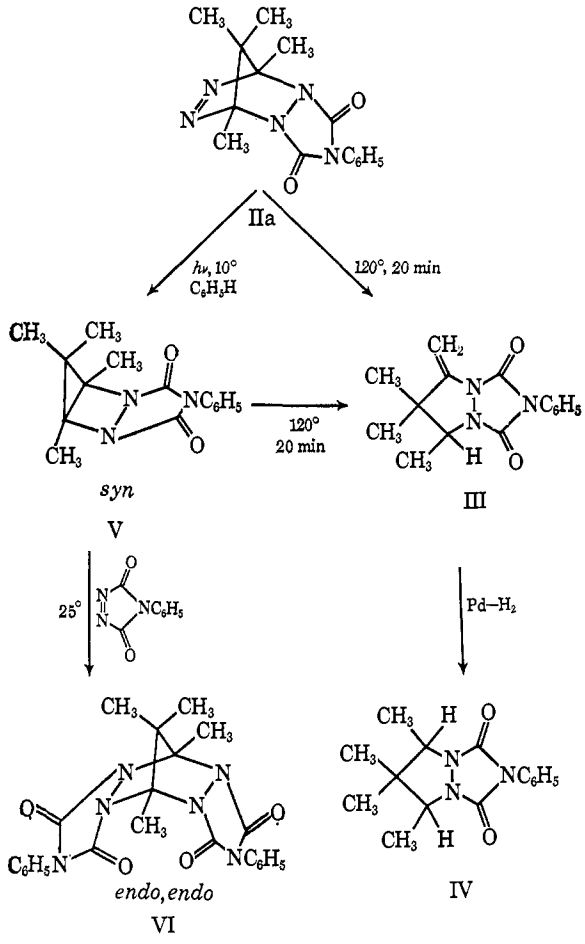
case, and neither simultaneous nor sequential inversions of the nitrogens in the rigid tricyclic ring systems of IIa, V, and VI are likely to be fast (on an nmr time scale) at −57°. Accordingly IIa and IIb are assigned the *endo* configuration and VI the *endo,endo* geometry. The fact that the low-field bridge methyl of IIa and the two bridge methyls of VI have virtually identical chemical shifts supports this assignment. The photoproduct V is assigned the *syn* configuration. Allred[11a] and Roth[11b] have shown that loss of nitrogen from 2,3-diazanorbornenes proceeds with inversion of the bridge. Roth has also demonstrated that carbocyclic [2.1.0] molecules react with 5-phenyl-1,2,4-triazoline-3,5-dione with inversion.[6c] These results should apply to our system yielding the geometries assigned in Scheme I.

Scheme I



The thermal isomerization of V to III must involve the dissociation of the weak central bond of V and intramolecular disproportionation of the resultant diradical. There is ample precedent for the disproportionation of 1,3 diradicals,[6b,12] although in nearly all these cases the migrating hydrogen atom comes from the 2 position. The thermal decomposition of the Diels–Alder adduct IIa to form III may involve the same diradical intermediate; it is not known, however, whether bond formation intervenes between loss of nitrogen and formation of the 1,3 diradical. A 1,3 diradical has been proposed as an intermediate in the thermal and photochemical decomposition of 2,3-diazabicyclo[2.2.1]hept-2-enes, although Roth has suggested another explanation.[6c] Our results demonstrate the plausibility of a diradical mechanism for both thermal and photochemical decomposition of IIa and IIb. In order to obtain further evidence we are examining the kinetics of the decomposition of analogs of II as well as attempting to characterize the intermediate(s) by electron spin resonance spectroscopy.

In addition to the isopyrazoles, acyclic 2,3-diazadienes react with 4-phenyl-1,2,4-triazoline-3,5-dione apparently in part by an analogous pathway. In systems examined thus far the product mixtures are complex and unstable.

(11) (a) E. L. Allred and R. L. Smith, *J. Am. Chem. Soc.*, **89**, 7133 (1967); (b) W. R. Roth and M. Martin, *Ann.*, **702**, 1 (1967).

(12) Pyrolysis of 1,4-dimethylbicyclo[2.1.0]pentane yields 1,3-dimethylcyclopentane and none of the *exo*-methylene anolog: R. Srinivasan, private communication.

