The Synthesis of Songorine: A Simplified Synthesis of the Aromatic Intermediate

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A simple conversion of the previously described (1) tricyclic ester **1** into the pentacyclic songorine intermediate **21** is described. The process is stereospecific and it operates in an overall yield of 7.8%.

On présente une méthode simple pour transformer l'ester tricyclique **1** décrit précédemment en intermédiaire pentacyclique **21** de la songorine. Le procédé est stéréospécifique et effectué avec un rendement global de 7.8%. [Traduit par le journal]

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We have described recently (1) a simple synthesis of the tricyclic ester **1** via the sequence **i** → **ii** → **iii** → **iv** → **1**. Compound **1** was then converted to the benzene sulfonyl aziridine **v** which selectively rearranged on acetolysis to compound **vi**.

The conversion of the tricyclic ester **vi** to the desired songorine intermediate **21** was also published in a preliminary report (1*b*, 2). Since large amounts of the intermediate **21** were required we wished to develop the synthetic process to a maximum of simplicity and efficiency. It turned out that the section of the synthesis between **vi** and **21** is the only one which could be fundamentally improved. The differential manipulation of the functions in compound **vi** required some five steps which might be eliminated by a suitable modification of the process.

Such a modification was indeed found, but it was necessary to abandon compound **vi** and to go back to the tricyclic ester **1** as starting material. Consequently we wish to describe in the present paper in detail the preferred and simplified route to the intermediate **21**. The overall yield in this new stereospecific conversion of **1** to **21** is 7.8% and thus this process provides a reliable platform for the continuation of the synthesis.

The tricyclic ester **1** was reduced with lithium aluminum hydride to the primary alcohol **2** and this compound was oxidized with *N*,*N*′-dicyclohexylcarbodiimide, dimethylsulfoxide, and pyridine in anhydrous benzene (3) to the aldehyde **3** in excellent yield.[1] The side chain destined to form ring A of songorine with its substituent was attached next. The aldehyde **3** was treated with an excess of the Grignard reagent prepared from 1-bromo-3-benzyloxybutane (4) in ether. A mixture of diastereoisomers represented by the formula **4** was obtained in a quantitative yield.

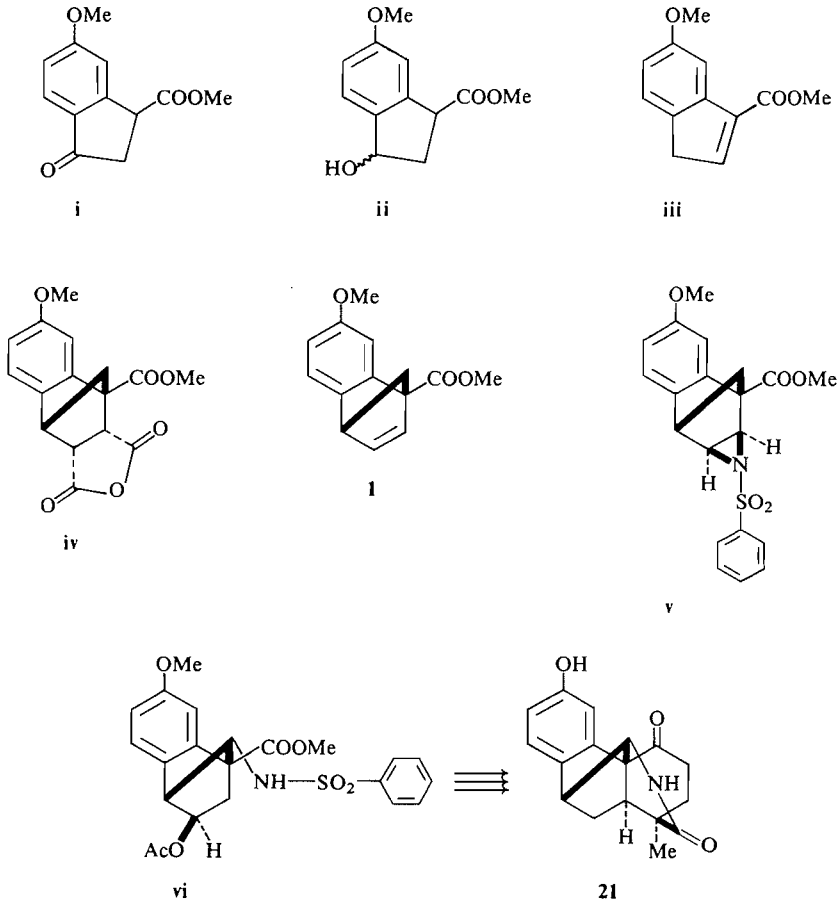
The oily mixture **4** was now converted to the *exo* benzenesulfonyl aziridine by treatment with an excess of benzenesulfonyl azide in benzene. The aziridine was quite unstable and it was consequently immediately subjected to acetolysis. Acetic acid and sodium acetate were added to the reaction mixture and stirring was continued at room temperature for several days. The crystalline mixture of diastereoisomers represented by the formula **5** was obtained in a yield of 84%. The mixture appeared to consist mainly of two components which differed in the configuration of the hydroxyl marked by the asterisk in formula **5**. For characterization the two components were separated by preparative t.l.c. and recrystallized for analysis. They were obtained in approximately equal quantities.

The aziridine rearrangement was completely regiospecific and the desired "compound" **5** was the only product detected in the reaction mixture. This clearly is due to the powerful influence of the aromatic methoxyl which increases the migratory aptitude of the bond in the *para* position.[2]

At this stage it was necessary to perform a reductive cleavage of the sulfonamide group and to replace it by an *N*-acetyl group. One of the subsequent steps in the synthesis involves the

[1] All spectral data for all compounds are recorded in the Experimental. They are mentioned in the Discussion only when specially relevant.

[2] For a full discussion of the influence of substituents on aziridine rearrangements see ref. 1*a*.

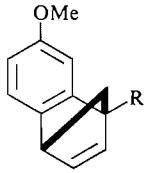


SCHEME 1

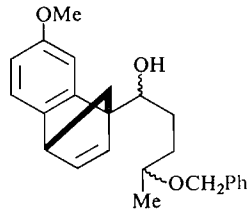
closure of ring A by an aldol condensation and the yield of this reaction is excellent if the nitrogen is blocked by acetylation but poor in the presence of the acidic sulfonamide group. The mixture of diastereoisomers **5** was reduced with an excess of $LiAlH_4$ in refluxing dioxane and the product was immediately acetylated with acetic anhydride and pyridine. The diastereoisomeric mixture **6** was obtained in a yield of 85%. The two major components of the mixture epimeric on the carbon marked by the asterisk in formula **6** were again isolated for characterization by preparative t.l.c.

