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SYNTHESIS IN THE SERIES OF DITERPENE ALKALOIDS VIII. A STEREOSPECIFIC SYNTHESIS OF PENTACYCLIC INTERMEDIATES WITH A BRIDGE IN RING B

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The synthesis of diterpene alkaloids with a bridge in ring B (for instance, songorine or various alkaloids of the delphinine type) requires the development of new methods, which are entirely different from the rather steroid-like approaches to the simpler diterpene bases (veatchine and atisine).

We wish to describe now a stereospecific synthesis of compound I. This compound has two of the usual oxygen substituents of the more complex diterpene alkaloids. It will be clear from the course of the synthesis, that the introduction of methoxyls into the benzene ring and methyl group will require only a suitable choice of starting materials and will thus not increase the complexity of the synthetic procedure. Consequently, we hope that the presently described method will prove useful in approaches to several alkaloids.

Our starting material was the ester II, the synthesis of which we have described recently (1). Lithium aluminum hydride reduction of II gave the corresponding primary alcohol III ($C_{12}H_{12}O$; m.p. 60°C.) in a 93% yield.*

Compound III was oxidized by the DMSO-carbodiimide method (2). The

* All crystalline compounds gave checking elemental analyses. Only the analytical data of compound I are given in full. Infrared and N.M.R. spectra (in $CHCl_3$ and $CDCl_3$) were recorded for all compounds, but are discussed only where specially relevant.

aldehyde IV was purified by chromatography on silica gel and obtained as an oil homogeneous in T.L.C. in a yield of 77%. [$C_{12}H_{10}O$; I.R.: 1720 cm^{-1} (aldehyde carbonyl); N.M.R.: singlet (1H) τ = 0.11 p.p.m. (aldehyde hydrogen).]

The aldehyde IV was treated with four moles of a Grignard reagent prepared from 3-benzyloxy-n-butyl bromide (3) in a refluxing ether solution for 15 hours. The product V was obtained in a yield of 96%. This material was immediately oxidized with the Jones' reagent to the corresponding ketone VI. Compound VI was an oil, purified by chromatography on silica gel and apparently homogeneous in T.L.C. It was obtained in a yield of 80%. [$C_{23}H_{24}O_2$; I.R.: 1700 cm^{-1} (ketone); N.M.R.: multiplet (11H) τ = 2.71 - 3.32 p.p.m. (aromatic and vinylic H), quadruplet (2H) τ = 5.50 p.p.m. (CH_2 of benzyl group), doublet (3H) τ = 8.79 p.p.m. (C-CH_3).]

The ketone VI was treated with an excess of benzenesulphonyl azide as described before (1). The product VII was isolated by chromatography on silica gel as an oil, apparently homogeneous in T.L.C., in a yield of 64%. [$C_{29}H_{27}O_4NS$; I.R.: 1705 cm^{-1} (ketone); N.M.R.: multiplet (14H) τ = 1.94 - 2.83 p.p.m. (aromatic H), quadruplet (2H) τ = 5.57 p.p.m. (CH_2 of benzyl group), doublet (3H) τ = 8.89 p.p.m. (C-CH_3).]

The rearrangement of the aziridine VII to the product VIII was performed as described before (1) by heating with an excess of glacial acetic acid to 100°C. for 45 minutes. The product VIII crystallized on removal of the solvent and it was recrystallized from chloroform. The yield of pure material was 49%. [$C_{31}H_{32}O_6NS$, m.p. 187°C.; I.R.: 1700, 1745 cm^{-1} (ketone and acetate); N.M.R.: multiplet (14H) τ = 2.01 - 3.03 p.p.m. (aromatic H), doublet (3H) τ = 8.77 p.p.m. (C-CH_3 in side-chain), singlet (3H) τ = 7.87 p.p.m. (acetate methyl).]

Compound VIII was refluxed with ethylene glycol and p-toluenesulphonic acid in benzene. The result was the ketalization of the keto group and a loss of the acetyl group by alcoholysis. The product IX was obtained in a 90% yield and purified by chromatography on alumina and crystallization from

ether. [$C_{31}H_{35}O_6NS$, m.p. 138°C.; N.M.R.: multiplet (14H) τ = 2.66 - 2.76 p.p.m. (aromatic H), singlet (4H) τ = 5.89 p.p.m. (dioxolane H).]

