Amine-Induced Rearrangements of 2-Bromo-1-(1*H*-indol-3-yl)-2-methyl-1-propanones: A New Route to α-Substituted Indole-3-acetamides, β-Substituted Tryptamines, α-Substituted Indole-3-acetic Acids and Indole β-Aminoketones

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The reaction of 2-bromo-1-(1*H*-indol-3-yl)-2-methyl-1-propanone (**1**) and 2-bromo-1-(1-methyl-1*H*-indol-3-yl)-2-methyl-1-propanone (**2**) with primary amines proceeds in good yields to produce rearranged amides by a proposed pseudo-Favorskii mechanism. These amides in turn can either be reduced to produce β-substituted tryptamines or hydrolyzed to produce substituted indole-3-acetic acids. When the reaction is carried out using bulky primary or secondary amines, β-aminoketones are produced by elimination of hydrogen bromide followed by Michael addition. When hindered secondary amines or tertiary amines are used, elimination to the α,β-unsaturated ketones occurs.

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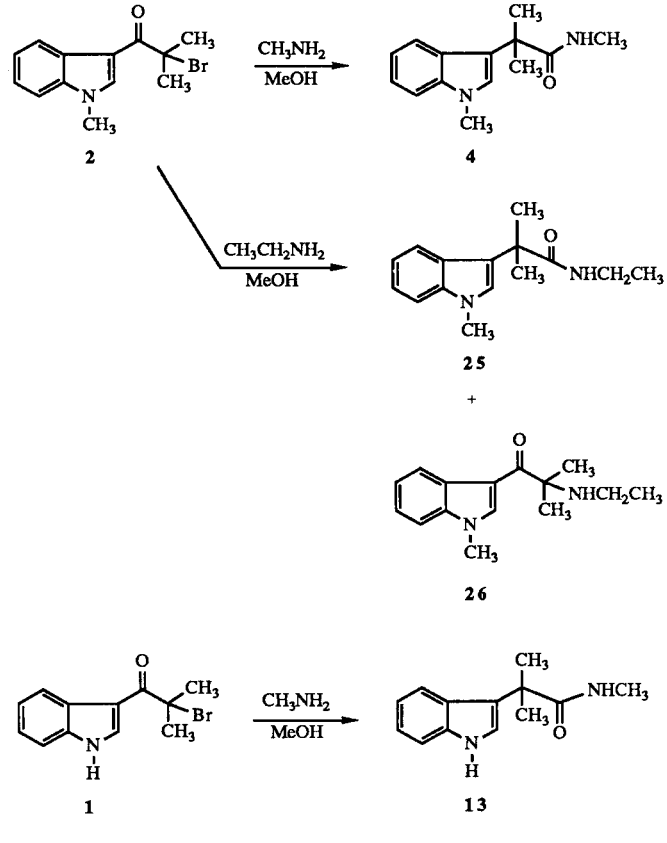
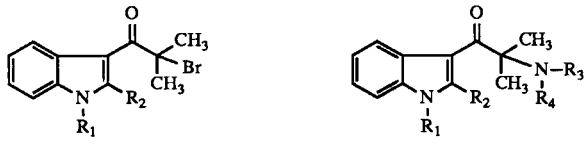
As part of our efforts to produce a series of 1*H*- and 1-alkylindol-3-yl-α-aminoketones **3**, a corresponding series of indol-3-yl-α-bromoketones **1, 2, 14** was prepared as potential intermediates [1]. Our originally planned synthesis of these compounds was by the direct displacement of the bromine atom with ammonia and small primary and secondary amines [2]. The initial reaction using 2-bromo-2-methyl-1-(1-methyl-1*H*-indol-3-yl)-1-propanone (**2**) and methylamine in methanol failed to produce any compounds containing a basic amine functionality (Scheme 1). However, from the neutral fraction of the reaction workup, *N*,α,α,1-tetramethyl-1*H*-indole-3-acetamide (**4**) was isolated in 80% yield. The formation of this product can be rationalized by postulating a pseudo-Favorskii mechanism [3]. The cyclopropanone intermediate **6** (see Scheme 2), can be formed either directly from **2** or *via* the ionic intermediate **5**. Attack on the carbonyl group by methylamine with loss of hydrogen bromide, gives the intermediate **7**. Reorganization of this intermediate as indicated by the arrows gives the observed amide **4**. Bergman and Backvall have reported a similar rearrangement of 3-(α-haloacyl)indoles using powdered sodium hydroxide in refluxing xylene (Scheme 3) to produce indole-3-acetic acids, *e.g.*, **10** in moderate yields [4]. They also postulated a cyclopropanone intermediate **9**, which in their case results from the initial formation of the anion **8** produced by the removal of the acidic 1-*H* from the bromoketone **1**. However, when

