Synthesis of 1-(2-Ethyl-3-indolyl)-1-(3-pyridyl)ethylene and Related Ellipticine Analogues

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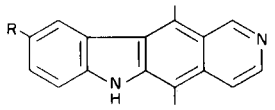
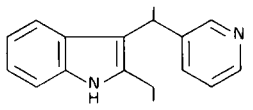
Indole, 2-methylindole, and 3-ethylindole have been condensed with acetyl- and propionylpyridine, respectively. When propionylpyridine was used as the reactant, the product always was a 1-(pyridyl)-1-indolylpropylene. Condensation of 2-substituted indoles with 3-acetylpyridine gave similar products, whereas a similar condensation with 4-acetylpyridine gave 1,2-bis(3-indolyl)-1-(4-pyridyl)ethanes (*e.g.* **7a**). Condensation of unsubstituted indole with 3- or 4-acetylpyridine respectively, gave 1,1-bis(3-indolyl)-1-(pyridyl)ethanes (*e.g.* **6c**).

Recent interest in the antitumour properties (1-3) of the indole alkaloids ellipticine (**1a**) and 9-methoxyellipticine (**1b**), has resulted in the synthesis of various structural analogues (3-6). This paper describes the synthesis of some analogues of the types **2** and **3**.



1

a R = H
b R = OCH_3



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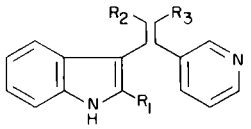
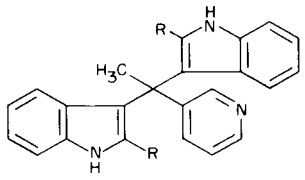


3

a $R_1 = R_2 = R_3 = H$
b $R_1 = CH_3$, $R_2 = R_3 = H$
c $R_1 = C_2H_5$, $R_2 = R_3 = H$
d $R_1 = H$, $R_2 = CH_3$, $R_3 = H$
e $R_1 = R_2 = H$, $R_3 = CH_3$
f $R_1 = C_2H_5$, $R_2 = H$, $R_3 = CH_3$
g $R_1 = C_2H_5$, $R_2 = CH_3$, $R_3 = H$



4

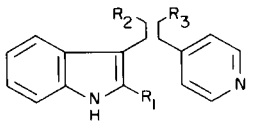
a R = H
b R = CH_3
c R = C_2H_5

In the first step in the ellipticine synthesis by Woodward *et al.* (7), indole is condensed with 3-acetylpyridine in acetic acid in the presence of zinc chloride (8). The product is a 1:2 condensation product, 1,1-bis(3-indolyl)-1-(3-pyridyl)ethane (**4a**), with compound **3a** as a plausible, but never isolated, intermediate (9). We have found that the compounds **3b** and **3c** are the products when 2-methylindole and 2-ethylindole, respectively, are condensed with 3-acetylpyridine (*cf.* ref. 9). The compounds **4b** and **4c** were not formed even when the 2-alkylindoles were used in excess. Steric hindrance of the 2-substituent readily accounts for this.

Catalytic hydrogenation of **3c** gave 2. The latter compound could be prepared without isolation of **3c**, if the condensation step was followed by a formate ion reduction step:

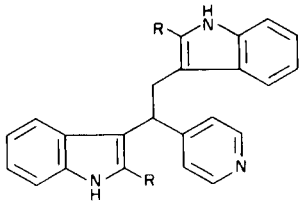
$$\mathbf{3c} \xrightarrow[195°/4h]{HCOO^-} \mathbf{2}$$

Condensation of 4-acetylpyridine with 2-ethylindole did not afford the 1:1 product **5b**, but the 1:2 product (10) **7b**. The isomeric 1:2 product, **6b**, was not formed.



