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SYNTHESIS IN THE SERIES OF DITERPENE ALKALOIDS VI.

A SIMPLE SYNTHESIS OF ATISINE

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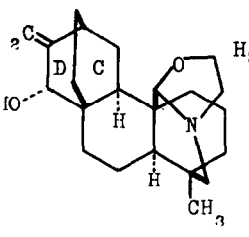
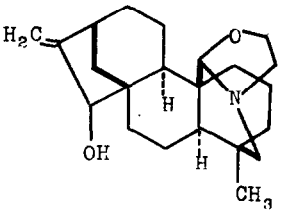
After the completion of the total synthesis of the alkaloid veatchine (1,2), it has been our goal to devise a synthesis of the related alkaloid atisine (I) which would not only be efficient and stereospecific but would also allow the possibility of a simple elaboration of the related skeleta of the veatchine (II) and kobusine (III) (3) type. We now wish to report a synthesis of atisine which satisfies these requirements.*



I



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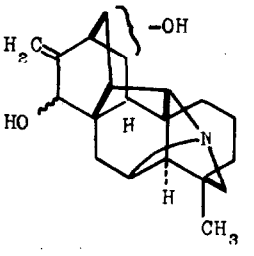


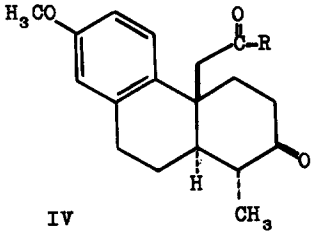
III

* Two syntheses of atisine based on different building principles have been reported by Nagata (4) and by Masamune (5).

The d,l-acid IV (R=OH), m.p. 149-150°, prepared from 2,6-dimethoxynaphthalene by the previously reported method (2,6), was treated in dry tetrahydrofuran with ethyl chloroformate and triethylamine and then with sodium azide to give an excellent yield of the acyl azide IV ($R=N_3$), infrared max. (CCl_4) 2135, 1725 cm^{-1}. A short treatment of IV ($R=N_3$) in refluxing benzene resulted in a complete conversion to the isocyanate V, infrared max. (CCl_4) 2270, 1720 cm^{-1}, which was without isolation treated with anhydrous p-toluenesulfonic acid in refluxing dry benzene for 18 hours (7). Chromatography of the product on alumina gave the keto lactam VI, m.p. 253-256°, infrared max. ($CHCl_3$) 3400, 1725, 1665 cm^{-1}, N.M.R. methyl singlet 8.67 τ, in 56% yield based on acid IV (R=OH). Keto lactam VII, m.p. 244-248°, infrared max. (KBr) 3250, 1725, 1675 cm^{-1}, N.M.R. methyl doublet centered at 8.91 τ, was isolated in 18% yield.

Lactam VI on treatment with ethane dithiol and BF_3-etherate gave the corresponding dithioketal which was reduced with Ra-nickel in ethanol to give lactam VIII, m.p. 241-242°, in 88% yield. A simple high-yield construction of the basic tetracyclic skeleton is thus completed.

To elaborate the C,D-ring system of atisine, VIII was reduced with lithium in a mixture of tetrahydrofuran, t-butanol and liq. ammonia and the resulting dienol ether was hydrolyzed with acid to give a 74% yield of ketone IX, m.p. 225-230°, infrared max. ($CHCl_3$) 3450, 1670, 1630 cm^{-1}, ultraviolet max. (ethanol) 239 mμ (ε 19,100), N.M.R. singlet (1 H) 4.07 τ.



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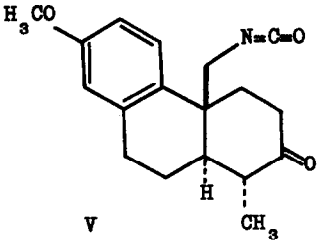

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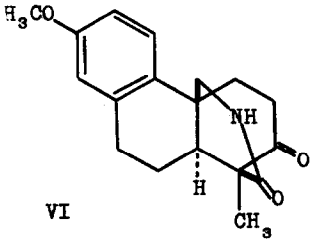

