The bromination–methanolysis of *N*-acetyl-2,3-dimethylindole[1]

SUSAN F. VICE AND GARY I. DMITRIENKO[2]

The Guelph–Waterloo Centre for Graduate Work in Chemistry, Waterloo Campus, Department of Chemistry, University of Waterloo, Waterloo, Ont., Canada N2L 3G1

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Bromination of *N*-acetyl-2,3-dimethylindole **11** in the presence of excess methanol at room temperature gave a mixture of products consisting of *cis* and *trans* *N*-acetyl-2,3-dimethoxy-2,3-dimethylindoline **17** and **18**, 3-methoxy-2,3-dimethylindolenine **19**, and *N*-acetyl-3-methoxymethyl-2-methylindole **21**. The same reaction performed at −40°C yielded a mixture of **17**, **18**, and *N*-acetyl-2-methoxy-2-methyl-3-methyleneindoline **22**. Bromination of **11** at low temperature in the presence of 1.5 equivalents of methanol followed by treatment with triethylamine yielded **22** quantitatively. Treatment of **22** with acidic methanol readily gave **21**. The mechanistic implications of these transformations are considered.

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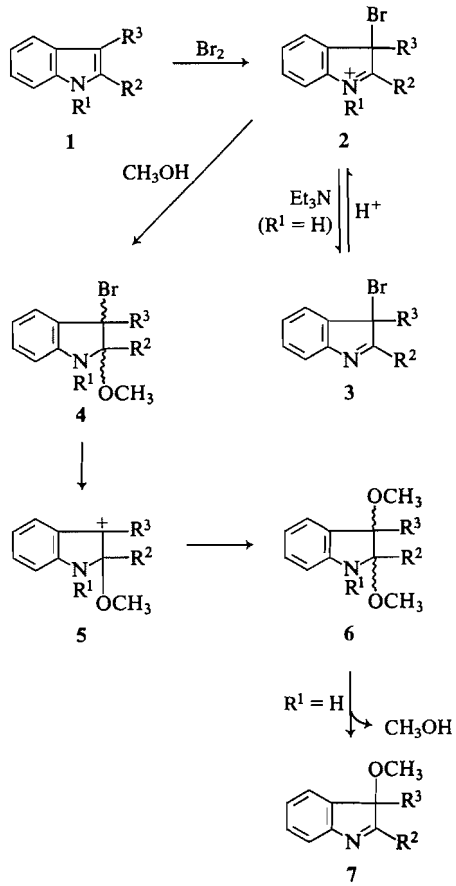
La bromation du *N*-acétyl diméthyl-2,3 indole **11**, en présence d'un excès de méthanol et à température ambiante, donne un mélange de produits comprenant les *N*-acétyl diméthoxy-2,3 diméthyl-2,3 indolines *cis* et *trans* **17** et **18**, le méthoxy-3 diméthyl-2,3 indolenine **19** et du *N*-acétyl méthoxyméthyl-3 méthyl-2 indole **21**. La même réaction effectuée à −40°C donne un mélange des isomères **17** et **18** et de *N*-acétyl méthoxy-2 méthyl-2 méthylène-3 indoline **22**. La bromation du composé **11** à basse température, en présence de 1,5 équivalent de méthanol, suivie d'une réaction avec la triéthylamine donne quantitativement le composé **22**. Ce dernier, en présence de méthanol acidulé, donne facilement le composé **21**. On considère le mécanisme de ces transformations.

[Traduit par le journal]

In connection with our interest in the development of new methods for the synthetic elaboration of 2,3-dialkylindoles **1**, we have recently reported the preparation of 3-methoxyindolenines **7** by bromination–methanolysis of 2,3-dialkylindoles (1). In the presence of triethylamine the corresponding bromindolenines **3** are moderately stable intermediates. Acidification of a solution of **3** in the presence of methanol has been shown to lead to the rapid formation of the methoxyindolenine **7**. We have argued (1*c*) that the methanolysis process likely proceeds via addition of methanol to the *N*-protonated bromoindolenine **2** to give, after deprotonation, the 2-methoxy-3-bromoindoline **4** (see Scheme 1). S_N1 type methanolysis of **4** would yield **6** (R^1 = H) which upon loss of methanol would generate the methoxyindolenine **7**.