The next task was to prepare the material for the closure of ring A by converting it into the diketone **9**. Fortunately, it turned out that the required partial hydrolysis of **6** to **7** proceeded with complete selectivity and practically quantitatively. The diastereoisomeric mixture **7** was converted into the diols **8** by hydrogenolysis and further into the mixture of the two epimeric diketones **9** by oxidation with chromium trioxide in pyridine. Both epimers **9** were crystalline and they were obtained in approximately equal quantities. They both showed in the i.r. spectrum a five-membered ketone at 1750 cm^{-1} and in the n.m.r. spectrum four methyl singlets. (β-epimer: τ 6.17 ($-OCH_3$), 7.84 ($-\overset{\overset{O}{\|}}{C}-CH_3$), 7.87 ($O-\overset{\overset{O}{\|}}{C}-CH_3$), and 7.94 p.p.m. ($N-\overset{\overset{O}{\|}}{C}-CH_3$)).

The mixture of the two diketones **9** was subjected to an aldol condensation in refluxing methanolic potassium carbonate. The two epimers **10** were obtained as a crystalline mixture in a yield of 88% and they were separated for



1 R = COOMe
2 R = CH_2OH
3 R = CHO



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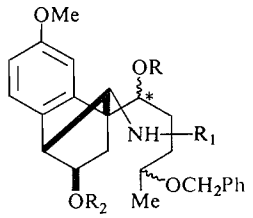
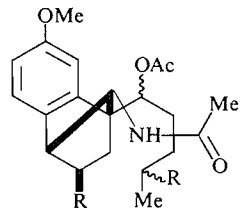


5 R = H; R_1 = SO_2Ph; R_2 = $-\overset{\overset{O}{\|}}{C}-Me$

6 R = R_1 = R_2 = $-\overset{\overset{O}{\|}}{C}-Me$

7 R = R_1 = $-\overset{\overset{O}{\|}}{C}-Me$; R_2 = H



8 R = OH
9 R = =O

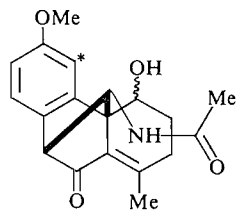
SCHEME 2

characterization by preparative t.l.c. The configuration of the hydroxyl in the two epimers **10** was assigned by n.m.r. spectroscopy. The aromatic hydrogen marked by the asterisk in formula **10** produces a narrow doublet at τ 3.24 p.p.m. in the β- and τ 2.87 p.p.m. in the α-epimer. This is due to the close proximity of this hydrogen and the ring A substituent in the α-epimer.[3]

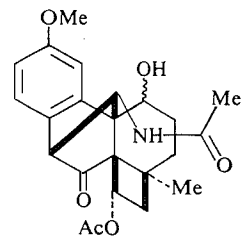
[3]In the case of the epimeric pair **10** the assignment of configuration was corroborated by a complete X-ray structure analysis performed by Dr. J. F. Blount (Hoffmann-La Roche, Nutley, New Jersey) on a heavy atom derivative of the β-epimer of compound **16**. A chemical proof of this configuration was the observation of an $N \rightarrow O$ acetyl migration in the course of the preparation of this derivative (*cf.* ref. 2).

The operation which faced us now was the stereospecific addition of a one carbon element in the β position of the α,β-unsaturated ketone system of **10** and the ring closure of this new function with the nitrogen. The method which we have developed for related systems, *i.e.*, the addition of cyanide (5), turned out to be useless in the present case since the cyanide ion added selectively *anti* to the nitrogen.

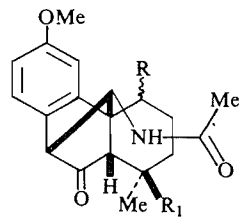
The problem was finally solved as follows. Photoaddition of vinyl acetate to the mixture of the two epimers **10** gave two epimers of compound **11**. For characterization they were separated by preparative t.l.c. and the α-epimer was crystalline. The configuration of the acetoxy group in both epimers **11** is tentative and there is no evidence for it apart from *a priori* considerations of more favorable geometry and orbital overlap. On the other hand the peculiar regiospecificity of the photoaddition and the stereochemistry of the cyclobutane ring are certain from subsequent transformations and n.m.r. spectroscopy. The most remarkable feature in the n.m.r. spectra of both epimers **11** is the extremely high field position of the carbon–methyl group singlet. (β-Epimer, τ 9.70 p.p.m.;



10



11



12 R = OH; R_1 = CH_2CHO
13 R = OAc; R_1 = CH=CHOAc
14 R = OAc; R_1 = CHO
15 R = OAc; R_1 = COOMe
16 R = OH; R_1 = COOMe
17 R = =O; R_1 = COOMe
18 R =  ; R_1 = COOMe

SCHEME 3

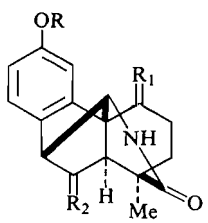
α-epimer, τ 9.66 p.p.m.). This is due to the shielding effect of the anisole ring on the methyl group and is only possible if the stereochemistry of the entire skeleton is as indicated in the formula **11**.

Saponification of "compound" **11** with methanolic potassium hydroxide gave a quantitative yield of the two epimers represented by formula **12**. They were oily and were separated for characterization by preparative t.l.c. The n.m.r. spectra of both compounds showed an aldehydic proton (β-epimer, τ −0.17 p.p.m.; α-epimer, τ −0.24 p.p.m.) and it was thus clear that after the hydrolysis of the acetoxy group the resulting alcohol opened by a reverse aldol reaction. Inspection of the n.m.r. spectra allowed also an unambiguous configurational assignment to the skeleton. Both epimers still showed a singlet for the carbon–methyl group at an abnormally high field (β-epimer, τ 9.54 p.p.m.; α-epimer, τ 9.50 p.p.m.). Consequently the AB *cis* stereochemistry of the photoadduct was preserved after the base catalyzed ring opening with simultaneous equilibration of the AB ring junction. We must therefore assume that this steric arrangement is more stable than the desired AB *trans* configuration. The operations which had to be executed at this point involved the shortening of the group R_1 in formula **12** by one carbon, epimerization of the AB ring junction and ring closure of the group R_1 with the nitrogen. The two epimers **12** were converted by enol acetylation to the two epimeric acetates **13**. These compounds were oxidized by osmic acid – periodate (6) to the noraldehydes **14** and oxidized further by the Jones method, followed by esterification with diazomethane to the acetoxy esters **15**. All these transformations were executed in excellent yields and the oily products were separated for characterization into the individual epimers by preparative t.l.c. The high-field methyl singlets in the n.m.r. spectra of these intermediates indicated that all of them had the same AB *cis* configuration. The structure and configuration of the β-epimer of compound **16** was furthermore rigorously confirmed when Dr. J. F. Blount, Hoffmann La Roche, Nutley, New Jersey, performed an X-ray analysis on a heavy atom derivative of this material (*cf.* ref. 2).

Mild alkaline hydrolysis of the epimers **15** yielded the hydroxy esters **16** and these were finally oxidized by the Jones method to the single crystalline diketo ester **17**, the synthesis of which was thus fully stereospecific.[4]

Ketalization of the diketone **17** with ethylene glycol and *p*-toluenesulfonic acid in benzene gave a quantitative yield of the crystalline ketal **18** which still showed the carbonyl maximum of the five-membered ring B ketone (1750 cm^{-1}) in the i.r. spectrum.

