The Absolute Configuration of Carpaine[1]

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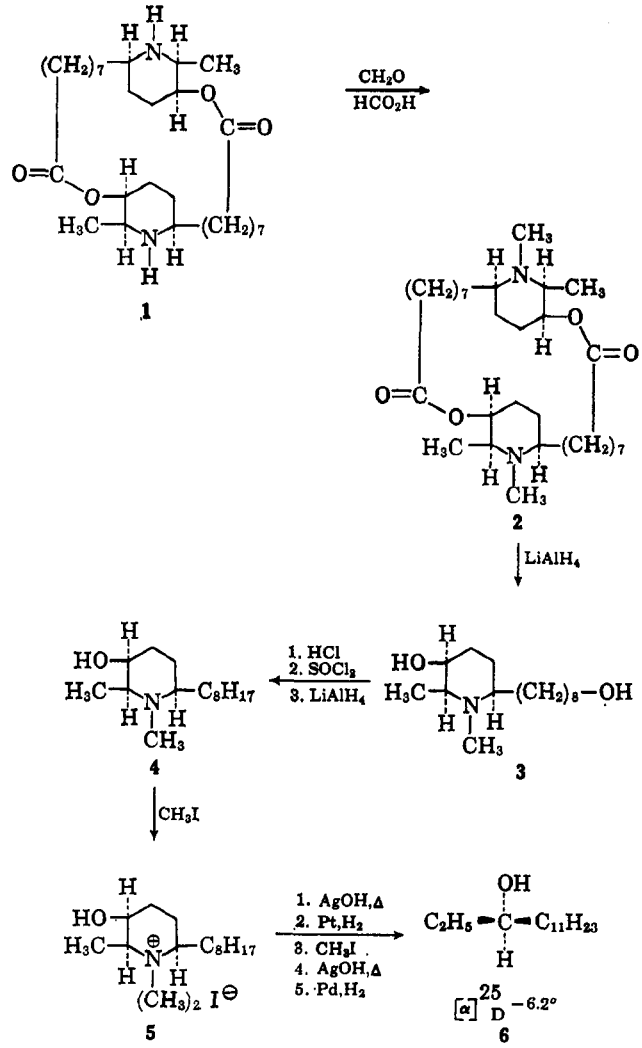
The absolute configuration of the papaya alkaloid carpaine has been determined. Carpaine was degraded to (*R*)-(−)-3-tetradecanol. The absolute configuration of (*R*)-(−)-3-tetradecanol was shown by its preparation from (*R*)-(+)-1,2-epoxybutane. The (*R*)-(+)-1,2-epoxybutane was reduced to (*S*)-(+)-2-butanol, the absolute configuration of which is known. The stereochemistry of related compounds is discussed.

The structure of the alkaloid carpaine (1) has been investigated by a number of workers. Rapoport and co-workers[3] and Govindachari and co-workers[4] have established the gross structure of the alkaloid. Govindachari and Narasimhan[5] provided convincing proof that the methyl group and the alkyl side chain are *cis* to each other on the piperidine ring. Tichy and Sicher[6] used infrared techniques to show that the hydroxyl group of methyl carpamate is axial on the piperidine ring. All this evidence was interpreted in favor of a relative configuration for carpaine in which all the groups attached to the piperidine ring are *cis*. A recent investigation[7] using mass spectral techniques has shown that carpaine consists of two identical substituted piperidine rings linked by two lactone groups Thus carpaine contains a novel 26-membered ring as shown in structure 1. Molecular weight determinations in the present work support this structure.

The problem of assigning the absolute configuration of carpaine then reduced itself to one of determining the absolute configuration of any one of the asymmetric centers present. We wish to report the results of a study in which the absolute configuration of carpaine has been determined.

Carpaine was degraded to 3-tetradecanol by reactions which left the absolute configuration of the lactone alcohol group of carpaine unaffected. The reactions involved are shown in Chart I. Carpaine (1) was converted to N,N′-dimethylcarpaine (2) which was in turn reduced to N-methylcarpamdiol (3) with lithium aluminum hydride. The primary alcohol function of 3 was removed by conversion to the monochloro compound and then reduction with lithium aluminum hydride to give N-methylcarpamol (4). Exhaustive methylation[8] with catalytic reduction at each stage gave levorotatory 3-tetradecanol (6), $[\alpha]^{25}D$ −6.2°.

