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Articles

Process Research and Development of Melatonin†

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Abstract:

A short, simple, and industrially feasible process for the preparation of melatonin (*N*-acetyl-5-methoxy tryptamine), starting from phthalimide and 1-bromo-3-chloropropane, in essentially four steps is discussed. The present article elucidates the preparative process along with the impurity profile of each intermediate.

Introduction

Much has been claimed about the therapeutic effects of the hormone melatonin in the recent past,[1] even to the extent of publication of two popular scientific books[2] maintaining that the hormone can alleviate the symptons of cancer, high blood pressure, Alzheimer's disease, AIDS, and coronary heart disease as well as improve sleep, sexual vitality, and longevity, thus making it a wonder drug of the 1990s. Melatonin was discovered in 1958 by a dermatologist, Aaron Lerner of Yale University. Its property of skin-lightening by the aggregation of the pigment melanin containing melanosomes within the skin cells of amphibians was reported, and since then, scientists have attempted to define the role of melatonin in animal and human physiology. Melatonin is mainly synthesised in the pineal gland, a pea-sized organ situated in the centre of the brain, and to a lesser extent in the retina.[3] Though the conclusions that melatonin might be useful in problems such as aging and coronary heart disease are speculative at present, it has created some interest among synthetic organic chemists, culminating in the development of several synthetic routes.[4]

Results and Discussion

Of all the schemes available in the literature, we selected two routes on the basis of their being seemingly feasible and commercially viable. The first route[4g] (Scheme 1) involves reacting 1-bromo-3-chloropropane **2** with an active methylene compound, **1** (ethylacetoacetate or diethylmalonate), followed by the Japp−Klingemann reaction[5] of the resulting keto ester **3** with a diazonium salt of *p*-anisidine to afford the 2-carbethoxy-5-methoxy tryptamine **4**. The ester **4** on hydrolysis gives the acid **5,** which on decarboxylation affords the 5-methoxy tryptamine **6,** which on acetylation yields melatonin **7**. The route worked out very well in terms of chemistry. Reaction of **2** and ethylacetoacetate **1**, in the presence of potassium carbonate in DMSO, gave compound **3** in about 75% yield after distillation under high vacuum. **3** on Japp−Klingemann reaction with the diazonium salt of *p*-anisidine resulted in the formation of **4** in 15−20% yield. This step became a bottleneck during scale-up trials. The tryptamine derivative **4** on hydrolysis afforded the corresponding acid **5** in ∼80% yield, which on subsequent decarboxylation gave **6** in ∼90% yield. Compound **6** on acetylation with acetic anhydride produced the required melatonin **7** in ∼80% purified yield. However, we faced a few problems during scale-up of this process:

(i) Compound **3** was a liquid, which had to be purified by high-vacuum distillation at a high temperature, and this posed problems during scale-up trials, resulting in reduction in yields due to partial charring of the compound.

(ii) The yield of the diazotisation step to produce **4** was very low (15−20%).

(iii) Though the remaining three steps proceeded quite comfortably, affording reasonably good yields, this route had to be abandoned on the basis of the cumbersome process and low overall yield (10%).

The second route[4i] (Scheme 2) involves the initial reaction of potassium phthalimide with 1,3-dibromopropane in the presence of sodium/ethanol to give the 3-bromopropyl-1-phthalimide **8a**, which upon reaction with ethylacetoacetate **1** affords the phthalimido keto ester **9**. The keto ester **9** on

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(1) (a) Skene, D. J. *Chem. Ind*. **1996**, 637. (b) Das, U. N. *Med. Sci. Res*. **1994**, *22*, 463.

(2) (a) Pierpaoli, W.; Regelson, W. *The melatonin miracle: Nature's age reversing, disease fighting, sex enhancing harmone*; Simon & Schuster: New York, 1995. (b) Reiter, R. J.; Robinson, J. *Melatonin: Your body's natural wonder drug*; Bantam Books: New York, 1995.

(3) Arendt, J. *Melatonin and the mammalian pineal gland*; Chapman Hall: London, 1995.