Finally the stage was set for the closure of the nitrogen ring. In compound **18**, of course, ring formation between the ester group and the nitrogen is sterically impossible because of the *cis* fusion of the rings A and B. However, we believed that in a solution sufficiently basic to enolize to a small extent the hydrogen next to the ring B ketone a certain amount of the AB *trans* isomer will be formed by reprotonation of the enolate ion. This material will then have opportunity to cyclize by lactam formation. Once cyclization occurs the system will be locked permanently and will be unable to go back to a *cisoid* derivative. This in fact turned out to be correct. The ketal ester **18** was heated under reflux with methanolic sodium methoxide and the beautifully crystalline lactam **19** was obtained in a yield of 80%. The i.r. spectrum of compound **19** showed carbonyl maxima at 1750 and 1675 cm^{-1} for the ketone and lactam and very significantly the carbon–methyl group singlet in the n.m.r. spectrum showed a normal expected chemical shift (τ 8.66 p.p.m.). In the *cisoid* ketal ester **18** the same carbon–methyl group singlet is located at τ 9.43 p.p.m.



19 R = Me; R_1 =  ; R_2 = =O

20 R = Me; R_1 =  ; R_2 = H_2

21 R = H; R_1 = =O; R_2 = H_2

SCHEME 4

[4]Since $LiAlH_4$ reductions of the ring A keto group in the songorine skeleton are known to yield stereospecifically "natural" β-hydroxy derivatives it is clear that the configuration of the ring A hydroxyl will also present no problems in the future. The ketone **17** was obtained not only from the mixture of the two epimers **15** but also from each epimer separately.

Wolff–Kishner reduction of compound **19** proceeded with no difficulty and yielded 89% of the highly crystalline ketal **20**.[5] Finally heating of the ketal **20** under reflux in a mixture of hydrobromic and acetic acid gave the high melting crystalline phenol **21** in an 86% yield. The process described in the present communication can supply very simply and efficiently the aromatic intermediate not only for songorine, but also if suitable modifications are introduced for a variety of other diterpene alkaloids. The chief advantage of the method is that it automatically provides the typical substitution pattern in rings A and B of delphinine type alkaloids simultaneously with the construction of the skeleton. This is an advantage which obviously is not fully utilized in the case of songorine.

The question remains whether the process described is the simplest and most efficient one possible. We do not believe this to be the case. It will probably turn out to be feasible to find a one carbon anionic reagent which will add to the α,β-unsaturated ketone **10** with the correct stereochemistry. Thus it should be possible to proceed from compound **10** directly to products of the type **16**. However, while we plan to return to these experiments in the future the present form of the synthesis is already highly satisfactory for our present purposes.

Experimental

*Reduction of the Ester **1** to the Alcohol **2***

To a cold stirred mixture of $LiAlH_4$ (3 g) in anhydrous ether (120 ml), a solution of the ester **1** (9.96 g) in anhydrous ether (110 ml) was added dropwise. The reaction mixture was stirred for 1 h at room temperature, and worked up by careful addition of wet ether (1000 ml) and then of 10% aqueous sodium hydroxide (2 ml). The white precipitate was filtered and the filtrate was evaporated to give 8.56 g of the pure alcohol **2** as an oil homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{13}H_{14}O_2$: 202. Found (mass spectroscopy): 202.

I.r. ($CHCl_3$): 3625 cm^{-1} (hydroxyl); n.m.r. ($CDCl_3$): τ 3.18 (m, 2H, vinylic protons), 5.71 (s, 2H, methylene of primary alcohol), 6.26 (s, 3H, aromatic methoxyl), 7.73 p.p.m. (q, 2H, apex protons).

*Oxidation of **2** to the Aldehyde **3***

Trifluoroacetic acid (1.76 ml) was added to a solution of the primary alcohol **2** (8.46 g), *N,N'*-dicyclohexylcarbodiimide (26 g), anhydrous dimethylsulfoxide (70 ml) and pyridine (3.54 ml) in benzene (80 ml). The solution was stirred for 12 h at room temperature and diluted with ether (300 ml) and *n*-hexane (700 ml). A solution of oxalic acid (7.96 g) in methanol (53 ml) was added slowly with stirring in order to destroy the excess of diimide and the white precipitate was removed by filtration. The filtrate was washed several times with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated to dryness. Chromatography of the yellow residue on silica gel and elution with benzene yielded 7.12 g (85%) of the oily aldehyde **3** homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{13}H_{12}O_2$: 200. Found (mass spectroscopy): 200.

I.r. ($CHCl_3$): 2950, 2848, 2740, 1725 cm^{-1} (aldehyde); n.m.r. ($CDCl_3$): τ −1.28 (s, 1H, aldehyde), 3.10 (m, 2H, vinylic protons), 6.02 (m, 1H, benzylic bridgehead proton), 6.23 (s, 3H, aromatic methoxyl), 7.25 p.p.m. (d, 2H, apex protons).

*Preparation of the Alcohol **4***

A solution of 1-bromo-3-benzyloxybutane (4) (14.6 g, two-fold excess) in absolute ether (200 ml) was added dropwise to a warm stirred mixture of magnesium turnings (1.5 g) in absolute ether (20 ml) in a nitrogen atmosphere. When the addition of the bromide solution was complete, reflux was maintained for about ½ h.

A solution of the aldehyde **3** (6 g) in absolute ether (120 ml) was added dropwise under reflux to the well-stirred Grignard solution. When the addition was completed, the reaction mixture was heated under reflux in a nitrogen atmosphere for 12 h. After cooling, ether (500 ml) was added and the unreacted magnesium metal was removed. A 10% aqueous ammonium chloride solution (200 ml) was added to the reaction mixture under stirring. After removal of the aqueous layer, the ether solution was washed with water, dried, and evaporated to dryness. The residue was chromatographed on silica gel, using ether–benzene (v/v 1:9) as eluant. The yield of the oily alcohol **4** was quantitative (10.6 g).

Mol. Wt. Calcd. for $C_{24}H_{28}O_3$: 364.2031. Found (high resolution mass spectroscopy): 364.2039.

I.r. ($CHCl_3$): 3615, 3415 cm^{-1} (hydroxyl); n.m.r. ($CDCl_3$): τ 3.06 (m, 2H, vinylic protons), 5.45 (q, 2H, benzylic protons), 5.60 (unresolved m, 1H, hydrogen unshielded by secondary hydroxyl), 6.27 (s, 3H, aromatic methoxyl), 8.75 p.p.m. (d, 3H, methyl protons).

*Preparation of the Rearranged Compound **5***

A solution of the unsaturated compound **4** (10 g) and an excess of benzenesulfonyl azide (20 g) in anhydrous benzene (50 ml) was stirred for 6 days at room temperature. Sodium acetate (6 g) and glacial acetic acid (70 ml) were added in one portion and the mixture was stirred for 5 days at room temperature. The reaction mixture was diluted with chloroform (1000 ml) and washed with saturated aqueous sodium bicarbonate (2 × 200 ml), followed by saturated aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow residue which was subjected to chromatography on silica gel. Elution with benzene–ether (8:2) gave 13.6 g (84%) of the crystalline product **5**.