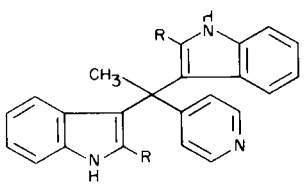
5

a $R_1 = CH_3$, $R_2 = R_3 = H$
b $R_1 = C_2H_5$, $R_2 = R_3 = H$
c $R_1 = C_2H_5$, $R_2 = H$, $R_3 = CH_3$
d $R_1 = C_2H_5$, $R_2 = CH_3$, $R_3 = H$
e $R_1 = R_2 = H$, $R_3 = CH_3$
f $R_1 = R_3 = H$, $R_2 = CH_3$



7

a R = CH_3
b R = C_2H_5
c R = H



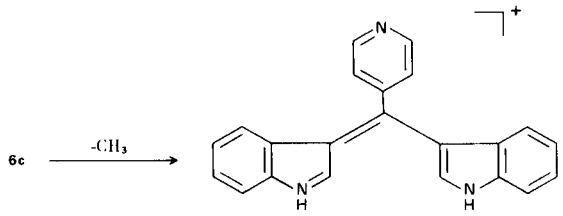
6

a R = CH_3
b R = C_2H_5
c R = H

A similar condensation with 2-methylindole gave **7a**. The compounds **5a** and **5b**, which could not be isolated, are plausible intermediates in the formation of **7a** respectively **7b**, and it is suggested that the 2-alkylindoles add to the 4-vinylpyridine moiety of **5a** and **5b** in much the same way as indole adds to 4-vinylpyridine or 2-vinylpyridine (11).

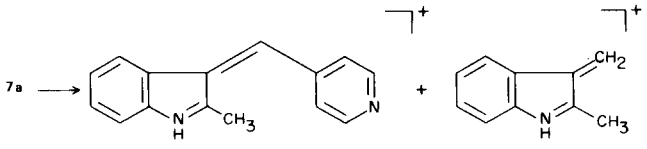
Condensation of 4-acetylpyridine with unsubstituted indole gave **6c** (12). The isomer **7c** could not be isolated. Condensation of 4-propionylpyridine with indole gave **5e** or its *cis-trans*-isomer **5f** (13). 4-Propionylpyridine and 2-ethylindole similarly gave **5c** or **5d**. Analogous products were produced from the condensation of 2-ethylindole with 2- and 3-propionylpyridine, respectively.

From these examples it is clear that introduction of alkyl substituents in the reactants has a powerful influence on the type of product formed.



m/e 322

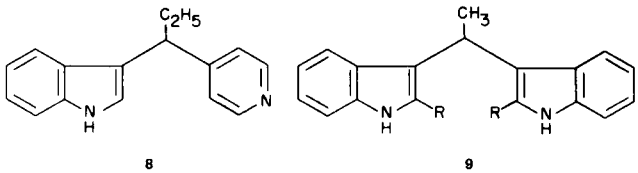
The structure of the new condensation products were proven by their nmr and mass spectra (see Experimental). The fragmentation pattern of the 1,1-(3)-indolyl- and 1,2-(3)-indolylethane derivatives (*e.g.* **6c** and **7a**) were strikingly different. Thus the spectrum of **6c**, which was nearly identical with that of **4a**, showed a dominant base peak corresponding to the M-15 ion, whereas the most intense peaks in the spectrum of **7a** were produced by α-cleavage as shown in Scheme **1** (14). The peak corresponding to the M-15 ion was negligible (less than 1% of the base peak).



SCHEME 1

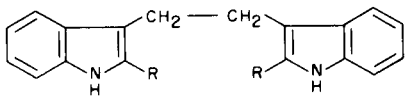
Peaks produced by loss of the pyridine moiety from the molecular ion represented a minor fragmentation pathway for compounds **4** and **6**, but were absent in the spectrum of **7**.

The general fragmentation pattern of **2** and **8** was similar to that of **4** and **6**. Less complicated 3-indolylethane derivatives could also easily be differentiated. Thus the spectrum of **10** showed a dominant base peak corresponding to the M/2 ion, whereas the base peak from **9** was produced by the M-15 ion.



8 **9**

a R = H
b R = CH_3



10

a R = H
b R = CH_3

EXPERIMENTAL

Melting points were determined on a micro hot stage and are uncorrected. Nmr spectra were determined with a Varian A-60 A spectrometer, using $DMSO_{d6}$ as solvent and TMS as internal standard.

Mass spectra were recorded with an LKB 9000 A instrument, using the direct inlet technique. The electron energy was 70 eV.

1-(2-Ethyl-3-indolyl)-1-(3-pyridyl)ethylene (**3c**).

