A synthesis in the series of aconitine and delphinine

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The synthesis of compound **3** is described. This synthesis represents the solution of most of the problems which will be encountered in the approach to the delphinine and aconitine aromatization products **1** and **2**. The synthetic compound **3** incorporates the complete skeleton and functionality of **1** and **2** except the substitution of ring A.

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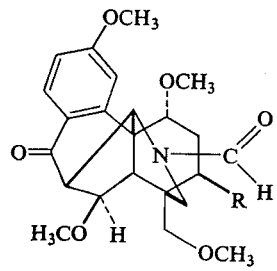
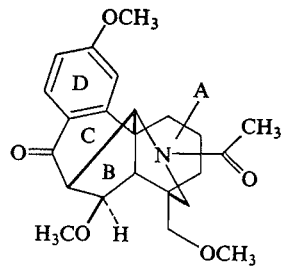
In 1959 we deduced the structures of the highly substituted and notorious aconite alkaloids delphinine (1*a*) and aconitine (1*b*).[1] In this structure determination aromatization products of the type **1** and **2** played a considerable role.[2] Our interest in these compounds is two-fold: (*a*) since they may be obtained in relatively good yields and only a few steps from delphinine and aconitine, the products **1** and **2** could serve as a relay in the total synthesis of complex poly-substituted aconite alkaloids; (*b*) the structure of the C/D ring system is one of the several features of aconitine and delphinine which follow with complete rigor from our chemical degradations (1*a*, 1*b*, 2, 3). Since the anisole ring of **1** and **2** has been generated from the C/D ring system of the parent alkaloids, while the remainder of the molecule remained completely intact, it is clear that a total synthesis of the aromatization products would represent a mathematically rigorous and simple structure proof for delphinine and aconitine, based on chemistry alone. This has not been accomplished in the past for too many natural products as complicated as the poly-substituted aconite alkaloids.

In view of our extensive and long standing interest in diterpene alkaloid chemistry we have decided to carry out the synthesis of **1** and **2** and thus to accomplish at least the second of the two objectives. The chief consideration in the total synthesis of the natural alkaloids themselves would then be the cost of such an undertaking. In the present communication we wish to describe the synthesis of compound **3** which represents the solution of most of the problems facing us in the synthesis of **1** and **2**. The synthesis of the fully



1 R = H
2 R = OH



3

SCHEME 1

substituted aromatization products and the correlation of "natural" and synthetic materials will be reported separately.

The synthetic strategy, which we developed in model experiments (4) involved the alkylation of the tetralone **4** with a long-chain iodide destined to form ring A, followed by an alkylation with allyl bromide (see Scheme 2). In the present synthesis it was consequently our first task to prepare the methoxy benzyloxy iodopentane **12** needed for the first alkylation step.

A convenient starting material was the γ-lactone **7** described by Leuchs *et al.* in 1912 (5). This lactone was hydrolyzed by aqueous alkali to the salt of the corresponding hydroxy acid and the hydrolysis mixture was treated with benzyl

[1]The latter was deduced jointly with Professor Büchi's group at the Massachusetts Institute of Technology.
[2]For a full discussion of these compounds, see reference 2.

chloride in benzene. The resulting acid **8** was esterified with methanolic hydrochloric acid and the ester **9** obtained in an overall yield of 80% was purified by distillation and characterized by its nuclear magnetic resonance (n.m.r.) spectrum, which showed quantitatively the presence of all three of its functional groups.[3]

The ester **9** was now reduced with lithium aluminium hydride to the alcohol **10**, this material was tosylated to **11**, and finally the iodide **12** was obtained by exchanging the tosyloxy group in **11** for iodine with sodium iodide in acetone. Compound **12** was an oil which was purified by chromatography and characterized by thin-layer chromatography (t.l.c.) and a quantitative evaluation of the n.m.r. spectrum. The overall yield of the conversion **8** → **12** was 72%.

With the side-chain **12** available, it was now possible to proceed with the necessary alkylations of the tetralone **4** (6). After unsuccessful preliminary attempts to introduce the allyl chain first and the methoxy benzyloxy pentyl chain in the second alkylation stage, we have turned our attention to the preparation of the compound **5**. This caused considerable difficulties, since the most obvious method, the Stork reaction, did not yield the desired product. Finally, we have been able to prepare **5** in a 50% yield by treating the tetralone **4** with 2 moles of the iodide **12** and 1 mole of sodium methoxide in methanol.

At this stage it should be pointed out that the seven intermediates of the synthesis between compounds **5** and **18**, inclusive, were mixtures of diastereoisomers resulting from the uncontrolled asymmetric centers marked by the asterisks. They were all purified by careful chromatography until they were apparently homogeneous on a thin-layer plate. Characterization was performed by a quantitative evaluation of the n.m.r. spectrum. This was considered very reliable since n.m.r. spectrography showed clearly the presence of all the functional groups, which were derived from all three components of the molecule (see Experimental). However, in spite of the confidence in this method, we were very relieved when we obtained the highly crystalline intermediates **21** and **22** which allowed not only spectral, but also a full classical characterization.