This material was a mixture (1:1) of two epimers, when analyzed by t.l.c. on silica gel using benzene–ether (7:4)

[5]In a derivative similar to **19** (R_1 = —OH, R_2 = =O) desulfurization of a thioketal and Wolff–Kishner reduction yielded the same ring B desoxy compound in both cases in a high yield.

as solvent. A small portion (100 mg) was separated by preparative t.l.c. and two epimeric alcohols were obtained in equal amount: the β-epimer (50 mg) with a larger R_F value and the α-epimer (50 mg) with a smaller R_F value. Both epimers were recrystallized from ether and they were homogeneous in t.l.c.

(*i*) β-Epimer, m.p. 146–147 °C.

Anal. Calcd. for $C_{32}H_{37}O_7NS$ (mol. wt. 579): C, 66.29; H, 6.43; N, 2.42. Found (mass spectroscopy 579): C, 66.30; H, 6.42; N, 2.52.

I.r. ($CHCl_3$): 3565 (hydroxyl), 3385 (NH), 1735 cm^{-1} (acetate); n.m.r. ($CDCl_3$): τ 2.86 (d, J = 8 Hz, 1H, hydrogen *meta* to aromatic methoxyl), 3.23 (d, J = 2.5 Hz, 1H, hydrogen *ortho* to aromatic methoxyl), 3.41 (q, J = 8 Hz, J = 2.5 Hz, 1H, hydrogen *ortho* to aromatic methoxyl), 4.08 (d, 1H, —N(H)—), 5.30 (m, 1H, proton unshielded by acetoxyl), 5.81 (m, 1H, proton unshielded by hydroxyl), 6.82 (broad s, 1H, benzylic bridgehead proton), 7.88 p.p.m. (s, 3H, acetoxy methyl).

(*ii*) α-Epimer, m.p. 167.5–168 °C.

Anal. Calcd. for $C_{32}H_{37}O_7NS$ (mol. wt. 579): C, 66.29; H, 6.43; N, 2.42. Found (mass spectroscopy 579): C, 66.14; H, 6.42; N, 2.54. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3455 (hydroxyl), 3375 (NH), 1740 cm^{-1} (acetate); n.m.r. ($CDCl_3$): τ 2.91 (d, J = 8 Hz, 1H, hydrogen *meta* to aromatic methoxyl), 2.99 (d, J = 2.5 Hz, 1H, hydrogen *ortho* to aromatic methoxyl), 3.37 (q, J = 8 Hz, J = 2.5 Hz, 1H, hydrogen *ortho* to aromatic methoxyl), 4.11 (d, 1H, —N(H)—), 5.33 (m, 1H, proton unshielded by acetoxyl), 5.85 (m, 1H, proton unshielded by hydroxyl), 6.98 (broad s, 1H, benzylic bridgehead proton), 7.89 p.p.m. (s, 3H, acetoxy methyl).

Conversion of Compound **5** *to the N-Acetyl Amide* **6**

To a stirred solution of compound **5** (13 g) in anhydrous dioxane (400 ml), an excess of $LiAlH_4$ (15 g) was added in one portion. The mixture was refluxed under nitrogen for 27 h. After cooling, the excess of hydride was decomposed by careful addition of wet ether (600 ml) and of 10% aqueous sodium hydroxide (6 ml). The white precipitate was removed by filtration and washed with tetrahydrofuran (8 × 100 ml). The combined filtrates were evaporated under reduced pressure to give 8.84 g of material which was immediately acetylated with acetic anhydride (20 ml) and anhydrous pyridine (80 ml) for 24 h at room temperature. Most of the solvent was evaporated *in vacuo* and the residue was dissolved in chloroform (1500 ml). The chloroform solution was washed with dilute hydrochloric acid, dilute aqueous sodium bicarbonate, and water. After drying over magnesium sulfate, evaporation gave a yellow residue which was chromatographed on silica gel. Elution with ether–benzene (3:7) yielded 9.98 g (85%) of the *N*-acetyl amide **6** as a thick oil. For analysis, the two epimers were separated by preparative t.l.c.

(*i*) β-Epimer (larger R_F value).

Mol. Wt. Calcd. for $C_{30}H_{37}O_7N$: 523.2570. Found (high resolution mass spectroscopy): 523.2566.

I.r. ($CHCl_3$): 3461 (NH), 1738 (acetate), 1678 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.63 (m, 1H, proton deshielded by acetoxyl), 5.26 (m, 1H, proton deshielded by acetoxyl), 6.25 (s, 3H, aromatic methoxyl), 6.68 (broad s, 1H, benzylic bridgehead proton), 7.91 (s, 3H, acetoxy methyl), 7.94 (s, 3H, acetoxy methyl), 7.99 (s, 3H, —N(C=O)—CH_3), 8.84 p.p.m. (d, 3H, methyl).

(*ii*) α-Epimer (smaller R_F value).

Mol. Wt. Calcd. for $C_{30}H_{37}O_7N$: 523.2570. Found (high resolution mass spectroscopy): 523.2557. The mass spectrum was identical with the mass spectrum of the β-epimer.

I.r. ($CHCl_3$): 3462 (NH), 1737 (acetate), 1678 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.45 (m, 1H, proton deshielded by acetoxyl), 5.21 (m, 1H, proton deshielded by acetoxyl), 6.26 (s, 3H, aromatic methoxyl), 6.59 (broad s, 1H, benzylic bridgehead proton), 7.90 (s, 6H, two acetoxy methyl), 7.99 (s, 3H, —N(C=O)—CH_3), 8.81 p.p.m. (d, 3H, methyl).

Selective Hydrolysis of the Diacetate **6** *to the Hydroxyacetate* **7**

The diacetate **6** (9 g) was dissolved in methanolic potassium carbonate (400 ml, p*H* 8.5) and the reaction mixture was stirred at room temperature. The course of the reaction was followed by t.l.c. In this case the reaction was allowed to proceed for 16 h, after which time the reaction mixture was neutralized with 5% hydrochloric acid (2 ml) and poured into saturated aqueous sodium chloride (600 ml). It was extracted with chloroform (5 × 200 ml) and the combined extracts were washed with saturated sodium chloride, dried, and evaporated to dryness. The hydroxyacetate **7** (8.16 g) was isolated as the sole product and the yield was quantitative. A small portion (100 mg) of the material was taken out and the two epimers separated by preparative t.l.c. (methanol–ether 4:96) as colorless foam homogeneous in t.l.c. Ratio of the epimers was 1:1.

(*i*) β-Isomer (larger R_F value).

Mol. Wt. Calcd. for $C_{28}H_{35}O_6N$: 481.2464. Found (high resolution mass spectroscopy): 481.2472.