(4) (a) Luigi, D. B.; Vittorio, D. B. Belgium Patent BE 824022, 1975. (b) Bertholet, R.: Hirsbrunner, P. European Patent EP 130303, 1985. (c) Somei, M.; Fukui, Y. *Heterocycles* **1993**, *36*, 1859. (d) Flaugh, M. E.; Crowell, T. A.; Clemens, J. A.; Sawyer, B. D. *J. Med. Chem*. **1979**, *22*, 63. (e) Shono, T.; Matsumura, Y.; Kanazawa, T. *Tetrahedron Lett.* **1983**, *24*, 1259. (f) Blickenstaff, R. T.; Brandstadter, S. M.; Reddy, S.; Witt, R. *J. Pharm. Sci*. **1994**, *83*, 216. (g) Szantay, Cs.; Szabo, L.; Kalaus, Gy. *Synthesis* **1974**, 354. (h) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707. (i) Franco, F.; Luigi, D. B.; Ermanno, D. European Patent EP 330625, 1989.

(5) Philips, R. R. *Org. React.* **1959**, *10*, 143.

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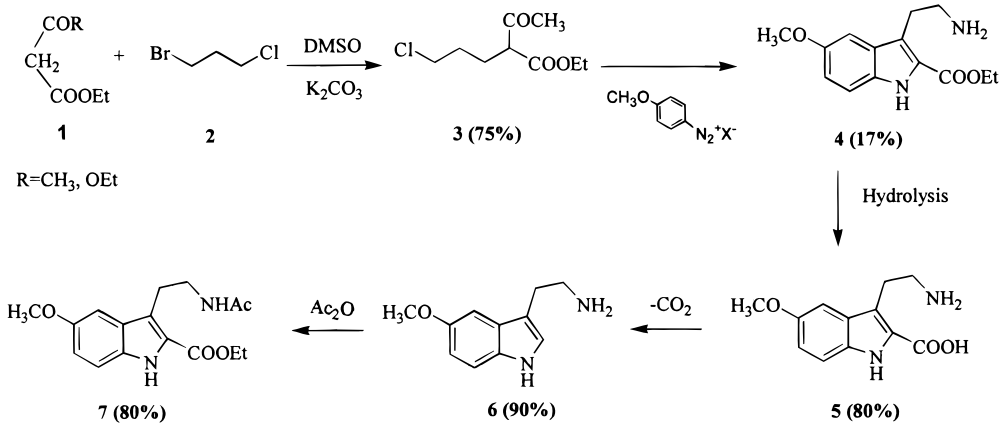
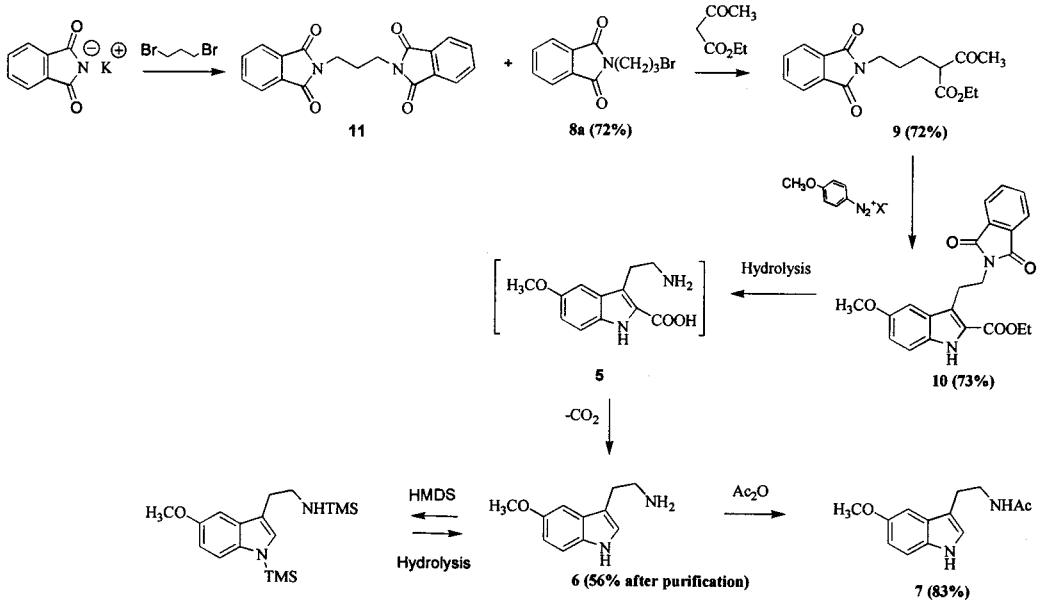
Scheme 1



