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SYNTHESIS AND REACTIONS OF SOME 3-(2-HALOACYL)INDOLES

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Abstract The reaction between indole and N-(2-haloacyl)pyridinium salts has been studied. With dioxan as solvent 1-(2-haloacyl)indole (2) was generally the product at low temperatures and 3-(2-haloacyl)indole (1) at high temperatures, as illustrated by the following α-bromopropionylation. Product ratio (1c/2a): 20° (0·01), 40° (0·8) and 60° (8·5). The fact that the α-bromobutyrylation at 60° gave 3-(N-(2-bromobutyryl)-1,4-dihydro-4-pyridyl)indole (6) as the main product, and 3-(2-bromobutyryl)indole (1d) only as a minor product, shows that the 3-acylation is affected by steric hindrance.

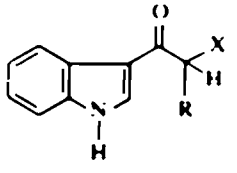
At high reaction temperature (> 60°) the yield of 1 decreased, owing to the formation of 3-indacylpyridinium salts (4).

It has recently been shown[1] that indole reacts with N-(α-chloroacyl)pyridinium salts to give α-chloro substituted 3-acylindoles, *e.g.* 3-chloroacetylindole (1a). Such compounds are of interest as starting materials in the synthesis of tryptamines[2,3] and several indole alkaloids.[4] Alternative starting materials such as indole 3-glyoxylyl chloride[5] and tryptophyl bromide,[6,7] have so far been used more frequently, owing to the relative inaccessibility of 3-(2-haloacyl)indoles.

The present study was undertaken in order to define more closely the scope and limitation of the reaction of N-(α-haloacyl)pyridinium salts with indole and to briefly study the possibility of using 3-(2-haloacyl)indoles as synthetic building blocks.

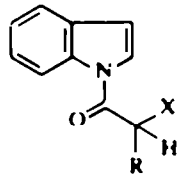
The reactions were carried out essentially as described earlier, *i.e.* slow addition of the α-haloacyl halide to pyridine and indole in dioxan or in some cases in toluene. The desired 3-isomer (1) was often accompanied by the 1-isomer (2). The isomers, which could easily be separated were assigned by IR spectroscopy. The assignations were further evidenced by NMR spectroscopy (Experimental).

The yield of the 3-isomer (1) increased, whereas the yield of the 1-isomer (2) decreased with increasing temperature. For the α-bromopropionylation of indole in dioxan the following product ratios (1c/2a) were determined: 20° (0·01), 40° (0·8), 60° (8·5). The 1-isomer could not be transformed



1

a R = H, X = Cl
b R = CH_3, X = Cl
c R = CH_3, X = Br
d R = Et, X = Br
e R = X = Cl
f R = Ph, X = Cl
g R = CH_3, X = N_3
h R = Et, X = N_3
i R = H, X = N_3



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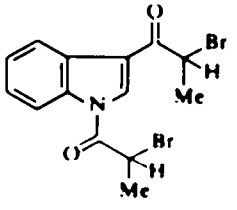
b R = Et, X = Br



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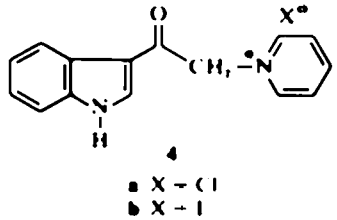

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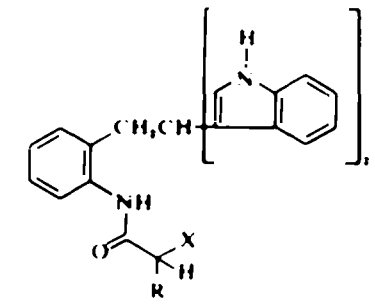
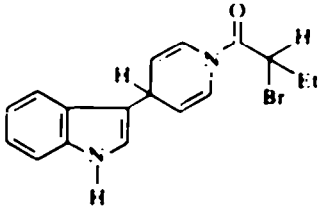
b X = I



5

a R = X = H
b R = X = Cl
c R = Me, X = Cl
d R = Me, X = Br
e R = Et, X = Br
f R = Ph, X = Cl



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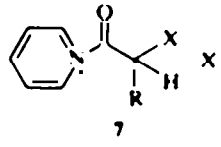

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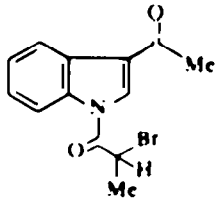