I.r. ($CHCl_3$): 3625 (hydroxyl), 3410 (NH), 1730 (acetate), 1675 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.63 (m, 1H, proton unshielded by acetoxyl), 6.21 (s, 3H, aromatic methoxyl), 6.89 (broad s, 1H, benzylic bridgehead proton), 7.92 (s, 3H, acetoxy methyl), 8.03 (s, 3H, —N(C=O)—CH_3), 8.81 p.p.m. (d, 3H, methyl).

(*ii*) α-Epimer (smaller R_F value).

Mol. Wt. Calcd. for $C_{28}H_{35}O_6N$: 481.2464. Found (high resolution mass spectroscopy): 481.2472. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3610 (hydroxyl), 3425 (NH), 1730 (acetate), 1675 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.70 (m, 1H, proton unshielded by acetoxyl), 6.25 (s, 3H, aromatic methoxyl), 6.90 (broad s, 1H, benzylic bridgehead proton), 7.94 (s, 3H, acetoxy methyl), 8.04 (s, 3H, —N(C=O)—CH_3), 8.80 p.p.m. (d, 3H, methyl).

Preparation of the Acetoxy Diol **8**

To a solution of the benzyloxy ether **7** (8 g) in methanol (200 ml), 10% palladium on charcoal (1 g) was added. The mixture was hydrogenated at atmospheric pressure and room temperature overnight. The catalyst was filtered off and washed with methanol. The methanolic solution was evaporated under reduced pressure and the diol **8** (6.4 g) was obtained as a colorless foam in a quantitative yield. For analysis, the two epimers were separated by preparative t.l.c.

(*i*) β-Epimer (larger R_F value).

Mol. Wt. Calcd. for $C_{21}H_{29}O_6N$: 391.1995. Found (mass spectroscopy): 391.2001.

I.r. ($CHCl_3$): 3610, 3460 (hydroxyl), 3400 (NH), 1731 (acetate), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.16 (d, J = 9 Hz, 1H, —N—H), 4.62 (m, 1H, proton unshielded by acetoxyl), 5.75 (d, J = 9 Hz, 1H, apex proton), 6.20 (s, 3H, aromatic methoxyl), 6.85 (broad s, 1H, benzylic bridgehead proton), 7.91 (s, 3H, acetoxy methyl), 7.98 (s, 3H, —N—C(=O)—CH_3), 8.82 p.p.m. (d, 3H, methyl).

(*ii*) α-Epimer (smaller R_F value).

Mol. Wt. Calcd. for $C_{21}H_{29}O_6N$: 391.1995. Found (mass spectroscopy): 391.2001. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3610 (hydroxyl), 3408 (NH), 1733 (acetate), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.49 (d, J = 9 Hz, 1H, —NH), 4.46 (m, 1H, proton unshielded by acetoxyl), 5.71 (d, J = 9 Hz, 1H, apex proton), 6.23 (s, 3H, aromatic methoxyl), 6.90 (broad s, 1H, benzylic bridgehead proton), 7.93 (s, 3H, acetoxy methyl), 8.05 (s, 3H, —N—C(=O)—CH_3), 8.84 p.p.m. (d, 3H, methyl).

Preparation of the Diketone **9**

A solution of the diol **8** (6.4 g) in pyridine (40 ml) was added slowly at room temperature to a stirred solution of chromium trioxide (7 g) in pyridine (50 ml). The mixture was stirred for 2 days at room temperature after which time it was diluted with ether (400 ml) and chloroform (100 ml). The brown precipitate was filtered and washed with ether. The combined filtrates were washed with dilute hydrochloric acid, 10% aqueous sodium bicarbonate and finally with water. Evaporation of the solvent and removal of the yellow color by filtration through a short neutral alumina column (100 g, activity grade II) gave 5.1 g (80%) of the diketone **9** as white crystals. The two epimers were separated by preparative t.l.c. (ether–methanol 9:1) and recrystallized for analysis. The ratio of the epimers was 1:1.

(*i*) β-Epimer (larger R_F value), m.p. 115°.

Anal. Calcd. for $C_{20}H_{23}O_6N$ (mol. wt. 387): C, 65.10; H, 6.50; N, 3.61. Found (mass spectroscopy, 387): C, 64.98; H, 6.52; N, 3.60.

I.r. ($CHCl_3$): 3430 (NH), 1750 (five-membered ketone), 1720 (ketone), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.64 (m, 1H, proton deshielded by acetoxyl), 6.17 (s, 3H, aromatic methoxyl), 6.40 (broad s, 1H, benzylic bridgehead proton), 7.84 (s, 3H, —C(=O)—CH_3), 7.87 (s, 3H, acetoxy methyl), 7.97 p.p.m. (s, 3H, —N—C(=O)—CH_3).

(*ii*) α-Epimer (smaller R_F value), m.p. 175°.

Anal. Calcd. for $C_{20}H_{23}O_6N$ (mol. wt. 387): C, 65.10; H, 6.50; N, 3.61. Found (mass spectroscopy 387): C, 64.99; H, 6.47; N, 3.58. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3450 (NH), 1750 (five-membered ketone), 1720 (ketone), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.30 (m, 1H, proton deshielded by acetoxyl), 6.07 (s, 3H, aromatic methoxyl), 6.30 (broad s, 1H, benzylic bridgehead proton), 7.80 (s, 3H, —C(=O)—CH_3), 7.84 (s, 3H, acetoxy methyl), 8.00 p.p.m. (s, 3H, —N—C(=O)—CH_3).

Preparation of the α,β-*Unsaturated Ketone* **10**

A solution of the diketone **9** (8.8 g) in saturated methanolic potassium carbonate (200 ml) was refluxed for 10 h in a nitrogen atmosphere. The mixture was neutralized by careful addition of dilute hydrochloric acid. Most of the solvent was removed *in vacuo* and the residue was suspended in saturated aqueous sodium chloride (300 ml). The aqueous phase was extracted with methylene dichloride (4 × 200 ml) and the combined extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the ketone **10** was obtained by crystallization from ether–chloroform. The yield was 6.62 g (88%). This crystalline material was a mixture (1:1) of two epimers when examined by t.l.c. on silica gel using chloroform–ether–methanol (70:30:6) as developing solvent. For analysis, samples of the two epimers were obtained by preparative t.l.c. and crystallized from ether.

(*i*) β-Epimer (larger R_F value), m.p. 205°.

Anal. Calcd. for $C_{19}H_{21}O_4N$ (mol. wt. 327): C, 69.69; H, 6.40; N, 4.20. Found (mass spectroscopy 327): C, 69.71; H, 6.39; N, 4.18.