We felt that an examination of the bromination–methanolysis of an *N*-acyl-2,3-dialkylindole **1** (R^1 = Ac) might offer some further insight into the nature of the intermediates involved in such processes. As a result, we have examined the bromination–methanolysis of *N*-acetyl-2,3-dimethylindole **11** and report the results of this investigation herein.

A survey of the literature revealed that the only previous studies of the bromination of *N*-acyl-2,3-



SCHEME 1

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[2]Author to whom communications may be addressed.

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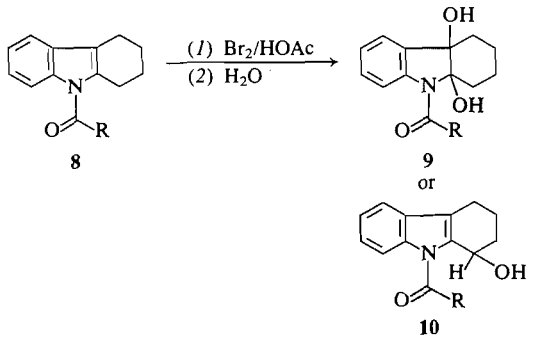
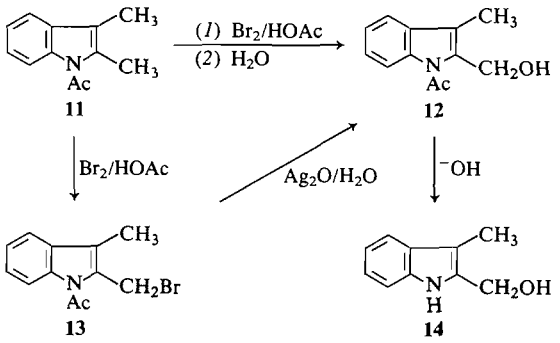


SCHEME 2

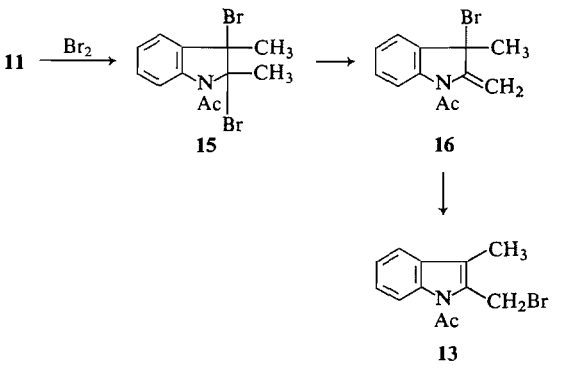
dialkylindoles were those reported by Plant and Tomlinson (2).[3] The bromination of several *N*-acetyltetrahydrocarbazoles **8** with bromine in acetic acid followed by addition of water yielded either *N*-acyl-2,3-dihydroxyindolines **9** or C2-side-chain hydroxylated products **10** (2*a*) (see Scheme 2). There was no apparent correlation between the nature of the *N*-acyl group and the nature of the product produced. In all cases products were isolated in low yield. Of the compounds examined by Plant and Tomlinson, *N*-acetyl-2,3-dimethylindole **11** was studied in greatest detail (2*b*). In this case the product of bromination–hydrolysis was *N*-acetyl-2-hydroxymethyl-3-methylindole **12** (see Scheme 3). In addition, a monobrominated product assumed to be *N*-acetyl-2-bromomethyl-3-methylindole **13** was isolated if the hydrolytic step was avoided. Hydrolysis of **13** in the presence of silver oxide yielded **12**, which upon alkaline hydrolysis gave **14**. Some years later, Taylor (3) provided proof for the assigned structure for **14** by an unambiguous synthesis.



SCHEME 3

The formation of **13** was rationalized as shown in Scheme 4. Bromination of **11** was assumed to give the dibromide **15** which upon elimination of HBr yielded the allylic bromide **16**. Allylic rearrangement of **16** would yield **13** and regenerate the aromatic indole ring system.