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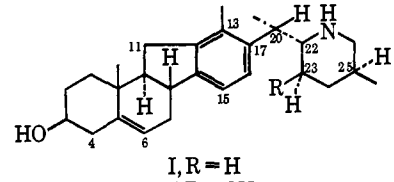
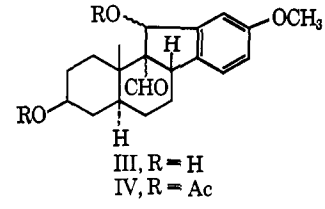
The Total Synthesis of Veratrum Alkaloids. I. Verarine[1,2]

Sir:

The synthesis of Veratrum alkaloids is of considerable interest, since members of this class possess the C-nor-D-homo steroid skeleton, a unique system among the steroidal alkaloids. Recently[3,4] synthetic routes to the alkaloids jervine and veratramine (II) have been described, and we now wish to present a total synthesis of verarine (I)[5,6] by a novel pathway which is also potentially applicable to veratramine and jervine. In general the approach involves the conversion of optically active 3β-acetoxyetiojervan-17-one (XII) to the natural series. Since the former compound is available by degradation[7,8] of the totally synthetic sapogenin, hecogenin,[9] the present work constitutes a total synthesis of this alkaloid. In addition, we have also completed in a separate series of experiments the total synthesis of





(1) Total Synthesis of Steroidal Derivatives. V.

(2) Presented in part at the IUPAC International Symposium on Natural Products, London, July 1968.

(3) T. Masamune, M. Takasugi, A. Murai, and K. Kobayashi, *J. Am. Chem. Soc.*, 89, 4521 (1967).

(4) W. S. Johnson, H. A. P. de Jongh, C. E. Coverdale, J. W. Scott, and U. Burckhardt, *ibid.*, **89**, 4523 (1967).

(5) T. Masamune, I. Yamazaki, and M. Takasugi, *Bull. Chem. Soc. Japan*, **39**, 1090 (1966).

(6) S. M. Kupchan and M. E. Suffness, *J. Am. Chem. Soc.*, **90**, 2730 (1968).

(7) H. Mitsuhashi and K. Shibata, *Tetrahedron Letters*, 2281 (1964).

(8) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965).

(9) Y. Mazur, N. Danieli, and F. Sondheimer, *J. Am. Chem. Soc.*, 82, 5889 (1960).

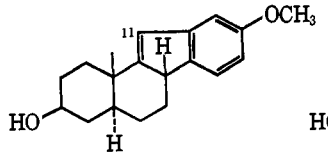
racemic XII by the elaboration of a previously published sequence.

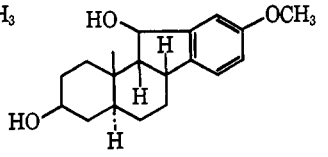
In a previous report[10] we described the total synthesis of the diol aldehyde III *via* a multistep sequence starting from β-naphthol. The conversion of this derivative to the racemic C-nor-D-homo intermediate XII is now discussed.

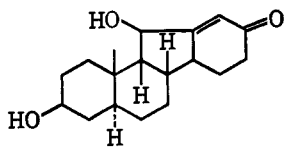
The diol aldehyde III was acetylated with pyridine and acetic anhydride to the diacetate IV,[11] mp 158.5–159.5°. This compound was converted by sodium acetate in refluxing acetic acid to the olefin V (mp 140–141°; λ_{max}^{MeOH} mμ (log ε): 305 (3.51), 293 (3.54), 263 (3.88), 239 (sh) (4.21), and 227 (4.41)), whose nmr spectrum[12] confirmed the presence of an olefinic proton at τ 3.80 (C_{11}–H, 1 H, singlet).

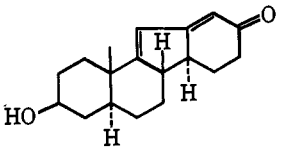
The introduction of the desired stereochemistry at C-9 was attempted by catalytic hydrogenation, Birch reduction, and hydroboration of the 9,11 olefinic linkage, but in each case only the undesired β epimer was isolated.[13] However, the hydroboration product VI obtained in 68% yield (mp 173–176°; λ_{max}^{EtOH} mμ (log ε): 288 (3.27) and 282 (3.33); doublet at τ 4.90 (C_{11}–H, 1 H, J = 12cps) in the nmr spectrum) provided a means of overcoming this problem.