I.r. ($CHCl_3$): 3550 (hydroxyl), 3400 (NH), 1725 (conjugated five-membered ketone), 1660 cm^{-1} (conjugated double bond and amide); u.v. (EtOH): λ_{max} 241[6] nm (log ε 4.01); n.m.r. ($CDCl_3$): τ 2.81 (d, J = 8 Hz, 1H, —N—H), 2.87 (d, J = 10 Hz, 1H, hydrogen-*meta* to methoxyl), 3.24 (d, J = 3 Hz, 1H, hydrogen-*ortho* to methoxyl), 3.32 (q, J = 10 Hz, J = 3 Hz, hydrogen-*ortho* to methoxyl), 5.60 (d, J = 8 Hz, 1H, apex proton), 6.24 (s, 3H, aromatic methoxyl), 6.30 (broad s, 1H, benzylic bridgehead proton), 7.87 (s, 3H, >C=C(—CH_3)—), 8.04 p.p.m. (s, 3H, —N—C(=O)—CH_3).

(*ii*) α-Epimer (smaller R_F value), m.p. 242°.

Mol. Wt. Calcd. for $C_{19}H_{21}O_4N$: 327.1471. Found

[6]These values were in error in the preliminary communication, *cf.* (2).

(high resolution mass spectroscopy): 327.1465. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3500 (hydroxyl), 3400 (NH), 1725 (conjugated five-membered ketone), 1660 cm^{-1} (conjugated double bond and amide); u.v. (EtOH): λ_{max} 239[6] nm (log ε 4.02); n.m.r. ($CDCl_3$): τ 2.81 (d, J = 10 Hz, 1H, hydrogen-*meta* to methoxyl), 2.87 (d, J = 3 Hz, 1H, hydrogen-*ortho* to methoxyl), 3.20 (d, J = 9 Hz, 1H, —N—H), 3.40 (q, J = 10 Hz, J = 3 Hz, 1H, hydrogen-*ortho* to methoxyl), 5.40 (d, J = 9 Hz, 1H, apex proton), 6.20 (s, 3H, aromatic methoxyl), 6.50 (broad s, 1H, benzylic bridgehead proton), 7.90 (s, 3H, —C=C—CH_3), 7.97 p.p.m. (s, 3H, —N—C—CH_3, O).

Preparation of the Photoadduct ***11***

To a solution of the α,β-unsaturated ketone **10** (15 g) in freshly distilled tetrahydrofuran (2000 ml), a great excess of distilled vinyl acetate (1000 ml) was added. The solution was irradiated continuously with a 400 W Hanovia Mercury lamp (Pyrex was used as filter) at −20° for 12 h under nitrogen. After evaporation of the solvent, the photoadduct **11** was purified by crystallization from ether. 7.4 g of the crystalline photoadduct was obtained and chromatography of the mother liquor on silica gel gave another 9.52 g. The yield was thus 16.92 g (89%). For analysis, the two epimers were separated by preparative t.l.c. on silica gel. The α-epimer crystallized from ether (m.p. 254–256°) while the β-epimer when pure remained a white foam. Both epimers were homogeneous in t.l.c.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{23}H_{27}O_6N$: 413. Found (mass spectroscopy): 413. The mass spectra of both epimers were completely identical.

I.r. ($CHCl_3$): 3500 (hydroxyl), 3420 (NH), 1750 (five-membered ketone), 1740 (acetate), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 3.00 (d, 1H, —N—H), 4.56 (q, 1H, proton unshielded by acetoxyl), 5.07 (t, 1H, proton unshielded by hydroxyl), 5.80 (d, 1H, apex proton), 6.11 (broad s, 1H, benzylic bridgehead proton), 6.17 (s, 3H, aromatic methoxyl, 7.84 (s, 3H, acetoxy methyl), 8.10 (s, 3H, —N—C—CH_3, O), 9.70 p.p.m. (s, 3H, methyl shielded by benzene ring).

(*ii*) α-Epimer.

Anal. Calcd. for $C_{23}H_{27}O_6N$ (mol. wt. 413): C, 66.81; H, 6.58; N, 3.39. Found (mass spectroscopy, 413): C, 66.80; H, 6.59; N, 3.37.

I.r. ($CHCl_3$): 3500 (hydroxyl), 3440 (NH), 1750 (five-membered ketone), 1738 (acetate), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 3.13 (d, 1H, —N—H), 4.54 (q, 1H, proton unshielded by acetoxyl), 5.10 (t, 1H, proton unshielded by hydroxyl), 5.74 (d, 1H, apex proton), 6.20 (s, 3H, aromatic methoxyl), 6.37 (broad s, 1H, benzylic bridgehead proton), 7.87 (s, 3H, acetoxy methyl), 8.07 (s, 3H, —N—C—CH_3, O), 9.66 p.p.m. (s, 3H, methyl shielded by benzene ring).

Hydrolysis of the Photoadduct ***11*** *to the Aldehyde* ***12***

The photoadduct **11** (16 g) was hydrolyzed in 1% methanolic potassium hydroxide (120 ml) for ½ h at room temperature. The mixture was poured into water and extracted with chloroform (5 × 200 ml). The combined extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 14.1 g of the aldehyde **12** as a foam. The yield was quantitative. The material consisted of two epimers (1:1) and a small portion was separated by preparative t.l.c. Both epimers were foams homogeneous in t.l.c.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{21}H_{25}O_5N$: 371.1674. Found (high resolution mass spectroscopy): 371.1679.

I.r. ($CHCl_3$): 3450–3300 (hydroxyl and NH), 2710 (aldehyde C—H), 1740 (five-membered ketone), 1715 (aldehyde), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ −0.17 (t, 1H, aldehydic proton), 2.40 (d, J = 3 Hz, —N—H), 5.34 (broad s, 1H, proton unshielded by hydroxyl), 5.97 (d, J = 3 Hz, apex proton), 6.20 (s, 3H, aromatic methoxyl), 7.30 (q, 2H, —C—CH_2—CHO), 8.00 (s, 3H, —N—C—CH_3, O), 9.54 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

(*ii*) α-Epimer.

Mol. Wt. Calcd. for $C_{21}H_{25}O_5N$: 371.1674. Found (high resolution mass spectroscopy): 371.1677. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3450–3300 (hydroxyl and NH), 2710 (aldehyde C—H), 1740 (five-membered ketone), 1715 (aldehyde), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ −0.24 (t, 1H, aldehydic proton), 2.37 (d, J = 7 Hz, 1H, —N—H), 5.70 (d, J = 7 Hz, 1H, apex proton), 6.03 (broad s, 1H, proton unshielded by hydroxyl), 6.20 (s, 3H, aromatic methoxyl), 7.40 (broad s, 2H, —C—CH_2—CHO), 7.94 (s, 3H, —N—C—CH_3, O), 9.50 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

Preparation of the Enol Acetate ***13***

A mixture of the aldehyde **12** (14 g), freshly fused sodium acetate (9 g) and distilled acetic anhydride (600 ml) was heated under reflux for 8 h under nitrogen. After removing the solvent *in vacuo* below 100°, a large amount of ether (1000 ml) and water (500 ml) was added to the residue. The organic layer was collected and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow residue which was chromatographed on silica gel. Elution with chloroform–methanol (98:2) gave

13.2 g of the product **13**. For analysis, the two epimers were isolated by preparative t.l.c.; both were thick oils homogeneous in t.l.c.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{25}H_{29}O_7N$: 455. Found (mass spectroscopy): 455.