Scheme 2



Japp−Klingemann reaction with a diazonium salt of *p*-anisidine gives the 2-carbethoxy-5-methoxy-3-((2-phthalimido)ethyl) indole **10**. The ester **10** on hydrolysis and decarboxylation gives 5-methoxy tryptamine **6**. Purification of the tryptamine derivative **6** involved silylation with HMDS, followed by distillation of the mono- and disilylated compound and subsequent hydrolysis to afford pure **6**. Acetylation of **6** yields melatonin **7**. Though Scheme 2 appeared to be seemingly straightforward, with a betteroverall yield (18%) compared to that of the first route (Scheme 1), a few problems were encountered:

(i) Preparation of potassium phthalimide adds one extra step to the process. On the other hand, procurement of the same would be an expensive affair.

(ii) Use of sodium (for the preparation of bromopropylphthalimide) in plant-scale reactions would be hazardous.

(iii) Initial attempts to prepare bromopropylphthalimide **8a** from potassium phthalimide and 1,3-dibromopropane gave the disubstituted product, 1,3-diphthalimidopropane **11**, as the predominant product.

(iv) Purification of **6** by the silylation/hydrolysis protocol appeared to be tedious on large scale.

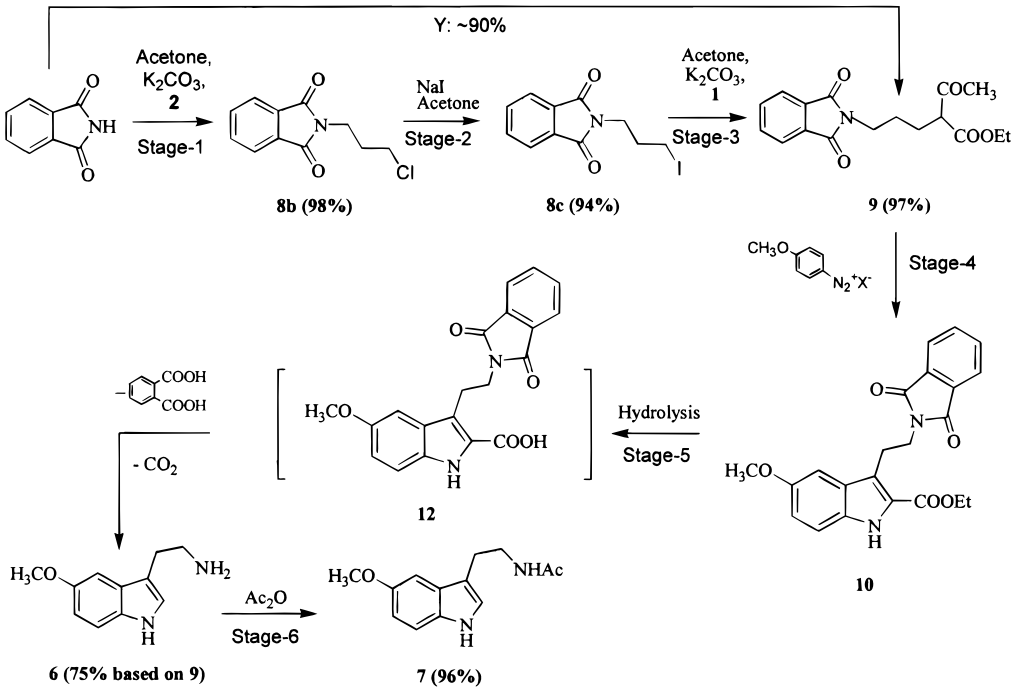
Process Improvement

A few important modifications were made to simplify the above process to make it more cost-effective, as shown in Scheme 3. The above synthetic route was changed little in terms of the chemistry, but the reagents, reaction conditions, and workup procedures were altered considerably to make the scale-up operations simpler and industrially viable.