Scheme 1

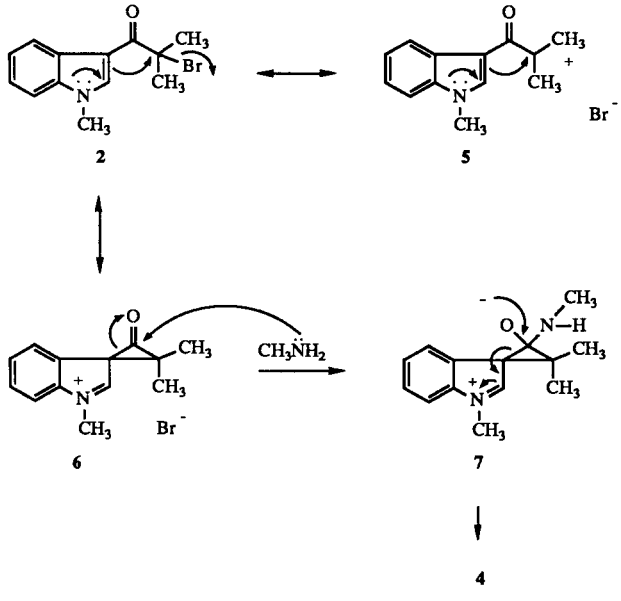




Formation of Substituted Indole-3-acetamides

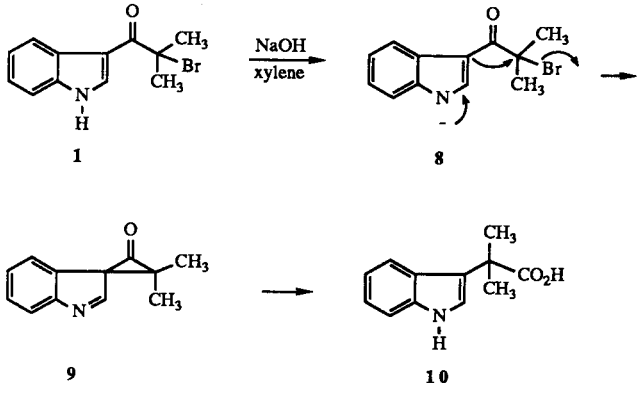
their reaction conditions were applied to 1-methylated indoles where the bromine was secondary, such as **11**, α-hydroxy ketones **12** were produced from the direct displacement of the α-halogen atom by hydroxide ion. Rearranged acids were not detected in any of these cases. Since the indole nucleus of **2** is already alkylated at the 1-position, the formation of an anion such as **8** to induce the initial formation of the cyclopropanone intermediate cannot occur. In our case, the existence of a small amount of **2** in the ionic form **6**, in a polar solvent such as methanol, may allow the formation of the observed amide to be an equilibrium shifting reaction, **2** → **6** → **4**.

Scheme 2



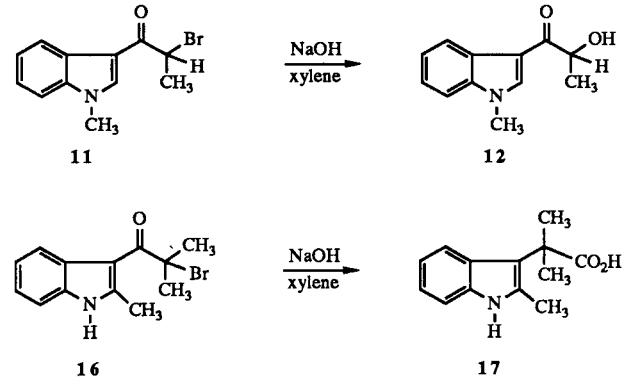
Mechanism of Formation of Substituted Amides

Scheme 3



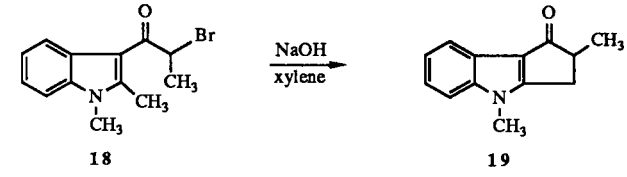
Mechanism for Formation of Substituted Indole-3-acetic Acids

The reaction of the 1-*H*-indole bromo ketone **1** with methylamine (Scheme 1) proceeded with rearrangement to produce the expected amide **13** in 74% yield. The formation of an anion such as **8** cannot be discounted in this case but in view of the results observed with the 1-substituted indole, it does not have to be invoked.