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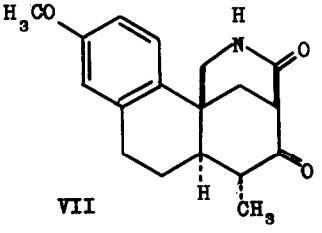

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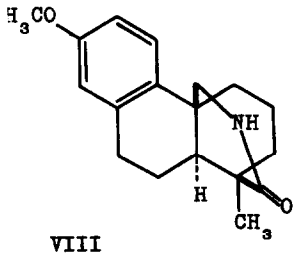

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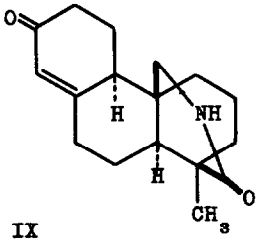

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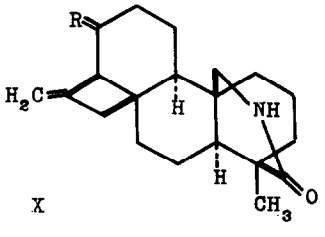
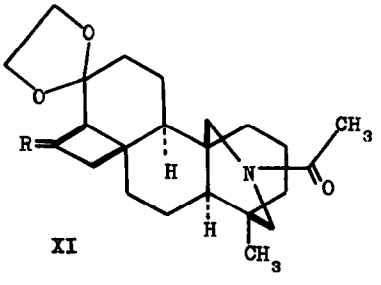


X



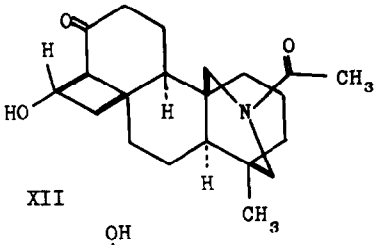
XI

A solution of IX in tetrahydrofuran was irradiated in the presence of a large excess of allene for 18 hours at -78° using a quartz mercury vapour lamp (Hanovia, 100 watts) and a Pyrex filter (7). Crystallization of the crude product gave an 80% yield of the photo-adduct X (R=O),* m.p. 269-272°, infrared max. ($CHCl_3$) 3400, 1695, 1655, 900 cm^{-1}, N.M.R. broad singlet (2 H) 5.06 τ. Treatment of X (R=O) with ethylene glycol and p-toluenesulfonic acid in benzene led to the dioxalane X (R=-O-CH_2-CH_2-O-), m.p. 304-306°, infrared max. ($CHCl_3$) 3400, 1650, 1100, 895 cm^{-1}, N.M.R. singlet (4 H) 6.06 τ, which after reduction with $LiAlH_4$ in boiling dioxane and subsequent acetylation gave the corresponding N-acetyl compound XI ($R=CH_2$), M.W. (mass-spec.) 385, infrared max. ($CHCl_3$) 1645, 1100, 895 cm^{-1}, N.M.R. singlet (3 H) 7.91 τ.

Oxidation of XI ($R=CH_2$) with osmium tetroxide and sodium metaperiodate in aqueous tetrahydrofuran afforded the cyclobutanone XI (R=O), m.p. 186-188°, infrared max. (CCl_4) 1785, 1645, 1090 cm^{-1}, which on subsequent reduction with $NaBH_4$ in methanol gave the alcohol XI (R=OH,H), infrared max. (CCl_4) 3550, 1645, 1095 cm^{-1}. Hydrolysis of XI (R=OH,H) with dilute hydrochloric acid in tetrahydrofuran gave an excellent yield of the pair of epimeric hydroxy ketones XIV, M.W. (mass-spec.) 345, infrared max. (CCl_4) 3650, 3400, 1725, 1640 cm^{-1}, obviously formed <u>via</u> XII and XIII.**

* The stereochemistry of the photo-addition follows from spectroscopic data and correlations with atisine degradation products described below.

** This construction of the C,D-ring system was first accomplished in a model series by Mr. A. Philipp in this laboratory (7).



