Synthesis and Reactions of *N*-Indol-3-ylmethylalkylamines and Related Compounds

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A series of new *N*-indol-3-ylmethylalkylamines (**1**) have been synthesized in excellent yields *via* transamination between gramine and the appropriate primary alkylamine. The use of tryptamine and propane-1,3-diamine in the exchange reaction afforded *N*-indol-3-ylmethyltryptamine (**2**), and *N,N'*-bis(indol-3-ylmethyl)propane-1,3-diamine (**3**) respectively, whereas the use of methylamine gave *N,N*-bis(indol-3-ylmethyl)methylamine (**4**). The exchange reaction has been extended by the use of amino acids to give *N,N*-bis(indol-3-ylmethyl)tryptophan (**6**) and *N,N*-bis(indol-3-ylmethyl)glycine (**8**). The secondary amines (**1**), (**2**) and the previously known bis(indol-3-ylmethyl)amine proved to be valuable intermediates for the synthesis of some new compounds related to gramine as well as to other indole alkaloids.

It appeared to us that while the syntheses of tertiary and secondary amines related to tryptamine with central nervous system activity have been reported,[1-3] little or no attention has been focused upon compounds related to gramine [*N*-indol-3-ylmethyldimethylamine], which, pharmacologically, is interesting in its own right.

Snyder and Matteson,[4] obtained *N*-indol-3-ylmethyl-t-butylamine in a 39% yield from t-butylamine, formaldehyde, and indole under typical Mannich conditions. With simpler primary amines, however, the formation of a mixture of products severely limits the usefulness of the Mannich reaction as a route to *N*-indol-3-ylmethylalkylamines. On the other hand, Walker and Moore[5] have reported the synthesis of secondary amines related to gramine by the reduction of imines, derived from indole-3-carbaldehyde and aralkyl, aryl and heteroaryl primary amines. However, their method was limited by the stability of the imines.

The ease with which tertiary Mannich bases undergo amine exchange reactions[6-9] provides an alternative route for the synthesis of the title compounds, in one step. Thus, the secondary amines (**1**) were readily obtained in nearly quantitative yields (80—95%), when gramine and an excess of the appropriate primary amine were heated at 100 °C. During these reactions dimethylamine was liberated and identified as its picrate.

R^1NHR^2 (**1**)
a; R^2 = Et
b; R^2 = Bu^i
c; R^2 = Bu^t
d; R^2 = $(CH_2)_7Me$
e; R^2 = Cyclohexyl
f; R^2 = R^1
g; R^2 = 2,3-dimethyl-1-phenyl-5-oxopyrazol-5-yl
R^1 = Indol-3-ylmethyl

$R^1NHCH_2R^1$ (**2**)

$R^1NH(CH_2)_3NH\ R^1$ (**3**)

$R^1{}_2NMe$ (**4**)

$R^1N(CH_2)_2NR^1(CH_2)_2$ (**5**)

The secondary amines (**1c**, **e**, **f**, and **g**) were isolated as crystalline solids, whereas no analytically pure samples of the other free bases could be prepared, since distillation under reduced pressure led to resinification. However, we have found that the hydrogen oxalate salts are not only more readily prepared in a crystalline form but are also stable and non-hygroscopic.

In an extension of this reaction, we obtained *N*-indol-3-ylmethyltryptamine (**2**) in 93% yield, by treating gramine with tryptamine. Similarly, treatment of gramine with propane-1,3-diamine afforded *N,N'*-bis(indol-3-ylmethyl)propane-1,3-diamine (**3**).

In addition to the correct analytical and spectral data, evidence confirming the structure of compounds (**1**)—(**3**) was obtained by preparing the previously reported,[4,5] 3-(t-butyl- and cyclohexyl-aminomethyl)-indoles (**1c**) and (**1e**), *via* an amine exchange reaction. In particular, the n.m.r. spectrum of (**2**) showed the aliphatic NH proton as a singlet at τ 8.33 and the CH_2CH_2N protons of the tryptamine moiety (which approach a singlet[10]) at τ 7.