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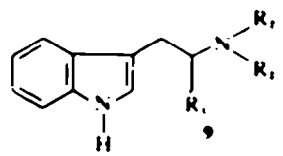
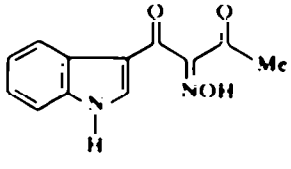


9

a R_1 = Me, R_2 = H
b R_1 = Et, R_2 = H
c R_1 = R_2 = Me
d R_1 = Ph, R_2 = Me
e R_1 = R_2 = H



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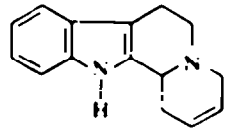

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CHART 1

into the 3-isomer by heating (70° 4 hr). At 30° and below, the 1-isomer was generally the dominant product. The best yields (40–80%) of the 3-isomers were obtained in the temperature range 55–60°. The small amounts of accompanying 1-isomers were easily removed by recrystallization or column chromatography. 1,3-Diacylated indoles could not be detected (TLC).

Strongly electron-deficient acyl halides seem, however, to be exceptional, judging by the fact that 3-dichloroacetylindole was the high-yield product from the reaction of indole with a pyridine-dichloroacetyl chloride reagent even at low (0°) temperatures. The same applies to trichloroacetyl chloride.

At high reaction temperatures (> 60°) the yield of the 3-(2-haloacyl)indole decreased, owing to the formation of 3-indacylpyridinium salts (4) and tars. Haloketene formation, with subsequent polymerisation, is suggested as one possible reason for the tar formation.

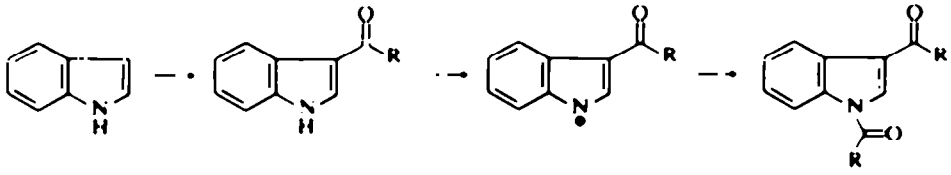
N-Acylated indole trimers (5) were formed as

by-products if pyridine was omitted or used in deficit relative to the α-haloacyl halide. The N-acylated trimers could often be isolated in excellent yields. 1-Acylindoles were formed as by-products. One exception was noted. The reaction between indole and trichloroacetyl chloride resulted in 3-trichloroacetylindole, whereas a similar reaction between indole and dichloroacetyl chloride gave the N-acylated trimer (5b). A semi-solid mass containing acylated indole oligomers, 1-acetylindole (*cf* Ref 8), was formed from indole and acetyl chloride. The reaction of indole and chloroacetyl chloride produced a similar mixture, but none of its components have been characterized.

In connection with these studies we have found that the nonacylated trimer (triindole) could be conveniently prepared by trimerization of indole by trifluoroacetic acid.

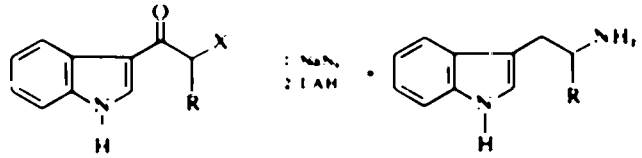
The results indicate that at least two competing reactions are operative. Bulky substituents in the starting acyl halide seem to decrease the rate of 1-acylation and thus favour the oligomerization. The influence of steric hindrance on the 3-acylation as well is apparent from the following example: Acylation of indole with a pyridine-α-bromopropionyl bromide reagent at 60° gave a good yield of 1c whereas attempted acylation with a pyridine-α-bromobutyryl bromide reagent at the same temperature yielded compound 6 as the main product, compound 1d being only a minor product. This example shows that a subtle balance between steric and electronic effects determines the reactivity of the essentially ambident reagent (7).

Replacement of pyridine with the much stronger base N-methylpiperidine gave 1,3-diacylindole as the readily isolated, main product. 1-Acylindole was a by-product. 3-Acylindoles, but not 1-acylindoles, could be substituted for indole as starting material in this synthesis. These facts suggest the following reaction mechanism:



1,3-Diacylindoles with different acyl groups (*e.g.* 8) could readily be prepared by this route.