In our hands, bromination of **11** in glacial acetic acid as described by Plant and Tomlinson (2*b*) or in methylene chloride gave **13** as the sole product with spectroscopic characteristics compatible with the assigned structure (1*a*). On the other hand, bromination of **11** at room temperature in methanol gave a mixture of products which were separated by column chromatography (Scheme 5). Two of the products were readily recognizable as the dimethoxyindolines **17** and **18**. The proton nmr spectra of the major and minor isomers are compared in Table



SCHEME 4

1. Although we suspect that the major isomer is the *trans*-product **17** and the minor isomer the *cis*-product **18**, the available data does not allow an unambiguous assignment. A very minor product identified in the mixture was 3-methoxy-2,3-dimethylindolenine **19** arising presumably via deacylation of **17** or **18**. In addition a crystalline product, **A**, with elemental composition $C_{13}H_{15}NO_2$ was isolated in 30% yield. Initially, we felt that **A** was *N*-acetyl-2-methoxymethyl-3-methylindole **20**, derivable, in principle, by methanolysis of **13**.

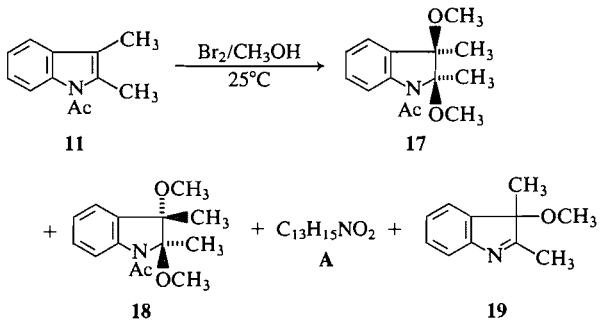
Since **17** and **18** are structurally analogous to the dihydroxyindolines produced in the bromination–hydrolysis of *N*-acyl tetrahydrocarbazoles, and since the monomethoxylated product **A** seemed to be an analog of **12** produced in the bromination–hydrolysis of **11**, it appeared that no new mechanistic information could be gleaned from our product study of the bromination–methanolysis of **11**. However, when authentic *N*-acetyl-2-methoxymethyl-3-methylindole **20** (see Scheme 6) was prepared by methanolysis of **13** it was found to be not identical with **A**. The similarity of the spectroscopic properties of **A** and **20** clearly required that **A** be the isomeric *N*-acetyl-3-methoxymethyl-2-methylindole **21**. This surprising finding prompted us to explore the bromination–methanolysis process further. We have found that, when the reaction is performed at

[3]For corrections of some of the work described by these authors see ref. 1*a*.

TABLE 1. Nuclear magnetic resonance spectral data: **17/18***

	C2 or C3—CH_3	C3 or C2—CH_3	—C(=O)—CH_3	C2 or C3—OCH_3	C3 or C2—OCH_3
Major isomer	1.46	1.76	2.36	2.87	3.07
Minor isomer	1.53	1.76	2.42	3.22	3.47

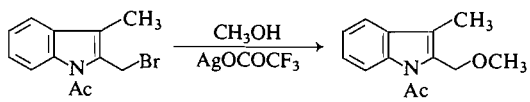
*All signals quoted are 3 proton singlets and chemical shifts are quoted on the δ scale.



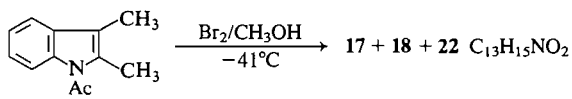
SCHEME 5

low temperature (−40°C), **21** is not observed. Instead, in addition to **17** and **18**, another isomer of **21**, compound **B**, with spectroscopic properties compatible with **22** or **23**, was obtained in 15% isolated yield.