On the other hand, when gramine was treated with methylamine, *N,N*-bis(indol-3-ylmethyl)methylamine (**4**) was obtained in 94% yield. It was shown to be a tertiary Mannich base from its analytical and spectral data, *e.g.* the n.m.r. spectrum showed a singlet at τ 6.3 (4 H, CH_2NCH_2), τ 7.75 (3 H, NMe), and the absence of a signal in the region τ 8—8.7 attributable to the aliphatic NH proton. The formation of (**4**) is in line with the reported formation of bis(indol-3-ylmethyl)-amine,[11] when gramine was treated with ammonium carbonate. The use of piperazine in the exchange reaction led to the formation of *N,N'*-bis(indol-3-ylmethyl)piperazine (**5**). Attempts to restrict the reaction to only one amine function failed.

Since the use of amino acids as the primary amines in the exchange reaction has been reported as a route to the amino acid Mannich bases[7] this reaction offers a potential method for the synthesis of *N*-indol-3-ylmethylamino acids. Therefore, gramine or its methiodide was treated with tryptophan to give *N,N*-bis(indol-3-ylmethyl)tryptophan (**6**). In an attempt to obtain *N*-indol-3-ylmethylglycine (**7**), as an isomer of tryptophan, by using glycine in the transamination reaction, we obtained *N,N*-bis(indol-3-ylmethyl)glycine (**8**). The formation of the bis compounds (**6**) and (**8**) is analogous to the reported formation of *N,N*-bis(β-benzoylethyl)glycine,[7] from the trans-amination reaction between β-diethylaminopropiophenone and glycine.

$R_2N{\cdot}CHR{\cdot}CO_2H$ (**6**)
$RNH{\cdot}CH_2{\cdot}CO_2H$ (**7**)
$R_2N{\cdot}CH_2{\cdot}CO_2H$ (**8**)
R = Indol-3-ylmethyl

In order to explore the synthetic potentialities of the secondary amines (**1**), as intermediates for the synthesis of

compounds related to gramine and, in particular, substances containing a carbazole or tetrahydrocarbazole nucleus, the amine (**1a**) was treated with formaldehyde and carbazole. Carbazol-9-ylmethyl(indol-3-ylmethyl)ethylamine (**9**) was formed *in accord* with earlier studies[12] of the Mannich type reactions of carbazole, in which 9-piperidinomethylcarbazole and dicarbazol-9-ylmethane were obtained.

On the other hand, tetrahydrocarbazole undergoes Mannich type reactions at the 1-position rather than on nitrogen.[13] However, in the present work a 1-substituted tetrahydrocarbazole (**11**) was synthesised by an alternative route. Thus, the exchange reaction between 2-(dimethylaminomethyl)-cyclohexanone and (**1a**) gave (**10**); Fischer indole cyclization of (**10**) took place quite smoothly and afforded 3-[ethyl(1,2,3,4-tetrahydrocarbazol-1-ylmethyl)aminomethyl]indole (**11**).

A similar treatment of (**1a**) with 3-(β-dimethylamino)propionylindole,[14] afforded *N*-indol-3-ylmethyl-*N*-(2-indol-3-ylcarbonylethyl)ethylamine (**12**).

$R^1{}_2NEt$
(**9**)
$R^1(Et)NCH_2CH_2COR^1$
(**10**)
$R^1(Et)N$(1,2,3,4-tetrahydrocarbazol-1-yl)
(**11**)
$R^1(Et)NOH_2CH_2COR^1$
(**12**)

$R^1CO{\cdot}CO{\cdot}NR^1R^2$	$(R^1CH_2)_2NR^2$
(**13**) R^2 = Et	(**16**) R^2 = Et
(**14**) R^2 = R^1	(**17**) R^2 = R^1
(**15**) R^2 = R^1CH_2	(**18**) R^2 = R^1CH_2