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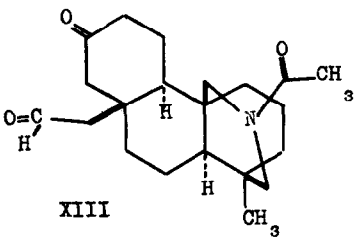

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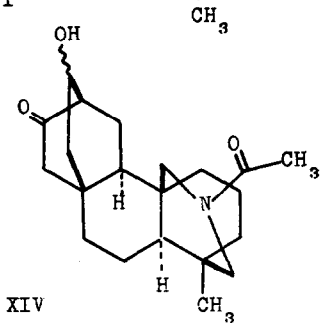

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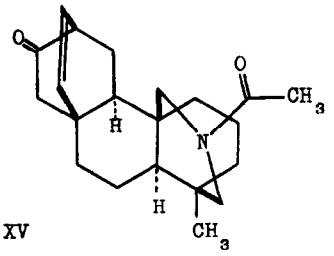

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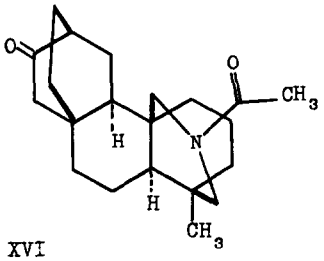

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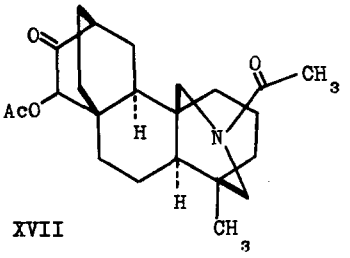

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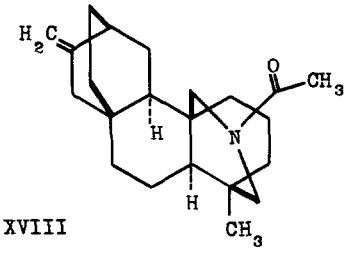


XVIII

Treatment of XIV with mesyl chloride in pyridine gave the corresponding mesyl derivative which without purification was heated under reflux in collidine to give the olefin XV, m.p. 188-190°, infrared max. (CCl_4) 1730, 1645 cm^{-1}, ultraviolet max. (ethanol) 295 mμ (ε 196), N.M.R. multiplet (2 H) 3.80 τ. Hydrogenation of XV with Pd-charcoal in ethanol gave the d,l-ketone XVI, m.p. 170-173°, infrared max. (CCl_4) 1725, 1645 cm^{-1}, N.M.R. singlets (3 H) 7.89 τ, (2 H) 8.02 τ and (3 H) 9.11 τ. The ketone XVI was obtained in a 20% overall yield from the ketal X (R=-O-CH_2-CH_2-O-).

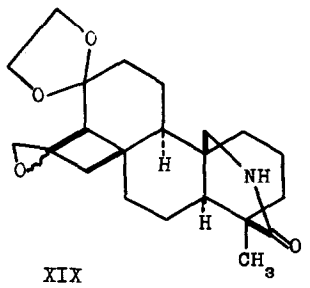
The corresponding optically active ketone XVI, m.p. 166-168°, was prepared from a previously reported atisine degradation product, the ketol acetate XVII (8), by reduction with calcium and liq. ammonia (9) followed by acetylation. The synthetic d,l-ketone XVI was found to be identical with ketone XVI, prepared by degradation of atisine, in solution infrared spectra, N.M.R. and mass-spectra and in t.l.c.

To complete the synthesis, the optically active ketone XVI was subjected to a Wittig reaction to give the methylene derivative XVIII, m.p. 155-158°, infrared max. (CCl_4) 1645, 885 cm^{-1}, N.M.R. doublet (2 H) centered at 5.30 τ, in 74% yield. Since the conversion of XVIII to atisine (I) has already been described (4,8,10), the preparation of d,l-ketone XVI represents a total synthesis of d,l-atisine.