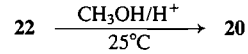
It was also found that **B** was very likely a precursor to **21** in the room temperature bromination–



SCHEME 6



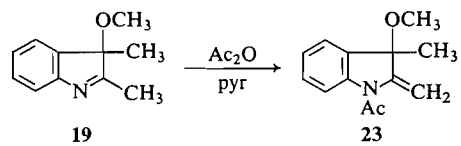
SCHEME 7



SCHEME 8

methanolysis of **11**, since treatment of **B** at room temperature with *p*-toluenesulfonic acid in methanol gave **21** in good yield. This chemical relationship between **B** and **21** clearly suggested that **B** was **22** and not **23**. This was confirmed by the synthesis of authentic **23** by the reaction of 3-methoxy-2,3-dimethylindolenine with acetic anhydride in pyridine (see Scheme 9). The most notable difference in the proton nmr spectra of **22(B)** and **23** is the fact that the methylene hydrogens in the former case appear as two one-proton singlets at δ 5.17 and 5.68 ppm whereas the methylene hydrogens in the latter case appear as two one-proton doublets (J = 2.0 Hz) at δ 5.10 and 5.38 ppm. In the ^{13}C spectra the methylene carbon of **22** appears at 104.5 ppm, significantly downfield from that of **23** at 96.8 ppm, reflecting the expected higher electron density of the β-carbon of the "enamide" system of **23**.

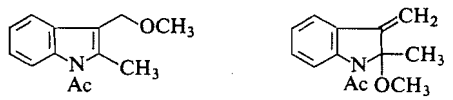
Although the formation of **21** seemed, at first, surprising in light of earlier results on bromination–hydrolysis of *N*-acetyl-2,3-dimethylindole, a re-examination of the mechanism suggested earlier for the bromination–methanolysis of 2,3-dialkyl-



SCHEME 9

indoles suggests that the formation of **21** and **22** can be readily rationalized with a minimum of additional mechanistic assumptions. Thus if the bromination of **11** proceeds as suggested for **1** in Scheme 1 (see Scheme 10), one would expect that in the presence of methanol a C2-methoxy-C3-bromoindoline **25** analogous to **4** would be produced. S_N1 type methanolysis of **25** via the stabilized carbonium ion **26** would give the mixture of dimethoxyindolines **17** and **18**. In addition, E_1 or possibly E_2 type elimination of HBr from **25** would give **22** at low temperature, and acid-catalyzed reaction of **22** with methanol would give the allylic rearrangement product **21** observed in the room temperature bromination–methanolysis of **11**.

Thus all of the observed products can be readily rationalized on the assumption that the 2-methoxy-3-bromoindoline **25** is an intermediate and hence our confidence in the intermediacy of **25** in such processes is bolstered. Furthermore, our confidence in the existence of **25** in the formation of **22** and **17** and **18** suggested that the formation of **22** might be favoured by the use of triethylamine to catalyze E_2 type elimination. It was found that bromination of **11** in methanol containing excess triethylamine led to a substantial increase in the ratio of **22** to **17** and **18**. However, under these conditions triethylamine

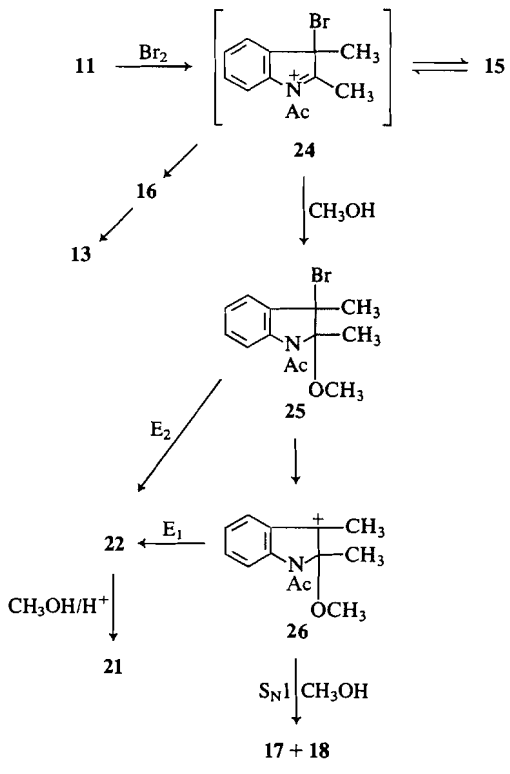


A ≡ 21 B ≡ 22

FIG. 1

catalyzes a reaction between methanol and bromine and as a result a large amount of unreacted **11** remained. Further experimentation has led us to the discovery that **22** can be produced quantitatively from **11** via a two-stage process. Thus treatment of **11** with one equivalent of bromine in methylene chloride in the presence of a limited amount of methanol (1.5 equivalents) at low temperature (−78°C) gives a colourless solution which upon treatment with triethylamine and aqueous work-up yields **22**.