CHART I



Levoratory 3-tetradecanol was shown to have the *R* absolute configuration by relating it chemically to (*S*)-(+)-2-butanol, the absolute configuration of which is known.[9] The reactions employed in this correlation are shown in Chart II. Racemic 1-dimethylamino-2-butanol, prepared from dimethylamine and 1,2-epoxybutane, was resolved with dibenzoyl (*R*)-(+)-tartaric acid to give (*R*)-(−)-1-dimethylamino-2-butanol. This was converted to the (*R*)-(−) methiodide which was in turn converted by a Hofmann elimination to (*R*)-

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(3) H. Rapoport, H. D. Baldridge, Jr., and E. J. Volcheck, Jr., *J. Am. Chem. Soc.*, **75**, 5290 (1953).

(4) T. R. Govindachari, N. S. Narasimhan, and S. Rajadurai, *J. Chem. Soc.*, 560 (1957).

(5) T. R. Govindachari and N. S. Narasimhan, *ibid.*, 1563 (1955).

(6) M. Tichy and J. Sicher, *Tetrahedron Letters*, 511 (1962).

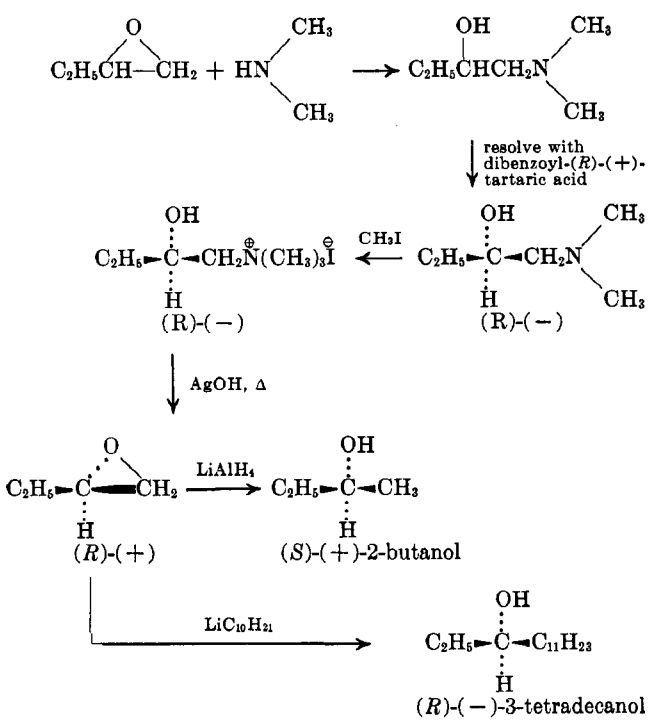
(7) M. Spiteller-Friedman and G. Spiteller, *Monatsh. Chem.*, **95**, 1234 (1964).

(8) A referee has questioned the stereochemical integrity of the asymmetric alcohol group in compound **5** after the initial Hofmann elimination, pointing out that the proton eliminated might be the one on the alcohol carbon. This might produce amino ketone with an optically active amino group. It was argued that this amino group might then control the stereochemistry of catalytic reduction of the ketone group, by asymmetric induction, to produce an alcohol group which was of the opposite absolute configuration to that present in compound **5** and hence in carpaine itself. This argument can be refuted by the following data. The initial crude Hofmann product of compound **5** showed only a faint trace of carbonyl absorption in the infrared spectrum and the (*R*)-(−)-3-tetradecanol from carpaine is, as nearly as we can tell, optically pure (see Experimental Section). It would indeed be surprising to find asymmetric induction of such a high degree. We do not know the exact course of the first Hofmann elimination on compound **5** except that neither a ketone nor an epoxide is produced. We are currently investigating Hofmann eliminations on compounds of this type and will report on this at a later date.

(9) (a) K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3891 (1952); (b) A. T. Bottini, V. Dev, and M. Stewart, *J. Org. Chem.*, **28**, 156 (1963); **28**, 3595 (1963); (c) P. A. Levine and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931); P. A. Levine and H. L. Haller, *ibid.*, **74**, 343 (1927).

(+)-1,2-epoxybutane.[9c] The absolute configuration of this epoxide, and hence all the other compounds in Chart II, was proven by reducing it to (*S*)-(+)-2-butanol.[9b] The (*R*)-(+)-1,2-epoxybutane was allowed to react with *n*-decyllithium to give (*R*)-(−)-3-tetradecanol (**6**). This proves the absolute configuration of the oxygen function on the piperidine ring of carpaine. As a further check on this, the same reactions were carried out as shown in Chart II except that dibenzoyl (*S*)-(−)-tartaric acid was used as the resolving agent. This was done in order to obtain (*S*)-(+)-3-tetradecanol for comparison.

Chart II



Since the absolute configuration of the alcohol group of carpaine (existing as the lactone) is now known we can write the complete structure for the alkaloid. If the conclusions reached by earlier workers[5,6] about the relative configuration of carpaine are correct, then the absolute configuration of carpaine must be that shown in structure **1**.

