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SYNTHESIS IN THE DITERPENE ALKALOID SERIES - II.

A TOTAL SYNTHESIS OF THE GARRYA ALKALOIDS

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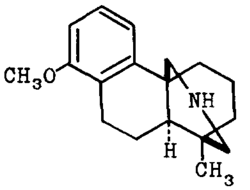
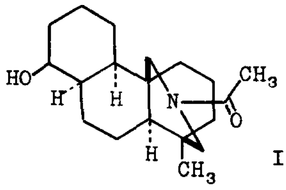
The synthesis of the d,l-amine I was announced recently (1). We now report the stereospecific conversion of I into the pentacyclic ketone XII which can be readily converted into the alkaloids garryine (XIV) and veatchine (XV).



I



II

The amine I, picrate m.p. 273–275°,[*] was acetylated with acetic anhydride in pyridine and the product hydrolyzed with conc. hydrobromic acid to give the corresponding N-acetylphenol, m.p. 278–281°, infrared max. (CCl_4) 3400, 3250, 1640 and 1580 cm^{-1}. A catalytic reduction of the phenol with platinum in acetic acid at atm. pressure[**]

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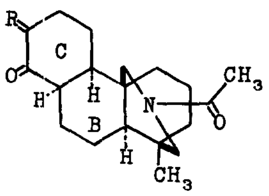
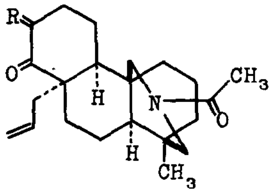
[*] Compounds for which m.p.'s are given gave correct analytical results. The remaining compounds were purified by chromatography and characterized spectroscopically.

[**] Platinum proved superior to ruthenium and nickel in this case.

yielded the oily alcohol II, infrared max. (CCl_4) 3400 and 1640 cm^{-1}, which without purification was oxidized with chromium trioxide in pyridine. Chromatography of the oxidation mixture on alumina yielded the crystalline ketone III, m.p. 187-190°, infrared max. (CCl_4) 1710 and 1650 cm^{-1}.

Treatment of III with sodium methoxide in ethyl formate gave the hydroxymethyleneketone IV,[*] infrared max. (CCl_4) 3250, 1725, 1710, 1640 and 1580 cm^{-1}, which was converted into the thiobutyl derivative V, infrared max. (CCl_4) 1640 and 1540 cm^{-1}, by a short reflux with butyl mercaptan and p-toluenesulfonic acid in benzene (2). Treatment of V with allyl bromide and sodium hydride in boiling tetrahydrofuran gave the allyl ketone VI, infrared max. (CCl_4) 1650,





III: $R = H_2$

IV: $R = C\genfrac{}{}{0pt}{}{H}{OH}$

V: $R = C\genfrac{}{}{0pt}{}{H}{\text{S-butyl}}$

VI: $R = C\genfrac{}{}{0pt}{}{H}{\text{S-butyl}}$

VII: $R = H_2$

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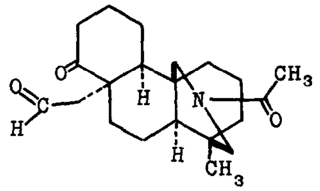
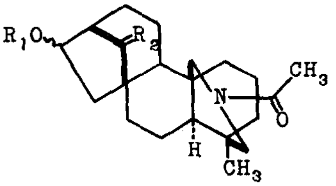
[*] The assignment of a *cis* B,C-ring juncture is based on the fact that compound IV isomerizes on prolonged treatment with sodium methoxide. It is assumed, but not proven, that no isomerization takes place during the formation of compound V.

1540 and 920 cm^{-1}, which was converted into VII, infrared max. (CCl_4) 1710, 1650 and 920 cm^{-1}, on a prolonged treatment with a boiling aqueous alcoholic sodium hydroxide solution. A chromatographic study of compound VII indicated the presence of only one isomer. On the basis of reported alkylations in comparable systems (3,4) and the screening of the β-side by the axially attached nitrogen bridge, it can be anticipated with confidence that the intermediate enolate ion would alkylate stereospecifically to form a cis-decalone as indicated in formulae VI and VII.



VIII



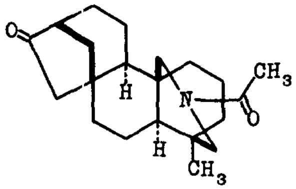
IX: $R_1 = H$; $R_2 = O$

X: R_1 = tetrahydropyranyl;
$R_2 = O$

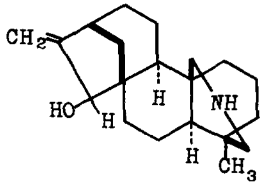
XI: $R_1 = H$; $R_2 = H_2$

The oxidation of ketone VII with sodium metaperiodate and osmium tetroxide in aqueous tetrahydrofuran (5) gave a good yield of the aldehyde VIII, infrared max. (CCl_4) 2720, 1730, 1710 and 1650 cm^{-1}, which was cyclized to IX, infrared max. (CCl_4) 3620, 3400, 1740 and 1650 cm^{-1}, on treatment with methanolic sulfuric acid. The method developed by Ireland in the diterpene series (6) was used in the conversion of

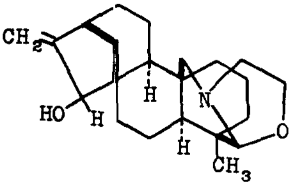
IX into XII. Treatment of IX with dihydro-γ-pyran and a trace of conc. HCl in chloroform (7) gave the tetrahydropyranyl derivative X, infrared max. (CCl_4) 1745, 1640 and 1030 cm^{-1}. This was reduced by a modified Wolff-Kischner method (8), the reduction product was subjected to an extensive chromatographic purification and then hydrolyzed with hot aqueous methanolic hydrochloric acid to give the alcohol XI, infrared max. (CCl_4) 3640, 3450 and 1640 cm^{-1}. Oxidation of XI with chromium trioxide in pyridine gave the ketone XII, infrared max. (CCl_4) 1745 and 1640 cm^{-1}.



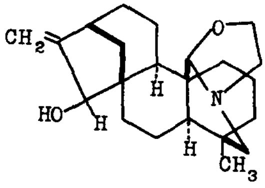
XII



XIII



XIV



XV

Veatchine (XV) was degraded by the method of Vorbrueggen and Djerassi (9) to the optically active ketone XII, m.p. 163–164°. The ''natural'' ketone was found to be identical with the racemic synthetic ketone XII by thin-layer chromatography and infrared spectroscopy. Furthermore, the two ketones gave superimposable mass-spectra. The ''natural'' ketone was reduced with sodium borohydride to give two epimeric alcohols which could be separated by alumina chromatography. One of the alcohols was found to be identical (infrared spectrum, t.l.c.) with the synthetic alcohol XI.

The synthesis of ketone XII constitutes a total synthesis of the Garrya alkaloids, since the conversion of XII into the amine XIII has already been announced by Masamune (10)* and the transformations of XIII into garryine (XIV) (11) and of garryine into veatchine (XV) (12) are also reported. Another method for the conversion of XII into XIII, involving the oxidation of XII with lead tetraacetate, followed by a Wittig reaction and a reduction with calcium in liquid ammonia, has been developed in our laboratory** and will be reported in detail in a full publication.

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* Ref. (10) reports an elegant total synthesis of the Garrya alkaloids. An interesting total synthesis has also been reported by Nagata and his co-workers (13).

** Unpublished results by Dr. H. Immer.

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