R^1 = Indol-3-ylmethyl

One of the specific objectives of this study was to prepare the tertiary amines (**16**)—(**18**), which have structural features related to gramine and tryptamine, *via* compounds of type (**1**) as key intermediates. Thus, following the Speeter–Anthony route[15] for the synthesis of tryptamines, the amines (**1a,f**) and (**2**) were treated with indol-3-yloxalyl chloride to give the corresponding amides (**13**), (**14**), and (**15**) respectively, in good yields. The i.r. spectra of these compounds showed absorptions at 1 745 cm^{-1} (antisymmetrical stretching for a 1,2-diketone) and 1 640 cm^{-1} (tert. amide). Reduction of the amides (**13**)—(**15**) with $LiAlH_4$ afforded the tertiary amines, *N*-ethyl-*N*-indol-3-yltryptamine (**16**), *N,N*-bis(indol-3-ylmethyl)tryptamine (**17**), and bis(2-indol-3-ylethyl)indol-3-ylmethylamine (**18**) respectively.

Experimental

M.p.s. were determined in capillaries and are uncorrected. I.r. spectra were measured on a Unicam SP 200 Grating Spectrophotometer. N.m.r. spectra, for the free bases, were determined on Perkin-Elmer R-32 (90MHz) spectrometer in $CDCl_3$ solution unless otherwise stated.

Amine Exchange Reactions of Gramine (N-*Indol-3-ylmethyldimethylamine*): *Formation of* N-*Indol-3-ylmethylalkylaminemethyl)indoles* (**1**).—Gramine (1.7 g, 10 mmol) was heated under reflux with an excess of the appropriate primary amine, until the evolution of dimethylamine had ceased (*ca.* 8 h). A slow stream of nitrogen was passed through the system to sweep out the dimethylamine formed by the reaction. In the case of compounds (**1a,b**), water (30 ml) was added to the cooled residue, and the oil that separated was extracted with ether, dried (Na_2SO_4), and evaporated to give yellow, highly viscous materials which failed to solidify. In the other cases, the excess of primary amine was removed under reduced pressure. If the product crystallised it was triturated with a small quantity of ether and dried. Non-crystalline products were converted into oxalates, by the addition of an ethereal solution of oxalic acid to the crude product in the same solvent. The precipitate was washed with ether and purified by crystallisation from methanol–ether.

N-*Indol-3-ylmethylethylamine* (**1a**). This was obtained in 94% yield; its oxalate had m.p. 164 °C (decomp.) (Found: C, 59.1; H, 6.0; N, 10.85. $C_{11}H_{14}N_2 \cdot C_2H_2O_4$ requires C, 59.07; H, 6.10; 10.60%).

N-*Indol-3-ylmethylbutylamine* (**1b**). This was obtained in 90% yield; its oxalate had m.p. 159 °C (decomp.) (Found: C, 61.85; H, 6.7; N, 9.75. $C_{13}H_{18}N_2 \cdot C_2H_2O_4$ requires C, 61.62; H, 6.89; N, 9.58%).

N-*Indol-3-ylmethyl-t-butylamine* (**1c**). This was obtained in 80% yield, m.p. 118—120 °C (lit.,[4] m.p. 115.5—119 °C).

N-*Indol-3-ylmethyl-n-octylamine* (**1d**). This was obtained in 80% yield, its oxalate had m.p. 162 °C (Found: C, 65.55; H, 8.15; N, 8.6. $C_{17}H_{26}N_2 \cdot C_2H_2O_4$ requires C, 65.49; H, 8.09; N, 8.04%).

N-*Indol-3-ylmethylcyclohexylamine* (**1e**). This was obtained in 91% yield, m.p. 115 °C (lit.,[5] m.p. 115 °C).

Bis(indol-3-ylmethyl)amine (**1f**). This was obtained according to a previously reported method,[11] m.p. 88 °C.

N-(2,3-*Dimethyl-1-phenyl-5-oxopyrazol-5-yl)indol-3-ylmethylamine* (**1g**). This was obtained in 72% yield, m.p. 210 °C (Found: C, 72.1; H, 5.9; N, 16.6. $C_{20}H_{20}N_4O$ requires C, 72.26; H, 6.06; N, 16.85%).