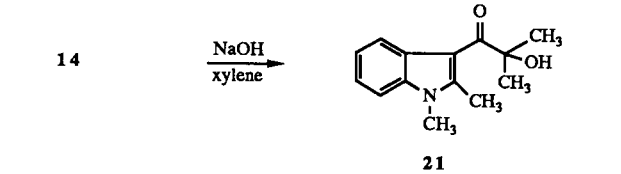
The possibility of the reactive 2-position of the indole nucleus interacting, as in the formation of tetrahydrocarbolines (Pictet-Spengler [5] and Bishler-Napieralski [6] reactions) or anion formation in 1,3-disubstituted indoles [7], to form some intermediate which could produce the observed results was explored. In order to discount this pathway, the reaction was repeated using 2-bromo-1-(1,3-dimethylindol-3-yl)-2-methyl-1-propanone (**14**). Again, the only isolated product (86%) was the rearranged amide **15**.

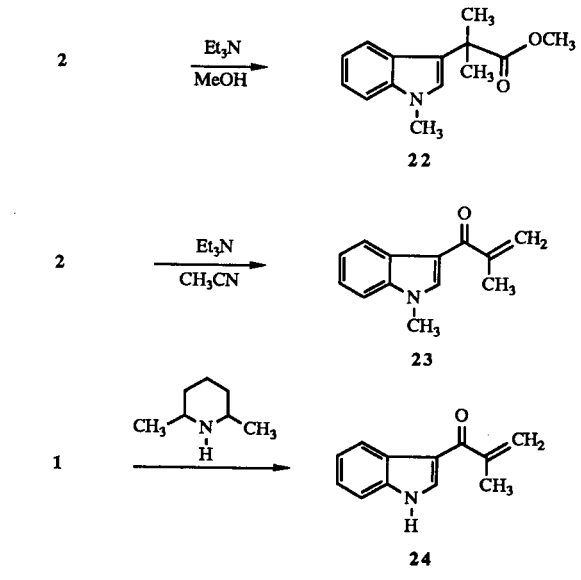
When Bergman and Backvall ran their reaction using the 1-*H*-indole analog **16**, they isolated 19% of the rearranged acid **17**. However, when they used 1-methylated secondary α-haloacylindole derivatives, such as **18**, they did not observe any rearranged acid. Instead, they isolated 2-substituted 3,4-dihydro-4-methylcyclopenta[*b*]indol-1(2*H*)-ones **19**, which arise from a displacement of the



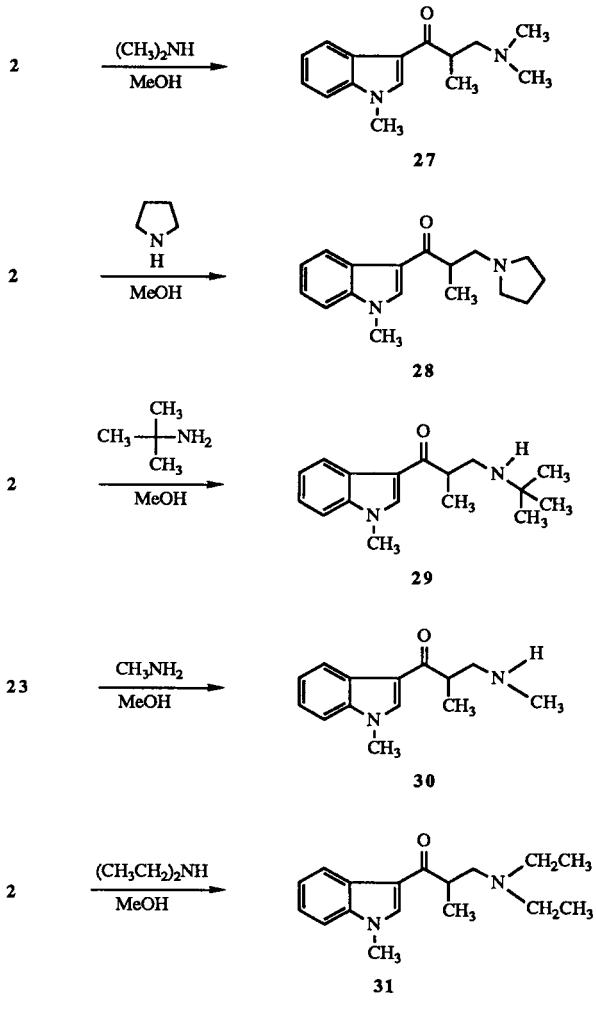
α-halogen by an anion formed from the 2-methyl group. If the halogen was tertiary, as in compound **14**, neither rearranged acids nor cyclopenta[*b*]indol-1(2*H*)-ones were isolated. The product was instead the α-hydroxyketone **21** as in the previous 1-substituted cases.