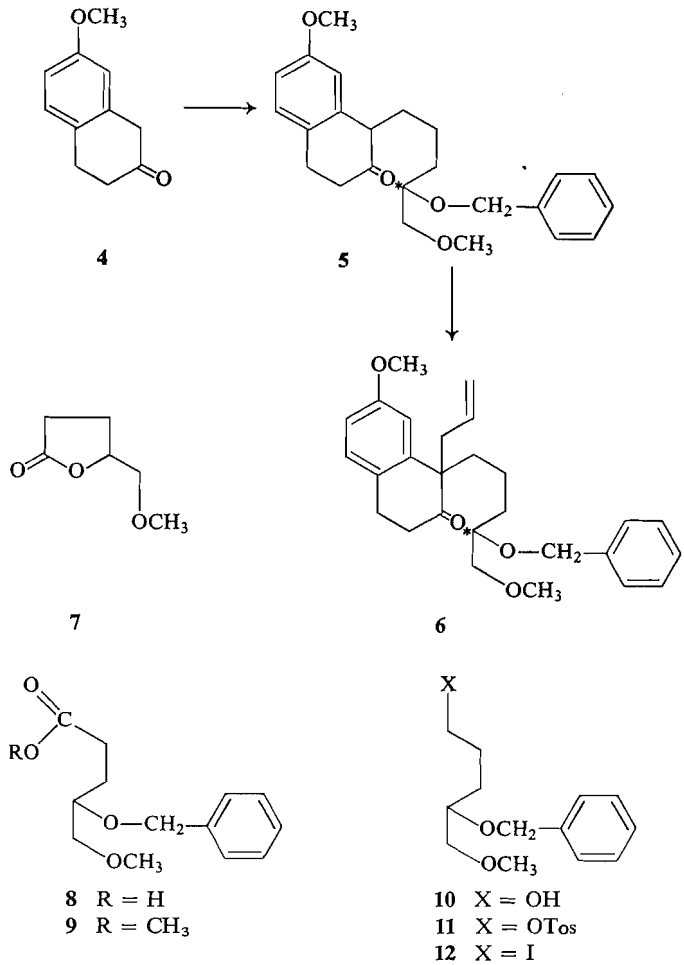
The introduction of the allyl group into the mono-substituted tetralone **5** was performed with allyl bromide and sodium hydride in dry benzene. The yield of the disubstituted tetralone **6** obtained in this manner was 90%. The next two steps, i.e. the hydroxylation of **6** to the diol **13** and the oxidation of this compound to the aldehyde **14** were accomplished in almost quantitative yield, and the products were found (by spectroscopy and t.l.c.) to be pure enough for further work. The hydroxylation was performed with a catalytic amount of osmic acid in the presence of an excess of sodium chlorate in aqueous tetrahydrofuran. The subsequent glycol cleavage was accomplished by metaperiodate in the same solvent.

The ring closure of the keto-aldehyde **14** to the tricyclic bridged hydroxy ketone **15** is a simple aldol condensation and is portrayed by the arrow in formula **14**. The reaction took place readily at 50 °C in aqueous methanolic sodium hydroxide in an 87% yield. The product was purified by chromatography in the form of its tetrahydropyranyl derivative **16**. The infrared (i.r.) spectrum of **16** showed a single sharp carbonyl band at 1755 cm^{-1} for the ketone in the apex of the 1,2,3-bicyclooctane system and no hydroxyl peak.

The next task which had to be accomplished was the conversion of the ketone in **16** to a primary amino group. The required configuration of this group was *anti* to the anisole ring. This was the first asymmetric center which had to be controlled, since all the others would be abolished in the further course of the synthesis. We have established already in our first model study (4) that reductive amination of the ketone with alcoholic ammonia and Raney nickel under high pressure yielded the most favorable proportion of the *anti* and *syn* isomers. In the present case this ratio turned out to be approximately 4:1 in favor of the desired *anti* isomer and the synthesis was thus almost stereospecific. Nevertheless, the two nitrogen epimers were separated only at a later stage, when all the remaining asymmetric centers disappeared.

The mixture of diastereoisomeric amino alcohols **17** which was obtained by the amination of compound **16** (yield 80%) was converted into the acetates **18** and this material was subjected to mild alkaline hydrolysis, hydrogenolysis with palladium on charcoal (to liberate the acetylated and benzylated alcoholic functions), and Jones' oxidation. All these processes gave good yields and the oxidation has reduced the number of

[3]Spectral data are discussed in the Theoretical section only in specially relevant cases. For spectral data of all compounds see the Experimental.



SCHEME 2

diastereoisomers to only two, i.e. the products **19** and **20**. These two epimeric acetylamino diketones were finally separated by careful chromatography on a column of silica gel. The ratio of **19** to **20** obtained in this manner was 4:1 and the required compound **19** crystallized as a waxy low-melting solid, which could not be recrystallized from a solvent.

