$[\alpha]_D$ −51.5° (c 11., chloroform);[21] mp 64°, $[\alpha]^{25}_D$ −60.5° (c 2.0, water);[22] mp 70–71°, $[\alpha]^{22}_D$ −57.3° (c 2.8, chloroform).[23]

Reaction of Phosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—Reactions involving phosphine were conducted in a closed glass system. Measured amounts of compound I and phosphine were introduced together in a small Vycor tube cooled in liquid nitrogen, cyclohexanol (5 ml) being used as the solvent. After sealing, the tubes were allowed to warm to 25° in an iron pipe containing a 2 × 10 cm slit and irradiated from a 200-W Hanovia S 654A-36 lamp at a distance of about 15 cm. At the end of irradiation, the unreacted phosphine was evacuated and cyclohexanol was distilled off. Addition of four volumes of ethyl ether precipitated a crude amorphous compound (V). The ether soluble portion was filtered and the filtrates were combined with the washings and evaporated to a yellow syrup which was dissolved in ethanol and oxidized by passing air or oxygen through the solution for 4–6 hr. The solution was then flowed through an Amberlite IR-45 column, eluted with 5% ammonium hydroxide solution and finally washed with water to neutrality. Redistilled cyclohexylamine was added to the collected effluent which was concentrated to a crystalline solid, and was recrystallized from an ethanol–acetone mixture to yield the pure cyclohexylammonium salt of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6-phosphonous acid (IV): mp 166°, $[\alpha]^{25}_D$ −10.9° (c 1.46, methanol).

Anal. Calcd for $C_{15}H_{30}NO_6P$: C, 51.25; H, 8.55; N, 3.99; P, 8.83. Found: C, 51.03; H, 8.47; N, 4.12; P, 8.47.

The infrared spectrum of the compound (potassium bromide pellet) showed absorption maxima at ν 3230 (OH), 2300 (P—H), 1635 (P=O), 1382, 1370 (CMe_2) cm^{-1}. Nmr data in deuterium oxide gave signals at τ 4.09 (one-proton doublet, $J_{1,2}$ = 3.6 Hz, H-1), 5.44 (one-proton doublet overlapping with OD peak), 5.91 (two-proton multiplet, H-3,4), 8.35 (15-proton multiplet, H-5,5′, H-6,6′, C_6H_{11}), 8.58, 8.75 (three-proton singlet, CMe_2), and 2.76 (one-proton doublet, J_{P-H} = 550 Hz, P–H).

The ether-insoluble material was recrystallized from hot ethanol to yield bis(5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-6)phosphine oxide (V): mp 190°, $[\alpha]^{25}_D$ −22.5° (c 1.70 in water).

Anal. Calcd for $C_{18}H_{31}O_9P$: C, 51.18; H, 7.35; P, 7.35; mol wt, 422. Found: C, 51.60; H, 7.46; P, 6.91; mol wt 412.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3350 (OH), 2340 (P—H), 1630 (P=O), 1368, 1380 (CMe_2) cm^{-1}.

Reaction of Phenylphosphine with 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose.—A 10-ml quartz tube was charged with 1.2 g of I, 6 g of phenylphosphine, and 0.5 ml of methanol and sealed with a rubber cap. The tube was irradiated with uv light from a 200-W Hanovia S 654-36 lamp at a distance of about 10 cm. After 48 hr, 50 ml of methanol was added and the azeotropic mixture of phenylphosphine and methanol was removed under reduced pressure (6 mm, 50°) to give a syrupy residue which was dissolved in benzene, and Skellysolve B was added to near turbidity. Compound VII slowly crystallized in the refrigerator to yield 1.56 g (75%). It was recrystallized from methanol–benzene–Skellysolve B: mp 145–147°, $[\alpha]^{25}_D$ −13.2° (c 0.64, methanol).

Anal. Calcd for $C_{15}H_{21}O_5P$: C, 57.70; H, 6.73; P, 10.06. Found: C, 57.74; H, 6.69; P, 9.58.

The infrared spectrum of the compound (potassium bromide pellet) exhibited absorption maxima at ν 3190 (OH), 2330 (P—H), 1590 (C_6H_5), 1382, 1370 (CMe_2), 1210 (P=O) cm^{-1}.

The nmr spectra in methanol showed one peak at τ −1.68, which is due to the phosphorus-bonded hydrogen. H-1 was observed at τ 4.08 as a doublet ($J_{1,2}$ = 3.05 Hz); isopropylidene protons were observed at τ 8.43 and 8.58. The rest of protons were obscured by the solvent peaks. Yields were not changed in several other runs using one-fourth the amount of reactants without the addition of methanol.