A solution of 2-ethylindole (14.5 g., 0.1 mole) and 3-acetylpyridine (12.1 g., 0.1 mole) in acetic acid (60 ml.) was refluxed for 24 hours. After cooling the solution was poured into aqueous sodium hydroxide (600 ml., 7%). The solid formed was dissolved in hot methanol. The crystals formed on cooling were recrystallized from toluene (with final cooling to -40°), yield, 13.5 g. (55%), m.p. 149-151°; nmr: (τ) 8.72 (t, 3, CH_3); 7.30 (q, 2, CH_2); 4.53 and 4.14 (2d, 2, $>=\langle^{H}_{H}$), J = 1.8 Hz; -0.9 (broad s, 1, NH).

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5; N, 11.3. Found: C, 82.1; H, 6.4; N, 11.1.

The following compounds were prepared similarly to **3c**.

1-(2-Methyl-3-indolyl)-1-(3-pyridyl)ethylene (**3b**).

Yield, 48%, m.p. 164-165°; nmr: (τ) 7.61 (s, 3, CH_3); 4.56 and 4.22 (2d, 2, $>=\langle^{H}_{H}$), J = 1.8 Hz; -0.9 (broad s, 1, NH).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 81.9; H, 5.8; N, 12.0.

1-(2-Ethyl-3-indolyl)-1-(3-pyridyl)propylene (**3f** or **3g**).

Yield, 45% (15), m.p. 147-149°; nmr: (τ) 8.82 (t, 3, CH_3); 8.35 (d, 3, CH_3), $J_{CH_3\text{-}H}$ = 6.9 Hz; 7.52 (q, 2, CH_2); 3.56 (q, 1, $>=\langle^{R}_{H}$), $J_{H\text{-}CH_3}$ = 6.9 Hz; -0.8 (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.0; H, 6.9; N, 10.8.

1-(3-Indolyl)-1-(3-pyridyl)propylene (**3d** or **3e**).

Yield, 53% (15), m.p. 182-184°; nmr: (τ) 8.15 (d, 3, CH_3); 3.77 (q, 1, >=$\langle^{R}_{H}$), $J_{CH_3\text{-}H}$ = 6.9 Hz; -0.9 (broad s, 1, NH).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 82.0; H, 6.0; N, 12.0.

1-(2-Ethyl-3-indolyl)-1-(4-pyridyl)propylene (**5c** or **5d**).

Yield, 58% (15), m.p. 160-161°; nmr: (τ) 8.82 (t, 3, CH_3); 8.35 (d, 3, CH_3), $J_{CH_3\text{-}H}$ = 6.9 Hz; 7.52 (q, 2, CH_2); 3.40 (q, 1, >=$\langle^{R}_{H}$), $J_{H\text{-}CH_3}$ = 6.9 Hz; -1.1 (broad s, 1 NH).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.1; H, 6.9; N, 10.7.

1-(3-Indolyl)-1-(4-pyridyl)propylene (**5e** or **5f**).

Yield, 47% (15), m.p. 188-189°; nmr (τ) 8.19 (d, 3, CH_3), $J_{CH_3\text{-}H}$ = 6.9 Hz; 3.53 (q, 1, >=$\langle^{R}_{H}$), $J_{H\text{-}CH_3}$ = 6.9 Hz; -0.8 (broad s, 1, NH).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 81.9; H, 6.1; N, 12.0.

1-(2-Ethyl-3-indolyl)-1-(2-pyridyl)propylene.

Yield, 51% (15), m.p. 153-154°; nmr (τ) 8.82 (t, 3, CH_3); 8.35 (d, 3, CH_3), $J_{CH_3\text{-}H}$ = 6.9 Hz; 7.52 (q, 2, CH_2); 3.45 (q, 1, >=$\langle^{R}_{H}$), $J_{H\text{-}CH_3}$ = 6.9 Hz; -1.0 (broad 2, 1, NH).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.2; H, 6.9; N, 10.7.

1-(2-Ethyl-3-indolyl)-1-(3-pyridyl)ethane (**2**).

Method A.

Compound **3c** (3.0 g.) in ethanol (100 ml.) was hydrogenated over 5% PD/C using standard conditions (15), yield, 2.8 g. (93%), m.p. 139-141°.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.6; H, 7.3; N, 11.2. Found: C, 81.7; N, 7.1; N, 11.0.

Method B.

