THE NATURE OF PYRACONITINE[1]

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ABSTRACT

A new investigation of pyraconitine and pyraconine has confirmed the presence of a skeletal carbonyl in these compounds. Reduction of pyraconitine with sodium borohydride produces a hydrolytic base which no longer contains a carbonyl group. The Wolff–Kishner reaction reduces the carbonyl in pyraconitine, eliminates the elements of methanol, and hydrogenates the resulting double bond as well as hydrolyzing off the benzoyl ester. These observations indicate the presence in aconitine of the sequence $R_2C(OAc).CHOH.CH(OCH_3)$-. On the basis of the structure of aconine previously derived from the X-ray structure of demethanolaconinone the foregoing results determine the skeletal position occupied by the labile acetoxy group in aconitine.

It has long been known (1) that aconitine ($C_{34}H_{47}O_{11}N$) when pyrolyzed eliminates acetic acid and gives rise to pyraconitine ($C_{32}H_{43}O_9N$). The loss of acetic acid has been variously interpreted as producing an epoxide (1, 2), an ethylenic linkage (3), or a carbonyl group (4). The last interpretation was based on the presence of a broad absorption band in the infrared spectrum of pyraconitine and a weak band in the spectrum of pyraconine hydrochloride. The ethylenic linkage suggested by Schneider (3) would, on the basis of his proposed structure for aconitine, require that the salts of pyraconitine be anhydronium salts, and neither the hydrochloride of pyraconitine nor that of its hydrolytic product pyraconine show the characteristic absorption of anhydronium salts in the infrared, so that this suggestion can be discarded. A new investigation of pyraconitine has therefore been undertaken, and the results obtained confirm the presence of a carbonyl in the pyrolytic products and permit the location of the acetoxy group in the carbon–nitrogen skeleton of the alkaloid.

Crystalline pyraconitine was prepared by heating aconitine to 185–190°. Its saponification product, pyraconine ($C_{25}H_{39}O_8N$), was isolated as the crystalline hydrochloride. The infrared spectrum of pyraconitine contained a split absorption band at 1696–1717 cm^{-1} due to the benzoyl ester carbonyl and a second carbonyl in a six-membered ring. The latter was confirmed by the presence of a weak band at 1709 cm^{-1} in the infrared spectrum of pyraconine, which no longer contains the benzoyl group. In order to ascertain whether this weak carbonyl band was significant a solution of pyraconine in chloroform, of known concentration, was used for the infrared spectrum. The carbonyl band had an extinction coefficient $\epsilon^{(a)}_{max}$ 300, thus showing it to be a true carbonyl absorption band, since the absorption is significant when $\epsilon^{(a)}_{max} > 200$ (5). Furthermore, this absorption peak no longer showed in the infrared spectrum of the Wolff–Kishner reduction product of pyraconitine. On treatment with sodium borohydride, pyraconitine underwent hydrolysis as well as reduction of the carbonyl group to a hydroxyl and gave rise to a compound, $C_{25}H_{41}O_8N$, which in the infrared showed no absorption in the region 1600–1850 cm^{-1}. Had the reaction not involved the reduction of a skeletal carbonyl the product should have been identical with pyraconine, but it proved to be quite different. These results, therefore, confirm the conclusion of Shima and Amiya (4) that the elimination of acetic acid in the pyrolysis of aconitine is accompanied by the formation of a carbonyl group.

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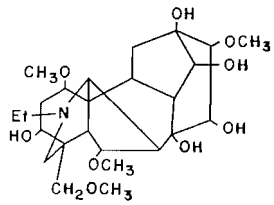
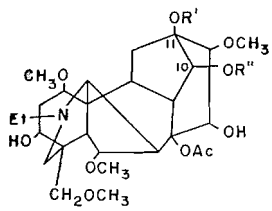
The Wolff–Kishner product of pyraconitine had the empirical formula $C_{24}H_{39}O_6N$, and contained only three methoxyl groups. Hence the reaction involved not only the reduction of the carbonyl to a methylene and saponification of the benzoyl group as expected; it also involved the loss of methanol and the hydrogenation of the resulting double bond. The absence of a double bond was evidenced by the infrared spectrum, which contained no absorption bands characteristic of such a function, and also by the attempted catalytic hydrogenation, which yielded the unchanged material. The Wolff–Kishner reaction is known to follow such a course when the carbonyl is α to a methoxyl, although in some cases the product is unsaturated (6).

In order that the elimination of acetic acid might give rise to a ketone it is necessary that the acetoxy group in aconitine be vicinal to a secondary hydroxyl, and to account for the behavior of pyraconine in the Wolff–Kishner reduction it is also necessary that this hydroxyl be vicinal to a methoxy group. It must be concluded, therefore, that aconitine contains the sequence of substituents $R_2C(OAc).CH(OH).CH(OCH_3)$- and that pyraconine contains the sequence $R_2CH.CO.CH(OCH_3)$-, which in the Wolff–Kishner reduction product becomes $R_2CH.CH_2.CH_2$-.