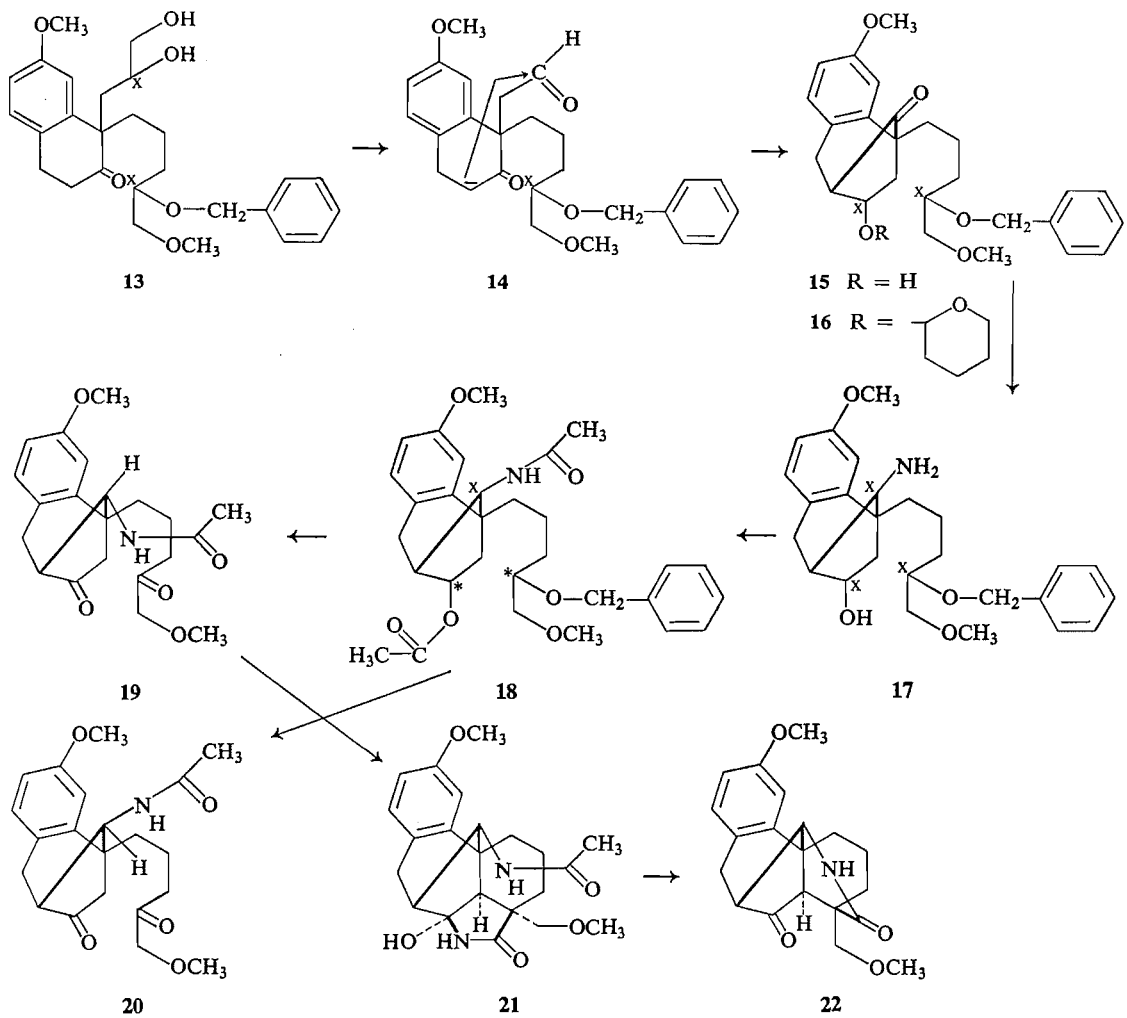
The i.r. spectrum of **19** showed ketonic maxima at 1750 and 1725 cm^{-1} (five-membered and side-chain ketones), an amide carbonyl group at 1675 cm^{-1}, and the NH of the secondary amide group at 3500 cm^{-1}.

The n.m.r. spectrum of **19** displayed two methoxyl singlets (3H each) at τ = 6.54 and 6.12 p.p.m., the methylenic group unshielded by the primary methoxyl as a singlet (2H) at τ = 5.93 p.p.m., the acetyl methyl group as a singlet (3H) at τ = 7.93 p.p.m., and the hydrogen unshielded by the acetylamino group as a doublet (1H) at τ = 5.28 and 5.43 p.p.m.

The spectral data of compound **20** were similar except that the hydrogen unshielded by the acetylamino group appeared in the n.m.r. spectrum of **20** as a multiplet centered at τ = 5.25 p.p.m.

One can see readily that the n.m.r. peak of the hydrogen unshielded by the acetylamino group is a significant indicator of the configuration at this center. Nevertheless we have not attempted to assign the configurations by a fundamental analysis of the n.m.r. spectra.

Since we have prepared previously configurationally defined model compounds (4) we knew empirically that the doublet displayed by compound **19** corresponded to the desired *anti* configuration of the acetylamino group. A rigorous



SCHEME 3

chemical corroboration of this preliminary configurational assignment followed subsequently from the conversion of compound **19** to the pentacyclic lactam **22**.

With the configurationally pure acetylamino diketone **19** in hand, the stage was set for the construction of ring A and the nitrogen ring. It was our intention to close ring A by an aldol condensation of diketone **19** and to complete the assembly of the entire carbon system by adding hydrogen cyanide across the double bond of the resulting α,β-unsaturated ketone.

We were not certain that this hydrocyanation reaction would yield a product possessing the required configuration with the nitrile and acetylamino groups *syn*. However, it would probably be simple to settle this point experimentally by ring formation between these two functional groups. As it turned out, the best method to perform the aldol condensation and hydrocyanation reactions was to combine them into one step. Prolonged reflux of the diketone **19** with a moderate excess of alcoholic potassium cyanide gave the highly crystalline sharply-melting lactamol **21** in an 80% yield. Clearly a hydrolysis of the nitrile group to a primary amide and interaction of this function with the five-membered ring B ketone followed the hydrocyanation. The analytical and spectral investigation of compound **21** (see Experimental) supported unambiguously

the structure assigned to it. On the other hand, the configuration of the lactamol which is portrayed in the formula **21** followed only from the success of the subsequent step, i.e. **21** → **22**.

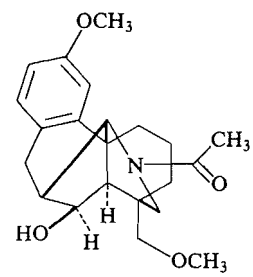
This crucial process, which gave us the final proof for the configurations of the intermediates **19** and **21** and at the same time completed the construction of the desired skeleton, was brought about in a yield of 80% by refluxing the lactamol **21** with a mixture of methanol and concentrated hydrochloric acid.

The keto lactam **22** was a beautifully crystalline substance, which gave a correct elemental analysis and a strong molecular ion in mass spectroscopy. Its i.r. and n.m.r. spectra left no doubt about the correctness of the structural assignment. The i.r. spectrum in chloroform showed the five-membered ketonic carbonyl at 1750 cm^{-1}, the lactam carbonyl at 1665 cm^{-1}, and the lactam NH at 3400 cm^{-1}. The n.m.r. spectrum displayed two methoxyls as singlets (3H each) at τ = 6.67 and 6.22 p.p.m., the methylenic group unshielded by the primary methoxyl as a singlet (2H) at τ = 6.55 p.p.m. and aromatic hydrogen (3H) at τ = 3.08–3.21 p.p.m.