The 3-(2-haloacyl)indoles could, *via* 3-(2-aminoacyl)indoles, be transformed to the corresponding tryptamines.[3] The first step was markedly catalyzed by iodide ions. Uncatalysed substitutions with bulky amines (e.g. diethylamine) were slow, especially with α-alkyl-substituted 3-(2-haloacyl)-indoles. For the synthesis of primary tryptamines this route is inconvenient, owing to formation of several (unidentified) by-products in the first step. The desired products could, however, be conveniently prepared using the route outlined below.



In connection with the synthesis of 3-(2-aminobutyl)indole (9b) *via* this route, the reduction of the oxime (10) with LAH was considered as an alternative route. The yield of the desired tryptamine (9b) was, however, low (20%).

3-Chloroacetylindole reacted at higher temperatures with pyridine, as reported by Sanna,[9] to give 3-indacylpyridinium chloride (4a). Attempts to prepare 4a in one step from indole, pyridine and chloroacetyl chloride, with pyridine as solvent, have so far given considerably lower yields. 3-Indacylpyridinium chloride (4a) could be reductively cyclized to 11, by applying the conditions described by Potts and Liljegren.[4] The starting material (4b) used by these authors was prepared *via* a King reaction from 3-acetylindole.

The nitrogen analyses of the azides (1g and 1h) were, not unexpectedly,[10] low (1%), and for this reason their mass spectra were recorded. The peak from the molecular ion was intense relative the peak corresponding to the M-28 ion (*cf* Ref 11), especially for compound 1g. The dominant base peak was produced by the ion $C_9H_6NO^+$ (*m/e* 144), which then lost[12-14] CO and HCN. The ion $C_9H_6NO^+$ was found to be the base peak for all 3-acylindoles described in this paper.

EXPERIMENTAL

M ps were determined on a microbot stage and are uncorrected. The mass spectra were recorded using an LKB 9000 A instrument, using the direct inlet technique. The electron energy was 70 eV, unless stated otherwise. Only fragment peaks stronger than 5% of the base peak are listed, unless stated otherwise. IR spectra from KBr disks were recorded using a Perkin Elmer No 237 instrument. The NMR spectra were determined with a Varian A60-A

spectrometer DMSO + d_6 was used as solvent unless stated otherwise.

Thin-layer chromatograms were run with CH_2Cl_2 on silica gel GF_{254} (Merck). All R_f values given were determined by TLC.

3-(2-Bromopropionyl)indole (1c). Method A. α-Bromopropionyl bromide (21.6 g, 0.1 mol) was added dropwise during 1 hr to a well-stirred soln of indole (11.7 g, 0.1 mol) and pyridine (8.1 ml, 0.1 mol) in dioxan (100 ml) at 60°. The mixture was stirred for another hr, cooled and poured into water (500 ml). The oil formed was separated and dissolved in MeOH. On standing (1–24 hr) crystals separated. Recrystallization from acetonitrile gave 3-(2-bromopropionyl)indole free from the 1-isomer, yield 15.2 g (60%), m.p. 210–212° (Found: C, 52.2; H, 4.0; N, 5.5; Br, 31.9. Calc. for $C_{11}H_{10}BrNO$: C, 52.4; H, 4.0; N, 5.6; Br, 31.6%); NMR (τ): 8.20 (d, 3, CH_3), 4.31 (q, 1, CH), 2.3 (broad s, 1, NH). IR: 3200 cm^{-1} (NH), 1627 cm^{-1} (C—O). MS: 253 (7.9), 251 (8.4), 145 (11.5), 144 (100), 116 (10.6), 89 (15.2), 63 (11.3). R_f – 0.22.

Method B. Method A was applied, except that dioxan (100 ml) was replaced by toluene (300 ml), yield 18.4 g (72%), m.p. 210–212°.

3-(2-Chloropropionyl)indole (1b). Method A was used, yield 52%, m.p. 193–194° (Lit.[3] 193–194°). NMR (τ): 8.26 (d, 3, CH_3), 4.42 (q, 1, CH), 2.2 (broad s, 1, NH). IR: 3200 cm^{-1} (NH), 1625 cm^{-1} (C—O).

3-(2-Bromobutyryl)indole (1d). Method A was used, substituting the pyridine (0.1 mol) with 2,4,6-trimethylpyridine (0.1 mol). The crude product was recrystallized from MeOH, yield 29%, m.p. 190–191°. If method B was used, yield 44%, m.p. 190–191° (Found: C, 54.0; H, 4.7; N, 5.0; Br, 29.8. Calc. for $C_{12}H_{12}BrNO$: C, 54.1; H, 4.5; N, 5.3; Br, 30.0%). NMR (τ): 8.99 (t, 3, CH_3), 7.90 (m, 2, CH_2), 4.56 (t, 1, CH), 2.2 (broad s, 1, NH). IR: 3202 cm^{-1} (NH), 1614 cm^{-1} (C—O). R_f – 0.30.