A solution of 2-ethylindole (14.5 g., 0.1 mole) and 3-acetylpyridine (12.1 g., 0.1 mole) in acetic acid (100 ml.) was refluxed for 24 hours. Formic acid (30 g.) and triethylamine (20 g.) were then added and the temperature increased to 195° by evaporation of solvent. After 4 hours at 195° the mixture was allowed to cool and then worked up as described for **3c** (15), yield, 59%; nmr: (τ) 8.78 (t, 3, CH_3); 8.25 (d, 3, CH_3); 7.27 (q, 2, CH_2); 5.51 (q, 1, CH); -0.8 (broad s, 1, NH); mass spectrum: 251 (10, M + 1), 250 (53, M), 235 (100), 236 (20), 221 (11), 220 (5), 219 (16), 172 (10, M - 78), 143 (4). Only peaks stronger than 3% of the base peak are listed.

1-(3-Indolyl)-1-(4-pyridyl)propane (**8**).

Procedure A above was used, yield, 72%, m.p. 169-170°; mass spectrum: 237 (6, M + 1), 236 (31), 208 (16), 207 (100), 206 (8), 205 (7), 180 (4), 158 (2), 152 (3), 103 (5). Only peaks stronger than 1% of the base peak are listed.

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.3; H, 6.8; N, 11.9. Found: C, 81.2; H, 6.9; N, 11.8.

1,1-Bis(3-indolyl)-1-(4-pyridyl)ethane (**6c**).

Indole (0.2 mole) and 4-acetylpyridine (0.1 mole) were refluxed in acetic acid (100 ml.) for 24 hours. After cooling the mixture was poured into aqueous sodium hydroxide (800 ml., 7%). The solid formed was extracted with acetonitrile. After evaporation of the extract the residue was crystallized twice from 85% ethanol, yield, 13 g. (39%), m.p. 223-224°; nmr: (τ) 7.69 (s, 3, CH_3); -0.6 (s, 2, 2 NH); mass spectrum: 338 (10, M + 1), 337 (39, M), 323 (24), 322 (100), 260 (3), 259 (16, M - 78), 243 (5), 205 (2), 168.5 (7, M^{2+}), 161.5 (4), 161 (9, $(M\text{-}15)^{2+}$); m*: 308 (337 → 322). Only peaks stronger than 2% of the base peak are given.

The residue from the acetonitrile extraction recrystallized from acetonitrile gave a product (m.p. >360°) whose mass spectrum (M = 440) indicates a 2:2-condensation product.

Anal. Calcd. for $C_{23}H_{19}N_3$: C, 81.9; H, 5.7; N, 12.5. Found: C, 81.6; H, 5.7; N, 12.4.

1,1,Bis-(3-indolyl)-1-(3-pyridyl)ethane (**4a**).

Indole (0.2 mole) and 3-acetylpyridine (0.1 mole) were refluxed in acetic acid (100 ml.) for 24 hours. After cooling the mixture was poured into aqueous sodium hydroxide (800 ml., 7%). The solid formed was recrystallized from 75% ethanol, yield, 23 g. (68%), m.p. 251-252° (lit. (7) 253 dec.); mass spectrum: 338 (9, M + 1), 337 (37, M) 323 (25), 322 (100), 260 (2), 259 (9, M - 78), 243 (5), 205 (4), 168.5 (5, M^{2+}), 161.5 (4), 161 (10, $(M\text{-}15^{2+})$; m*: 308 (337 → 322). Only peaks stronger than 2% of the base peak are listed. Nmr: (τ) 7.66 (s, 3, CH_3); -0.6 (2s, 2, 2 NH).

The following two compounds were prepared using the procedure described for **4a**.

1,2-Bis(2-methyl-3-indolyl)-1-(4-pyridyl)ethane (**7a**).

Yield, 70%, m.p. 262-263°; nmr: (τ) 8.25 (s, 3, CH_3); 8.08 (s, 3, CH_3); 6.40 (d, 2, CH_2); 5.51 (t, 1, CH); -0.2 (s, 1, NH); -0.4 (s, 1, NH); mass spectrum: 366 (1, M + 1), 365 (3, M), 364 (1), 363 (3), 223 (17), 222 (100), 221 (23), 220 (3), 219 (5), 206 (1), 205 (2), 204 (2), 203 (2), 145 (7), 144 (54), 143 (9), 129 (3), 115 (3), 77 (5). Only peaks stronger than 1% of the base peak are listed.