Preparations on a smaller scale, with irradiation from an ultraviolet handlamp, gave comparable yields of VII after longer periods of irradiation.

Registry No.—I, 7284-07-3; IV cyclohexylamine, 16355-03-6; V, 16355-04-7; VII, 16355-05-8.

Acknowledgment.—This work was supported by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-7662(71) (Journal Paper No. 3234 of the Purdue Agricultural Experiment Station, Lafayette, Ind.), administered by the Northern Regional Laboratory, Peoria, Ill.

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(23) D. Horton and W. N. Turner, *Carbohyd. Res.*, **1**, 444 (1966).

The Pyrolysis and Structure of Jesaconitine

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Received November 24, 1967

The structure of jesaconitine has been determined by an examination of the nmr spectrum of this alkaloid and its pyrolysis products. The pyrolysis was carried out in an nmr tube and continuously monitored by nmr spectroscopy to provide evidence for the elimination product. This method of pyrolysis constitutes a rapid and convenient way of establishing the presence of certain C-8 ester groups in these diterpene alkaloids using small amounts of material.

Jesaconitine (*Aconitum fischeri* Reich,[2] A. subcunlatum,[3,4] A. sachalinense,[3,4] A. yesoense,[3] and A. mitakense[5]) on hydrolysis affords acetic acid, anisic acid, and the amino alcohol aconine (I).[4] Since the absolute stereochemistry of aconine (Figure 1) is known from X-ray crystallographic studies,[6] the structure of jesaconitine follows once the placement of the two ester groups on the aconine skeleton is determined.

Jesaconitine has been reported to undergo pyrolysis to form pyrojesaconitine.[4] Pyrolysis is a well-characterized reaction for aconitine-type alkaloids bearing an ester functional group at C-8.[7,8] When a C-16 hydroxyl is present, the pyrolytic product exists in the keto form.[9,10] Unfortunately, early workers did not report whether acetic acid or anisic acid was the elimination product of the pyrolysis. However, as a

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(2) K. Makoshi, *Arch. Pharm.* (Weinheim), **247**, 243 (1909); *Chem. Abstr.*, **3**, 2707 (1909); **5**, 674 (1911).

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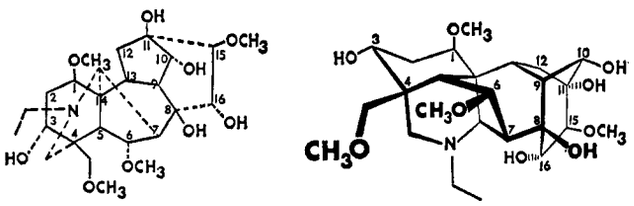


I

Figure 1.—The structure of aconine.

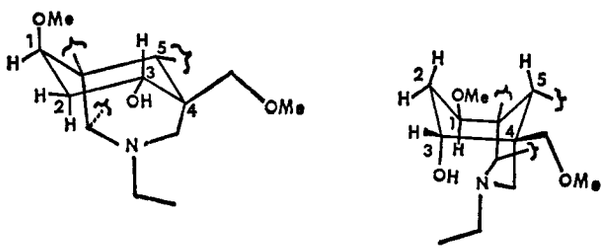
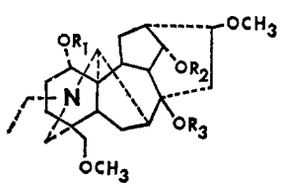


Figure 2.—The conformations of ring A.

working hypothesis it was assumed that one of the two ester moieties is located at C-8.

It then became apparent that the second site of esterification should be relatively easily deduced from the nmr spectrum of jesaconitine itself, for, based on the data gathered from the nmr spectra of other diterpene alkaloids of this type, some rather accurate predictions can be made as to the chemical shift, signal pattern, and coupling constants of the proton geminal to the ester moiety at each of the four possible remaining sites in aconine (C-3, C-10, C-11, C-16). If the second ester group is at C-3, the geminal proton of that position would be expected to exhibit a signal at τ 5.1–5.4 which should be either a quartet, triplet, or a broad multiplet, depending upon the conformation of ring A. If ring A exists in the chair conformation (Figure 2), the dihedral angles between the geminal C-3 proton and the adjacent C-2 equitorial and axial protons are quite different and the signal should be split into a quartet with coupling constants of about 7 and 10 Hz. If ring A is in the boat conformation where the two dihedral angles in question are nearly the same (50–60°), the signal would be expected to be a triplet with a coupling constant of about 3 Hz, and, if ring A is in a rapid equilibrium between the two conformations, the signal of the C-3 geminal proton would be a multiplet. The basis for the above predictions can be discerned from molecular models and is substantiated by a study of the nmr spectra of some ring-A acetate and benzoate esters of condelphine (II) and isotalatizidine (III).[11,12]



II, $R_1 = R_3 = H$; $R_2 = Ac$
III, $R_1 = R_2 = R_3 = H$
IV, $R_1 = R_2 = R_3 = Ac$

(11) S. W. Pelletier, L. H. Keith, and P. C. Parthasarathy, *Tetrahedron Lett.*, **35**, 4217 (1966).