3-Dichloroacetylindole (1e). Method A was used, yield 82%, m.p. 246–248 (Lit.[3] 202°). IR (KBr): 3190 cm^{-1} (NH), 1631 cm^{-1} (C—O). MS: 229 (7.9), 227 (12.5), 164 (6.7), 145 (10.7), 133 (100), 116 (14.5), 89 (13.2).

3-(α-Chlorophenylacetyl)indole (1f). α-Chlorophenylacetyl chloride[4] (18.9 g, 0.1 mol) was added dropwise during 1 hr to a well-stirred soln of pyridine (8.1 ml) and indole (11.7 g, 0.1 mol) in toluene (250 ml) at 55°. A brownish oil, which soon solidified, separated during the addition. The mixture was stirred for another hr, whereupon water (300 ml) and MeOH (50 ml) was added. After 1 hr the solid was collected and crystallized from acetonitrile, yield 18.5 g (70%), m.p. 218–220° (lit.[5] 202–204°). (Found: C, 71.2; H, 4.6; N, 5.4; Cl, 13.1. Calc. for $C_{16}H_{12}ClNO$: C, 71.2; H, 4.5; N, 5.2; Cl, 13.1%). MS: 271 (1.1), 269 (3.2), 207 (4.8), 205 (3.6), 145 (9.8), 144 (100), 116 (13.0), 89 (14.7), 63 (5.1). Only peaks stronger than 3% of the base peak are listed.

3-Chloroacetylindole (1a). The same procedure as for 1f was used, yield 48%, after recrystallization from EtOH, m.p. 230–232°, lit.[3] 230–232°.

3-Chloroacetyl-2-methylindole. The same procedure as for 1f was used, yield 75% after recrystallization from acetonitrile, m.p. 220–221°, lit.[6] 220°.

1-(2-Bromopropionyl)indole (2a). Method A as described for 1c was used at 20°. The crude product was recrystallized from MeOH (with final cooling to −20°), yield 75%, m.p. 107–108° (Found: C, 52.4; H, 4.0; N, 5.6; Br, 31.6. Calc. for $C_{11}H_{10}BrNO$: C, 52.4; H, 4.0; N, 5.6; Br, 31.6%). NMR (τ): 8.10 (d, 3, CH_3), 4.29 (q, 1, CH), 3.24 (d, 1, 3-H), 2.03 (d, 1, 2-H). IR: 1682 cm^{-1} (C—O). MS: 253 (14.0), 251 (15.1), 144 (7.7), 118 (11.6), 117 (100), 116 (16.2), 109 (5.5, $C_5H_4Br^+$), 107 (5.8, $C_7H_6Br^+$), 90 (8.6), 89 (17.2), 63 (9.8). R_f – 0.69.

1-(2-Bromobutyryl)indole (2b). The same procedure as for 2a was used, yield 52%, m.p. 91–92° (Found: C, 53.8; H, 4.7; N, 5.1; Br, 30.3. Calc. for $C_{12}H_{12}BrNO$: C, 54.1; H, 4.5; N, 5.3; Br, 30.0%). NMR (τ): 8.92 (t, 3, CH_3), 7.81 (m, 2, CH_2), 4.47 (t, 1, CH), 3.23 (d, 1, 3-H), 1.98 (d, 1, 2-H). IR: 1676 cm^{-1} (C—O). R_f – 0.75.

1,3-Di(2-bromopropionyl)indole (3). Method A, as described for 1c was used, the pyridine being replaced by N-methylpiperidine (22.6 g, 0.2 mol) and the amount of α-bromopropionyl bromide increased to 0.2 mol, yield 28% after recrystallization from acetonitrile, m.p. 181–182°, Lit.[3] 168–170°. 1-(2-Bromopropionyl)indole (yield 19%) could be isolated from the acetonitrile mother liquor. NMR (τ): 8.08 (2d, 6, CH_3), 4.17 (m, 2, CH), 0.87 (s, 1, 2-H). IR: 1721, 1702, 1670, 1654 cm^{-1} (C—O). R_f – 0.55.

In method B, α-bromopropionyl bromide (21.6 g, 0.1 mol) was added dropwise during 1 hr to a well-stirred soln of 3-(2-bromopropionyl)indole and N-methylpiperidine (11.3 g, 0.1 mol) in dioxan (150 ml) at 60°. After further 2 hr the mixture was cooled and poured into water (500 ml). The solid formed was separated and recrystallized from acetonitrile, yield 90%, m.p. 181–182°.