This transformation not only represents a facile route to a relatively rare example of a C3-alkylidene indoline, but, coupled with the facile conversion of **22** to **21**, also represents a potentially simple and efficient route to C3 side-chain functionalization of 2,3-dialkylindoles.[4] Continuing studies in our laboratory are aimed at exploiting the synthetic utility of these transformations in the preparation of more complex indole-derived natural products.



SCHEME 10

[4]For an example of the preparation of a C3-alkylidene indoline by reaction of singlet oxygen with C3-vinylindoles, see ref. 4.

Experimental

Melting points were determined on a Fisher Mel-temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrometer and the frequency (cm^{-1}) of significant peaks is reported. A Beckman Model 35 spectrophotometer was used for uv spectra and wavelengths (nm) of absorption bands are reported followed by extinction coefficients (ε) in parentheses. Nuclear magnetic resonance spectra were recorded on a Varian T-60 or Bruker WP80 spectrometer (chloroform-*d* solvent unless otherwise indicated) and chemical shifts are reported on the δ scale, followed in parentheses by an account of the multiplicity and number of protons concerned. Mass spectra were recorded on a VG-7070 mass spectrometer. Microanalyses were performed by Galbraith Laboratories and Guelph Chemical Laboratories. *N*-Acetyl-2,3-dimethylindole was prepared by the method of Dave and Warnhoff (5).

Bromination of N-*acetyl-2,3-dimethylindole* ***11*** *in methylene chloride*

N-Acetyl-2,3-dimethylindole **11** (0.510 g; 2.73 mmol) was dissolved in methylene chloride (30 mL) and cooled in an ice bath. A solution of bromine (1.1 equivalents) in methylene chloride (3.8 mL) was added dropwise with stirring in a nitrogen atmosphere. After five minutes the solvent was removed *in vacuo* to yield *N*-acetyl-2-bromoethyl-3-methylindole **13** quantitatively as a homogeneous crystalline solid which soon turned purple upon exposure to a normal atmosphere; uv (CH_2Cl_2): 290 (11 480); ^1H nmr: 2.23 (s, 3, C3—CH_3), 2.76 (s, 3, —CO—CH_3), 5.01 (s, 2, —CH_2—Br), 7.02–7.90 (m, 4, Ar—H). Molecular ions at *m/e* 267 (m^+ ^{81}Br) and *m/e* 265 (m^+ ^{79}Br).

An analogous result was obtained with acetic acid rather than methylene chloride as solvent.

Methanolysis of N-*acetyl-2-bromomethyl-3-methylindole*

To a stirred solution of *N*-acetyl-2-bromomethyl-3-methylindole **13** (0.426 g; 1.60 mmol) in methanol (50 mL) was added silver trifluoroacetate (0.365 g; 1.76 mmol). The mixture was stirred for 20 min in a nitrogen atmosphere and then filtered through Celite. The Celite was washed with methylene chloride. The combined filtrate was washed with water and saturated aqueous sodium chloride. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness on a rotary evaporator to give *N*-acetyl-2-methoxymethyl-3-methylindole in 90% yield as a homogeneous viscous oil which could not be induced to crystallize. Infrared (neat): 1675 (s, C=O); uv MeOH: 237 (16 900), 260 (10 700), 288 (6500), 297 (6370); ^1H nmr: 2.26 (s, 3, C3—CH_3), 2.72 (s, 3, —COCH_3), 3.32 (s, 3, —OCH_3), 4.66 (s, 2, C2—CH_2), 7.19–7.53 (m, 3, C4,5,6—H), 8.09–8.21 (m, 1, C7—H). *Exact mass* calcd. for. $C_{13}H_{15}NO_2$: 217.1103; found: (ms): 217.1093.