(12) S. W. Pelletier, L. H. Keith, and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, **89**, 4146 (1967).

Although the later alkaloids bear no C-3-hydroxyl group, their corresponding geminal C-1 hydrogen is β, as is the geminal C-3 hydrogen of jesaconitine, and models show that the dihedral angles involved, as well as the magnetic environments, are the same between the C-3 proton and the C-2 protons of jesaconitine as between the C-1 proton and the C-2 protons of condelphine and isotalatizidine. Actually, if the C-3 hydroxyl of jesaconitine were esterified, the expected conformation of ring A would be the chair form for there would then be no possible intramolecular hydrogen bonding to help offset the higher energy of the boat conformation.[12]

If the second ester is substituted at C-10, the signal of the geminal proton should be split into a doublet, coupling with the C-9 bridgehead proton, with a coupling constant of about 4.5 Hz. The basis of this prediction is the correlation of the signals of the C-10 geminal protons of a number of diterpene alkaloids which are esterified at C-10.[12,13] In each case, a doublet or triplet was observed (depending on whether C-11 is substituted with a hydroxyl group or a hydrogen) with a coupling constant of 4.5 Hz.

If the second ester is located at C-11, there would be no signal arising from a geminal proton since there is none present.

If the C-16 hydroxyl is the second site of esterification, the signal of the geminal proton should be a very close doublet with a coupling constant of only about 1.0 Hz since the dihedral angle between this proton and the C-15 proton is about 70°. However, esterification of this hydroxyl might also be expected to interfere with the pyrolysis reaction.

An examination of the nmr spectrum of jesaconitine (Figure 3) immediately revealed the position of the second ester moiety as C-10; the signal of the geminal proton appears as a doublet (J = 4.5 Hz) at τ 5.38. Also evident are the two low field doublets of the aromatic protons, the doublet at τ 2.11 (J = 9 Hz) being attributed to the two protons (H_a) flanking the carbonyl group and the doublet at τ 3.15 (J = 9 Hz) arising from the two protons (H_b) flanking the methoxyl. The five singlets at τ 6.19, 6.28, 6.76, 6.78, and 6.87 are assigned to the five methoxyl groups, the one at lowest field being the aromatic methoxyl. The triplet at τ 8.91 (J = 7 Hz) is characteristic of an N-ethyl group and close to it at 8.64 is the highly shielded signal of the acetoxy protons. This highly shielded signal is further confirmation of a C-8–C-10-diester substitution. Analogous shielding has been observed in all diterpene alkaloids examined which contain a C-10-benzoyloxy–C-8-acetoxy substitution pattern. This phenomenon was first noted by Tsuda and Marion[13] who explained that the upfield shift is caused by the diamagnetic anisotropy of the aromatic ring which can easily come in close proximity to the acetoxy protons. The normal signal of the C-8-acetoxy protons of triacetylisotalatizidine (diacetylcondelphine) (IV) appears at τ 8.07.[12]

At this point there was still no rigorous proof that the aromatic and aliphatic ester moieties of jesaconitine were not switched from their usual deployment in other alkaloids of this type, for a C-8-*p*-methoxybenzoyloxy group and a C-10-acetoxy would be expected to show

(13) Y. Tsuda and L. Marion, *Can. J. Chem.*, **41**, 1634 (1963).

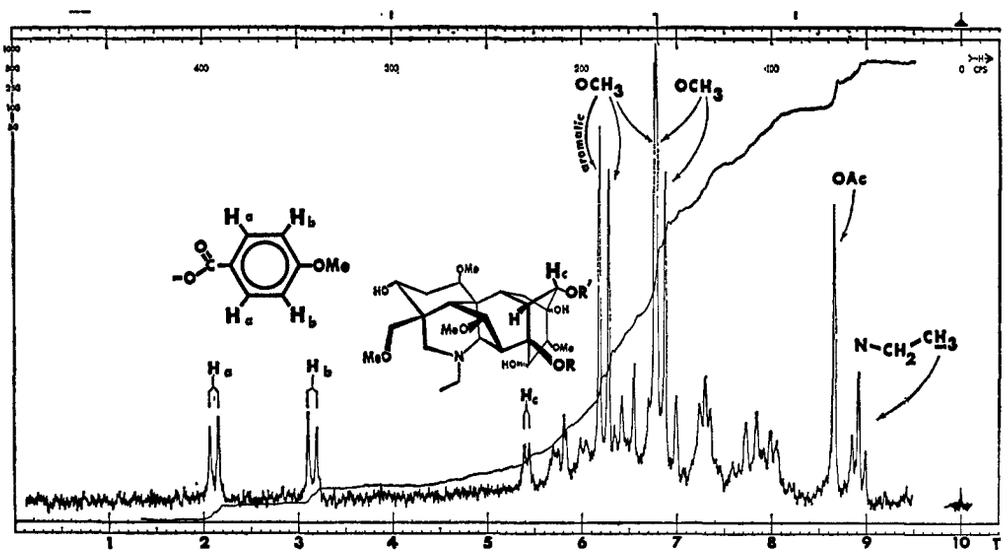
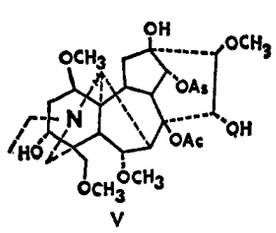