The synthesis of compound **22** was reported in a preliminary communication (7) by two of the present authors (K.W. and J.Š.). It was subsequently repeated on a larger scale (by W.K.) and the individual steps were not only corroborated, but the overall yield was increased by a factor of 3.

The stage was consequently set for the final adjustment of the functional groups. To this end it was necessary to change the ketone of compound **22** into an *exo*-methoxyl and to introduce a new keto group into conjugation with the anisole ring.

The reduction of the keto group in compound **22** caused considerable difficulties and about 500 mg of substance were consumed in attempts to find a stereospecific method. Finally the keto lactam **22** was reduced with lithium aluminium hydride, the product was acetylated, and the *O*-acetyl group saponified by mild reflux with methanolic alkali. All three steps proceeded in good yields (about 90%) and gave a mixture of the *N*-acetyl alcohols **23** and **24** (ratio about 5:4). These two epimers were readily separated by chromatography and subjected (separately) to methylation with dimethyl sulfate and sodium hydride in dry dioxane. The desired *exo*-methoxy compound **25** obtained by methylation of **23** crystallized nicely from ether and showed,



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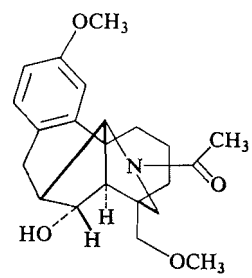

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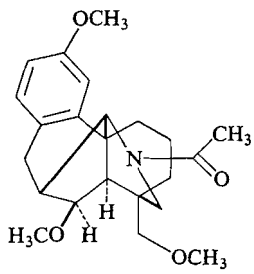

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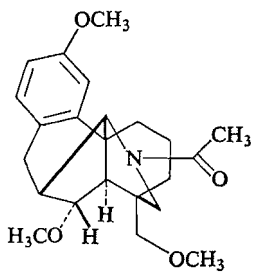

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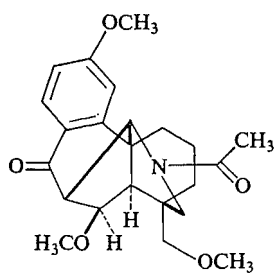

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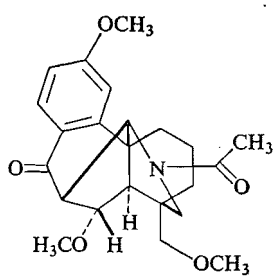

27

besides a correct molecular ion in mass spectroscopy, i.r. and n.m.r. spectral properties in agreement with expectations; n.m.r.: singlet (3H) τ = 6.27 p.p.m. (aromatic —OCH_3), singlet (6H) τ = 6.75 p.p.m. (two aliphatic —OCH_3), singlet (3H) τ = 7.98 p.p.m. (acetyl —CH_3), multiplet (3H) centered at τ = 3.20 p.p.m. (aromatic hydrogen); i.r.: no —OH or NH band, amide carbonyl at 1651 cm^{-1}.

The *endo*-methoxy compound **26** remained amorphous even when it was completely pure (t.l.c.). Its mass spectrum was identical with the mass spectrum of **25**, which is good evidence for the epimeric relationship of the two products. The i.r. spectra of **25** and **26** showed small but distinct differences only in the finger-print region. However, the n.m.r. spectrum of **26** displayed a major difference with respect to the spectrum of

25 and this enabled us to assign to the two products the configurations portrayed in the formulae. The secondary methoxyl singlet which in the n.m.r. spectrum of **25** coincides with the primary methoxyl at $\tau = 6.75$ p.p.m. is shifted in the n.m.r. spectrum of **26** strongly up-field to $\tau = 6.93$ p.p.m. The aromatic and primary methoxyl signals of **25** and **26** are at almost identical τ values and also the remaining peaks in both spectra are very similar. On inspection of the models of compounds **25** and **26** the reason for this n.m.r. behavior becomes clear. The secondary methoxyl of **26** is located in the shielding region of the anisole ring and thus its n.m.r. peak is shifted up-field.[4]

The last operation which faced us in the synthesis was the introduction of a new carbonyl group into conjugation with the anisole ring. No difficulties were encountered in this task, which was accomplished in a yield of 77% by Jones' oxidation. In this way the two compounds **25** and **26** were converted to the final products **3** and **27**, respectively.

This time the *endo*-methoxy product **27** was crystalline and the desired *exo*-methoxy derivative **3** remained amorphous, although it was completely homogeneous on t.l.c. in several systems. Both products gave not only correct molecular ion peaks in mass spectroscopy, but the entire mass spectra were practically identical. The i.r. spectrum of **3** showed no peak in the OH—NH region and three peaks in the carbonyl region at 1680, 1642, and 1600 cm^{-1}. The i.r. spectrum of **27** was practically the same and showed only small differences in the finger-print region. The ultraviolet (u.v.) spectra of **3** and **27** were identical and superimposable on the spectrum of the "natural" aromatization products **1** and **2** [$\lambda_{max} = 278$ mμ ($\log \varepsilon = 4.12$), $\lambda_{max} = 230$ mμ ($\log \varepsilon = 4.09$)].

Our final compound **3** contains the complete functionality of the aromatization products **1** and **2** except the substitution of ring A. In order to synthesize by the same method the "natural" compound **1** itself, it is clearly necessary to prepare an analogue of the intermediate **19** with an additional methoxyl suitably placed in the side-chain. This task is very laborious, but it has now been accomplished on a small scale by two routes.[5] It will be reported in due course.