I.r. ($CHCl_3$): 3400 (NH), 1750 (ketone and acetate), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.75 (d, J = 12 Hz, 1H, vinylic proton), 4.00 (d, J = 12 Hz, 1H, vinylic proton), 4.23 (broad s, 1H, proton unshielded by acetoxyl), 6.20 (s, 3H, aromatic methoxyl), 6.34 (broad s, 1H, benzylic bridgehead proton), 7.90 (s, 6H, acetoxy methyl), 8.04 (s, 3H, —N—C(=O)—CH_3), 9.54 p.p.m. (s, 3H. tertiary methyl shielded by benzene ring).

(*ii*) α-Epimer.

Mol. Wt. Calcd. for $C_{25}H_{29}O_7N$: 455. Found (mass spectroscopy): 455. The mass spectra of both epimers were completely identical.

I.r. ($CHCl_3$): 3400 (NH), 1750 (ketone and acetate), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.89 (d, J = 12 Hz, 1H, vinylic proton), 4.14 (d, J = 12 Hz, 1H, vinylic proton), 5.07 (t, 1H, proton unshielded by acetoxyl), 6.14 (aromatic methoxyl), 6.37 (broad s, 1H, benzylic bridgehead proton), 7.87 (s, 6H, acetoxy methyl), 8.04 (s, 3H, —N—C(=O)—CH_3), 9.47 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

*Cleavage of Compound **13** to the Nor-aldehyde **14***

A mixture of the enol acetate **13** (13.2 g), osmium tetroxide (1.2 g) and acetic acid (5 ml) in tetrahydrofuran (600 ml) was stirred for 3½ h at room temperature. During this process the mixture turned dark, and sodium metaperiodate powder (12 g) in water (50 ml) was added to the dark solution. The mixture was stirred for an additional 4 h at room temperature. The precipitate was filtered off and washed thoroughly with tetrahydrofuran (200 ml). The filtrate was partially evaporated *in vacuo* and the residue was dissolved in chloroform (1000 ml). The chloroform solution was washed with water (3 × 400 ml), dried and evaporated to dryness. Column chromatography of the residue on silica gel yielded 8 g (70%) of the product **14** as a waxy material. A small portion was separated by preparative t.l.c. Both epimers were thick oils homogeneous in t.l.c. in several solvent systems.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{22}H_{25}O_6N$: 399.1704. Found (high resolution mass spectroscopy): 399.1709.

I.r. ($CHCl_3$): 3450 (NH), 2820, 2710 (aldehyde C—H), 1740 (ketone and acetate), 1730 (aldehyde), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ −0.40 (s, 1H, aldehyde), 4.27 (m, 1H, proton unshielded by acetoxyl), 6.20 (s, 3H, aromatic methoxyl), 6.37 (broad s, 1H, benzylic bridgehead proton), 7.94 (s, 3H, acetoxy methyl), 8.04 (s, 3H, —N—C(=O)—CH_3), 9.70 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

(*ii*) α-Epimer.

Mol. Wt. Calcd. for $C_{22}H_{25}O_6N$: 399. Found (mass spectroscopy): 399. The mass spectra of both epimers were entirely identical.

I.r. ($CHCl_3$): 3450, 3400 (NH), 2820, 2710 (aldehyde C—H), 1740 (ketone and acetate), 1735 (aldehyde), 1685 cm^{-1} (amide); n.m.r. $CDCl_3$): τ −0.40 (s, 1H, aldehyde), 5.00 (t, 1H, proton unshielded by acetoxyl), 6.17 (s, 3H, aromatic methoxyl), 6.30 (broad s, 1H, benzylic bridgehead proton), 7.87 (s, 3H, acetoxy methyl), 8.00 (s, 3H, —N—C(=O)—CH_3), 9.40 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

*Conversion of the Aldehyde **14** to the Keto Ester **15***

Jones' reagent (5 ml) was added dropwise to a stirred solution of the aldehyde **14** (8.56 g) in 10% aqueous sulfuric acid (5 ml) and acetone (50 ml). The mixture was stirred at room temperature for 1 h. Saturated aqueous sodium chloride was added and the solution was extracted exhaustively with methylene dichloride. The combined extracts were dried over anhydrous sodium sulfate and evaporated to give 8.61 g of the crude acid which was converted to the methyl ester by treatment with an excess of diazomethane in methanol–ether at room temperature. Removal of the solvent and chromatography of the crude product on silica gel gave 7.43 g (80%) of the keto ester **15** as a thick oil. For analysis, the two epimers were separated by preparative t.l.c. Both epimers were thick oils, homogeneous in t.l.c.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{23}H_{27}O_7N$: 429.1816. Found (high resolution mass spectroscopy): 429.1819.

I.r. ($CHCl_3$): 3350 (NH), 1750 (ketone), 1728, 1720 (acetate, ester), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.20 (m, 1H, proton unshielded by acetoxyl), 6.17 (s, 3H, aromatic methoxyl), 6.24 (s, 3H, —C(=O)—OCH_3), 6.34 (broad s, 1H, benzylic bridgehead proton), 7.84 (s, 3H, acetoxy methyl), 7.94 (s, 3H, —N—C(=O)—CH_3), 9.44 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

(*ii*) α-Epimer.

Mol. Wt. Calcd. for $C_{23}H_{27}O_7N$: 429.1816. Found (high resolution mass spectroscopy): 429.1818. The mass spectra of both epimers were identical.

I.r. ($CHCl_3$): 3420 (NH), 1750 (ketone), 1735, 1730 (acetate, ester), 1690 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 4.96 (t, 1H, proton unshielded by acetoxyl), 6.15 (s, 3H, aromatic methoxyl), 6.26 (s, 3H, —C(=O)—OCH_3), 7.90 (s, 3H, acetoxy methyl), 7.97 (s, 3H, —N—C(=O)—CH_3), 9.37 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

Preparation of the Hydroxy Ester ***16***

The acetoxy ester **15** (7.2 g) was dissolved in methanol (30 ml) and 1% aqueous potassium hydroxide (10 ml) was added. The solution was stirred for 3 h at room temperature. After work-up in the usual manner, 6.24 g (96%) of the hydroxy ester **16** was obtained as a colorless oil. The analytical samples of the two epimers were obtained by preparative t.l.c. and both were oils homogeneous in t.l.c.

(*i*) β-Epimer.

Mol. Wt. Calcd. for $C_{21}H_{25}O_6N$: 387.1682. Found (high resolution mass spectroscopy): 387.1684.

I.r. ($CHCl_3$): 3500 (hydroxyl), 3440 (NH), 1750 (ketone), 1725 (ester), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.34 (d, J = 8 Hz, 1H, —N(H)—), 5.34 (broad s, 1H, proton unshielded by hydroxyl), 5.87 (d, J = 8 Hz, 1H, apex proton), 6.20 (s, 3H, aromatic methoxyl), 6.30 (s, 3H, —C(=O)—OCH_3), 7.97 (s, 3H, —N(—C(=O)—CH_3)—), 9.44 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

(*ii*) α-Epimer.