Birch reduction of VI with lithium in ammonia, dioxane, and 2-propanol led on subsequent acid hydrolysis to the intermediate VII which was readily dehydrated under the reaction conditions to form the dienone VIII (48%); mp 199–203°; λ_{max}^{EtOH} 295 mμ (log ε 4.38); $\nu_{max}^{CHCl_3}$ 1635 cm^{-1}; vinyl protons at τ 4.05 and 4.25 (broad singlets, C_{11}–H and C_{13}–H).


V


VI


VII


VIII

Hydrogenation of the dienone VIII in ethanol over platinum on charcoal resulted in the formation of a mixture of saturated ketone IX and monounsaturated ketone X. The ketone IX, a viscous oil (bp 125° (0.1 mm); $\nu_{max}^{CHCl_3}$ 1698 cm^{-1}; τ 9.22 (C_{19}–CH_3, singlet), no nmr signals below τ 6), was transformed by bromine in acetic acid followed by dehydrobromination over magnesium oxide in dimethylformamide to the enone X (over-all yield 51%), which distilled at 142° (0.1 mm) to form a clear glass: λ_{max}^{EtOH} 238 mμ (log ε 4.20); $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}; τ 4.13 (C_{13}–H, 1 H, broad singlet) and 9 22 (C_{19}–CH_3, 3 H, singlet).

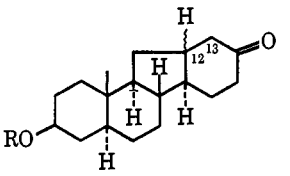
(10) J. P. Kutney, A. By, T. Inaba, and S. Y. Leong, *Tetrahedron Letters*, 2911 (1965).

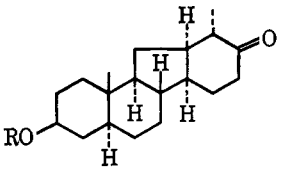
(11) Satisfactory elemental analyses were obtained for all new compounds reported. In addition, high-resolution mass spectrometry was employed in many cases to confirm the molecular formulas.

(12) Nmr spectra were measured on a Varian HA-100 spectrometer in deuteriochloroform solutions with tetramethylsilane as internal reference.

(13) Allocation of the stereochemistry at C-9 results from a detailed study of nmr data which will be presented in our full paper.

The next step in the sequence, introduction of a methyl group at C-13, was achieved by addition of methyl iodide to a solution of the enone X and lithium in ammonia and dioxane. The product of this reaction (XI) was acetylated with pyridine and acetic anhydride to yield XII: mp 169–171.5°; $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; nmr


IX, R = H
X, R = H; 12,13 double bond


XI, R = H
XII, R = Ac
XIII, R = Ac; 12,13 double bond

signals at τ 9.02 (C_{18}–CH_3, 3 H, doublet, J = 12 cps) and 9.20 (C_{19}–CH_3, 3 H, singlet) which was shown to be identical (tlc, ir, nmr, mass spectra) with 3β-acetoxyetiojervan-17-one obtained from hecogenin.[7,8,14]

Reintroduction of the 12,13 olefinic linkage was achieved by the bromination and dehydrobromination procedure used to convert XI to X. The product of this reaction, XIII (mp 167–168°; λ_{max}^{EtOH} 246 mμ (log ε 4.19); $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}), was then coupled with the appropriately substituted pyridine by addition of the former to a solution of 2-ethyl-5-methylpyridine and methyllithium in anhydrous tetrahydrofuran. The reaction was quenched with water and the product reacetylated with pyridine and acetic anhydride to afford a mixture of epimers (58%) from which the desired isomer[15] XIV (mp 189–190°; λ_{max}^{MeOH} mμ (log ε): 269 (3.62), 276 (sh), and 265 (sh); $\nu_{max}^{CHCl_3}$ 1709 (acetate), 1600, 1567 (pyridine), 3280 cm^{-1} (hydroxyl)) was isolated. The nmr spectrum with signals at τ 8.88 (3 H, doublet, J = 7 cps, C_{21}–CH_3), 8.28 (3 H, singlet, C_{18}–CH_3), 4.20 (1 H, broad singlet, C_{17}–O*H*), 2.92 (1 H, doublet, J = 8 cps, C_{23}–H), 2.70 (1 H, quartet, J_o = 8 cps and J_m = 2 cps, C_{24}–H), and 1.75 (1 H, doublet, J = 2 cps, C_{27}–H) was in good accord with the assigned structure XIV.