N-*Indol-3-ylmethyltryptamine* (**2**).—This compound was prepared in essentially the same manner as that described above, but from tryptamine hydrochloride (1.9 g, 10 mmol) in aqueous ethanol 50% (70 ml), containing sodium carbonate (0.7 g). After the reaction mixture had been heated under reflux for 24 h, it was worked up as described above to yield a brown oily product (1.9 g, 67%). The *oxalate* formed white crystals from methanol–ether, m.p. 156—158 °C (decomp.) (Found: C, 66.2; H, 5.75; N, 10.8. $C_{19}H_{19}N_3 \cdot C_2H_2O_4$ requires C, 66.47; H, 5.58; N, 11.07%); τ 8.3 (1 H, s, aliphatic NH), 7 (4 H, br s, CH_2CH_2N), 6.2 (2 H, s, indolyl-CH_2N), and 3—2.5 (12 H, m, indolic protons).

N,N-*Bis(indol-3-ylmethyl)propane-1,3-diamine* (**3**)—A mixture of gramine (1.7 g, 10 mmol) and propane-1,3-diamine (0.4 g, 5 mmol) in aqueous ethanol 50% (40 ml), was refluxed for 6 h. Ethanol was removed under reduced pressure and treatment of the residue with water gave a white solid. This was triturated with ether (5 ml), filtered, and washed with ether (2 × 4 ml) to give (0.3 g, 9%) of the crude product, m.p. 110 °C. Two recrystallisations from acetone–methylcyclohexane (1:1) gave the pure product, m.p. 120—122 °C (Found: C, 75.05; H, 7.0; N, 16.4. $C_{21}H_{24}N_4$ requires C, 75.86; H, 7.27; N, 16.85%).

N,N-*Bis(indol-3-ylmethyl)methylamine* (**4**).—Following the same procedure as that used for the preparation of compounds (**1**), gramine (1.7 g) and methylamine (33% in ethanol) (20 ml) in water (20 ml), gave a brown oil (1.5 g, 52%). The *oxalate* of this formed white crystals from methanol, m.p. 195 °C (decomp.) (Found: C, 66.2; H, 5.65; N, 10.75. $C_{19}H_{19}N_3 \cdot C_2H_2O_4$ requires C, 66.47; H, 5.58; N, 11.07%); τ 7.75 (3 H, s, NCH_3), 6.3 (4 H, s, CH_2NCH_2), and 3—2.5 (12 H, m, indolic protons).

N,N′-*Bis(indol-3-ylmethyl)piperazine* (**5**).—A mixture of gramine (2.6 g, 15 mmol), piperazine (0.65 g, 7.5 mmol), and aqueous ethanol 50% (80 ml) was refluxed for 24 h. Evaporation of ethanol under reduced pressure gave a pale yellow solid (2 g, 77.5%) crystallisation of which from acetone–cyclohexane (1:1) gave the pure material, m.p. 227 °C (Found: C, 76.6; H, 6.85; N,

16.1. $C_{22}H_{24}N_4$ requires C, 76.71; H, 7.02; N, 16.26%); τ 7.35 [8 H, s, $N(CH_2CH_2)_2N$], 6.35 (4 H, s, 2 indolyl-CH_2N), and 3.1—2.7 (12 H, m, indolic protons).

N,N-*Bis*(*indol*-3-*ylmethyl*)*tryptophan* (**6**).—A solution of gramine (0.5 g) or its methiodide (0.95 g, 3 mmol) and DL-tryptophan (0.6 g, 3 mmol) in water (20 ml) was refluxed for 6 h, while a slow stream of nitrogen was passed over it. The solid that separated was dissolved in aqueous sodium hydroxide (25%) (15 ml) and ethanol (20 ml) at 70 °C, and then filtered free from a little gummy material. The hot filtrate was acidified with acetic acid and diluted with water (20 ml). The pure *product* obtained on cooling was filtered off and washed with aqueous ethanol (50%) (2 × 3 ml); yield 0.3 g (23%), m.p. 186 °C (decomp.) (Found: C, 76.0; H, 5.35; N, 12.35. $C_{29}H_{26}N_4O_2$ requires C, 75.30; H, 5.66; N, 12.11%).