Mol. Wt. Calcd. for $C_{21}H_{25}O_6N$: 387.1682. Found (high resolution mass spectroscopy): 387.1685. The mass spectra of both epimers were completely identical.

I.r. ($CHCl_3$): 3500 (hydroxyl), 3440 (NH), 1750 (ketone), 1725 (ester), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$) τ 2.33 (d, J = 7 Hz, 1H, —NH), 5.69 (d, J = 7 Hz, 1H, apex proton), 6.11 (t, 1H, proton unshielded by hydroxyl), 6.19 (s, 3H, aromatic methoxyl), 6.30 (s, 3H, —C(=O)—OCH_3), 7.90 (s, 3H, —N(—C(=O)—CH_3)—), 9.41 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

Oxidation of ***16*** *to the Diketone* ***17***

Compound **16** (6.24 g) dissolved in acetone (80 ml) was oxidized at 0° with a slight excess of Jones' reagent for 2 h. The reaction mixture was poured into water and the product was extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 5.18 g (83%) of the diketone **17** which was crystallized from ether–chloroform as white crystals homogeneous in t.l.c. in several solvent systems. An analytical sample was prepared by recrystallization from ether, and melted at 109°.

Anal. Calcd. for $C_{21}H_{23}O_6N$ (mol. wt. 385): C, 65.45; H, 6.02; N, 3.64. Found (mass spectroscopy, 385): C, 65.41; H, 6.09; N, 3.63.

I.r. ($CHCl_3$): 3450 (NH), 1750 (five-membered ketone), 1725 (ester), 1710 (six-membered ketone), 1680 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 2.98 (d, J = 7 Hz, 1H, —N(H)—), 5.33 (d, J = 7 Hz, 1H, apex proton), 4.03 (broad s, 1H, benzylic bridgehead proton), 6.20 (s, 3H, aromatic methoxyl), 6.23 (s, 3H, —C(=O)—OCH_3), 8.03 (s, 3H, —N(—C(=O)—CH_3)—), 9.40 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

Preparation of the Keto Ketal ***18***

The diketone **17** (5.18 g) was dissolved in anhydrous benzene (300 ml) to which ethylene glycol (2 ml) and *p*-toluenesulfonic acid (850 mg) were added. The solution was heated under reflux for 1½ h with a water separator. The cooled reaction mixture was worked up by the usual procedure. The ketal **18** was crystallized from ether and melted at 245°. The yield was quantitative.

Anal. Calcd. for $C_{23}H_{27}O_7N$: C, 64.32; H, 6.33; N, 3.26. Found: C, 64.29; H, 6.32; N, 3.29.

I.r. ($CHCl_3$): 3410 (NH), 1750 (five-membered ketone), 1720 (ester), 1670 cm^{-1} (amide); n.m.r. ($CDCl_3$): τ 5.93 (m, 4H, dioxolane hydrogen), 6.20 (s, 3H, aromatic methoxyl), 6.25 (s, 3H, —C(=O)—OCH_3), 8.00 (s, 3H, —N(—C(=O)—CH_3)—), 9.43 p.p.m. (s, 3H, tertiary methyl shielded by benzene ring).

Cyclization of Compound ***18*** *to the Keto Lactam* ***19***

A solution of the keto ester **18** (5.71 g) in absolute methanol (50 ml) was added to a solution of sodium methoxide prepared by dissolving sodium metal (2 g) in absolute methanol (50 ml). The mixture was heated under reflux for 26 h in a nitrogen atmosphere. Most of the methanol was removed *in vacuo* and the residue was dissolved in ice water (200 ml). The solution was extracted with chloroform (4 × 150 ml) and the combined extracts were washed with water, dried, and evaporated to dryness. Crystallization of the solid residue from chloroform–ether gave the pure lactam **19**, m.p. 264°. The yield was 3.75 g (80%).

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.55; H, 5.87; N, 3.97.

I.r. ($CHCl_3$): 3400 (NH), 1750 (ketone), 1675 cm^{-1} (lactam); n.m.r. ($CDCl_3$): τ 5.80 (m, 4H, dioxolane hydrogen), 6.23 (s, 3H, aromatic methoxyl), 8.66 (s, 3H, tertiary methyl).

Wolff–Kishner Reduction of the Keto Lactam ***19***

A mixture of the lactam **19** (3.6 g), 95% hydrazine (48 g), hydrazine dihydrochloride (9.6 g) and triethylene glycol (150 ml) was heated at 130° (oil bath temperature) for 4 h with stirring. Potassium hydroxide pellets (13 g) were added in portions with stirring and the temperature was gradually raised to 190° (oil bath). The solution was stirred at that temperature for 5 h. The whole process was operated in a nitrogen atmosphere. After cooling, saturated aqueous sodium chloride (200 ml) was added and the mixture was extracted with chloroform (4 × 200 ml). The chloroform extracts were washed with water, dried, and evaporated to dryness. The pure reduction product **20** (3.1 g, 89%) was obtained by crystallization from ether and it melted at 233°.

Anal. Calcd. for $C_{20}H_{23}O_4N$ (mol. wt. 341): C, 70.36;

H, 6.79; N, 4.10. Found (mass spectroscopy, 341): C, 70.49; H, 6.80; N, 4.06.

I.r. ($CHCl_3$): 3400 (NH), 1665 cm^{-1} (lactam); n.m.r. ($CDCl_3$): τ 3.63 (broad s, 1H, —NH), 5.80 (m, 4H, dioxolane hydrogen), 6.20 (s, 3H, aromatic methoxyl), 6.46 (broad s, 1H, apex proton), 6.83 (m, 1H, benzylic bridgehead proton), 8.76 p.p.m. (s, 3H, tertiary methyl).

Preparation of the Phenol ***21***

A solution of compound **20** (2.6 g) in 48% hydrobromic acid (50 ml) and glacial acetic acid (35 ml) was refluxed for 4 h under nitrogen. After cooling, water was added and the product was extracted with methylene dichloride. Evaporation of the solvent yielded 1.82 g (86%) of the highly crystalline phenol **21**. The analytical sample was prepared by recrystallization from chloroform–methanol to a constant melting point of 301° (dec.).

Mol. Wt. Calcd. for $C_{17}H_{17}O_3N$: 283.1214. Found (high resolution mass spectroscopy): 283.1208.

I.r. ($CHCl_3$): 3500–3300 (OH and NH), 1718 (ketone in six-membered ring), 1655 cm^{-1} (lactam); n.m.r. ($CDCl_3$—CD_3OD): τ 3.12 (d, J = 8 Hz, 1H, aromatic hydrogen), 3.13 (d, J = 3 Hz, 1H, aromatic hydrogen), 3.52 (q, J = 8 Hz, J = 3 Hz, 1H, aromatic hydrogen), 6.43 (broad s, 1H, apex proton), 6.67 (m, 1H, benzylic bridgehead proton), 8.82 p.p.m. (s, 3H, tertiary methyl).

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