1-(2-Bromopropionyl)-3-acetylindole (8). Method B, as described for 3, was used, starting with 3-acetylindole (0.1 mol). The crude product was recrystallized twice from MeOH (with final cooling to −20°). Yield 17.9 g (61%), m.p. 129–130° (Found: C, 53.3; H, 4.2; N, 4.7; Br, 26.9. Calc. for $C_{13}H_{12}BrNO_2$: C, 53.1; H, 4.1; N, 4.8; Br, 27.2%). NMR ($CDCl_3$) (τ): 8.07 (d, 3, CH_3), 7.53 (s, 3, $COCH_3$), 4.96 (q, 1, CH).

Trindole. In method A, trifluoroacetic acid (5.8 g, 0.05 mol) was added to indole (11.7 g, 0.1 mol) in ether (80 ml). After 2 days at 20° MeOH (10 ml) was added and the solvent slowly removed. Some oil adhering to the crystals formed (10.7 g, m.p. 122–129°) was washed off with ether, and the crystals dissolved in MeOH (40 ml). This soln was added to KOH (3.0 g) in MeOH (40 ml). The mixed soln was poured into water (500 ml), and the ppt formed was collected, dried and crystallized from benzene, yield 8.2 (70%), m.p. 168–170°, Lit.[8] 169–170.5°. R_f – 0.08, (diindole R_f – 0.28).

In method B, indole (11.7 g) and pyridinium chloride (5.0 g) in dioxan (100 ml) were heated (80°) while stirring for 5 hr. The mixture was poured into water (400 ml) and the solid was filtered off, dissolved in EtOH and the soln made alkaline with 0.5 M NaOH. The crude product was purified as described above. The mother liquor contained diindole (TLC), yield 5.7 g (49%), m.p. 168–170°.

Acetyltrindole (5a). In method A, pyridine (8.1 ml) was added at 20–25° to acetyl chloride (7.1 ml) in dioxan (80 ml). After 3 min the ppt of N-acetylpyridinium chloride was filtered off without protective gas. Indole (11.7 g) was dissolved in the filtrate. After 2 hr water (300 ml) was added and the solid formed was crystallized from EtOH, yield 9.5 g (73%), m.p. 210–211°, Lit.[8] 211–212°. NMR (acetone-d_6) (τ): 8.45 (s, 3, CH_3CO), 6.42 (d, 2, CH_2), 5.27 (t, 1, CH).

Acetyltrindole (5a). Method B.

Reaction of indole with acetic-trifluoroacetic anhydride. AcOH (3.0 ml) was added to trifluoroacetic anhydride (10.5 g) in ether (10 ml). Indole (5.85 g) in ether (20 ml) was added at 20° (cooling was not necessary). After 2 days

at 20°, acetyltrindole (2·2 g, 34%) had separated from the dark soln. The solid was crystallized from EtOH, m.p. 210–211°, Lit.[29] 211–212°. The mother liquor contained acetyldiindole and several other compounds as shown by TLC.

Dichloroacetyltrindole (5b). In method A, dichloroacetyl chloride (4·9 g, 0·13 mol) was added dropwise during 1 hr to a well-stirred soln of indole (11·7 g, 0·1 mol) in dioxan (100 ml) at 30°. The mixture was stirred for 4 hr, cooled and the solid collected and washed with water. Recrystallization from EtOH gave dichloroacetyltrindole containing crystal-ethanol, which could be removed by drying at 105°/8 mm, yield 10·4 (68%), m.p. 177–179° (Found: C, 67·7; H, 4·4; N, 9·0; Cl, 15·5. Calc for $C_{20}H_{17}Cl_2N_3O$: C, 67·6; H, 4·6; N, 9·1; Cl, 15·3%).

In method B, trindole was acylated as described by Kuryla,[31] yield: 85%. The following compounds were prepared by method A, as described for 5b.

α-Chloropropionyltrindole (5c), yield 65%, m.p. 167–168° (Found: C, 73·2; H, 5·6; N, 9·6; Cl, 8·0. Calc for $C_{21}H_{19}ClN_3O$: C, 73·5; H, 5·5; N, 9·5; Cl, 8·0%). NMR (τ): 8·41 (d, 3, CH_3), 6·40 (d, 2, CH_2), 5·38 (t, 1, CH), 5·05 (t, 1, CH), 0·4 (s, 1, NH), 0·8 (s, 2, NH).