N,N-*Bis*(*indol*-3-*ylmethyl*)*glycine* (**8**). This was prepared in 45% yield from glycine following the same procedure (reaction time 2 h) described above, m.p. 144 °C (Found: C, 72.4; H, 5.35; N, 12.4. $C_{20}H_{19}N_3O_2$ requires C, 72.05; H, 5.74; N, 12.60%).

Carbazol-9-*ylmethyl*(*indol*-3-*ylmethyl*)*ethylamine* (**9**).—A mixture of carbazole (1.67 g, 10 mmol), ethanol (40 ml), formalin (37%) (0.9 ml, 0.011 mol of CH_2O), and (**1a**) (1.8 g, 10 mmol) was heated under reflux for 1 h. The solution was chilled to give the crude product (2.55 g, 73%). Recrystallisation from ethanol gave the pure *product*, m.p. 220 °C (Found: C, 82.0; H, 6.1; N, 11.55. $C_{24}H_{23}N_3$ requires C, 81.55; H, 6.55; N, 11.88%).

N-*Indol*-3-*ylmethyl*-N-(1,2,3,4-*tetrahydrocarbazol*-1-*ylmethyl*)*ethylamine* (**11**).—A mixture of 1-dimethylaminomethylcyclohexanone hydrochloride (1.9 g, 10 mmol) and an equimolar quantity of *N*-indol-3-ylmethylethylamine (**1a**), dissolved in aqueous ethanol (50%) (80 ml) was refluxed for 40 h under nitrogen. Water (20 ml) was added and the separated oily product was extracted with ether (2 × 50 ml) and the extract was dried (Na_2SO_4). Evaporation under reduced pressure gave the crude N-*indol*-3-*ylmethyl*-N-(2-*oxocyclohexyl*)-*ethylamine* (**10**), as a brown highly viscous material (2.2 g, 76%). The material gave a single spot on t.l.c. but would not crystallise; $\nu_{max.}$(film) 1 730 cm^{-1}.

A mixture of crude (**10**) (1 g) and an equimolar quantity of phenylhydrazine in acetic acid (20 ml) was refluxed for 15 min and then filtered whilst hot. The filtrate was diluted with water (6 ml) and cooled to give the indole (**11**) as a brown solid (70%), which was crystallised from dilute acetic acid, m.p. 145 °C (Found: C, 80.1; H, 7.2; N, 11.45. $C_{24}H_{27}N_3$ requires C, 80.63; H, 7.61; N, 11.75%); τ 8.9 (3 H, t, CH_3), 8.1 (4 H, m, 2- and 3-H_2), 7.25—7.4 (3 H, br s, 1-H and 4-H_2), 6.55—6.8 (4 H, m, $CHCH_2NCH_2CH_3$), 6.3 (2 H, s, indolyl-CH_2-N), and 3—2.5 (11 H, m, indolic protons).

N-*Indol*-3-*ylmethyl*-N-(2-*indol*-3-*ylcarbonylethyl*)*ethylamine* (**12**).—This compound was prepared in essentially the same manner as that described above for compound (**10**), but from (**1a**) (0.9 g, 5 mmol) and *N*-(2-indol-3-ylcarbonylethyl)dimethylamine (1 g, 5 mmol) (reaction time 50 h). The crude product, obtained as a yellow solid (1.4 g, 81%), was crystallised twice from ethanol–benzene (1:1), m.p. 165 °C (Found: C, 76.25; H, 7.1; N, 12.0. $C_{22}H_{23}N_3O$ requires C, 76.49; H, 6.71; N, 12.16%); $\nu_{max.}$ (Nujol) 1 650 cm^{-1}.

Treatment of Compounds (**1a**), (**1f**) *and* (**2**) *with Indol*-3-*yloxalyl Chloride*; *Formation of the Amides* (**13**)—(**15**).—To a stirred solution of the secondary amine (**1a**) (5 mmol) in dry benzene (100 ml) was added over 10 min solid indol-3-yloxalyl chloride (1 g, 5 mmol). The mixture was stirred for 2 h after which the precipitated product was filtered off, and crystallised from 70% aqueous methanol.

