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A NOVEL RING CONTRACTION LEADING TO THE VERATRAMINE NUCLEUS

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IN connection with a program directed toward the total synthesis of the veratrum alkaloids, we have studied the contraction of ring C of the previously known acetoxy-methoxy-methyldodecahydrochrysene I.[1] One of the approaches examined involved the use of 11,12-dehydro I which is readily available from substance I by acetoxylation (at C-12) with lead tetraacetate, followed by elimination of acetic acid.[2] Ozonization of the dehydro compound at -78°, followed by treatment with triethylamine, afforded the dialdehyde II in 70% yield, m.p. 128-131°, $\lambda_{max}^{95\%\ EtOH}$ 318 mμ (ε 7,250), 257 (7,000); λ_{max} 3.7 μ, 5.85, 5.98 (Found: C, 71.0; H, 7.6). This aldehyde, on treatment with refluxing methanolic sodium hydroxide, was converted into a very insoluble isomeric substance which crystallized

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[1] W. S. Johnson, W. A. Vredenburgh and J. E. Pike, J. Amer. Chem. Soc. 82, 3409 (1960).

[2] W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman and W. F. Johns, J. Amer. Chem. Soc. 78, 6312 (1956).

directly from the reaction mixture in 90% yield, m.p. 275-277°; $\lambda_{max}^{95\%\ EtOH}$ 276 mμ (ε 1,240), 272 (1,240); λ_{max}^{mull} 3.0 μ, 3.1, 3.7, 5.90 (Found: C, 72.7; H, 8.0). The spectral data are consistent with the aldol structure III which was confirmed by the following transformations. Acetylation yielded a diacetate, m.p. 82-84°. The NMR spectrum[3] showed absorption for 3 protons as a singlet at δ = 1.38 p.p.m. (19-CH_3), 3 protons as a singlet at 1.90 (acetate-CH_3), 3 protons as a singlet at 2.00 (acetate-CH_3), 1 proton as a quartet at 3.33-3.67 (H at C-8), 3 protons as a singlet at 3.80 (CH_3O), 1 proton as a broad band at 4.67-5.00 (H at C-3), 4 protons as a multiplet at 6.66-7.50 (H at C-11 and 3 aromatic H), and 1 proton at 9.87 as a singlet (aldehyde H). Oxidation with Jones' reagent[4] afforded the diketo aldehyde IV, m.p. 170-172° (Found: C, 73.5; H, 6.7), $\lambda_{max}^{95\%\ EtOH}$ 318 mμ (ε 4,000), 264 (8,450), which on treatment with aqueous potassium hydroxide in dioxane underwent deformylation to give a mixture of two diketones, A, m.p. 126-128° (Found: C, 76.2; H, 7.6), and B (dimorphic), m.p. 133-135° and 142-145° (Found: C, 76.3; H, 7.5). That these were the expected C-9 epimers was shown by their base-catalyzed interconversion. In the accompanying communication[5] evidence is given to show that diketone-A corresponds to the 9β and diketone-B to the 9α isomer.

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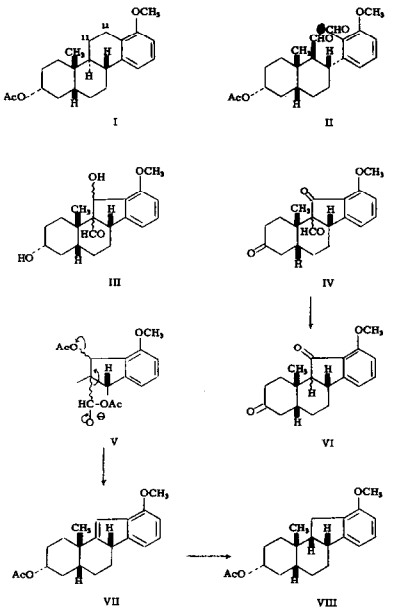
[3] NMR spectra were determined at 60 megacycles. Deuterochloroform was employed as the solvent and tetramethylsilane as an internal standard.

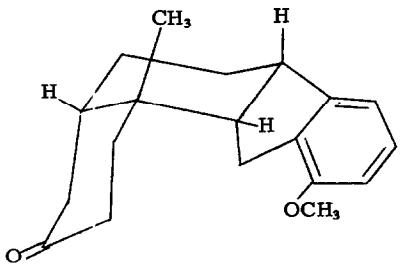
[4] C. Djerassi, R. R. Engle and A. Bowers, J. Org. Chem. 21, 1547 (1956).