α-Bromopropionyltrindole (5d), yield 71%, m.p. 148–150° (Found: C, 66·7; H, 4·8; N, 8·6; Br, 16·2. Calc for $C_{21}H_{18}BrN_3O$: C, 66·7; H, 5·0; N, 8·6; Br, 16·4%). NMR (τ): 8·32 (d, 3, CH_3), 6·44 (d, 2, CH_2), 5·34 (t, 1, CH), 5·12 (t, 1, CH), 0·5 (s, 1, NH), 0·7 (s, 2, NH). R_f – 0·12. The mother liquor contained 1-(2-bromopropionyl)-indole.

α-Bromobutyryltrindole (5e), yield 70%, m.p. 155–157° (Found: C, 67·1; H, 4·9; N, 8·5; Br, 16·2. Calc for $C_{22}H_{20}BrN_3O$: C, 67·4; H, 5·2; N, 8·4; Br, 16·0%). NMR (τ): 9·08 (t, 3, CH_3), 8·05 (m, 2, CH_2), 6·41 (d, 2, CH_2), 5·50 (t, 1, CH), 5·08 (t, 1, CH), 0·4 (s, 1, NH), 0·8 (s, 2, NH). R_f – 0·13. The mother liquor contained 1-(2-bromobutyryl)indole.

α-Chlorophenylacetyltrindole (5f), yield 85%, m.p. 160–161° (Found: C, 76·0; H, 5·3; N, 8·3; Cl, 7·2. Calc for $C_{27}H_{22}ClN_3O$: C, 76·1; H, 5·4; N, 8·3; Cl, 7·0%).

3-[N-(2-Bromobutyryl)-1,4-dihydro-4-pyridyl]indole (6). α-Bromobutyryl bromide (0·1 mol) was added to indole (0·1 mol) and pyridine (0·1 mol) in dioxan as described for 1c (Method A). The crude product was recrystallized from EtOH (with final cooling to −20°), yield 28%, m.p. 128–129° (Found: C, 59·7; H, 5·1; N, 8·1; Br, 22·8. Calc for $C_{17}H_{17}BrN_2O$: C, 59·4; H, 5·0; N, 8·1; Br, 23·1%). IR (KBr): 3320 cm^{-1} (NH), 1650 cm^{-1} (C=O), 1628 cm^{-1}. R_f – 0·34.

3-(2-Bromobutyryl)indole formed (8% yield) along with 6 may be isolated by column chromatography of the evaporated methanolic mother liquor obtained.

Indacylpyridinium chloride (4a). A mixture of 3-chloroacetylindole (9·7 g, 0·05 mol) and pyridine (60 ml) was heated at 80° for 0·5 hr. On cooling of the clear soln obtained, crystals of 4a separated, yield 18·7 g (69%), m.p. 252–254°, Lit.[9] 258°.

3-(2-Azidopropionyl)indole (1g). 3-(2-Bromopropionyl)-indole (8·4 g) was added in 10 portions during 15 min to a well-stirred suspension of sodium azide (3·3 g) in DMSO (40 ml) at 25°. After completed addition the mixture was stirred for 2 hr, and then poured into water (400 ml) and the mixture extracted with ether. The ether phase was washed with water, dried and evaporated. The residue recrystallized from ether–light petroleum gave 5·2 g (73%), m.p. 125–126° (Found: C, 61·7; H, 4·8; N, 25·1. Calc for $C_{11}H_{10}N_4O$: C, 61·7; H, 4·7; N, 26·1%). MS: 214 (4·2), 186 (1·5), 145 (9·7), 144 (100), 116 (14·1), 115 (3·1), 89 (13·5), 63 (5·0), 62 (3·2), 28 (3·2). Only peaks stronger than 3% of the base peak, except the M-28 peak, are given. IR: 3220 cm^{-1} (NH), 2120 cm^{-1} (N_3), 2085 cm^{-1} (N_3), 1630 cm^{-1} (C=O).

3-(2-Azidobutyryl)indole (1h). The same method as for (1g) was used except that 3-(2-bromopropionyl)indole (8·4 g) was replaced by 3-(2-bromobutyryl)indole (8·8 g), yield: 6·2 g (82%), m.p. 115–116° (Found: C, 63·3; H, 5·4; N, 23·6. Calc for $C_{12}H_{12}N_4O$: C, 63·1; H, 5·3; N, 24·6%). MS: 228 (1·6), 200 (7·0), 145 (14), 144 (100), 116 (12·5), 89 (12), 28 (11). IR: 3214 cm^{-1} (NH), 2110 cm^{-1} (N_3), 2082 cm^{-1} (N_3), 1636 cm^{-1} (C=O).