Preparation of N-*acetyl-2-methyl-3-methoxymethylindole* ***21***

To a solution of *N*-acetyl-2-methoxy-2-methyl-3-methylene indoline **22** in methylenechloride prepared from *N*-acetyl-2,3-dimethylindole (0.216 g; 1.15 mmol) as described below was added methanol (40 mL) followed by a solution of *p*-toluenesulfonic acid (0.360 g) in methanol (2 mL) at room temperature. After 15 min the mixture was washed with water, 10% aqueous ammonia, and saturated aqueous sodium chloride. Removal of solvent from the dried organic phase *in vacuo* yielded **21** as a crystalline solid in quantitative yield. This material was identical in all respects with material isolated from the room temperature bromination of **11**, mp 55°C.

Preparation of N-*acetyl-2-methoxy-2-methyl-3-methylene indoline* **22**

To a solution of *N*-acetyl-2,3-dimethylindole **11** (0.101 g; 0.54 mmol) in methylene chloride (40 mL) containing methanol (0.81 mmol, 1.5 equivalents) cooled to −78°C was added dropwise a solution of bromine (0.59 mmol) in methylene chloride (0.76 mL). After 20 min, triethylamine (0.11 mL; 1.5 equivalents) was added and the solution allowed to warm to room temperature. Methylene chloride (20 mL) was added and the organic phase was washed with water and saturated aqueous sodium chloride. Removal of solvent from the dried organic phase *in vacuo* gave a quantitative yield of **22** as a colourless thick oil which could not be induced to crystallize and which darkened rapidly on standing. Infrared (neat): 1665, (N—$COCH_3$); uv ($CHCl_3$): 250 (18 200), 268 (14 400), 317 (3770), 327 (3580); ^{1}H nmr: 1.74 (s, 3, C2—CH_3), 2.49 (s, 3, —$COCH_3$), 3.03 (s, 3, OCH_3), 5.22 (s, 1, =CH_2), 5.72 (s, 1, =CH_2), 6.96–7.55 (m, 3, C4,5,6—H), 8.36–8.46 (m, H, C7—H). *Exact mass* calcd. for $C_{13}H_{15}NO_2$: 217.1103; found (ms): 217.1100.

Preparation of N-*acetyl-3-methoxy-3-methyl-2-methylene-indoline* **23** *from 2,3-dimethyl-3-methoxyindolenine* **19**

To a solution of freshly prepared 2,3-dimethyl-3-methoxy indolenine **19** (1) (0.292 g; 1.68 mmol) in pyridine (2 mL) was added acetic anhydride (1 mL). The solution was heated at 100°C in a nitrogen atmosphere for 19 h. Methylene chloride (20 mL) was added and the solution was washed with water and saturated aqueous sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness on a rotary evaporator.

The residue was chromatographed on silica gel with elution by a 1:1 mixture of ether – petroleum ether (60–80°C) to give **23** as colourless analytically pure crystals, mp 52–54°C, in 42% yield. Infrared ($CHCl_3$): 1657 (C=O); uv (MeOH): 257 (13 400), sh 312 (1500); ^{1}H nmr: 1.58 (s, 3, C3—CH_3), 2.54 (s, 3, —$COCH_3$), 2.90 (s, 3, —OCH_3), 5.10 (d, J = 2 Hz, 1, C2=CH_2), 5.38 (d, J = 2 Hz, 1, C2=CH_2); ms *m/e* 217 (molecule ion). *Anal.* calcd. for $C_{13}H_{15}NO_2$: C 71.86, H 6.96, N 6.45; found: C 71.94, H 6.89, N 6.58.

Low temperature bromination – methanolysis of N-*acetyl-2,3-dimethylindole*

To a cooled (−40°C) solution of **11** (0.538 g; 2.87 mmol) in methanol (175 mL) was added dropwise a solution of bromine (1.0 equivalents) in acetic acid (3.7 mL). After four minutes the solution was poured into cold aqueous (10% v/v) ammonia and the mixture was extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. Removal of solvent *in vacuo* yielded a brown oily product (0.76 g). The crude mixture was chromatographed on silica gel with elution by a step-wise gradient of ether – petroleum ether (60–80°C) increasing in ether content in 5% increments at 100-mL intervals from 10% to 50% v/v.