Anal. Calcd. for $C_{25}H_{23}N_3$: C, 82.1; H, 6.3; N, 11.5. Found: C, 82.0; H, 6.5; N, 11.5.

1,2-Bis(2-ethyl-3-indolyl)-1-(4-pyridyl)ethane (**7b**).

Yield, 75%, m.p. 256-258°; nmr: (τ) 9.26 (t, 3, CH_3); 9.22 (t, 3, CH_3); 7.80 (m, 4, 2 CH_2); 6.41 (d, 2, CH_2); 5.45 (t, 1, CH); -0.2 (s, 1, NH); -0.4 (s, 1, NH); mass spectrum: 393 (1, M), 250 (2), 248 (3), 237 (18), 236 (100), 235 (19), 333 (4), 221 (7), 220 (5), 219 (8), 218 (2), 159 (7), 158 (46), 144 (6), 143 (14), 130 (6). Only peaks stronger than 1% of the base peak are listed.

Anal. Calcd. for $C_{27}H_{27}N_3$: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.0; H, 7.0; N, 10.8.

1,2-Bis(2-methyl-3-indolyl)ethane (**9b**).

Boron trifluoride etherate (10.0 g.) in diglyme (30 ml.) was added dropwise with stirring to bis-(2-methylindol-3-yl)glyoxal (16) (3.16 g.) and sodium borohydride (2.0 g.) in diglyme (100 ml.) at 25°. After completed addition the temperature was raised to 80° for 2 hours. Water (300 ml.) was then added slowly while stirring to the cooled reaction mixture. The solid formed was collected and recrystallized from dichloromethane, yield, 2.4 g. (84%), m.p. 220-221° (lit. (16) 220-222°; mass spectrum: 289 (3, M + 1), 288 (17, M), 145 (22), 144 (100), 143 (9), 128 (1), 115 (2), 103 (2), 78 (3). Only peaks stronger than 1% of the base peak are listed.

1,2-Bis(3-indolyl)ethane (**9a**).

The same procedure as for **9b** was used. The starting material bis(indolyl-3-yl)glyoxal, was prepared as described by Zee (17), yield, 80%, m.p. 256-257° (lit. (17) 258-259°); mass spectrum: 261 (2, M + 1), 260 (15, M), 131 (26), 130 (100), 129 (12), 103 (8), 78 (5). Only peaks stronger than 1% of the base peak are listed.

1,1,Bis(2-methyl-3-indolyl)ethane (**10b**).

2-Methylindole and paraldehyde were condensed as described by Fischer (18, 15), yield, 74%, m.p. 210-212° (lit. (18, 17), 191°, 210-212°), mass spectrum: 289 (8, M + 1), 288 (42, M), 287 (7), 274 (20), 273 (100), 257 (11), 158 (9), 157 (54), 156 (26), 144 (8), 131 (42), 130 (60).

1,1,Bis(3-indolyl)ethane (**10a**)

This compound was prepared as described earlier (19), m.p. 161-162° (lit. (19) 161-162°); mass spectrum: 261 (10, M + 1), 260 (53, M), 259 (12), 246 (22), 245 (100), 218 (19), 217 (18), 144 (5), 123 (11), 122.5 (16), 122 (7). Only peaks stronger than 5% of the base peak are listed.

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(8) We have, however, found that omission of zinc chloride gives a more pure product.

(9) Condensation of 2-methylindole with acetophenone gives 1-(2-methyl-3-indolyl)-1-phenylethylene in a reasonable yield. M. S. Fawcett and W. E. Noland [quoted by D. C. Johnson, *Dissertation, University of Minnesota, Minneapolis*, p. 6 (1962)].

(10) Compound **5b** could not be isolated even when 4-acetylpyridine was used in excess.

(11) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, 79, 3554 (1957).

(12) A 2:2 product was also isolated, but its structure has not been elucidated.

(13) Catalytic hydrogenation gave **8**.

(14) The base peak appeared, however, at m/e 222. To account for this a McLafferty rearrangement is suggested.

(15) The crude solid was crystallized from acetonitrile.

(16) A. N. Yao, *M. S. Thesis, University of Minnesota, Minneapolis*, (1963).

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