THE ABSOLUTE CONFIGURATION OF MAJORIDINE

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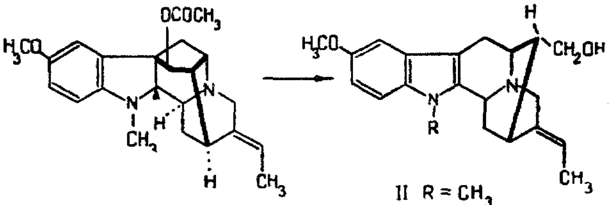
Majoridine, with the composition $C_{23}H_{28}N_2O_3$ and mp 222°–223° C, $[\alpha]_D^{20}$ −26.6° (chloroform), has been isolated [1] from the plant Vinca major L. var. major [2]. The structure of 10-methoxy-O-acetyltetrafilicin (I), from which the relative configuration of the individual asymmetric centers follows, was deduced for this substance.

In the present paper the transformation of majoridine into N-methyllochnerine (II) and lochnerine (III) is described; the configuration of the latter is known [4].

The oxidation of compound (I) with chromium trioxide in pyridine and subsequent reduction with sodium borohydride in an alkaline medium under the conditions given for the analogous degradation of 21-deoxyajmaline [4] gave lochnerine (III) [5, 6] and a new substance, N-methyllochnerine (II). The UV spectrum of N-methyllochnerine, like the spectrum of lochnerine itself [7], shows absorption characteristics for the indole chromophoric system: λ_{max} 230 and 280 mμ (log ε 3.41 and 3.93 respectively). The IR spectrum of N-methyllochnerine exhibits bands of free (3600 cm^{-1}) and associated hydroxymethyl groups (3130 and 3330 cm^{-1}), and also the vibrations of a substituted indole (1585 and 1621 cm^{-1}). Substance (II) forms an O-acetyl derivative the IR spectrum of which lacks the bands of free and associated hydroxymethyl groups, while a new band of an $OCOCH_3$ group appears (1735 cm^{-1}). We obtained the N-methyllochnerine from O-acetyllochnerine [8] by the action of sodium and methyl iodide in liquid ammonia and subsequent alkaline saponification of the reaction product.

Thus, majoridine has an absolute configuration of the substituents at C_{15} similar to that of other indole and dihydroindole alkaloids [9–11]:



I

II R = CH_3

III R = H

Experimental

Oxidation of majoridine by chromium trioxide in pyridine. With cooling, a solution of 101 mg of majoridine in 15 ml of pyridine was added to an oxidizing mixture consisting of 125 mg of chromium trioxide and 5 ml of pyridine. The mixture was shaken for 20 hr at room temperature. Then it was diluted with 100 ml of methylene chloride, the solution was passed through a layer of alumina (activity grade II) and elution was carried out with methylene chloride. After the solvent had been distilled off, 86 mg of a dry powder remained, which was dissolved in 2 ml of aqueous methanol (4 : 1); with stirring, then 150 mg of sodium borohydride was added to the solution over 45 min. The aqueous methanolic solution was evaporated to dryness (57 mg). The residue consisted of a mixture of crystals with mp 171°–173° C. A thin-layer chromatogram in the ethyl acetate–methanol (9 : 1) system showed two spots with R_f 0.51, corresponding to the R_f value of N-methyllochnerine, and R_f 0.31 corresponding to lochnerine.

N-Methyllochnerine (II). A solution of 45 mg of the mixture of crystals in ethyl acetate was chromatographed on alumina, elution being carried out with ethyl acetate. The 3rd–11th fractions yielded 24 mg of N-methyllochnerine with mp 220°–221° C (from acetone); $[\alpha]_D^{28}$ + 56° (c 1.03; acetone); + 36.88° (c 1.465; pyridine), R_f 0.69 in the butan-1-ol–acetic acid–water (20 : 1 : 20) system.