[4]In this connection it might be mentioned that the "natural" aromatization products of aconitine (2) display methoxyl signals exactly like the epimer **25** and unlike **26**. However, we do not wish to use this as a corroboration of our assignment, which is quite unambiguous in its own right, since one of the purposes of the present work is a rigorous synthetic structure proof for aconitine.

Addendum

While this paper was being refereed and a high resolution mass spectrum of the final product obtained at the suggestion of the referee, we finally succeeded in securing a sufficient supply of pure aconitine to prepare the aromatization product **2** and convert it into the optically active forms of **25** and **3**. These "natural" compounds were shown to be identical with the corresponding synthetic racemates by t.l.c. (in six different systems using two adsorbents), i.r., n.m.r., and mass spectroscopy. This work completes a rigorous purely chemical structure proof for aconitine and delphinine, and also proves the configuration of the ring B methoxyl in these alkaloids. The entire structural argument will be reviewed in a future publication.

Experimental

Preparation of the Methoxy Benzyloxy Methyl Ester **9**

The lactone **7** (5) (13 g) was added to a mixture of dioxane (35 ml) and sodium hydroxide (20 g). The resulting suspension was stirred for 1 h at 80°. After this time the suspension was diluted with dry benzene (100 ml) and benzyl chloride (40 ml) was added dropwise over a period of 10 h. In the course of this addition the temperature was maintained at 80° and rapid stirring was continued. The acid **8** was isolated from the reaction mixture in the usual manner. The yield was 21 g (88%) and it was converted to the ester **9** without further purification. The acid **8** (23.8 g) was dissolved in absolute methanol (100 ml) and the solution was cooled to −15°. Gaseous hydrogen chloride was introduced for 30 min and the solution was allowed to stand overnight at room temperature. The solution was then neutralized with sodium bicarbonate, the methanol evaporated *in vacuo*, and the residue dissolved in ether. The ether solution was washed with water, dried, and the ether distilled off. The residue was fractionated *in vacuo*. The fraction boiling at 115–120° (0.2 mm Hg) was the pure ester **9** homogeneous in t.l.c. and g.l.c. The yield was 22.8 g (90%). Infrared spectrum: no OH band; 1740 cm^{-1} (ester carbonyl). Nuclear magnetic resonance spectrum: singlet (5H) $\tau = 2.75$ p.p.m. (aromatic hydrogen); singlet (2H) $\tau = 5.40$ p.p.m. (benzylic hydrogen); two singlets (3H each) $\tau = 6.35$ and 6.60 p.p.m. (2 $-OCH_3$). Mass spectrum: strong peaks at *m/e* 207 ($CH_3O_2C(CH_2)_2CHOCH_2C_6H_5$); 45 ($CH_2$-

[5]C. Demerson, E. Jay, and T. Kanno. Unpublished results.

OCH_3); 59 (CO_2CH_3); 91 ($CH_2C_6H_5$); 115 (CH_3CO_2-$(CH_2)_2CO$).

Preparation of the Methoxy Benzyloxy Iodopentane **12**

The ester **9** (25.2 g) was heated under reflux in dry ether (250 ml) with lithium aluminium hydride (3.7 g). Work-up in the usual manner gave the alcohol **10** (22.5 g) as a colorless oil in a quantitative yield. It was pure in t.l.c. and was immediately used for further work. Infrared spectrum: 3480 cm^{-1} (hydroxyl); no carbonyl peak. Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.67 p.p.m. (aromatic hydrogen); singlet (2H) τ = 5.46 p.p.m. (benzylic hydrogen); singlet (3H) τ = 6.60 p.p.m. (—OCH_3).

The alcohol **10** (22.4 g) was dissolved in dry pyridine (40 ml) and cooled to −15°. Tosyl chloride (20 g) was gradually added under vigorous stirring and cooling. After the addition was completed the stirring was continued at 0° for 1 h. After this period, water (250 ml) and crushed ice were added and the oily suspension was extracted with ether. The ether solution was washed with dilute hydrochloric acid, aqueous bicarbonate and water, dried, and evaporated to dryness. The yield was 34 g (90%) of the crude tosylate **11**. This material (37.9 g) was dissolved in dry acetone, the solution was cooled to 0° and sodium iodide (75 g) was added to it. The mixture was stirred for 12 h after which time the acetone was distilled off *in vacuo* and water (300 ml) and crushed ice were added. The aqueous mixture was extracted with ether and the combined ether extracts were washed with a 10% thiosulfate solution and with water. After drying and evaporation to dryness the crude oily product was chromatographed on silica gel. Ether in benzene (5%) eluted the iodo compound **12**. It was homogeneous in t.l.c. and was obtained in a yield of 80% (26.8 g).

Mol. Wt. Calcd. for $C_{13}H_{19}O_2I$: 334. Found (mass spectrometry): 334.

Infrared spectrum: no OH and carbonyl band. Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.61 p.p.m. (aromatic hydrogen); singlet (2H) τ = 5.37 p.p.m. (benzylic hydrogen); singlet (3H) τ = 6.52 p.p.m. (—OCH_3); multiplet (4H) centered at τ = 8.34 p.p.m. (C—CH_2—CH_2—C).