[5] D. M. Bailey, D. P. G. Hamon and W. S. Johnson, Tetrahedron Letters No. 9, 555 (1963).

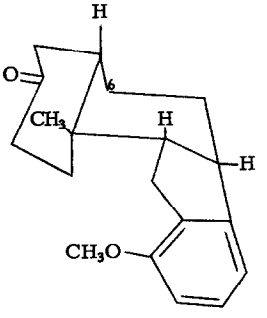


The diacetate of III, on heating with sodium acetate in acetic acid, underwent an interesting fragmentation reaction represented schematically by the partial formula V to give, in 90% yield, the olefin VII, m. p. 156-157° (Found: C, 77.3; H, 8.0), $\lambda_{max}^{95\%\ EtOH}$ 308 mμ (ε 3,900), 298 (4,600), 269 (9,700), 260 (11,700), 231 (8,300), 224 (10,800), 210 (12,800); λ_{min} 304 mμ (ε 3,600), 278 (1,100), 265 (8,500), 239 (3,700); λ_{max} 5.80 μ, 6.20, 6.28-6.35. The NMR spectrum[3] showed absorption for 3 protons as a singlet at δ = 1.22 p.p.m. (19-CH_3), 3 protons as a singlet at 1.93 (acetoxy-CH_3), 1 proton as a quartet at 3.17-3.50 (H at C-8), 3 protons as a singlet at 3.85 (CH_3O), 1 proton as a broad band at 4.50-5.00 (H at C-3), 4 protons as a multiplet at 6.58-7.25 (vinyl H at C-11 and 3 aromatic

H). This substance VII promises to be a useful intermediate for the synthesis of veratramine. Catalytic reduction of VII over palladium-on-carbon proceeded stereospecifically with the absorption of one mole-equivalent of hydrogen to give, in practically quantitative yield, a single product, m.p. 134-135° (Found: C, 76.6; H, 8.7), $\lambda_{max}^{95\%\ EtOH}$ 275 mμ (ε 930), 267 (820). Models of the substance VII indicate that the alpha side of the molecule is highly hindered; hence the hydrogen atom at C-9 must be β-oriented, and the configuration of the product is cis-syn-cis (formula VIII). Saponification of the acetate VIII afforded the corresponding alcohol, m.p. 110.5-112° (Found: C, 79.5; H, 9.4), which, on oxidation with Jones' reagent, was transformed into the ketone IX, m.p. 105-107° (Found: C, 80.2; H, 8.8). This last substance has been used in the proof of configuration of the diketones A and B which in turn have provided the basis for evidence for the configuration of veratramine at C-9.[5]



IX-a



IX-b

Confirmation of the configuration of the 107° ketone was afforded by a study of the stereochemical course of reduction of the keto group. With sodium in liquid ammonia the reduction was strikingly non-stereoselective

and the 3α-hydroxy compound could be isolated as the acetate VIII in only 24% yield. This result is to be compared with the sodium borohydride reduction which, in contrast, was moderately stereoselective, giving the 3α-acetoxy compound VIII in 60% yield. This extraordinary behavior may be rationalized if the 107° ketone has the cis-syn-cis configuration which permits it to undergo a conformational inversion between the "steroid" and "non-steroid" forms IX-a and IX-b respectively.* Now the alcohols produced by reduction can undergo similar conformational inversion; hence it is possible for the hydroxyl group to be equatorial irrespective of its configuration. Thus the 3α-hydroxyl group is equatorial in the steroid conformation (cf. formula IX-a) and the 3β-hydroxyl group is equatorial in the non-steroid form (cf. formula IX-b). The non-stereoselectivity of the reduction with sodium therefore is explicable on the assumption that these two equatorial epimers have comparable stability. Since the course of the reduction with borohydride is subject more to steric approach control, ketone IX would be expected to give a preponderance of reduction to the 3α-hydroxy compound, irrespective of which form, IX-a or IX-b, is attacked. The approach of the reagent is hindered from the alpha face of IX-b by a 1,3-diaxial interaction with the methylene group at C-6, while attack of form IX-a is controlled by the same factors involved in the reduction of an A/B cis 3-keto steroid.

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* The L-forms only are shown (formulas IX-a and IX-b).