Found, %; C 73.85, 73.90; H 7.93, 7.96; N 8.16, 8.28. Calculated for $C_{21}H_{26}N_2O_2$, %: C 74.54; H 7.74; N 8.27.

N-Methyl-O-acetyllochnerine. A solution of 45 mg of the substance in 2 ml of acetic anhydride was heated on a boiling water bath for 3 hr. The excess acetic anhydride was diluted with water, and the mixture was made alkaline with 30% caustic potash solution and extracted with ether. Evaporation of the ether gave 25 mg of N-methyl-O-acetyllochnerine, with mp 126°-127° C (from ether); $[\alpha]^{21}_{D}$ −13.06° (c 1.723; pyridine), R_f 0.75 in the butan-1-ol–acetic acid-water (20: 1: 20) system.

Lochnerine (III). From the 17th–23rd fractions was isolated 15.5 mg of lochnerine with mp 201°-202° C (from methanol); $[\alpha]^{21}_{D}$ + 68° (c 0.56; methanol). Its IR spectrum was identical with that of a sample of natural lochnerine.

O-acetyllochnerine. A mixture of 115 ml of lochnerine and 6 ml of acetic anhydride was heated to 100° C for 3 hr. The acetic anhydride was distilled off under vacuum and the residue was recrystallized from a mixture of benzene and petroleum ether. This gave 52 mg of white crystals with mp 240°-242° C; $[\alpha]^{23}_{D}$ + 46° (methanol).

N-Methyllochnerine (II). 1.5 mg of $Fe(NO_3)_3$ and 10 mg of sodium were added to 10 ml of liquid ammonia. The mixture was stirred; a colorless solution formed in the course of a few minutes. To this was added 55 mg of O-acetyllochnerine, which dissolved in the course of 15 min with stirring. After cooling, the reaction mixture was treated with 0.02 ml of methyl iodide in 0.2 ml of absolute ether, and the resulting mixture was stirred for 2 hr at room temperature. The remainder of the ammonia was distilled off under vacuum and the base was extracted with methylene chloride. The yield of amorphous powder crystallizing after the addition of ethanol was 60 mg. Paper chromatography showed the presence of three substances in the mixture: N-methyl-O-acetyllochnerine (R_f 0.95), N-methyllochnerine (R_f 0.3), and lochnerine (R_f 0.02) (S_6 system [12], Whatman No. 1 paper).

The mixture was subjected to hydrolysis by being treated for 15 hr with 1 ml of 1 N caustic soda in ethanolic solution. After the solvent had been distilled off under vacuum, the residue was extracted with methylene chloride. A substance was obtained which included N-methyllochnerine and traces of lochnerine. Recrystallization from ethanol yielded N-methyllochnerine with mp 230°-235° C (Kofler), $[\alpha]^{25}_{D}$ + 87° (ethanol); the IR spectrum was identical with that of the substance formed by oxidation and subsequent reduction of majoridine. The melting point of a mixture of the two substances showed no depression.

Oxidation of majoridine with lead tetraacetate. N-Methyllochnerine. A solution of 100 mg of the base in 100 ml of glacial acetic acid was treated with 140 mg of lead tetraacetate. The mixture was left at room temperature for 24 hr. Then it was diluted with 50 ml of water, made alkaline with 30% caustic potash solution, and extracted with ether. This yielded 94 mg of a brown noncrystalline substance which was dissolved in 5 ml of aqueous methanol (9 : 1). With stirring, 200 mg of sodium borohydride was added to this solution. The reaction mixture was diluted with water and extracted with ether. The yield of N-methyllochnerine was 58 mg.

The sample of lochnerine was kindly supplied to us by Dr G. Svoboda and Dr N. R. Farnsworth (University of Pittsburgh, USA).

Summary

The oxidation of majoridine with chromium trioxide and lead tetraacetate with subsequent reduction of the oxidation product has yielded lochnerine and N-methyllochnerine and has thereby shown the absolute configuration of majoridine as 10-methoxy-O-acetyltetrafilicin.

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