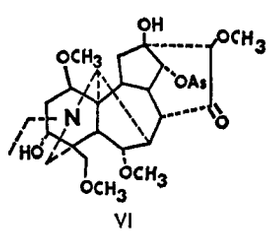
Figure 3.—The 100-MHz spectrum of jesaconitine in carbon tetrachloride at 28°.

the same highly shielded acetoxy signal as a C-8-acetoxy and a C-10-*p*-methoxybenzoyloxy substitution.

Accordingly, in order to determine the exact deployment of the two ester moieties between C-8 and C-10, 10 mg of jesaconitine was pyrolyzed in an nmr tube and the reaction was continuously monitored by nmr over a 2-hr period.[14] The shielded acetoxy signal at τ 8.46 was observed to slowly disappear while another signal at 7.98 correspondingly appeared and grew to the approximate height of the former signal (Figure 4). There was no change in the signals of the aromatic protons. Acetic acid under conditions identical with those described above exhibited a signal at τ 7.98 thus confirming the elimination of acetic acid during the pyrolysis as well as confirming the site of the acetoxy group at C-8. The *p*-methoxybenzoyloxy group is then at C-10. The structures of jesaconitine and pyrojesaconitine are thus V and VI, respectively.

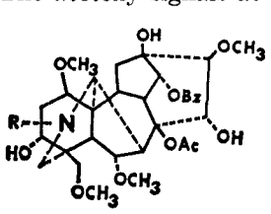


V



VI

The applicability of this method for the determination of similar C-8–C-10 aliphatic–aromatic ester substitutions in aconitine-type alkaloids was confirmed by subjecting 10-mg samples of aconitine (VII) and mesaconitine (VIII) to the pyrolytic conditions described above and monitoring the pyrolysis by nmr spectroscopy. The acetoxy signals at τ 8.48 and 8.49



VII, R = C_2H_5
VIII, R = CH_3

(14) L. H. Keith and S. W. Pelletier, *Chem. Commun.*, 993 (1967).

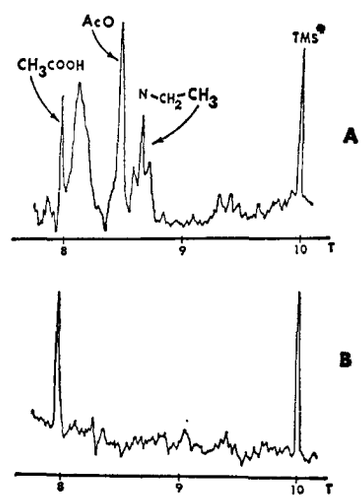


Figure 4.—(A) The nmr spectrum of jesaconitine during pyrolysis (after 45 min); (B) the nmr spectrum of acetic acid under the identical conditions of pyrolysis.

in aconitine and mesaconitine, respectively, were observed to slowly disappear while the corresponding signal of acetic acid at 7.98 appeared and grew to the approximate size of the former signals. This method of monitoring the pyrolysis by nmr presents a rapid and convenient way of establishing the presence of certain C-8-ester groups in the aconitine-type skeleton without sacrificing relatively large amounts of material as required for conventional studies of the pyrolytic products of these alkaloids.

Experimental Section

The spectra were obtained with a Varian HA-100 spectrometer. The samples (10 mg) were dissolved in 0.4 cc of glycerol containing a trace of D_2SO_4 and 2–3 mg of the sodium salt of 3-(trimethylsilyl)propanesulfonic acid as an internal standard. The methylene proton signal of the solvent supplied the lock signal. Pyrolysis was carried out by maintaining the sample temperature at 185° over a 2-hr period.

Registry No.—V, 16298-90-1; VI, 16298-91-2.

Acknowledgment.—This work was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service.