Preparation of the Monoalkylated Tetralone **5**

The methoxy tetralone **4** (6) (35.2 g) was added to a solution of sodium (4.6 g) in absolute methanol (1000 ml) under nitrogen. The solution was stirred for 1 h after which time the iodide **12** (120 g) was added and the stirring was continued at 25° for 48 h. The methanol was evaporated and water (500 ml) was added to the residue. The aqueous phase was extracted with ether (5 × 200 ml) and 2% aqueous sodium hydroxide (50 ml) was added to the combined ether extracts. Air was vigorously bubbled through both phases for a short time, after which the aqueous alkaline phase was separated and discarded. This operation destroyed the remaining starting material **4** while leaving the product **5** unaffected. The ether layer was now dried, evaporated to dryness, and the residue chromatographed on silica gel (3.2 kg). The product **5** was eluted with benzene–ether (10:1) as a colorless oil. The yield was 39 g (51%) and the product was apparently homogeneous in t.l.c. Infrared spectrum: no OH band; 1710 cm^{-1} (ketone). Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.72 p.p.m. (aromatic hydrogen of the benzyl group); multiplet (3H) τ = 2.97–3.38 p.p.m. (aromatic hydrogen of the anisole ring); singlet (2H) τ = 5.48 p.p.m. (benzylic hydrogen); singlets (3H each) τ = 6.25 and 6.66 p.p.m. (2 —OCH_3).

Preparation of the Dialkylated Tetralone **6**

Compound **5** (38.2 g) was added to dry benzene (250 ml) containing a 50% emulsion (3.1 g) of sodium hydride in mineral oil. The mixture was stirred at room temperature for 1 h, after which time it was cooled in an ice bath and allyl bromide (24.2 g) was added over a period of 30 min. The temperature was then gradually raised to 45° and the stirring was continued for 24 h. After cooling, the reaction mixture was washed with water, dried, evaporated to dryness, and the residue was chromatographed on silica gel (2 kg). The product **6** was eluted with benzene–ether (20:1). It was a colorless oil homogeneous in t.l.c. and was obtained in a yield of 90%. Infrared spectrum: no OH band; 1720 cm^{-1} (ketone); 928 cm^{-1} (C=CH_2). Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.77 p.p.m. (aromatic hydrogen of the benzyl group); multiplet (3H) τ = 3.02–3.22 p.p.m. (aromatic hydrogen of the anisole ring); multiplet (3H) centered around τ = 5.06 p.p.m. (vinylic hydrogen); singlet (2H) τ = 5.53 p.p.m. (benzylic hydrogen); two singlets (3H each) τ = 6.23 and 6.68 p.p.m. (2 —OCH_3).

Preparation of the Aldehyde **14**

The disubstituted tetralone **6** (21 g) was dissolved in tetrahydrofuran (100 ml) and a solution of osmium tetroxide (0.06 g) in tetrahydrofuran (6 ml) was added. The mixture was stirred for 10 min at room temperature, after which time sodium chlorate (6 g) in water (25 ml) was added. The stirring was continued at room temperature for 48 h. After this period most of the tetrahydrofuran was distilled off *in vacuo*, water was added, and the aqueous layer was exhaustively extracted with ether. After drying and evaporation to dryness the ether extract gave a quantitative yield (22.8 g) of a compound which was apparently homogeneous in t.l.c. and showed a strong hydroxyl band in the i.r. spectrum. It was converted to the aldehyde **14** without purification. To this end the above material (22.8 g) was dissolved in aqueous tetrahydrofuran (1:1, 400 ml) and sodium metaperiodate (81.1 g) was added to the solution. The mixture was vigorously stirred under nitrogen for 5 h at room temperature. During this time a heavy precipitate was formed. It was filtered off and washed thoroughly with ether. The ether was in turn washed with water, dried, and evaporated to dryness. The residue was the practically pure (t.l.c.) aldehyde **14** (21.2 g) obtained in quantitative yield. It was purified by chromatography on silica gel and stored under nitrogen. Infrared spectrum: no OH band, 2710 cm^{-1} (aldehyde); 1730 and 1725 cm^{-1} (aldehyde and ketone carbonyls); no vinyl group around 900 cm^{-1}. Nuclear magnetic resonance spectrum: narrow multiplet (1H) τ = 0.61 p.p.m. (aldehyde hydrogen); singlet (5H) τ = 2.73 p.p.m. (aromatic hydrogen of the benzyl group); multiplet (3H) τ = 3.26–3.38 p.p.m. (aromatic hydrogen of the anisole ring); singlet (2H) τ = 5.50 p.p.m. (benzylic hydrogen); two singlets (3H each) τ = 6.24 and 6.70 p.p.m. (2 —OCH_3).

Preparation of the Tetrahydropyranyl Ketone **16**

The keto aldehyde **14** (21.2 g) was dissolved in methanol (700 ml) and sodium hydroxide (2 g) in water (30 ml) was added under vigorous stirring. The stirring was continued under nitrogen at 50–55° for 24 h. After this time the methanol was partly evaporated *in vacuo*, ice water (150 ml) was added, and the solution was extracted with ether. After washing and drying the ether extract was evaporated to dryness. The yield was 18.15 g (86.5%) of the crude hydroxy ketone **15**. For purification it was converted into the tetrahydropyranyl derivative **16**. Infrared spectrum of crude **15**: 3500 cm^{-1} (OH); 1755 cm^{-1} (five-membered ketone). The crude hydroxy ketone **15** (21.2 g) was dissolved in dry chloroform (250 ml) and dihydropyran (22 g) was added to the solution. After the addition of two drops of concentrated hydrochloric acid the solution was allowed to stand for 24 h at room temperature. The chloroform was then washed with a dilute sodium bicarbonate solution and water, dried, and evaporated to dryness. The residue was chromatographed on neutral alumina (1.1 kg). Petroleum ether – dry chloroform (1:1) eluted 18.2 g (72%) of the t.l.c. homogeneous compound **16**. Infrared spectrum: no OH band; 1755 cm^{-1} (five-membered ketone). Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.70 p.p.m. (aromatic hydrogen of the benzyl group); multiplet (3H) τ = 3.26–3.38 p.p.m. (aromatic hydrogen of the anisole ring); singlet (2H) τ = 5.34 p.p.m. (benzylic hydrogen); multiplet (13H) between singlets at τ = 6.24 and 6.58 p.p.m. (hydrogens unshielded by oxygen plus the two methoxyls).