In an attempt to isolate a stable compound which would indicate the presence of the proposed ionic intermediate **6**, the bromoketone **2** was reacted with triethylamine in methanol in hopes of shifting the proposed equilibrium





Scheme 4



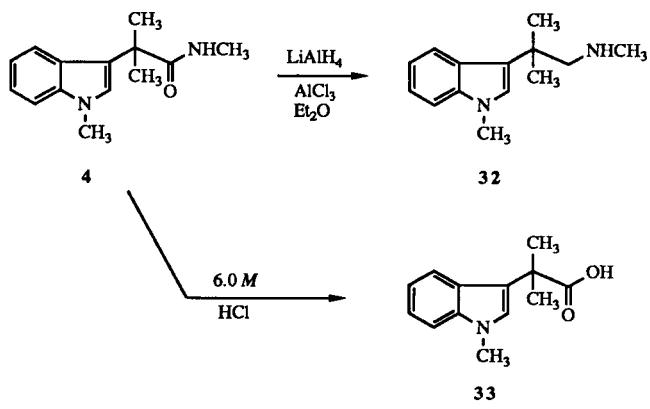
Formation of β-Aminoketones

reaction **2** → **6** to favor the cyclopropanone compound. The only compound isolated was the rearranged ester, methyl α,α,1-trimethyl-1*H*-indole-3-acetate (**22**), in 75% yield. The reaction was rerun in acetonitrile in an attempt to prevent the capture of any discernable intermediates by reactive solvent molecules. The only product isolated under these conditions resulted from the elimination of hydrogen bromide from the bromoketone to give the alkenylindole **23**, 87% yield. The corresponding 1-unsubstituted analog **24** was prepared by reacting the bromoketone **1** with 2,6-dimethylpiperidine.

In order to explore the scope of this reaction, the bromo ketone **2** was reacted with ethylamine using conditions identical to those previously described for methylamine. The reaction went with rearrangement to afford the *N*-ethylamide **25** in 86% yield (Scheme 1). However, in this case it was possible to isolate a small amount (5%) of the α-aminoketone **26** which arises from the direct displacement of bromine by ethylamine. The reaction of **2** with dimethylamine failed to produce any insoluble amounts of rearranged amide (Scheme 4). However, the basic product isolated was not the α-aminoketone which would arise from direct displacement of the bromine, but the β-aminoketone **27** which results from an elimination of hydrogen bromide from the bromoketone followed by a Michael addition [8]. This was also the case when **2** was reacted with pyrrolidine, the only isolated product being the β-aminoketone **28** which occurred nearly quantitatively (98%).

To try to determine the cross over point between rearrangement, direct displacement and elimination-addition, **2** was reacted with *t*-butylamine. The only isolated product (84%), in this case, was the β-aminoketone **29** which arises from elimination-addition. To establish that addition to the double bond of **23** is a viable route for the production of the observed β-aminoketones, the alkene was reacted with methylamine in methanol to provide the expected β-aminoketone **30** in 69% yield. To complete the series, **2**

Scheme 5



Transformations of Substituted Indole-3-acetamides

was reacted with diethylamine to give the β-aminoketone **31** in 73% yield.

Since tryptamines are compounds which possess many interesting biological effects [9], we examined whether these highly substituted amides could be reduced to produce novel tryptamine analogs. The initial rearranged amide **4** was chosen for the model reaction and the use of lithium aluminum hydride and aluminum chloride in ether gave the desired tryptamine analog **32**, in 82% yield (Scheme 5) [10].

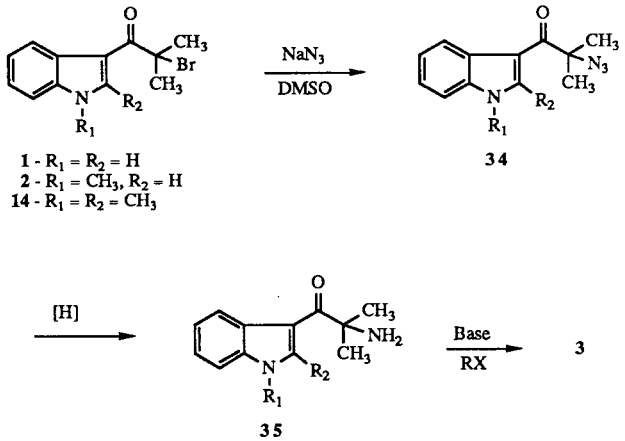
Another example of compounds which are of biological importance and should be readily available from the products of this rearrangement are substituted indole-3-acetic acid [11]. Hydrolysis of the rearranged amides would produce highly α-substituted examples such as **33**. Attempted base hydrolysis under vigorous conditions failed to provide any conversion, however, hydrolysis under acidic conditions smoothly converted the amide **4** into the desired acid **33** in excellent yield (94%).