Compound IX was reduced with lithium and liquid ammonia in the presence of ethanol. Work-up gave a 70% yield of compound X which was purified by crystallization from ether. [$C_{18}H_{25}O_4N$, m.p. 154°C.; N.M.R.: multiplet (4H) τ = 2.86 p.p.m. (aromatic H), singlet (4H) τ = 5.85 p.p.m. (dioxolane H), doublet (3H) τ = 8.8 p.p.m. (C-CH_3).]

The amino alcohol X was acetylated with acetic anhydride and pyridine to the corresponding N,O-triacetate XI which was purified by crystallization from ether-pet. ether. The yield was 85%. [$C_{24}H_{31}O_7N$, m.p. 150°C.; I.R.: 1740, 1680 cm^{-1} (esters and amide); N.M.R.: singlet (9H) τ = 7.91 p.p.m. (3 acetyl methyls), doublet (3H) τ = 8.18 p.p.m. (C-CH_3).]

Compound XI was hydrolysed with 1% methanolic potassium hydroxide to the N-acetyl diol XII.

Compound XII was purified by crystallization from ether-chloroform and was obtained in a yield of 83%. [$C_{20}H_{27}O_5N$, m.p. 189°C.; I.R.: 1670 cm^{-1} (amide); N.M.R.: singlet (3H) τ = 7.96 p.p.m. (acetyl methyl), doublet (3H) τ = 8.84 p.p.m. (C-CH_3).]

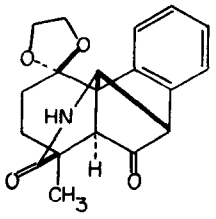
Compound XII was oxidized with chromium trioxide in pyridine. The product XIII was purified by chromatography on neutral alumina and crystallization from ether and was obtained in a yield of 60%. [$C_{20}H_{23}O_5N$, m.p. 201°C.; M.W. (mass spec.) = 357; I.R. (KBr): 1740, 1710, 1685 cm^{-1} (ketones and amide); N.M.R.: singlet (3H) τ = 7.83 p.p.m. (acetyl methyl), singlet (3H) τ = 7.99 (methyl ketone).]

Compound XIII was refluxed with one mole of potassium hydroxide in methanol for 3 hours. The product XIV was obtained in a yield of 92%. It was crystallized from ether. [$C_{20}H_{21}O_4N$, m.p. 200°C.; M.W. (mass spec.) = 339; I.R. (KBr): 1724, 1672, 1650 cm^{-1} (ketone, amide, double bond); N.M.R.: singlet (3H) τ = 7.84 p.p.m. (acetyl methyl), singlet (3H) τ = 8.04 p.p.m. (vinylogous methyl ketone); U.V.: $\lambda_{max.}$ = 253 mμ (log ε = 3.82).]

Compound XIV was subjected to the hydrocyanation reaction (4) in dimethyl formamide and ammonium chloride for 16 hours. The reaction mixture obtained from 800 mg. of XIV was separated by preparative T.L.C. on silica gel into 123 mg. of starting material, 98 mg. of the minor product XVa and 594 mg. of the major product XVb. Since both XVa and XVb are convertible to I they must be epimeric on the carbon marked with the asterisk. XVa: [$C_{21}H_{22}O_4N_2$, m.p. 244°C.; M.W. (mass spec.) = 366; I.R.: 2225, 1750, 1695 cm^{-1} (nitrile, ketone, amide); N.M.R.: singlet (3H) τ = 8.14 p.p.m. (acetyl methyl), singlet (3H) τ = 8.36 p.p.m. (C-CH_3).] XVb: [$C_{21}H_{22}O_4N_2$, m.p. 239°C.; M.W. (mass spec.) = 366; I.R.: 2225, 1750, 1690 cm^{-1} (nitrile, ketone, amide); N.M.R.: singlet (3H) τ = 7.98 p.p.m. (acetyl methyl), singlet (3H) τ = 8.30 p.p.m. (C-CH_3).] The entire mass spectra of compounds XVa and XVb were identical.