The synthetic versatility of the photo-adduct X (R=O) and the stereospecificity of its formation could be further tested by the following series of reactions. Oxidation of X

(R=-O-CH_2-CH_2-O-) with perbenzoic acid in chloroform gave a high yield of the mixture of epimeric epoxides XIX, infrared max. ($CHCl_3$) 3400, 1650, 1110, 1080 cm^{-1}, which on reduction with lithium borohydride in dry tetrahydrofuran furnished the tertiary alcohols XX, infrared max. ($CHCl_3$) 3600, 3400, 1650, 1095 cm^{-1}, in over 80% yield. Treatment of the crude product with a mixture of dilute HCl and tetrahydrofuran gave the keto alcohols XXI, infrared max. ($CHCl_3$) 3650, 3400, 1725, 1650 cm^{-1}. Dehydration of crude XXI with p-toluenesulfonic acid in boiling benzene gave the olefin XXII (R=O), m.p. 259-263°, infrared max. ($CHCl_3$) 3400, 1725, 1650 cm^{-1}, ultraviolet max. (ethanol) 295 mμ (ε 185), N.M.R. singlets (1 H) 4.16 τ, (3 H) 8.16 τ, in 65% yield based on XX.

Removal of the ketone function was achieved by treatment of XXII (R=O) with ethane dithiol and BF_3-etherate followed by desulfurization with Ra-nickel in methanol to give the olefin XXII ($R=H_2$), M.W. (mass-spec.) 299, infrared max. ($CHCl_3$) 3400, 1650 cm^{-1}, N.M.R. singlets (1 H) 4.4 τ, (3 H) 8.23 τ.



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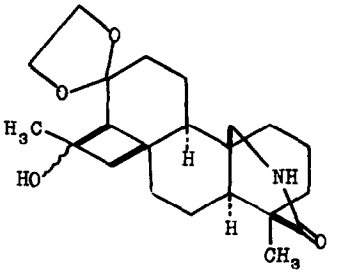
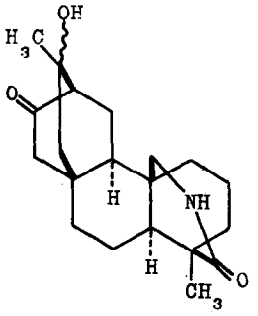
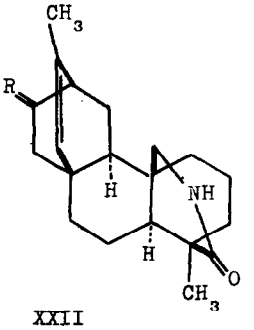


XX

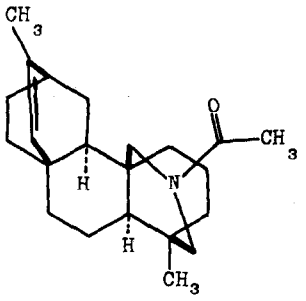


XXI

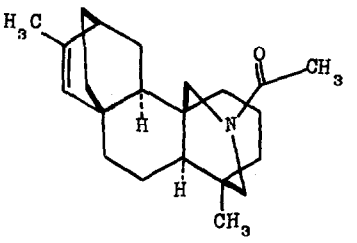


XXII

Reduction of XXII (R=H_2) with $LiAlH_4$ in dioxane followed by acetylation gave the corresponding N-acetyl derivative XXIII, M.W. (mass-spec.) 327, infrared max. ($CHCl_3$) 1645 cm^{-1}. This synthetic racemic compound, when compared to the ''natural'' olefin XXIV, M.W. (mass-spec.) 327, infrared max. ($CHCl_3$) 1645 cm^{-1} simply prepared from XVIII on treatment with p-toluenesulfonic acid in benzene, showed a virtually identical fragmentation pattern in the mass-spectrum and very similar infrared spectrum, but distinctly different N.M.R. spectrum and different R_f values in thin-layer chromatography. Significantly, t.l.c. study showed that no detectable amount of racemic XXIV was present in crude olefin XXIII.



XXIII



XXIV

The stereospecificity of the photo-addition is thus demonstrated by two synthetic series. The configuration of the C,D-ring system in X and its products follows not only from the completed synthesis, but also from the fact the double-bond in olefins XV and XXIII exerts a profound influence upon the N.M.R. chemical shifts and splitting pattern of the $-CH_2-N-CH_2-$ grouping, whereas the N.M.R. appearance of the same grouping in olefin XXIV is comparable to that of saturated compounds.

Experiments designed to convert suitable intermediates of the presently described synthetic series into compounds of the veatchine type (II) by rearrangement and the kobusine type (III) by bridging reactions are under study.

ACKNOWLEDGMENT. The support of this work by the National Research Council, Ottawa, is gratefully acknowledged.

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