The rearrangement of highly substituted indol-3-yl bromoketones under the influence of small primary amines has been explored. The formation of α-substituted amides which can either by hydrolyzed to indole-3-acetic acids or reduced to give β-substituted tryptamines, provides a facile entry into these biologically important compounds.

The reaction of the bromo ketones with either bulky primary amines of secondary amines produces β-aminoketones by elimination of hydrogen bromide followed by Michael addition to the double bond. When hindered secondary amines or tertiary amines are used, the vinyl ketones which are intermediates in the formation of the β-aminoketones can be isolated.

The desired series of α-aminoketones **3** was successfully prepared (Scheme 6) by the direct displacement of the bromine atom by azide ion in dimethyl sulfoxide, in high yield, to produce the 2-indol-3-yl-(α-azido)ketones **34**.

Scheme 6



1 - $R_1 = R_2 = H$
2 - $R_1 = CH_3$, $R_2 = H$
14 - $R_1 = R_2 = CH_3$

34

35

Synthetic Route to Indole α-Aminoketones

These azido ketones could be reduced under a variety of mild conditions to afford the initial aminoketones **35** which could then be alkylated by standard methods to produce the desired target series **3**.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm resolution. Proton magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 35-40° and pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry nitrogen atmosphere. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer.

N,α,α,1-Tetramethyl-1*H*-indole-3-acetamide (**4**).

A solution of 28.0 g (0.1 mole) of **2** [1] in 300 ml of methanol was saturated with gaseous methylamine without external cooling. The reaction mixture was heated at gentle reflux for 18 hours and the solvent was removed *in vacuo*. The residue was partitioned between ether and water. The organic layer was washed with 1.0 *M* hydrochloric acid, water, 1.0 *N* sodium hydroxide, dried and concentrated *in vacuo*. The residue was triturated with pentane and the resulting solid was removed by filtration, washed with pentane, and dried *in vacuo* to give 18.5 g (80%) of **4**, mp 125-130°. A sample recrystallized from toluene-petroleum ether had, mp 128-130°; ir (potassium bromide): 3400 (NH), 1660, and 1550 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.67 (s, 6H), 2.66 (d, 3H), 3.82 (s, 3H), 5.72 (br s, 1H), 7.05 (s, 1H), 7.29 (m, 4H).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.86; H, 7.85; N, 12.13.

N,α,α-Trimethyl-1*H*-indole-3-acetamide (**13**).

A solution of 16.6 g (0.1 mole) of **1** [1] in 250 ml of methanol was saturated with gaseous methylamine, reacted and worked up as in the preparation of **4** to give 16.1 g (74%) of **13**, mp 170-172°; ir (potassium bromide): 3405 and 3352 (NH), 1652, and 1631 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.52 (s, 6H), 2.50 (s, 3H), 7.15 (m, 5H).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.44; H, 7.40; N, 13.08.

N,α,α,1,2-Pentamethyl-1*H*-indole-3-acetamide (**15**).

A suspension of 29.5 g (0.1 mole) of **14** [4] was saturated with gaseous methylamine, reacted and worked up as in the preparation of **4** to give 21.0 g (86%) of **15**, mp 121-123°; ir (potassium bromide): 3345 (NH), 3306 (NH), 1650, and 1544 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.70 (s, 6H), 2.35 (s, 3H), 2.68 (d, 3H), 3.63 (s, 3H), 5.68 (br s, 1H), 7.15 (m, 3H), 7.68 (s, 1H).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.83; H, 8.35; N, 11.54.

Methyl α,α,1-Trimethyl-1*H*-indole-3-acetate (**22**).

A solution of 28.0 g (0.1 mole) of **2** in 300 ml of methanol was treated with 15.2 g (0.15 mole) of triethylamine and the mixture

was heated at reflux for 18 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was washed with 1.0 *M* hydrochloric acid, water, dried, filtered, and concentrated *in vacuo*. The residue was triturated with hexane and the resulting solid was removed by filtration, washed with hexane, and dried *in vacuo* to give 17.2 g (75%) of **22**, mp 104-105°; ir (potassium bromide): 1728 (C=O); ^{1}H nmr (deuteriochloroform): δ 1.68 (s, 6H), 3.61 (s, 3H), 3.66 (s, 3H), 6.91 (s, 1H), 7.21 (m, 3H), 7.66 (s, 1H).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.85; H, 7.36: N, 6.07.