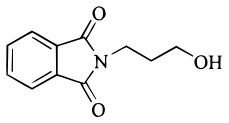
Stage 1. The preparation of **8a** from potassium phthalimide and 1,3-dibromopropane using potassium carbonate as base has been reported in the literature,[4i] but as mentioned earlier, in our hands use of 1,3-dibromopropane led to the predominant formation of **11**. Hence, it was decided to employ the same Gabriel synthesis,[6] albeit using 1-bromo-3-chloropropane **2**, which would probably reduce the formation of **11**, as the reactivities of chloro and bromo substituents differ significantly. We also attempted to use phthalimide directly instead of converting it to its potassium salt, and the reaction worked very well, yielding about 98% of chloropropylphthalimide **8b,** with a HPLC purity of ~98%.

(6) (a) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224. (b) Gibson M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919.

Scheme 3



The use of phthalimide and 1-bromo-3-chloropropane not only simplified the process but also proved to be less expensive. GC−MS analysis of the mother liquors indicated the presence of the following impurities. Apart from small quantities of the bromopropylphthalimide **8a** and the corresponding hydroxy compound **13**, the major impurity was found to be the 1,3-diphthalimidopropane **11**.



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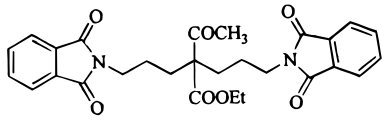
Stage 2. We had some trouble in the direct condensation of chloropropylphthalimide **8b** with ethylacetoacetate, as the reaction was very sluggish. Hence, we performed a Finkelstein substitution[7] on **8b**, employing sodium iodide (1.5 equiv) in refluxing acetone, to yield the iodopropylphthalimide **8c** in 94% yield. GC−MS analysis of the mother liquors indicated the presence of a small amount of the unreacted starting material **8b,** apart from the other carried-over impurities **8a**, **13**, and **11**.

Stage 3. The condensation reaction between ethylacetoacetate (1.05 equiv) in refluxing acetone/potassium carbonate (5 equiv) and **8c** was smooth and facile to yield **9** in 97%. With an intention of further simplifying the process of preparing **9**, the first three steps were clubbed, as all three steps required acetone as the solvent and, in two steps, potassium carbonate as the base. The inorganic salts were filtered after each step, and the next step was carried out by adding the calculated amounts of the required reagents without isolating the products. This procedure produced **9** in the same yield as that of the stepwise reaction, although the purity came down by 2−3%, which we found would not interfere in the subsequent steps. LC−MS analysis of the mother liquors indicated the presence of the following impurities. The three halopropylphthalimides **8a**, **8b**, and **8c** were found to be present to the extent of ∼0.1−0.5% each, while two other minor dialkylated impurities, **14** and **15**, were also found to the tune of ∼0.2−0.3% each.



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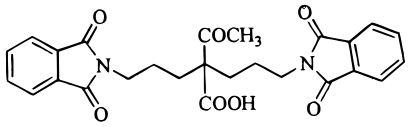

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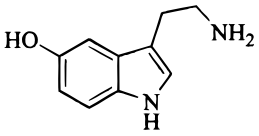
Stage 4. Ethyl-2-acetyl-5-phthalimido pentanoate **9** on Japp−Klingemann reaction with the diazonium salt of *p*-anisidine gave **10** in about 80% yield with 80% HPLC purity. We established the fact that the low purity of **10** does not pose any problem in the subsequent steps, as the two major impurities present in **10** were identified to be the hydrolyzed product **12**, 5-methoxytryptamine **6,** and 5-methoxy tryptamine-2-carboxylic acid **5**. LC−MS analysis of the mother liquors indicated the presence of the following impurities apart from **12**, **6,** and **5**. While the compounds **5**, **10,** and **12** do not pose any problem in the subsequent step, as all of them lead to the same product **6**, there were other minor impurities, such as the unreacted starting material **9** and the carried-over impurities **14** and **15**.

