr. Towards the end of the addition of Na additional external heat was required to dissolve all of the metal. The soln was heated for an additional 1 hr ar reflux and then allowed to cool. The solid mass (EtONa) was added to water and extracted with benzene. The organic extract was washed well with water, dried and concentrated to afford 4·27 g (93%) of a white solid. Crystallization from ether or pet ether (30–60°) gave pure material as fluffy colorless needles, m.p. 128–129°. TLC showed only a yellow-brown spot with lower R_f than starting material. The UV spectrum (EtOH) exhibited 266 mμ (ε 6600), 279 mμ (ε 5700) and 288 mμ (ε 3700). The NMR spectrum showed absorption at 6·32 ppm (3-indole proton) and typical indole aromatic and piperidine absorption. The indole N—H appeared at 9·2 ppm. The IR spectrum exhibited sharp absorption at 3490 cm^{-1} (indole N—H). (Found: C, 78·21; H, 8·12; N, 13·76. $C_{13}H_{16}N_2$ requires: C, 77·96; H, 8·05; N, 13·99%).

2-[2-(N-*Carboethoxypiperdyl*)]*indole* (**19**). A soln of 700 mg 2-(2-piperidyl) indole in 25 ml CH_2Cl_2 and 1 ml pyridine was cooled to 0° and treated with 0·3 ml ethyl chlorocarbonate. The resulting mixture was stored at 0° overnight and processed in the usual manner. The crude urethan was crystallized from benzene–hexane to afford 681 mg of pure material m.p. 149–151°. (Found: C, 70·40; H, 7·64; N, N, 10·55. $C_{16}H_{22}N_2O_2$ requires: C, 70·56; H, 7·40; N, 10·29%).

2-[2-(N-*methylpiperidyl*)]*indole* (**17**)*from urethan* **19**. A sample of **19** was reduced with LAH hydride in THF soln to afford after the usual workup a sample of pure 2-[2-(N-methylpiperidyl)]indole m.p. 76–78° (lit.[23] m.p. 154°) which was identical with the material obtained from the 3-vinylindole 15.* (Found: C, 78·28; H, 8·45; N, 13·28. $C_{14}H_{18}N_2$ requires: C, 78·46; H, 8·47; N, 13·07%).

* Polymorphism is probably responsible for the large melting point difference between our preparation of 2-[2-(N-methylpiperidyl)] indole and that prepared by Sugasawa *et al.*[23]

3-(1-*Cyanoethyl)indole.*† A soln of 3-vinylindole (800 mg), prepared by the method of Noland and Sundberg,[14] 600 mg NaCN in 140 ml 70% EtOH–water was refluxed overnight. The usual, processing afforded a mixture from which 3-(1-cyanoethyl)indole, 330 mg (60%) could be isolated by chromatography over alumina. The 3-(1-cyanoethyl) indole, m.p. 48–52°, obtained in this manner showed m.p. 58–60·5° after crystallization from benzene. The UV spectrum showed normal indole absorption and the NMR spectrum showed a doublet (3H) at 1·64 ppm and a quartet at 4·08 ppm (1H). The IR spectrum exhibited a peak at 2250 cm^{-1} (C≡N). The same compound was obtained by treating 3-(1-piperidylethyl) indole prepared by the procedure of Albright and Snyder,[27] with MeI and then NaCNaq. (Found: C, 77·32; H, 5·93; N, 16·41. $C_{11}H_{10}N_2$ requires: C, 77·62; H, 5·92; N, 16·46%).

* This experiment was performed by Mrs. Zahra Esfandiari.

REFERENCES

[1] L. J. Dolby and G. W. Gribble, *J. Org. Chem.* **32**, 1391 (1967).
[2] J. A. Ballantine, C. B. Barrett, R. J. Beer, R. G. Boggiano, S. Eardly, B. E. Jennings and A. Robertson, *J. Chem. Soc.* 2227 (1957).
[3] M. Gorman, N. Neuss, N. J. Cone and J. A. Deyrup, *J. Am. Chem. Soc.* **82**, 1142 (1960).
[4] B. Douglas, J. L. Kirkpatrick, B. P. Moore and J. A. Weisbach, *Austral. J. Chem.* **17**, 246 (1964).
[5] M. F. Bartlett, R. Sklar, A. Smith and W. I. Taylor, *J. Org. Chem.* **28**, 2197 (1963).
[6] L. J. Dolby and S. Sakai, *Tetrahedron* **23**, 1 (1967).
[7] J. A. Weisbach and B. Douglas, *Chem. & Ind.* 623 (1965).
[8] L. J. Dolby and D. L. Booth, *J. Org. Chem.* **30**, 1550 (1965).
[9] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Am. Chem.* **82**, 2184 (1960).
[10] Unpublished observations of Dr. P. D. Lord.
[11] H. Budzikiewicz, C. Djerassi, and D. H. Williams, *Mass Spectrometry of Organic Compounds*, p. 134. Holden-Day, San Fransisco, California (1967).
[12] J. Levy, G. Ledouble, J. LeMan and M.-M. Janot, *Bull. Soc. Chim. Fr.* 1917 (1964).
[13] U. Renner, D. A. Prins, A. L. Burlingame and K. Biemann, *Helv. Chim. Acta* **46**, 2186 (1963).
[14] W. E. Noland and R. J. Sundberg, *J. Org. Chem.* **28**, 884 (1963).
[15] K. F. Jennings, *J. Chem. Soc.* 497 (1957).
[16] T. Shiouri, K. Ishizumi and S. Yamada, *Chem. Pharm. Bull.* **15**, 1010 (1967).
[17] E. Leete, *J. Am. Chem. Soc.* **81**, 6023 (1959).
[18] J. C. Powers, *Tetrahedron Letters* 655 (1965).
[19] R. J. Gritter and T. J. Wallace, *J. Org. Chem.* **24**, 1951 (1959).
[20] W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.* **123**, 3242 (1923).
[21] F. Walls, O. Collera and A. Sandoval, *Tetrahedron* **2**, 173 (1958).
[22] British Patent 804,786: *Chem. Abstr.* **53**, 16160h (1959).
[23] S. Sugasawa, M. Terashima, and Y. Kanaoka, *Pharm. Bull. (Japan)*, **4**, 16 (1956).
[24] J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.* **81**, 2239 (1959).