N-*Ethyl*-(N-*indol*-3-*ylmethyl*)*indol*-3-*yloxalamide* (**13**). This was obtained in 97% yield, m.p. 188 °C (decomp.) (Found: C, 72.85; H, 5.4; N, 11.95. $C_{21}H_{19}N_3O_2$ requires C, 73.02; H, 5.54; N, 12.16%).

N,N-*Bis*(*indol*-3-*ylmethyl*)*indol*-3-*yloxalamide* (**14**). This was obtained from (**1f**) similarly in 67% yield, m.p. 210 °C (Found: C, 75.1; H, 4.9; N, 12.8. $C_{28}H_{22}N_4O_2$ requires C, 75.31; H, 4.96; N, 12.54%).

N-*Indol*-3-*ylmethyl*-N-(2-*indol*-3-*ylethyl*)*oxalamide* (**15**). This was obtained from (**2**) in 66% yield, m.p. 170 °C (Found: C, 75.55; H, 5.1; N, 12.0. $C_{29}H_{24}N_4O_2$ requires C, 75.63; H, 5.25; N, 12.16%). Compounds (**13**)—(**15**) showed $\nu_{max.}$ (Nujol) 1 745 and 1 640—1 645 cm^{-1}.

Reduction of the Amides (**13**)—(**15**).—To a stirred solution of lithium aluminium hydride (0.5 g, 13 mmol) in dry THF (15 ml) was added, dropwise, a warm solution of the amide (**13**) (0.5 g, 1.4 mmol) in dry THF (20 ml). The mixture was refluxed under nitrogen for 6 h, cooled, and the excess of hydride destroyed carefully with cold water; it was then basified with 40% ammonia and filtered. The filtrate was evaporated, extracted with ether, and the extract dried. Ethereal oxalic acid was then added to the latter to give the oxalate which was crystallised from methanol–ether.

N-*Ethyl*-N-*indol*-3-*ylmethyltryptamine* (**16**). This was obtained in 72% yield; its oxalate had m.p. 194 °C (decomp.) (Found: C, 67.65; H, 5.95; N, 10.05. $C_{21}H_{23}N_3 \cdot C_2H_2O_4$ requires C, 67.79; 6.18; N, 10.31%).

The oxalate was basified with aqueous sodium hydroxide (2%), extracted with ether, dried (K_2CO_3), and evaporated under reduced pressure to give the free amine (**16**) as a glassy solid which would not crystallise; τ 8.8 (3 H, t, CH_3), 7.1 (4 H, br s, CH_2CH_2N), 6.75 (2 H, q, CH_2CH_3), 6.2 (2 H, s, indolyl-CH_2N), and 3—2.6 (12 H, m, indolic protons).

N,N-*Bis*(*indol*-3-*ylmethyl*)*tryptamine* (**17**). This was obtained in 64% yield; its oxalate had m.p. 213 °C (decomp.) (Found: C, 70.6; H, 5.25; N, 10.75. $C_{28}H_{26}N_4 \cdot C_2H_2O_4$ requires C, 70.85; H, 5.55; N, 11.02%). The free amine, obtained as above, was crystallised from ethyl acetate–benzene (1:1), m.p. 134 °C; τ 7 (4 H, br s, CH_2CH_2N), 6.3 (4 H, s, [(indolyl-CH_2)$_2$N], and 3—2.6 (18 H, m, indolic protons).

N-*Indol*-3-*ylmethyl*-N,N-*bis*(2-*indol*-3-*ylethyl*)*amine* (**18**). This was obtained from (**15**) in 61% yield; its oxalate had m.p. 187 °C (decomp.) (Found: C, 71.1; H, 5.6; N, 10.5. $C_{29}H_{28}N_4 \cdot C_2H_2O_4$ requires C, 71.24; H, 5.78; N, 10.72%). The free amine, obtained as above, was a glassy solid which would not crystallise; τ 7.05 [8 H, br s, (indolyl-CH_2CH_2)$_2$N], 6.35 (2 H, s, indolyl-CH_2N), and 3—2.5 (18 H, m, indolic protons).

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