(7) (a) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528. (b) Smith, W. B.; Branum, G. D. *Tetrahedron Lett.* **1981**, *22*, 2055.

Stage 5. Compound **10** (contaminated with **6** and **12**) was hydrolyzed in 12% aqueous potassium hydroxide solution, and without isolating **12**, the reaction mass was directly subjected to treatment with 5% hydrochloric acid to give **6** in about 75% yield based on **9** with a HPLC purity of ~99%. The aqueous phase was freeze-dried to give 85 g of a solid, which was subjected to LC−MS analysis to identify the following impurities. This stage was found to be the most complicated of all in terms of its impurity profile. Apart from the 5-methoxy tryptamine derivatives **4**, **5**, **10**, **12**, **17**, and **18**, the 5-hydroxy derivatives **16** and **19** also were found, arising due to demethylation. It is worth mentioning that the heterocyclic skeleton present in compounds **17** and **19** is interesting, as some biologically active compounds such as incasan[8] and canthin[9] derivatives possess this skeleton.



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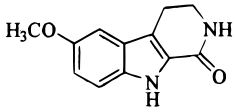

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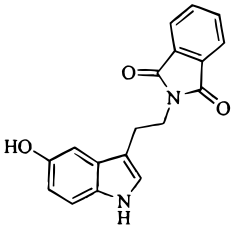

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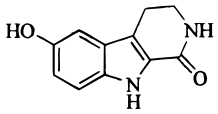

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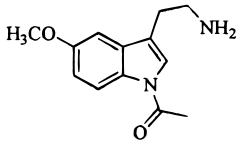
Stage 6. The conversion of 5-methoxytryptamine **6** by acetylation to melatonin **7** gave an isolated yield of ~80% with pharmaceutically acceptable quality. The mother liquors were concentrated to give a gummy mass, which was used for the impurity profile study. Apart from the unreacted starting material **6**, the indole *N*-acetylated compound **20** and the diacetyl compound **21** also were present in the mother liquor.



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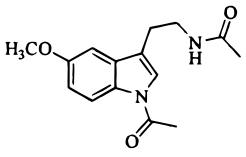

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(8) (a) Zaitsev, S. A.; Glushkov, R. G.; Andreeva, N. I.; Mashkovskii, M. D. *Khim.-Farm. Zh.* **1990**, *24*, 112. (b) Askinazi, B. Z.; Vekshina, L. I.; Kogan, N. A.; Kozarinskaya, N. *Khim.-Farm. Zh.* **1981**, *15*, 70.

(9) Narayanan, K.; Schindler, L.; Cook, J. M. *J. Org. Chem.* **1991**, *56*, 359.

Scale-Up Trials. With the procedures fully optimised, for stage 1 to stage 6 of Scheme 3, the scale-up trials were performed at 5−10 kg scale. This route was operated routinely and reliably, affording the expected yields and purities in all stages of the synthesis, demonstrating the robustness and viability of the process.

Conclusions

A short, simple, and inexpensive industrially feasible process for the preparation of melatonin has been developed. Preparations of **9** and **6** have been simplified without compromising on their yield and purity. A simple way of conducting the impurity profile study has been employed by enriching the impurities in the mother liquor. The following are the advantages of the present process:

(i) Importantly, the process is cost-effective. A simple, commercially viable, and short synthetic route has been developed. Phthalimide, which is relatively inexpensive and more easily available than its potassium salt, has been used as one of the starting materials.

(ii) Another inexpensive chemical, 1-bromo-3-chloropropane, is used in the place of the expensive 1,3-dibromopropane as reported in the literature.[4i] This not only makes the route more cost-effective but also helps in reducing the diphthalimidopropane impurity.

(iii) Potassium carbonate is used, which is relatively inexpensive and easy to handle, compared to sodium in ethanol as reported in the literature.[4i]

(iv) A short synthesis of ethyl-2-acetyl-5-phthalimido pentanoate **9** is developed by combining three stages.

(v) The synthetic route is simplified by combining the hydrolysis and decarboxylation steps into a single-pot operation to produce **6**.