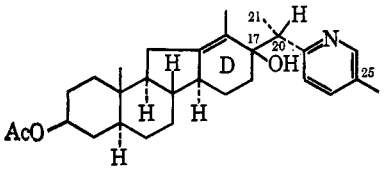
Aromatization of ring D of XIV results on heating a finely ground mixture of the compound with 10% palladium on charcoal at 200°. The product XV, an oil, distilled at 195° (0.1 mm). Its nmr spectrum showed in the aromatic region the typical signals corresponding to two AB spin systems resulting from protons at C_{15}, C_{16}, C_{23}, and C_{24}, as well as a quartet at τ 5.58 (J = 7.5 cps, C_{20}–H).

Selective hydrogenation[16] of the pyridine ring led to a mixture of isomers from which 3-O-acetyl-5α,6-dihydroverarine (XVI) (15%) was isolated. This compound was converted to 3-O,N-diacetyl-5α,6-dihydroverarine (XVII) with pyridine and acetic anhydride and subsequently to N-acetyl-5α,6-dihydroverarine (XVIII) by selective hydrolysis of the 3-O-acetate function with 0.1 *M* potassium hydroxide in refluxing methanol. Compound XVIII, mp 248–249°, was identical with an

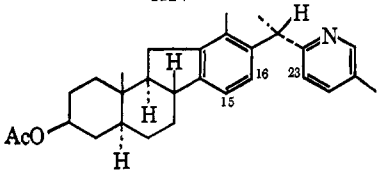
(14) Compounds III–XII are racemic. The structural identity of synthetic XII with the natural material was established by spectral comparison as noted. In this instance, the melting point of the synthetic *dl* compound was also identical with the natural optically active material. From this point in the synthesis, 3β-acetoxyetiojervan-17-one (XII) obtained from hecogenin was utilized as starting material.

(15) The stereochemistry shown at C-20 is inferred from later experimental data, while that at C-17 is not definitively assigned at present.

(16) R. L. Augustine, "Catalytic Hydrogenation, Techniques and Applications in Organic Chemistry," Marcel Dekker, Inc., New York, N. Y., 1965, pp 104–105.

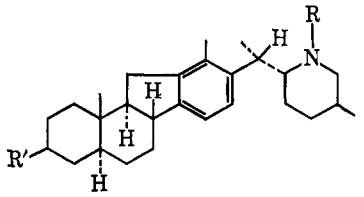


XIV



XV

authentic sample (melting point, ir, tlc, nmr) prepared from veratramine.[5]



XVI, R = H; R′ = OAc
XVII, R = Ac; R′ = OAc
XVIII, R = Ac; R′ = OH
XIX, R = Ac; R′ = O
XX, R = Ac; R′ = O; 4,5 double bond
XXI, R = Ac; R′ = OH; 5,6 double bond

Oxidation of N-acetyl-5α,6-dihydroverarine (XVIII) with Jones reagent yielded the 3-ketone XIX which was converted to the α,β-unsaturated ketone XX by the method of Evans, *et al.*[17] This compound (XX, $\nu_{max}^{CHCl_3}$ 1661 cm^{-1}; τ 4.22 (1 H, singlet, C_4–H)) was then converted into the β,γ-unsaturated alcohol XXI by the procedure of Dauben.[18] Compound XXI, N-acetylverarine, was identical with authentic material (melting point, ir, tlc, nmr) prepared as cited above.[5]

The final step in the sequence, removal of the N-acetyl group, was achieved with 10% potassium hydroxide in refluxing ethylene glycol. The resulting product was shown to be verarine (I), mp 174–176°, by comparison with authentic material (melting point, ir, tlc, nmr).[19]

It is now clear that, by utilization of the appropriately substituted pyridine derivative in the condensation reaction mentioned above, a route to veratramine and jervine is available. Results in this direction will be presented in future communications.