From the X-ray crystallographic study of demethanolaconinone hydriodide trihydrate (7) it follows that the structure of aconine is that represented by formula I. If we assume that no ring enlargement accompanies the pyrolytic reaction, then structure I presents



I



II

only one choice for the location of the acetoxy group in aconitine whose structure is shown by formula II where either R′ or R″ = C_6H_5CO and the other is H. It has previously been shown that the secondary hydroxyl in ring A is unsubstituted (8) and hence the benzoyl ester group can only be in either position 10 or 11 (cf. for numbering see ref. 8). It is hoped from current work to determine which of these two positions is occupied by the benzoyl ester group.

Aconitine possesses many points of similarity with delphinine. Like it, it possesses a bicyclo(1,2,3)octane system (9) which, however, contains one more hydroxyl group due to which the pyrolytic derivatives obtained from the two alkaloids are of a different nature. Jacobs and Pelletier (10) have shown that in delphinine it is a secondary hydroxyl on a five-membered ring that is esterified with benzoic acid. On the assumption that a similar situation exists in aconitine, the structure II (R′ = H, R″ = COC_6H_5) is preferred.

EXPERIMENTAL

All infrared absorption spectra were measured on nujol mulls, unless otherwise mentioned, with a Perkin–Elmer double beam spectrometer Model 21B. The melting points were determined on a Kofler hot stage and were not corrected.

Pyraconitine

Aconitine (1 g) was heated at 185–190° (metal bath) in a slow stream of nitrogen until effervescence ceased. The pale yellow liquid was cooled and dissolved in the minimum quantity of hot acetone. Hexane was added dropwise until a slight turbidity was observed. After some time pyraconitine crystallized as colorless needles (510 mg), m.p. 167–168° (literature gives 167.5° (1)). It had $[\alpha]_D^{24}$ −103° (*c*, 1.21 in ethanol) and pK_a 7.72 (determined in 50% ethanol). Found: C, 65.26; H, 7.21. Calc. for $C_{32}H_{43}O_9N$: C, 65.62; H, 7.46%. Infrared spectrum: 1696 cm^{-1} (skeletal carbonyl), 1717 cm^{-1} (ester carbonyl), the hydriodide crystallized as pale yellow rosettes from acetone–ether, m.p. 218–220°. Infrared spectrum: 1720 cm^{-1} (broad) due to ester and skeletal carbonyl groups.

Pyraconine

Pyraconitine was saponified with alcoholic sodium hydroxide and the product isolated as the hydrated hydrochloride, which separated from water as colorless prisms, m.p. 135° (literature (2) gives m.p. 135°), $[\alpha]_D^{22}$ −126.7° (*c*, 1.20 in water). Infrared spectrum: 1709 cm^{-1} (six-membered ring carbonyl).

Wolff–Kishner Reduction of Pyraconitine

Pyraconitine (230 mg) was dissolved in triethylene glycol (3 ml) and 95% hydrazine (2.5 ml) added to the solution. The reaction mixture was maintained at 150° for 1 hour under an atmosphere of nitrogen. Solid potassium hydroxide (1 g) was then added to the mixture and the temperature raised and maintained at 185° for a further hour. The dark reaction mixture was cooled and water (10 ml) was added. The aqueous solution was then extracted with six 20-ml portions of ether and the combined extract dried over magnesium sulphate. Evaporation of the ether extract yielded a gum (105 mg) that failed to crystallize, but formed a perchlorate that crystallized from a mixture of acetone and ether as colorless prisms, m.p. 258–259° (decomp.), $[\alpha]_D^{22}$ +61.9 (*c*, 1.25 in ethanol). Found: C, 53.70; H, 7.05; OMe, 17.03. Calc. for $C_{24}H_{39}O_6N.HClO_4$: C, 53.55; H, 7.26; $3OCH_3$, 17.36%.

Sodium Borohydride Reduction of Pyraconitine

Pyraconitine (370 mg) was dissolved in 80% methanol (10 ml) and sodium borohydride (150 mg) was added to the solution. After 1 hour, the solution was evaporated *in vacuo* and the residue dissolved in water (5 ml). The solution was extracted with five 10-ml portions of chloroform and the dried extract evaporated. There was left a gummy residue (280 mg) which formed a hydrochloride that crystallized from aqueous acetone as colorless prisms. The melting point was variable but fusion started at 155–156°, $[\alpha]_D^{21.5}$ −23.4 (*c*, 2.70 in water). Found (sample dried at 50° for 2 hours): C, 54.57; H, 8.27. Calc. for $C_{25}H_{41}O_8N.HCl.2H_2O$: C, 54.10; H, 8.27%. Found (sample dried at 100° at 0.1 mm for 3 days): C, 55.95; H, 8.45. Calc. for $C_{25}H_{41}O_8N.HCl.H_2O$: C, 55.84; H, 8.10%.

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