(vi) The purification of 5-methoxy tryptamine **6** is simplified, unlike the cumbersome silylation and hydrolysis sequence reported in the literature.[4i]

(vii) The final product is obtained in ~99.5% purity directly with a pharmaceutically acceptable quality.

(viii) There is an overall improvement in yield and purity using inexpensive chemicals and simplified single-pot syntheses in two stages.

(ix) Workup procedures are simplified.

Experimental Section

General. Solvents and reagents were obtained from commercial sources and were used as such without any further purification, unless specified. The melting points were recorded on a Buchi-535 apparatus and are uncorrected. The ^{1}H NMR spectra were obtained using a 200-MHz Varian Gemini spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded using a Perkin-Elmer model 1640 instrument. Mass spectra were recorded on an MS Engine, Hewlett Packard model 5989, at DIP 20 eV. HPLC equipment consisted of a Waters 510 pump, a Waters 486 UV−vis detector, a Waters 746 data module, and a Novapack C^{18} column.

Preparation of Chloropropyl Phthalimide (8b). One hundred grams of phthalimide, 2.5 L of acetone, and 187 g

of potassium carbonate were taken into a 5-L four-neck round-bottom flask fitted with a mechanical stirrer and a refluxing condenser. Next, 117 g of 1-bromo-3-chloropropane **2** was added rapidly under stirring at room temperature, and the reaction mixture was refluxed for 16 h. Progress of the reaction was monitored by TLC. The reaction mass was cooled to room temperature, and the insoluble inorganic salts were filtered, dried, and used for the analysis of inorganic salts. The filtrate was concentrated to give crude **8b**, which was triturated with petroleum ether (300 mL) to afford 150 g of pure **8b** (yield, 98%; purity, 98%; mp 70 °C). HPLC analysis: Novapack C^{18} 150-mm column, mobile phase 0.01 M KH_2PO_4/CH_3CN in 55:45 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 5 min. IR: 1773, 1718, 1395, 1110, 1032, 870, 724 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.8 (m, 4H), 3.9 (t, 2H), 3.6 (t, 2H), 2.2 (m, 2H). Mass: 223, corresponding to $C_{11}H_{10}NO_2Cl$.

Preparation of Iodopropylphthalimide (8c). One hundred grams of the chloropropylphthalimide **8b** and 66 g of sodium iodide were taken into a 2-L round-bottom flask. One litre of acetone was added, and the mixture was refluxed for a period of 12 h. Though the reaction can be monitored by TLC by the multiple run technique, it is generally preferred to monitor the reaction by either GC or HPLC, as both **8b** and **8c** elute with almost the same R_f on TLC. After the reaction was complete, the reaction mass was cooled to room temperature, and the insoluble salts were filtered and analysed for inorganic salts. The filtrate was concentrated to give ~160 g of crude **8c**, which was triturated with chilled MeOH to give 134 g of **8c** (yield, 94%; purity, 97%; mp 85−88 °C). HPLC analysis: Novapack C^{18} 150-mm column, mobile phase 0.01 M KH_2PO_4/CH_3CN in 55:45 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 6.5 min. IR: 1763, 1703, 1402, 1198, 722 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.8 (m, 4H), 3.8 (t, 2H), 3.2 (t, 2H), 2.25 (m, 2H). Mass: 316 (M + 1), corresponding to $C_{11}H_{10}NO_2I$.

Preparation of Ethyl-2-acetyl-5-phthalimido Pentanoate (9). A 217-g portion of potassium carbonate and 1 L of acetone were taken into a 2-L round-bottom flask. Next, 43 g of ethylacetoacetate was added, and the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature, and then 100 g of **8c** was added over a period of 15 min. The reaction mixture was again refluxed for a further period of 4 h, monitoring the reaction by TLC. After the completion of the reaction, the reaction mass was cooled to room temperature, and the insoluble inorganic salts were filtered and analysed. The solvent was concentrated to yield 130 g of residue, to which 150 mL of water was added, and the mixture was acidified to pH 4, followed by extraction into dichloromethane. The solvent was distilled off, and the residue was triturated with chilled petroleum ether to give 97 g of **9** (yield, 97%; purity, 97%; mp 56−58 °C, lit.[4i] mp 60 °C). HPLC analysis: Novapack C^{18} 150-mm column, mobile phase 0.01 M KH_2PO_4/CH_3CN in 55:45 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 4.2 min. IR: 1739, 1713, 1401, 1244, 1192, 1145, 1043, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75 (m, 4H), 4.15 (q, 2H), 3.7 (t, 2H), 3.5 (t, 1H), 2.25 (s, 3H), 1.5−2.0 (m, 4H), 1.25 (t, 3H). Mass: 317, corresponding to $C_{17}H_{19}NO_5$).

