THE ALKALOIDS OF FUMARIACEOUS PLANTS

LV. THE STRUCTURE OF CULARIDINE

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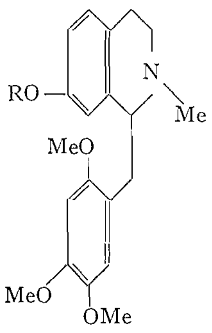
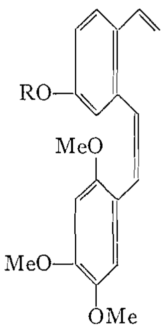
ABSTRACT

Cularidine, which on O-methylation yields cularine, has one phenolic hydroxyl group. It was O-ethylated with diazoethane, and the resultant O-ethylcularidine was degraded to asaronic and 4-ethoxyphthalic acids via sodium – liquid ammonia fission, O-methylation, double Hofmann degradation, and oxidation. These fragments prove the structure of cularidine to be that shown by III.

The alkaloid cularidine has been isolated from *Dicentra cucullaria* (L.) Bernh. (1) and from *Corydalis claviculata* (L.) DC. (2). It is monophenolic and upon methylation with diazomethane is converted into cularine; therefore, it can have only one of three possible structures. It is evident that the procedure used in determining the structure of cularine (3), when applied to cularidine O-ethyl ether, will give an unambiguous answer. The experimental difficulties, however, are twofold: difficult O-methylation and poor yields on oxidation; hence pilot experiments with cularine were carried out first.



I



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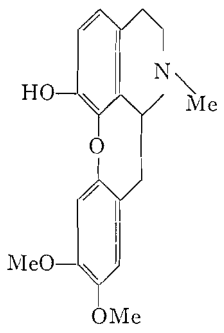

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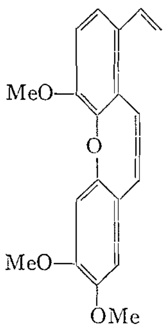

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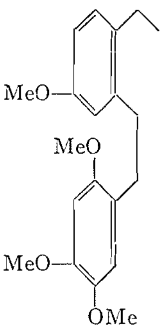

V

The scission of the diphenyl ether bridge with sodium in liquid ammonia is almost quantitative, but the methylation of the resultant phenolic base offered considerable difficulty until the method of Rodionow (4) was used; then moderate yields of the tetramethoxybenzylisoquinoline (I, R = Me) were obtained. The exhaustive methylation of this base also proceeded in moderate yields to give II (R = Me). However, the oxidation of the latter, although it gave the phthalic acid derivative in acceptable yields, gave asaronic (2,4,5-trimethoxybenzoic) acid in very poor yields, presumably because it is attacked rather easily by the oxidizing agent (permanganate). Nevertheless, a very small amount of asaronic acid was obtained not only from the cularine degradation but also from cularidine O-ethyl ether. This observation alone indicates that III is the structure of cularidine; however, it was also possible to isolate 4-ethoxyphthalic acid in better yield from the degradation products, and this fact alone is also sufficient to establish the suggested structure. The ethoxyphthalic anhydride showed the characteristic anhydride infrared peaks at 1 773 and 1 840 cm^{-1} and was characterized as its N-methylimide. A nuclear magnetic resonance spectrum of the latter clearly showed the signals associated with the O-ethyl group (a quartet at τ 5.92 (2H, J = 7.0 c.p.s.) and a triplet at τ 8.53 (3H, J = 7.0 c.p.s.)) as well as the singlet of the methyl protons (at τ 6.85 shifted to lower field because of the deshielding of the two electronegative carbonyl groups).

An attempt to obtain recognizable degradative fragments from cularine by another route failed at the penultimate stage. When the doubly unsaturated product (IV) of the second stage of the Hofmann degradation was treated with sodium in liquid ammonia, the product was not the phenolic vinylstilbene but a phenolic ethyldibenzyl which, on O-methylation, generated the fully saturated ethyltetramethoxydiphenylethane V, the nuclear magnetic resonance spectrum of which was entirely consistent with this structure.

The help of Dr. Kju Hi Shin in interpreting the nuclear magnetic resonance spectra is gratefully acknowledged.