The separate conversion of XVa and XVb into I gave identical results. Consequently, we describe here an experiment in which the unresolved mixture of the two compounds was utilized, thus avoiding the preparative T.L.C. in the course of the synthesis.

The mixture of XVa and b (450 mg.), potassium hydroxide (380 mg.) and potassium cyanide (380 mg.) in 80 ml. of 10% water-methanol were refluxed for three days. The two main products of the reaction were compounds XVI (200 mg.) and I (120 mg.). They were separated by careful chromatography on alumina. Compound XVI: [$C_{21}H_{24}O_5N_2$, m.p. 213°C.; M.W. (mass spec.) = 384; I.R.: 3400, 1700, 1685 cm^{-1} (OH-NH, lactam, amide); N.M.R.: multiplet (4H) τ = 2.69 - 2.88 p.p.m. (aromatic H), singlet (3H) τ = 7.96 p.p.m. (N-acetyl), singlet (3H) τ = 8.69 p.p.m. (C-CH_3).] Compound I (recrystallized from ether), m.p. 228°C.: [$C_{19}H_{19}O_4N$; Found: C, 70.31; H, 5.91; N, 4.28%. Calc.: C, 70.14; H, 5.89; N, 4.30%; M.W. (mass spec.) = 325; I.R.: 3200, 1726, 1680 cm^{-1} (NH, ketone, lactam); N.M.R.: multiplet (4H) τ = 2.80 p.p.m. (aromatic H), doublet (1H) τ = 4.05 p.p.m. (NH), narrow multiplet (4H) τ = 6.25 p.p.m. (dioxolane H), singlet (3H) τ = 8.72 p.p.m. (C-CH_3).] The



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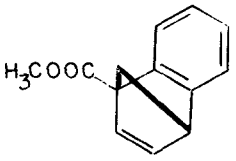

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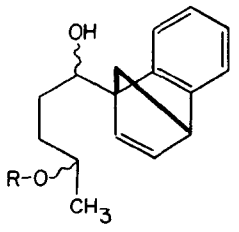

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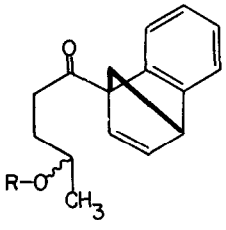

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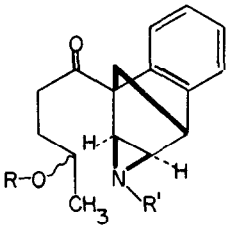

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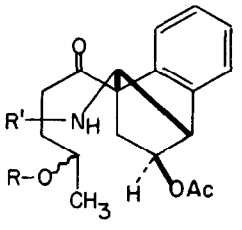

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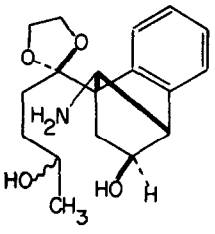
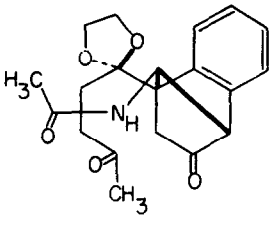


X



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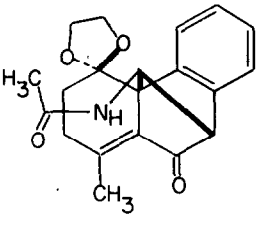
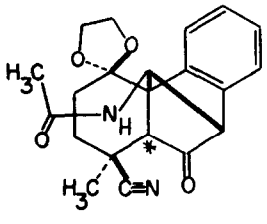


XIV



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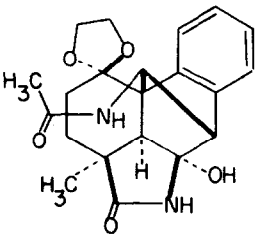

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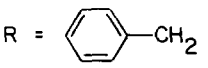

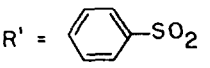

lactamol XVI was heated with potassium hydroxide (1.7 g.) in 10% water-methanol for 5 days. The result was a 60% conversion into compound I and recovery of 40% of starting material.

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