2-Methyl-1-(1-methyl-1*H*-indol-3-yl)-2-propen-1-one (**23**).

A solution of 56.0 g (0.2 mole) of **2**, 30.3 g (0.3 mole) of triethylamine and 350 ml of acetonitrile was heated at reflux for 18 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The ether layer was washed with water, 1.0 *M* hydrochloric acid, water, dried, filtered, and evaporated *in vacuo* to give 34.4 g (86%) of **23**, mp 60-65°. An analytical sample recrystallized from ether-pentane had, mp 65-66°; ir (potassium bromide): 1609 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.09 (s, 3H), 3.80 (s, 3H), 5.58 (d, 2H), 7.31 (m, 3H), 7.58 (s, 1H), 8.46 (m, 1H).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.29; H, 6.50; N, 6.95.

1-(1*H*-Indol-3-yl)-2-methyl-2-propen-1-one (**24**).

A solution of 26.6 g (0.1 mole) of **1** in 200 ml of 2,6-dimethylpiperidine was heated at reflux for 8 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was washed with water, 1.0 *M* hydrochloric acid, water, dried filtered, and evaporated *in vacuo* to give 16.1 g (87%) of **24**, mp 150-152°; ir (potassium bromide): 3218 (NH), 1596 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.08 (s, 3H), 5.63 (d, 2H), 7.28 (m, 3H), 7.72 (d, 1H), 8.37 (m, 1H), 9.75 (br s, 1H).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.86; H, 5.95; N, 7.51.

N-Ethyl-α,α,1-trimethyl-1*H*-indole-3-acetamide (**25**).

A solution of 28.0 g (0.1 mole) of **2** in 125 ml of methanol was saturated with gaseous ethylamine and heated at reflux for 3 hours, resaturating with ethylamine after 2 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was extracted with 1.0 *M* hydrochloric acid (2 × 50 ml), washed with water, dried, clarified with Norit, filtered through Celite, and evaporated *in vacuo* to give 21.1 g (86%) of **25**, mp 109-110°; ir (potassium bromide): 3306 (NH), 1640 and 1543 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.89 (t, 3H), 1.61 (s, 6H), 3.15 (q, 2H), 3.74 (s, 3H), 5.68 (br s, 1H), 6.97 (s, 1H), 7.23 (m, 4H).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.75; H, 8.28; N, 11.54.

2-(Ethylamino)-2-methyl-1-(1-methyl-1*H*-indol-3-yl)-1-propanone Hydrochloride (**26**).

The combined acid water extracts from the isolation of **25** were made basic with 20% sodium hydroxide and extracted with ether (2 × 100 ml). The combined ether layers were washed with water, dried, filtered, and evaporated *in vacuo*. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 1.5 g (5%) of **26**, mp 329-330°. The spectra were identical to an authentic sample [1].

3-Dimethylamino-2-methyl-1-(1-methyl-1*H*-indol-3-yl)-1-propanone Hydrochloride (**27**).

To a solution of 50 g (1.11 moles) of dimethylamine in 150 ml of methanol was added 28.0 g (0.1 mole) of **2**. The reaction mixture was stirred at reflux for 18 hours and the solvent was removed *in vacuo*. The residue was partitioned between ether and water and the organic layer was extracted with 1.0 *M* hydrochloric acid (2 × 50 ml). The combined acid water layers were made basic with 20% sodium hydroxide and extracted with ether (2 × 200 ml). The combined ether layers were washed with water, dried, filtered, and evaporated *in vacuo*. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 18.4 g (65%) of **27**, mp 183-190°. Recrystallization of a sample from methanol-ether provided an analytical sample, mp 194-196°; ir (potassium bromide): 1643 (C=O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.61 (d, 3H), 3.21 (s, 3H), 3.68 (m, 3H), 3.99 (s, 3H), 5.08 (HDO + exchangeable protons), 7.53 (m, 3H), 8.32 (m, 1H), 8.45 (s, 1H).

Anal. Calcd. for $C_{15}H_{20}N_2O$·HCl: C, 64.15; H, 7.54; N, 9.98. Found: C, 64.30; H, 7.75; N, 9.86.

Examination of the neutral ether layers from the isolation of **27** failed to indicate the presence of any identifiable compounds.