Preparation of Ethyl-2-acetyl-5-phthalimidopentanoate (9) by Combining the First Three Stages. (a) First, 100 g of phthalimide, 2.5 L of acetone, and 187 g of potassium carbonate were taken into a 5-L four-neck round-bottom flask fitted with a mechanical stirrer and a reflux condenser. Next, 117 g of 1-bromo-3-chloropropane **2** was added rapidly under stirring at room temperature, and the reaction mixture was refluxed for 16 h. The progress of the reaction was monitored by TLC. The reaction mass was cooled to room temperature, and the insoluble inorganic salts were filtered. The filtrate containing **8b** was used as such for the next step.

(b) A 99-g portion of sodium iodide was added, and the mixture was refluxed for a period of 12 h. Though the reaction can be monitored by TLC by the multiple run technique, it is generally preferred to monitor the reaction by GC/HPLC, as both **8b** and **8c** elute with almost the same R_f on TLC. After the reaction was complete, the reaction mass was cooled to room temperature, and the insoluble salts were filtered. The filtrate containing **8c** was used as such for the next step.

(c) A 435-g portion of potassium carbonate and 86 g of ethylacetoacetate were added to the above acetone solution, and the solution was refluxed for 4 h, monitoring the reaction by TLC. After the completion of the reaction, the reaction mass was cooled to room temperature, and the insoluble inorganic salts were filtered. The solvent was concentrated, and the residue was taken in water, acidified to pH 4, and extracted into dichloromethane. The solvent was distilled off, and the residue was triturated with chilled petroleum ether to give 194 g (yield, 90% based on phthalimide; purity, ~96%; mp 56−58 °C) of **9**.

Preparation of 2-Carboxyethyl-3-(2-phthalimidoethyl)-5-methoxy Indole (10). Part A. One hundred grams of ethyl-2-acetyl-5-phthalimidopentanoate **9** and 1 L of methanol were taken into a 2-L four-neck round-bottom flask. Next, 206 g of sodium acetate was added to the reaction flask under stirring over 5 min, and the solution was stirred at room temperature for 1 h. Meanwhile, part B material was prepared.

Part B. A 39-g portion of *p*-anisidine, 125 mL of methanol, and 185 mL of water were taken in a 1-L four-neck round-bottom flask, stirred, and cooled to 0 °C. Next, 125 mL of concentrated hydrochloric acid was added to the reaction mixture over 30 min under stirring. The reaction mixture was allowed to stir at 0 °C for 10 min. Freshly prepared sodium nitrite solution (24 g in 90 mL of water) was added slowly to the reaction mixture from −5 to 0 °C over 30 min. After addition, the reaction mixture was allowed to stir at 0 °C for 30 min.

The part A mixture was cooled to 0 °C, and the part B mixture was added slowly over 30 min, and then the resulting reaction mixture was allowed to warm to room temperature with stirring and maintained at room temperature for a further 3 h. The reaction mass was extracted with dichloroethane (1 L), washed with water to attain neutral pH, and distilled. The residue thus obtained was transferred with 100 mL of