Acknowledgment. Financial aid from the National Research Council of Canada, Medical Research Council of Canada, President's Research Fund, University of British Columbia, and Smith, Miller and Patch, Inc., is gratefully acknowledged.

(17) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(18) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, 73, 4463 (1951).

(19) We are very grateful to Dr. J. Tomko, Slovak Academy of Sciences, Bratislava, Czechoslovakia, for a sample of this material.

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Received May 25, 1968

Inhibition of Coenzyme Q Systems by Chloroquine and Other Antimalarials[1,2]

Sir:

Basic studies on the metabolism of malarial parasites (*Plasmodium*) have led to new data showing that chloroquine, primaquine, quinacrine, and a naphthoquinone antimalarial inhibit, *in vitro*, the mitochondrial oxidation of DPNH and succinate by coenzyme Q (CoQ). The inhibitory effects of chloroquine and the naphthoquinone are the most pronounced, and the effects of the four antimalarials differ considerably in nature and degree. While these inhibitions of electron transfer involving CoQ by certain antimalarials are newly evident, and the presence of CoQ in the metabolism of *Plasmodium* is now known, any correlation between such inhibition and antimalarial activity remains a subject for study. This specific correlation would support only one of many mechanisms for antimalarial activity.

Stemming largely from the research of Fieser and Leffler and their many respective coworkers,[3a] the two naphthoquinones (I, II, or M-1916 and M-2350) were found in the late 1940's to show antimalarial activity in man. Of M-1916, it was said "effect was not satisfactory, but enough to show that M-1916 has definite antimalarial activity in man."[3b] Of M-2350, it was stated "two patients with primary vivax infection were given 2 g ... for 4 days .... The results were dramatic. ...The patients left the hospital in perfect condition with no parasites in the blood. ... or without relapse."[3c] The chemical, biological, and medical research on naphthoquinones during the World War II period was prodigious and seemed to imply that vitamin K was intrinsic in the metabolism of *Plasmodium*. This was a reasonable implication at that time, since it was known that vitamin K is a product of microbial metabolism, and such antimalarial naphthoquinones produced hemorrhagic symptoms in rats which were prevented by vitamin K.[4] Nevertheless, there were no data during those years which proved the participation of vitamin K in the metabolism of the *Plasmodium*.

Recent recognition of the resistance of certain strains of *Plasmodium* to otherwise effective drugs, and the world implications of this resistance, prompted our research for basic knowledge on the electron-transfer mechanisms of *Plasmodium*. Not only was a specific search made for the presence of vitamin K in *Plasmodium*, but a search for CoQ was also made, since the latter closely related quinone was discovered subsequent to the World War II antimalarial program. It was surprisingly discovered[5,6] that CoQ_8 and possibly CoQ_9

(1) Coenzyme Q. CVIII.

(2) This investigation was partially supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2784. This is Contribution No. 421 from the Army Research Program on malaria.

(3) (a) L. F. Fieser, E. Berliner, F. J. Bondhus, F. C. Chang, W. C. Dauben, M. G. Ettlinger, G. Fawaz, M. Fields, M. Fieser, C. Heidelberger, H. Heymann, A. M. Seligmann, W. R. Vaughan, A. G. Wilson, E. Wilson, M. Wu, M. T. Leffler, K. E. Hamlin, R. J. Hathaway, E. J. Matson, E. E. Moore, M. B. Moore, R. T. Rapala, and H. E. Zaugg, *J. Am. Chem. Soc.*, 70, 3151 (1948); (b) *ibid.*, 70, 3154 (1948); (c) *ibid.*, 70, 3155 (1948).

(4) C. C. Smith, R. Fradkin, and M. D. Lackey, *Proc. Soc. Exptl. Biol. Med.*, 61, 398 (1946); 64, 45 (1947).

(5) P. J. Rietz, F. S. Skelton, and K. Folkers, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. M-23.