3-(2-Azidoacetyl)indole (1i). The same method as for 1g was used except that 3-(2-bromopropionyl)indole (8·4 g) was replaced by 3-chloroacetylindole (5·7 g), yield: 90%, m.p. 184–186°, Lit.[32] 184–186°. MS: 200 (9·7), 172 (13·4), 145 (12·2), 144 (100), 115 (5·5). IR: 3222 cm^{-1} (NH), 2105 cm^{-1} (N_3), 2082 cm^{-1} (N_3), 1635 cm^{-1} (C=O).

3-[α-(Dimethylamino)phenylacetyl]indole (1, R = Ph, X = NMe_2). A mixture of 3-(α-chlorophenylacetyl)-indole (5·38 g, 0·02 mol), EtOH (100 ml) and dimethylamine (2·5 g) was refluxed for 3 hr, concentrated and treated with 0·5 M HCl (200 ml). After washing with ether the base was liberated by conc NH_4OH. Recrystallization from EtOH gave the pure product, yield 3·8 g (69%), m.p. 207–208° (Found: C, 77·6; H, 6·5; N, 9·9. Calc for $C_{18}H_{18}N_2O$: C, 77·7; H, 6·5; N, 10·0%). NMR (τ): 7·80 (s, 6, CH_3), 5·32 (s, 1, CH), 1·20 (s, 1, NH).

3-(α-Dimethylaminopropionyl)indole (1, R = Me, X = NMe_2). The method described above, starting with 1c, was used, yield 3·0 g (70%), m.p. 192–193°, Lit.[33] 192–193°, 186–188°.

3-(2-Morfolinopropionyl)indole, yield 78%, m.p. 200–202° (Found: C, 69·5; H, 7·1; N, 11·0. Calc for $C_{15}H_{18}N_2O_2$: C, 69·7; H, 7·0; N, 10·9%).

5-Methoxy-3-(N,N-dimethylaminoacetyl)indole, yield: 80%, m.p. 191–193° (Found: C, 67·5; H, 6·8; N, 12·0. Calc for $C_{13}H_{16}N_2O_2$: C, 67·2; H, 6·9; N, 12·1%). NMR (τ): 7·70 (s, 6, $N(CH_3)_2$), 6·43 (s, 2, CH_2), 6·20 (s, 3, OCH_3).

3-(2-Dimethylaminobutyryl)indole (1, R = Et, X = NMe_2). 3-(2-Bromoburyryl)indole (5·3 g, 0·02 mol), aqueous dimethylamine (33%, 7·0 ml) and NaI (3·0 g) in EtOH (100 ml) was refluxed for 20 hr. The soln was concentrated to *ca* 25 ml and then poured into aqueous 0·5 M HCl (200 ml). The acid soln was extracted with ether and the base liberated by addition of conc NH_4OH. The crude base was recrystallized from EtOH, yield 3·0 g (65%), m.p. 200–201° (Found: C, 72·9; H, 7·8; N, 12·1. Calc for $C_{14}H_{20}N_2O$: C, 73·0; H, 7·9; N, 12·2. The following compounds were similarly prepared.

3-(2-Diethylaminopropionyl)indole (1, R = Me, X = NEt_2), yield 3·7 g (77%) from MeOH, m.p. 142–144° (Found: C, 73·9; H, 8·1; N, 11·5. Calc for $C_{15}H_{20}N_2O$: C, 73·7; H, 8·3; N, 11·5%). NMR (τ): 8·9 (m, 9, $3CH_3$), 7·4 (q, 4, $2CH_2$), 5·9 (q, 1, CH), 1·8 (broad s, 1, NH).

3-(2-Hydroximino-1,3-dioxobutyl)indole (10). $NaNO_2$ (1·25 g) in water (3·0 ml) was added to a mixture of 3-acetoacetylindole[34] (4·0 g) and HOAc (20 ml) at 12–15°. On completed addition a homogeneous soln was obtained from which crystals soon (1–5 min) separated. The crystals were collected and washed with cold MeOH, yield 3·6 g (78%) (Found: C, 62·8; H, 4·3; N, 12·1. Calc for $C_{12}H_{10}N_2O_3$: C, 62·6; H, 4·4; N, 12·2%). MS: 231 (6·5), 230 (45·2), 201 (5·0), 187 (5·1), 171 (5·6), 170 (31·5), 161 (13·7), 145 (11·6), 144 (100), 117 (13·0).