Preparation of the N,O-Diacetyl Derivative **18**

The tetrahydropyranyl ketone **16** (18 g) was dissolved in methanol (60 ml) and the solution was saturated with ammonia. The solution was then hydrogenated at 2500 p.s.i. for 8 h in the presence of Raney nickel (4 g) at 165°. The catalyst was filtered off and the filtrate was evaporated to dryness. The basic fraction was separated in the usual manner and yielded 12 g of crude compound **17**. This material was dissolved in methylene dichloride (100 ml) and triethylamine (25 g) was added to the solution. The solution was then cooled in an ice bath and acetyl chloride (12.5 g) was added dropwise with vigorous stirring. The stirring was continued at room temperature for 24 h. After this time the mixture was diluted with chloroform, washed with dilute hydrochloric acid, aqueous sodium bicarbonate and water, dried, and evaporated to dryness. The residue was chromatographed on silica gel (600 g). The diacetyl compound **18** was eluted with ether–methanol (10:1) as an oil (11 g), apparently homogeneous in t.l.c. Infrared spectrum: 3450 cm^{-1} (NH); 1730 cm^{-1} (O—CO—CH_3); 1670 cm^{-1} (N—CO—CH_3). Nuclear magnetic resonance spectrum: singlet (5H) τ = 2.78 p.p.m. (aromatic hydrogen of the benzyl group); multiplet (3H) τ = 3.10–3.36 p.p.m. (aromatic hydrogen of the anisole ring); singlet (2H) τ = 5.48 p.p.m. (benzylic hydrogen); two singlets (3H each) τ = 6.30 and 6.66 p.p.m. (2 —OCH_3); two singlets (3H each) τ = 7.97 and 8.15 p.p.m. (2 —C—CH_3).

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Preparation of the Acetylamino Diketone **19**

Compound **18** (10 g) was dissolved in methanol (200 ml) and 10% aqueous sodium hydroxide (40 ml) was added. The solution was refluxed for 1 h after which time the methanol was evaporated *in vacuo*, water (200 ml) was added, and the product extracted with chloroform. The chloroform extracts were washed with dilute hydrochloric acid, aqueous bicarbonate and water, dried, and evaporated to dryness. The residue (6.5 g) was practically homogeneous in t.l.c. and showed no acetoxy band in the i.r. spectrum. It was dissolved in ethanol (200 ml) and acetic acid (2 ml) was added. The solution was hydrogenated for 24 h at atmospheric pressure with 10% palladium on charcoal (2 g). The hydrogenation mixture was worked up as usual and gave after chromatography on silica gel (200 g, eluant chloroform–methanol 10:1) an oily product (4 g) which showed the absence of both the acetoxy and the benzyl group in the i.r. and the n.m.r. spectrum. This material was dissolved in acetone (250 ml) and the solution was cooled in an ice-bath to 5°. Jones' reagent was then added dropwise with stirring until the solution became orange. Stirring was continued for 20 min after which period the reaction mixture was neutralized with a saturated solution of sodium bicarbonate in water. The precipitate which had formed was filtered off and the filtrate was evaporated to dryness. The residue was suspended in water (50 ml) and extracted with chloroform (6 × 50 ml). The chloroform extract was dried, evaporated to dryness, and the residue was chromatographed on silica gel (400 g). Chloroform–methanol (25:1) eluted the pure epimer **19** as an oil which gradually crystallized to a low melting solid and was homogeneous in several t.l.c. systems. The yield was 2 g (50%).

Mol. Wt. Calcd. for $C_{21}H_{27}NO_5$: 373. Found (mass spectrometry): 373.

For the i.r. and n.m.r. spectra, see the Theoretical section.

Preparation of the Lactamol **21**

The diketone **19** (1.015 g) was dissolved in ethanol (50 ml) and a solution of potassium cyanide (0.54 g) in water (4 ml) was added. The mixture was heated under reflux for 18 h. The solvent was evaporated *in vacuo*, the residue was taken up in water (40 ml), and extracted with chloroform (6 × 50 ml). The chloroform extract was washed with dilute hydrochloric acid and water, dried, and evaporated to dryness. The crude product was chromatographed on silica gel (40 g). Chloroform–methanol (100:3) eluted the pure crystalline lactamol **21**. It was recrystallized from methanol to a melting point of 236–238°. The yield was 0.86 g (80%).

Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 66.00; H, 7.00; N, 7.00. Found: C, 65.89; H, 6.69; N, 6.96.

Infrared spectrum (KBr pellet): 1670 and 1715 cm^{-1} (*N*-acetyl and five-membered lactam). Nuclear magnetic resonance spectrum: singlets (3H each) τ = 6.20 and 6.70 p.p.m. (2 —OCH_3); singlet (2H) τ = 6.54 p.p.m. (CH_2 unshielded by primary methoxyl); singlet (3H) τ = 8.10 p.p.m. (—C—CH_3). Mass spectrum: strong peak at *m/e*

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382 (M—H_2O).

Preparation of the Keto Lactam **22**

The crystalline lactamol **21** (1.2 g) was heated under reflux with a mixture of methanol (30 ml) and concen-

trated hydrochloric acid (70 ml) for 24 h. After this time the solution was evaporated to dryness *in vacuo*. The residue was dissolved in chloroform and filtered through a column of neutral alumina (50 g). Evaporation of the filtrate yielded the pure crystalline keto lactam **22**. It was recrystallized from methanol and melted at 185–186°. The yield was 820 mg (80%).