The first material eluted was **11** (0.021 g; 0.11 mmol). Further elution gave **22** (0.093 g; 0.43 mmol) as a colourless oil which darkened on standing, could not be induced to crystallize, and was identical in all respects with the material obtained by stepwise bromination–elimination of **11** described above.

After a number of mixed fractions of **22** and **17** (0.074 g of a 1:4 mixture), pure **17** (0.258 g; 1.04 mmol) was obtained as a crystalline solid, mp 49°C (from petroleum ether (60–80°C)). Infrared (film): 1675 (N$COCH_3$); uv (MeOH): 248 (13 500), 278 sh (2480), 285 sh (1900); ^{1}H nmr: 1.46 (s, 3, C3 or C2—CH_3), 1.76 (s, 3, C2 or C3—CH_3), 2.36 (s, 3, N$COCH_3$), 2.87 (s, 3, C3 or C2—OCH_3), 3.07 (s, 3, C2 or C3—OCH_3), 6.83–7.70 (m, 4, Ar—H). *Exact mass* calcd. for $C_{14}H_{19}NO_3$: 249.1365; found (ms): 249.1353. *Anal.* calcd. for $C_{14}H_{19}NO_2$: C 67.44, H 7.68, N 5.62; found: C 67.62, H 7.81, N 5.63.

Finally, after a mixed fraction of **17** and **18** (0.109 g, 0.48 mmol), pure **18** (0.060 g; 0.241 mmol) was obtained as a solid, mp 50°C (from petroleum ether (60–80°C)). Infrared (film): 1668 (N—$COCH_3$); uv (MeOH): 250 (11 200), 278 sh (2440), 288 sh (1600); ^{1}H nmr: 1.53 (s, 3, C3 or C2—CH_3), 1.66 (s, 3, C2 or C3—CH_3), 2.42 (s, 3, N$COCH_3$), 3.22 (s, 3, C2 or C3—OCH_3), 3.47 (s, 3, C3 or C2—OCH_3), 6.98–7.37 (m, 3, C4,5,6—H), 7.91–8.18 (m, 1, C7—H). *Exact Mass* calcd. for $C_{14}H_{19}NO_3$: 249.1365; found (ms): 249.1344. *Anal.* calcd. for $C_{14}H_{19}NO_3$: C 67.44, H 7.68, N 5.62; found: C 67.37, H 7.65, N 5.57.

Room temperature bromination–methanolysis of N-*acetyl-2,3-dimethylindole*

To a stirred solution of **11** (1.00 g; 5.35 mmol) in methanol (60 mL) was added dropwise a solution of bromine (1.1 equivalents) in glacial acetic acid (7.6 mL). After 10 min, the mixture was diluted with water (75 mL) and made basic with 10% aqueous ammonia. The mixture was extracted with methylene chloride and the dried organic extract was evaporated to dryness *in vacuo* to yield a brown residue (1.17 g). Part of the crude product (1.09 g) was chromatographed on silica gel with elution by a stepwise gradient of ether – petroleum ether increasing in ether content from 5% to 50% v/v. The first component eluted was the starting material **11** (0.30 g; 1.60 mmol). Further elution gave a mixture of **17** and **21** (0.361 g of a 49:51 mixture) and finally a small fraction (0.007 g) which consisted of a mixture of **18** and **19** in a ratio of 2.8:1.0 as indicated by tlc and nmr analysis.

The mixture of **17** and **21** was chromatographed on silica gel with elution by methylene chloride to give pure **21** as a waxy solid, mp 55°C (white needles from hexane). Infrared ($CHCl_3$): 1700 (C=O); uv: 242 (16 000), 263 (10 300), 289 (4900), 297 (4800); ^{1}H nmr: 2.58 (s, 3, C2—CH_3), 2.67 (s, 3, C=O—CH_3), 3.32 (s, 3, C3—OCH_3), 4.50 (s, 2, C3—CH_2—), 7.02–8.00 (m, 4, Ar—H); ms *m/e* 217 (molecule ion). *Anal.* calcd. for $C_{13}H_{15}NO_2$: C 71.86, H 6.96, N 6.45; found: C 71.99, H 7.16, N 6.37.

Further elution by methanol – methylene chloride (5:95) gave pure **17** identical in all respects with that obtained from the low temperature bromination–methanolysis.

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