3-(2-*Aminopropyl)indole* (9a). 3-(2-Azidopropionyl)-indole (3·5 g) in dry THF (50 ml) was added to a well-stirred mixture of LAH (4·0 g) in dry THF (100 ml). After a reflux period (23 hr) the excess of LAH was destroyed by addition of KOH (2M, 5 ml). The mixture was filtered and the solid inorganic phase carefully washed with ether. The ether phase was dried and evaporated. The residue recrystallized from n-hexane–EtOAc gave 2·1 g (74%), m.p. 100–102°, Lit.[28] 97–100°.

3-(2-*Aminobutyl)indole* (9b). In method A, 3-(2-azidobutyryl)indole (6·2 g) in THF (50 ml) was added to LAH (6·0 g) in THF (100 ml). The mixture was then treated as described above, yield: 4·4 g (86%), m.p. 99–101°, Lit.[29] 97–99°.

In method B, **10** (2·3 g, 0·01 mol) was added in portions to a refluxing mixture of LAH (3·0 g) and THF (60 ml). After completed addition the reflux was continued for 12 hr. The excess of LAH was destroyed by addition of KOH (2M, 4 ml). The mixture was filtered and water (300 ml) and ether (300 ml) was added to the filtrate. After washing (3 × 300 ml H_2O) the ether phase was extracted with 2% HCl aq (2 × 150 ml). The acid extract was rendered alkaline and extracted with ether (2 × 200 ml). After drying and evaporation the crude base was recrystallized from n-hexane–EtOAc, yield 0·38 g (20%).

3-(2-*Dimethylaminopropyl)indole* (9c). 3-(2-Dimethylaminopropionyl)indole (2·7 g) in THF (50 ml) was reduced with LAH (2·7 g) in THF (60 ml) as described for 9a, yield: 1·65 g (66%) after recrystallization from benzene–n-hexane, m.p. 109–110° (Lit.[30,31] 108°, 113–14°, 58–60°). A further recrystallization from n-pentane did not change the m.p.* MS 202 (0·6), 158 (1·0), 157 (0·5), 156 (0·5), 144 (0·6), 143 (1·2), 131 (0·5), 130 (3·4), 129 (0·7), 128 (0·5), 117 (0·6), 115 (0·7), 103 (0·8), 77 (0·9), 73 (4·9), 72 (100), 71 (1·3), 70 (1·2), 57 (0·9), 56 (1·8), 44 (1·8), 42 (1·5). Only peaks stronger than 0·5% of the base peak are listed.

3-(2-*Aminoethyl)indole* (9e). 3-(2-Azidoacetyl)indole was reduced using method A above, yield: 90%, m.p. 117–118°, Lit.[28] 118°.

3-(2-*Dimethylamino-2-phenylethyl)indole* (9d). 3-[α-(dimethylamino)phenylacetyl]indole (2·8 g, 0·01 mol) in THF (80 ml) was reduced with LAH (2·7 g) in THF (60 ml) as described for 9a, yield: 2·1 g (80%) after recrystallization from benzene–MeOH, m.p. 82–83° (Found: C, 81·8, H, 7·6, N, 10·6. Calc for $C_{18}H_{20}N_2$: C, 81·8, H, 7·6, N, 10·6%). MS 264 (0·07), 220 (1·2), 219 (0·7), 218 (1·3), 217 (1·3), 135 (12·5), 134 (100), 132 (1·4), 130 (2·3), 119 (0·7), 118 (4·2), 117 (0·8), 116 (0·8), 103 (1·3), 91 (4·0), 78 (2·5). Only peaks stronger 0·5% of the base peak are listed.

5-*Methoxy-N,N dimethyltryptamine hydrochloride*. 5-Methoxy-3-(*N,N*-dimethylaminoacetyl)indole (4·0 g) was added in portions while stirring to a mixture of LAH (1·0 g) in dry THF (150 ml). After reflux (8 hr), the mixture was cooled and water cautiously added. The mixture was then poured into 3% NH_4Cl aq (400 ml) and extracted with ether (2 × 200 ml). The combined extracts were dried (K_2CO_3) and the base transformed to its HCl-salt by N_2-diluted $HCl_{(g)}$, yield 3·5 g (81%), m.p. 145–146°, Lit.[29] 145–146°.

*Our product is identical with a sample kindly provided by Dr Heath-Brown. The reason for the low m.p. reported by Ganellin *et al.*[3] is not clear. A mass spectrum of the low melting product, kindly provided by Dr Ganellin, is, however, nearly identical with that of our product.

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