2-Methyl-1-(1-methyl-1*H*-indol-3-yl)-3-(1-pyrrolidinyl)-1-propanone Hydrochloride (**28**).

A solution of 28.0 g (0.1 mole) of **2** in 150 ml of pyrrolidine was heated at reflux for 3 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and 1.0 *N* sodium hydroxide. The ether layer was washed with water, dried, filtered, and evaporated *in vacuo*. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 30.1 g (98%) of **28**, mp 202-207°. A sample recrystallized from 2-propanol had, mp 211-212°; ir (potassium bromide): 3440 (NH·HCl), 1640 (C=O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.59 (d, 3H), 2.01-2.46 (m, 4H), 3.38-3.87 (m, 6H), 3.98 (s, 3H), 5.09 (s, HOD + exchangeable protons), 7.52 (m, 3H), 8.38 (m, 1H), 8.54 (s, 1H).

Anal. Calcd. for $C_{17}H_{22}N_2O$·HCl: C, 66.54; H, 7.55; N, 9.13. Found: C, 66.40; H, 7.70; N, 9.10.

2-(*t*-Butylamino)-2-methyl-1-(1-methyl-1*H*-indol-3-yl)-1-propanone Hydrochloride (**29**).

A solution of 28.0 g (0.1 mole) of **2** in 100 ml of *t*-butylamine and 150 ml of *t*-butyl alcohol was refluxed for 72 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The ether layer was extracted with 1.0 *M* hydrochloric acid (2 × 75 ml) and the combined aqueous acid layers were washed with ether and made basic with 20% sodium hydroxide. After extracting with ether (2 × 250 ml), the combined ether layers were washed with water, dried, filtered, and evaporated *in vacuo* to give 23.1 g of the crude free base of **29**. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 25.9 g, (84%) of **29**, mp 194-196°; ir (potassium bromide): 3420 (br NH·HCl), 1638 (C=O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.62 (d, 3H), 1.70 (br s, 12H), 3.36-3.72 (m, 3H), 3.93 (s, 3H), 5.10 (s, HOD + exchangeable protons), 7.50 (m, 3H), 8.35 (m, 2H).

Anal. Calcd. for $C_{17}H_{24}N_2O$·HCl: C, 66.11; H, 8.16; N, 9.07. Found: C, 65.93; H, 8.36; N, 9.20.

2-Methyl-3-(methylamino)-1-(1-methyl-1*H*-indol-3-yl)-1-propanone Hydrochloride (**30**).

A solution of 9.9 g (0.05 mole) of **23** in 200 ml of methanol was saturated with gaseous methylamine without external cooling. After heating at gentle reflux for 18 hours, the solvent was partitioned between ether and water. The organic layer was washed with water (4 × 100 ml), dried, filtered, and concentrated *in vacuo*. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 9.2 g (69%) of **30**, mp 190-193°. An analytical sample recrystallized from 2-propanol-ether had, mp 192-193°; ir (potassium chloride): 3345 (br NH·HCl), 1685 (C=O) cm^{-1}; ^1H nmr (deuterium oxide): δ 1.62 (d, 3H), 3.08 (s, 3H), 3.36-3.77 (m, 3H), 3.89 (s, 3H), 5.05 (s, HOD + exchangeable protons), 7.47 (m, 3H), 8.36 (m, 1H), 8.53 (s, 1H).

Anal. Calcd. for $C_{14}H_{18}N_2O$·HCl: C, 63.03; H, 7.18; N, 10.50. Found: C, 63.10; H, 7.33; N, 10.43.

3-(Diethylamino)-2-methyl-1-(1-methyl-1*H*-indol-3-yl)-1-propanone Hydrobromide (**31**).

A suspension of 28.0 g (0.1 mole) of **2** in 150 ml of diethylamine was heated at gentle reflux for 72 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was extracted with 1.0 *M* hydrochloric acid (2 × 100 ml) and the combined aqueous layers were washed with ether and made basic with 20% sodium hydroxide. After extracting with ether (2 × 250 ml), the combined ether layers were washed with water, dried, clarified with Norit, filtered through Celite, and concentrated *in vacuo*. The residue was converted to its hydrobromide salt by dissolving in 2-propanol and bubbling in hydrogen bromide. Precipitation was completed by diluting with ether to give 25.6 g (73%) of **31**, mp 133-135°; ir (potassium chloride): 1618 (C=O) cm^{-1}; ^1H nmr (deuterium oxide): δ 1.35-1.64 (m, 9H), 3.20-3.58 (m, 4H), 3.62-3.96 (m, 3H), 3.98 (s, 3H), 5.05 (s, HOD + exchangeable protons), 7.48 (m, 3H), 8.38 (m, 2H).