Anal. Calcd. for $C_{20}H_{23}NO_4$ (mol. wt. 341): C, 70.50; H, 6.75; N, 4.12. Found (mol. wt. by mass spectrometry, 341): C, 70.49; H, 6.74; N, 4.36.

For i.r. and n.m.r. spectra, see the Theoretical section.

*Preparation of the Epimers **25** and **26***

The keto lactam **22** (400 mg) was dissolved in dry dioxane (20 ml) and heated under reflux for 24 h with an excess of lithium aluminium hydride (800 mg). After work-up in the usual manner 314 mg (85%) of reduced material were obtained. It was dissolved in dry pyridine (6 ml), acetic anhydride (5 ml) was added, and the mixture was allowed to stand overnight at room temperature. Work-up in the usual manner yielded 373 mg (92%) of the *N,O*-diacetate. This material was dissolved in methanol (6 ml) and a 10% aqueous potassium hydroxide solution (5 ml) was added to it. The reaction mixture was stirred overnight at room temperature. After this time the methanol was evaporated *in vacuo*, water (25 ml) was added, and the mixture was extracted with chloroform (7 × 50 ml). The chloroform solution was washed, dried, and evaporated to dryness. It yielded 311 mg of a colorless oil which showed two spots corresponding to the two epimeric alcohols **23** and **24** in a thin-layer chromatogram. The two epimers were separated by chromatography on silica gel (34 g). The epimer **23** (122 mg) was eluted with methanol–ether (3:100) and the epimer **24** (110 mg) with methanol–ether (5:100). Both compounds were oils homogeneous in t.l.c.

Compound **23** has an i.r. spectrum: 3395 cm^{-1} (—OH); 1621 cm^{-1} (N—C—CH_3; $\underset{\underset{O}{\|}}{}$); and an n.m.r. spectrum: multiplet (3H) τ = 2.99–3.15 p.p.m. (aromatic hydrogen); singlets (3H each) τ = 6.22, 6.69, and 7.88 p.p.m. (2 —OCH_3, N—C—CH_3; $\underset{\underset{O}{\|}}{}$).

Compound **24** has an i.r. spectrum: 3395 and 3595 cm^{-1} (—OH); 1625 cm^{-1} (N—C—CH_3; $\underset{\underset{O}{\|}}{}$); and an n.m.r. spectrum: multiplet (3H) τ = 2.95–3.15 p.p.m. (aromatic hydrogen); singlets (3H each) τ = 6.22, 6.71, and 7.93 p.p.m. (2 —OCH_3, N—C—CH_3; $\underset{\underset{O}{\|}}{}$).

The acetylamino alcohol **23** (130 mg) was dissolved in dry dioxane (7 ml) and a suspension of sodium hydride in mineral oil (30 mg) was added. The mixture was stirred overnight at room temperature. After this time dimethyl sulfate (0.25 ml) was added and the solution was heated under reflux for 12 h. The reaction mixture was cooled, water (20 ml) was added, and the solution was extracted with chloroform (7 × 50 ml). The chloroform extract was washed, dried, and evaporated to dryness. The crude product was chromatographed on silica gel (8.5 g). The compound **25** was eluted with benzene–chloroform (1:1) and recrystallized from ether to a constant melting point of 128–130°. The yield was 79 mg.

Mol. Wt. Calcd. for $C_{23}H_{31}NO_4$: 385. Found (mass spectrometry): 385.

For the i.r. and n.m.r. spectra, see the Theoretical section.

The methylation of the acetylamino alcohol **24** to compound **26** was performed in exactly the same manner. From 134 mg of **24** 87 mg of pure compound **26** were obtained. This material remained oily, but was completely homogeneous in t.l.c. and gave a mass spectrum identical with the mass spectrum of the crystalline epimer **25**.

Mol. Wt. Calcd. for $C_{23}H_{31}NO_4$: 385. Found (mass spectrometry): 385.

Infrared spectrum: no OH band; 1655 cm^{-1} (N—C—CH_3; $\underset{\underset{O}{\|}}{}$). Nuclear magnetic resonance spectrum: multiplet (3H) around $\tau \approx 3.20$ p.p.m. (aromatic hydrogen), singlets (3H each) τ = 6.30, 6.73, 6.93, and 7.99 p.p.m. (3 —OCH_3, N—C—CH_3; $\underset{\underset{O}{\|}}{}$).

*Preparation of the Compounds **3** and **27***

The compound **25** (50 mg) was dissolved in pure acetone (20 ml) and the solution was cooled to 5°. Jones' reagent was added dropwise with stirring until the color of the reaction mixture changed from green to orange. Stirring was continued for 3 h 30 min after which time methanol (5 ml) was added and the mixture was neutralized with sodium bicarbonate. The precipitate was filtered off, the filtrate evaporated to dryness, dissolved in water (10 ml), and extracted with chloroform (6 × 25 ml). After washing and drying, the chloroform extract was evaporated to dryness and the residue was chromatographed on silica gel (15 g). Methanol–ether (8:92) eluted the pure compound **3**. It was an oil homogeneous in t.l.c. Its mass spectrum was identical with the mass spectrum of the crystalline epimer **27**. The yield was 40 mg.

Mol. Wt. Calcd. for $C_{23}H_{29}NO_5$: 399.2046. Found (mass spectrometry): 399.2042.

For the i.r. and u.v. spectra, see the Theoretical section.

The oxidation of compound **26** was performed in exactly the same manner. From 40 mg of **26** 30 mg of compound **27** were obtained. The material was purified by preparative t.l.c. on silica gel and crystallization from ether. It melted at 197–199°.

Mol. Wt. Calcd. for $C_{23}H_{29}NO_5$: 399. Found (mass spectrometry): 399.

Infrared spectrum (KBr pellet): 1678, 1645 and 1600 cm^{-1}. For the u.v. spectrum, see the Theoretical section.

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