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SYNTHESIS IN THE DITERPENE ALKALOID SERIES - I

THE STEREOSPECIFIC SYNTHESIS OF AN INTERMEDIATE AND ITS IDENTIFICATION WITH A NATURAL DEGRADATION PRODUCT

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ALMOST nine years ago, the structures of the first two diterpenoid alkaloids, veatchine and atisine, were deduced in this laboratory. Later work here and elsewhere clarified the relative and absolute configuration I and II, respectively, of these two compounds.[1] The present communication describes the first phase of our work directed towards their total synthesis. By a series of unambiguous steps, we have been able to synthesize the racemic anisole-amines III and IV which appear well suited for further synthetic elaboration.

The tetralones Va and Vb (R_3 = H),[2] prepared by Na-EtOH reduction of the appropriate dimethoxynaphthalenes,[3] were alkylated with ethyl bromoacetate using the enamine method.[4] The resulting liquid esters Va and Vb

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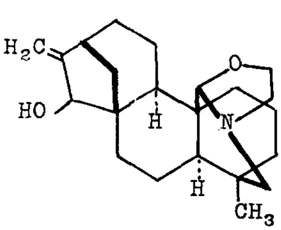
[1] For structures, see K. Wiesner, R. Armstrong, M.F. Bartlett and J.A. Edwards, Chem. & Ind. 132 (1954); J. Amer. Chem. Soc. 76, 6068 (1954). For configuration of veatchine, see K. Wiesner and J.A. Edwards, Experientia 11, 255 (1955); H. Vorbrüggen and C. Djerassi, Tetrahedron Letters 119 (1961) and later papers. For configuration of atisine, see D. Dvornik and O.E. Edwards, Tetrahedron 14, 54 (1961). Experimental connection of I and II, S.W. Pelletier, J. Amer. Chem. Soc. 82, 2398 (1960). The evidence for the indicated absolute configuration is summarized in ref. 12.

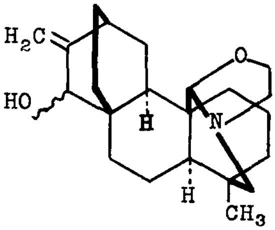
[2] Throughout the paper, $R_1 = OCH_3$, R_2 = H in series "a"; R_1 = H, $R_2 = OCH_3$ in series "b".

[3] J.W. Cornforth and Sir R. Robinson, J. Chem. Soc. 1855 (1949).

[4] G. Stork and H.K. Landesman, J. Amer. Chem. Soc. 78, 5128, 5129 (1956); G. Stork, U.S. Patent 2,773,099; Chem. Abstr. 51, 9703 (1957).



I



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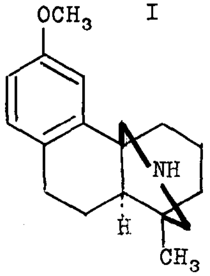

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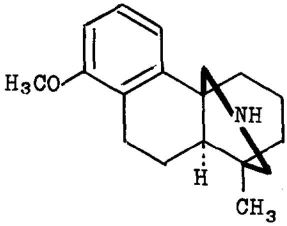

IV

(R_3 = $CH_2COOC_2H_5$) were converted into the unsaturated keto-acids VIa, $C_{18}H_{20}O_4$,[5] m.p. 165-175° (45 per cent yield) and VIb, m.p. 170-174° (30 per cent yield)[6] on treatment with the methiodide of diethylaminopentanone and K-ethoxide in ethanol-benzene.[3] Reduction with lithium in ammonia gave the saturated keto-acids VIIa, $C_{18}H_{22}O_4$, m.p. 173-184° (methyl ester, m.p. 104-105°) and VIIb,[7] m.p. 205-210°, in a variable yield (max.70 per cent).

Reflux of acids VII with p-toluenesulfonic acid in benzene gave the desired diketones VIIIa, $C_{18}H_{20}O_3$, m.p. 146-148° and VIIIb, m.p. 153-156°. In both series, the isomeric cyclopentanones formed by attack of the acylium ion at C_2 were also formed. It was found, however, that a prolonged treatment converted them to the desired diketones VIII.[8]

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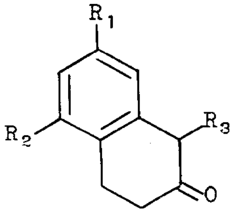
[5] Satisfactory elementary analyses were obtained for all new synthetic compounds described in this communication.

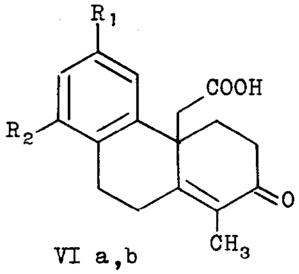
[6] Both acids contained variable amounts of the corresponding γ-lactones (I.R.). These did not have to be separated, since they reopened during the Li-NH_3 reduction.