Anal. Calcd. for $C_{17}H_{24}N_2O$·HBr: C, 57.79; H, 7.13; N, 7.93. Found: C, 57.63; H, 7.26; N, 7.84.

N,α,α,1-Tetramethyl-1*H*-indole-3-ethanamine Hydrochloride (**32**).

To a suspension of 3.8 g (0.1 mole) of lithium aluminum hydride and 4.5 g (33 mmoles) of aluminum chloride in 250 ml of ether was added a solution of 3.0 g (13 mmoles) of **4** in 100 ml of ether (in 10 ml portions). The mixture was stirred at room temperature for 3 hours and worked up by the consecutive dropwise addition of 4 ml of water, 3 ml of 40% sodium hydroxide and 8 ml of water, titrating the final addition to give a fine granular precipitate. The ether was removed by filtration, the precipitate was washed with ether and the filtrate was concentrated *in vacuo*. The residue was converted to its hydrochloride salt using 2-propanolic hydrogen chloride to give 2.7 g (82%) of **32**, mp 208-212°. An analytical sample from 2-propanol-ether had, mp 212-214°; ir (potassium bromide): 3440 (br NH·HCl) cm^{-1}; ^1H nmr (deuterium oxide): δ 1.65 (s, 6H), 2.78 (s, 3H), 3.55 (s, 2H), 3.93 (s, 3H), 5.02 (s, HOD + exchangeable protons), 7.53 (m, 3H), 8.02 (m, 2H).

Anal. Calcd. for $C_{14}H_{20}N_2$·HCl: C, 66.51; H, 8.38; N, 11.08. Found: C, 66.70; H, 8.46: N, 11.07.

1,α,α-Trimethylindole-3-acetic Acid (**33**).

A solution of 1.0 g (4.3 mmoles) of **4** in 10 ml of 6.0 *M* hydrochloric acid was heated at reflux for 18 hours. The solvent was evaporated *in vacuo* and the residue was suspended in 15 ml of water and dissolved to *p*H 11.0 with 10% sodium hydroxide. After filtering through a fiber glass pad to clarify, the filtrate was adjusted to *p*H 1.5 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration washed with water and dried *in vacuo* to give 0.88 g (94%) of **33**, mp 176-178°; ir (potassium bromide): 1695 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95 (s, 6H), 3.98 (s, 3H), 7.36 (m, 1H), 7.54 (m, 2H), 7.96 (d, 1H).

Anal. Cacld. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.71; H, 6.89; N, 6.36.

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[3a] The term Favorskii rearrangement is used to indicate a mechanism which involves the formation of a cyclopropanone intermediate formed by the abstraction of an α-hydrogen from an α-haloketone. For example see: A. A. Akhrem, T. K. Ustynyuk, and Y. A. Titov, *Russ. Chem. Rev.*, **39**, 732-746 (1970); D. H. Hunter, J. B. Strothers and E. W. Warnhoff, in P. de Mayo, Rearrangements in Ground and Excited States, Vol **1**, pp 437-461, Academic Press, New York, 1980; C. Rappe, in S. Patai, The Chemistry of the Carbon-Halogen Bond, Part **2**, pp 1084-1101, John Wiley and Sons, New York, 1973; A. Kende, *Org. React.*, **11**, 261-316 (1960); R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

[3b] The term quasi-Favorskii rearrangement is used to indicate a semi-Benzilic rearrangement which does not involve the formation of a cyclopropanone intermediate from an α-haloketone possessing an α-hydrogen. For an example see: E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **81**, 1201 (1959).

[3c] The term pseudo-Favorskii rearrangement is used to indicate the formation of a cyclopropanone intermediate with the assistance of the electron pair on the nitrogen of an α-haloketone without the presence of an α-hydrogen. For examples see Reference 4.

[3d] Other examples of the formation of cyclopropane and aziridine intermediates using this mechanism can also be shown. See: M. Julia, H. Igolen, and J. Lenzi, *Bull. Soc. Chim.*, 2291 (1966); W. D. Clossen, S. A. Roman, G. T. Kwiatkowski, and D. A. Corwin, *Tetrahedron Letters*, 2271 (1966); M. Cohen, *Tetrahedron Letters*, 2165 (1970).

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[10] As proof of structure of the original rearranged amide, the reduced tryptamine analog was prepared by trimethylating indole-3-acetonitrile, reducing to the tryptamine and monomethylating the amine function. The physical and spectroscopic properties were identical with **32**.

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