methanol into a 1-L four-neck round-bottom flask fitted with a mechanical stirrer and heated to reflux. Next, 10% anhydrous HCl in methanol (500 mL) was added slowly through a pressure-equalising dropping funnel over 30 min at refluxing temperature. Solid was seen separating out by the time about 350−400 mL of 10% HCl in methanol was added. Addition was continued under stirring, and the mixture was refluxed for a further 2 h after complete addition of the 10% HCl/MeOH. The reaction mass was cooled to 5 °C under stirring for 30 min, and the solid was filtered and washed with chilled methanol (200 mL). The crude compound **10** weighed 98 g and had a HPLC purity of ∼80%. HPLC analysis: Novapack C^{18} 150-mm column, mobile phase 0.01 M KH_2PO_4/CH_3CN in 55:45 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 9 min. IR: 3324, 1772, 1719, 1683, 1393, 1261, 1219, 1017, 716 cm^{-1}. ^1H NMR (DMSO + $CDCl_3$): δ 11.3 (br s, 1H), 7.8 (m, 4H), 7.3 (d, 1H), 7.0 (s, 1H), 6.8 (d, 1H), 4.3 (q, 2H), 3.9 (t, 2H), 3.7 (t, 2H), 1.4 (t, 3H). Mass: 392, corresponding to $C_{22}H_{20}N_2O_5$. This compound was used as such for the next step without any further purification.

Preparation of 5-Methoxy Tryptamine (6). One hundred grams of the crude compound **10** was taken into a 5-L round-bottom flask fitted with a mechanical stirrer and refluxing condenser. Next, 425 mL of 12% aqueous potassium hydroxide solution was added, and the mixture was heated to reflux for 3 h. Progress of the reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass, containing mostly **12** and a small quantity of **6**, was directly acidified with 5% HCl, followed by refluxing for 8 h. The progress of the reaction was again monitored by TLC. After the completion of the reaction, the reaction mass was cooled to 0−5 °C, and the solid (4.5 g; mp 195−198 °C) thus obtained was filtered. This solid was found to be phthalic acid. The filtrate thus obtained after the removal of phthalic acid was cooled to 0 °C and basified with 50% sodium hydroxide solution (200 mL). The separated solid was filtered and washed with 100 mL of water to give 57 g of **6** (yield, 75% based on **9**; purity, 99%; mp 116−119 °C, lit.[4i] mp 120 °C). HPLC anaylsis: Novapack C^{18} 300-mm column, mobile phase 0.05 M NH_4OAc/CH_3CN in 80:20 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 4 min. IR: 3349, 3197, 1662, 1499, 1215, 1110, 1024, 808, 776 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.2 (br s, 1H), 7.25 (m, 1H), 7.0 (m, 2H), 6.8 (m, 1H), 3.8 (s, 3H), 2.8−3.1 (m, 4H), 2.5 (br s, 2H). Mass: 190, corresponding to $C_{11}H_{14}N_2O$).

Preparation of Melatonin (7). Thirty grams of **6** was taken into a 1-L four-neck round-bottom flask. Next, 400 mL of dichloroethane was added, and the mixture was cooled to 0 °C. Then, 30 mL of acetic anhydride in 50 mL of dichloroethane was added at the same temperature during 30 min, and the mixture was maintained at 0 °C for 1 h. The progress of the reaction was monitored by TLC, and after the completion of the reaction, 150 mL of dichloroethane was added to the reaction mass, which was then washed with 400 mL of sodium bicarbonate solution. The organic layer was concentrated after being treated with activated charcoal (5 g) and triturated with petroleum ether to give 35 g of pure melatonin **7** (yield, ∼96%; purity, 99.8%; mp 116−117 °C, lit.[4i] 116−117 °C). HPLC analysis: Novapack C^{18} 300-mm column, mobile phase 0.05 M NH_4OAc/CH_3CN in 80:20 ratio, flow 1 mL/min, $\lambda = 230$ nm, retention time 10.5 min. IR: 3304, 1629, 1586, 1555, 1489, 1212, 1176, 1041 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.1 (br s, 1H), 7.3 (d, 1H), 7.05 (br s, 2H), 6.9 (d, 1H), 5.6 (br s, 1H), 3.9 (s, 3H), 3.6 (m, 2H), 2.95 (t, 2H), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.4, 153.6, 131.5, 127.5, 122.9, 112.0, 111.9, 100.2, 55.7, 39.7, 25.0, 23.0. Mass: 232, corresponding to $C_{13}H_{16}N_2O_2$.

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