[7] The trans A/B ring-juncture follows from analogous reductions [see e.g. M.E. Kuehne, J. Amer. Chem. Soc. 83, 1492 (1961)].

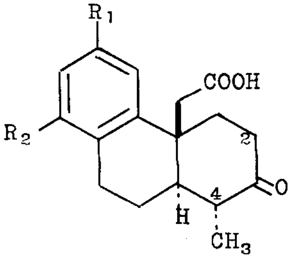
[8] The reaction must therefore be reversible and the diketones VIII must be more stable than their C_2-isomers. The N.M.R. signal of the C_4-methyl group was used for structural assignments.



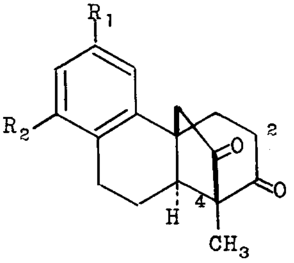
V a,b



VI a,b



VII a,b



VIII a,b

The reaction with $(CH_2SH)_2$ in the presence of $ZnCl_2$ in anhydrous benzene attacked the cyclohexanone specifically to give the dithioketal-ketones IXa, $C_{20}H_{24}O_2S_2$, m.p. 179-181° and IXb, m.p. 218-220°. Vigorous reduction with RaNi in ethanol then gave the alcohols Xa, $C_{18}H_{24}O_2$, and Xb, m.p. 146-149°.[9] The conversion VII ⟶ X was accomplished in an overall yield of 45 per cent in both series. Both alcohols were treated with benzoyl chloride in pyridine and the isolated benzoates were pyrolyzed at 320° to give the liquid olefins XIa, $C_{18}H_{22}O$ (51 per cent yield), and XIb (70 per cent yield). The N.M.R. spectra of both olefins contained quadruplets centered at 4.6 p.p.m. corresponding to the 2 olefinic hydrogens.

The nitrogen bridge was introduced in the following way. The treatment of the olefins with 1 mole of OsO_4 in pyridine gave the vic.-diols XIIa, $C_{18}H_{24}O_3$,[10] (80 per cent yield) and XIIb, m.p. 136-137°, (80 per cent

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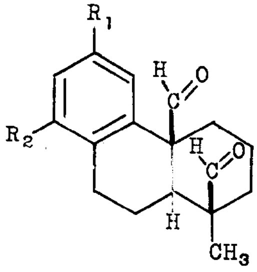
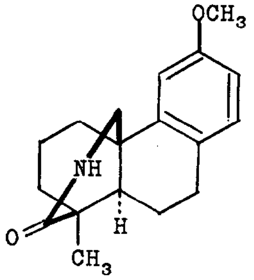
[9] In some runs, it was necessary to complete the ketone reduction with $NaBH_4$. No attempt was made at this stage to isolate pure epimers.

[10] Compounds X-XII in series "a" were oily. They were purified by chromatography on Al_2O_3 and sublimed for analysis.

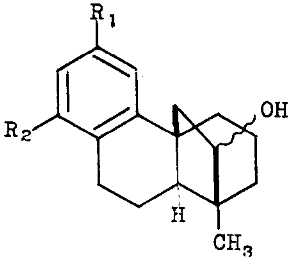


XIII a,b

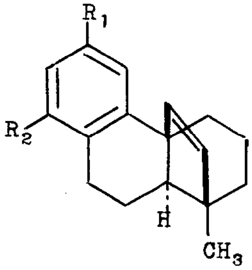


XIV

yield), which were oxidized with Pb(OAc)$_4$ in glacial HOAc to the dialdehydes XIIIa, $C_{18}H_{22}O_3$, and XIIIb, m.p. 127-131°, in an almost quantitative yield.[11] Treatment with a large excess of NH_2OH in boiling pyridine followed by a catalytic reduction with PtO_2 in HOAc then yielded the desired amines III, $C_{18}H_{25}NO$, m.p. 120-122° (picrate, m.p. 204-205°), and IV (picrate, m.p. 273-275°), in approximately 50 per cent yield.



X a,b



XI a,b

The synthetic d,l-base III showed an infrared spectrum (CCl_4) identical to that of the amine (picrate, m.p. 218-220°) formed by $LiAlH_4$ reduction of the optically active lactam XIV.[12] Furthermore, the rich KBr spectra of the two amine picrates were virtually identical. This correlation provides a synthetic structure proof for the rings A, B, C and E in veatchine and atisine.

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[11] Because of their instability, the two dialdehydes were not analyzed.

[12] J.W. ApSimon and O.E. Edwards [Canad. J. Chem. 40, 896 (1962)] prepared this lactam from podocarpic acid and correlated it with a degradation product of atisine, showing that the two series are antipodal. We thank Dr. O.E. Edwards for a sample of lactam XIV.