EXPERIMENTAL

2-Methyl-7,2′,4′,5′-tetramethoxy-1-benzyltetrahydroisoquinoline (I, R = Me)

The phenolic base obtained by the sodium – liquid ammonia fission of cularine (4 g) was added to phenyltrimethylammonium hydroxide (prepared from 8 g of the corresponding *p*-toluenesulfonate), and the mixture was heated at 110–120° for 1 h. Steam was passed into the reaction mixture to remove the dimethylaniline and then the solution was extracted with ether. The washed ether solution was dried over solid potassium hydroxide and the solvent largely removed. The base (2.5 g) crystallized shortly, and when it was recrystallized from dry ether – hexane it was obtained as stout colorless prisms melting sharply at 98°.*

Anal. Calcd. for $C_{21}H_{27}O_4N$: four OMe, 34.76. Found: OMe, 34.54, 34.38.

Degradation of Cularidine

A solution of cularidine (1.5 g) in ethanol was treated with an ethereal solution of diazoethane, and after 24 h the excess reagent was removed. The base, in ether solution, was washed with water and dried over potassium hydroxide. It was then added to ca. 50 cc liquid ammonia and treated with a dilute solution of sodium in the same solvent until the blue color was permanent for 1 min. After evaporation of the ammonia, the residue was extracted with ether and the residue from the ether extract was heated with an excess of phenytrimethylammonium hydroxide. The non-phenolic base was isolated as described above and converted into the nitrogen-free compound (II, R = Et) by a double Hofmann degradation (3). The resultant product weighed 0.24 g and consisted of a colorless resin. It was dissolved in acetone and treated with a saturated aqueous solution of potassium permanganate until the color was permanent for 30 min. The acetone was boiled off, a little calcium chloride added, and the hot mixture filtered through a layer of Filtercel. The acidified filtrate was exhausted with ether and the residue from the extract sublimed from a distillation tube. There was a small amount of sublimate at 110° and 0.2 mm which melted at 130–141° either alone or in admixture with asaronic acid. This quantity was insufficient for further characterization. A second distillate was obtained at ca. 150° and 0.2 mm; this, when resublimed, melted at 65–70° either alone or in admixture with 4-ethoxyphthalic anhydride. It was treated in methanol with methylamine, the mixture evaporated, and the residue sublimed (140° at 0.2 mm). The crystalline sublimate, when recrystallized from ether–hexane, melted at 108° either alone or in admixture with an authentic specimen of N-methyl 4-ethoxyphthalimide.

4-Ethoxyphthalic Anhydride

This compound has been described by Fritsch (5), but for the present it was prepared by ethylating 4-hydroxyphthalic acid (6) with ethyl sulfate and alkali. From 12 g of diethyl 4-aminophthalate via the hydroxy acid was obtained 5.5 g of twice-sublimed 4-ethoxyphthalic anhydride which, when recrystallized from dry ether, melted at 76°. The *methylimide*, which had been prepared from the anhydride, sublimed *in vacuo*, and recrystallized from dry ether, melted at 109°. The *ethylimide*, similarly prepared and purified, melted at 102°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98. Found: C, 65.39, 65.34; H, 5.66, 6.13.

O-Ethylcularidine

Though the free base could not be obtained in crystalline form, it gave an acid oxalate (m.p. 218°) which was only sparingly soluble in cold methanol. The *picrate*, crystallized from acetone–methanol, melted at 210°. The hydrochloride was obtained as colorless needles melting at 172° when recrystallized twice from hot acetone, in which it is moderately soluble. It appears to be a monohydrate.

Anal. Calcd. for $C_{21}H_{25}O_4N{\cdot}HCl{\cdot}H_2O$: C, 61.54; H, 6.84. Found: C, 61.34, 61.99; H, 7.28, 7.27.

When this hydrochloride was recrystallized from methanol a solvated form melting at 195° was obtained. The *methiodide* of the O-ethyl ether melted at 236° and the *methine methiodide* prepared therefrom consisted of fine needles, which were sparingly soluble in methanol and which melted at 205° without darkening.

**All melting points are corrected.*

2-Ethyl-5,2′,4′,5′-tetramethoxy-1,2-diphenylethane (V)

A solution of compound IV (3) in tetrahydrofuran was added to liquid ammonia in which a small piece of sodium had been dissolved. The blue color was discharged at once. Sodium in small pieces was added until the blue color of the solution remained for 5 min. The ammonia was then evaporated in a current of air, and the residue was treated with an excess of sodium bicarbonate and extracted with ether. The phenolic residue from the washed and dried ether solution did not crystallize. It was methylated with an excess of dimethyl sulfate and caustic soda; the non-phenolic product thus obtained was dried in ether solution with potassium hydroxide. Partial evaporation of the ether and the addition of hexane to the concentrate gave a nearly quantitative yield of the saturated compound (V), m.p. 93°. It was stable to permanganate in acetone solution.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.61, 72.44; H, 7.82, 7.83.

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