This work is relevant to the absolute configuration of a number of other compounds. The alkaloid pseudocarpaine is reported[10] to be identical with carpaine except that it has the opposite absolute configuration at the lactone oxygen function. Rigorous proof of this is lacking. In view of the present structure of carpaine there is some doubt as to the exact structure of pseudocarpaine. Assuming it is not an artifact, it is possible that pseudocarpaine is a dilactone made up of two nonidentical halves. We will reserve further comments until work on this problem has been finished. It is not yet known whether the alkaloid cassine[11] has the same stereochemistry as carpaine or not. Work is in progress to relate these two alkaloids.

(10) T. R. Govindachari, B. R. Pai, and N. S. Narasimhan, *J. Chem. Soc.*, 1847 (1954).

(11) R. J. Highet, *J. Org. Chem.*, **29**, 471 (1964).

Experimental Section[12]

Isolation of Carpaine (1).—Carpaine was isolated from granulated *Carica papaya* leaves purchased from S. B. Penick and Co. The leaves were continuously extracted in batches of 7 kg. for 4 days with a solution of 89% ethanol, 10% water, and 1% acetic acid. The resulting extracts were evaporated under vacuum to give a dark green tar which was shaken with 2 l. of water containing 50 ml. of acetic acid. This mixture was continuously extracted with ether to remove all acid-insoluble material. The aqueous solution was then made basic with 160 g. of potassium carbonate and extracted with ether to obtain the bases. The ether solution of bases was washed several times with water and extracted with 5% hydrochloric acid until all the bases were extracted. These aqueous acid extracts were combined, basified, and extracted with ether. The ether solutions were combined, dried, and concentrated. The solid which crystallized was isolated by filtration to yield about 4 to 5 g. of carpaine, m.p. 118–120°, for each 7 kg. of dried leaves (lit.[13] m.p. 119–120°). Molecular weight determinations at 0.005 to 0.10 *M* concentrations in benzene showed a molecular weight 493 ± 10 (calcd. mol. wt. 479).

N,N′-Dimethylcarpaine (2).—The procedure of Govindachari and Narasimhan[5] was followed. A mixture of 10.0 g. (0.0209 mole) of carpaine, 11.5 ml. of 37% aqueous formaldehyde, 11.5 ml. of 85% formic acid, and 10 ml. of toluene was heated at reflux for 5 hr. The reaction mixture was cooled, diluted with 250 ml. of water, and made basic with concentrated potassium carbonate solution. The resulting two-phase system was extracted several times with ether. The ether solutions were combined, washed several times with water, and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a solid which was crystallized from acetone–water to yield 9.2 g. (87%) of N,N′-dimethylcarpaine, m.p. 79–81° (lit.[5] m.p. 84°).

N-Methylcarpamdiol (3).—A solution of 19.0 g. (0.0376 mole) of N,N′-dimethylcarpaine in 400 ml. of ether was added slowly with good stirring to a suspension of 7.6 g. of lithium aluminum hydride in 200 ml. of ether. The resulting mixture was stirred at reflux for 4 days and was then decomposed by careful successive addition of 8 ml. of water, 6 ml. of 20% sodium hydroxide, and 28 ml. of water. The ether layer was decanted and the solid aluminum hydroxide was washed several times with ether. The ether solutions were combined, dried over magnesium sulfate, and evaporated. The residue was distilled under vacuum to give 17.0 g. (88%) of N-methylcarpamdiol, b.p. 167–168° (0.7 mm.).

Anal. Calcd. for $C_{15}H_{31}NO_2$: C, 69.99; H, 12.14. Found: C, 70.06; H, 12.02.

N-Methylcarpamol (4).—A solution of 17.0 g. (0.0659 mole) of N-methylcarpamdiol in 500 ml. of ether was treated with dry hydrogen chloride until no more insoluble material formed. The ether was removed under vacuum and 200 ml. of ethanol-free chloroform was added. The resulting two-phase system was cooled to 0° and 4.8 ml. of thionyl chloride was added. After being stirred for 3 days at 25° the mixture was homogeneous. The chloroform was removed under vacuum and a solution of 20 g. of sodium hydroxide in 300 ml. of water was added with cooling. The basic solution was extracted several times with ether. The ether solutions were combined, dried, and evaporated to give a thick oil. This oil was taken up in 150 ml. of dry tetrahydrofuran and the resulting solution was added slowly with stirring to a mixture of 11.4 g. of lithium aluminum hydride and 500 ml. of dry tetrahydrofuran at reflux. The mixture was stirred and heated at reflux under nitrogen for 30 hr. The reaction mixture was worked up by cooling in an ice bath and successive additions of 12 ml. of water, 9 ml. of 20% sodium hydroxide, and 42 ml. of water. The resulting mixture was filtered and dried over magnesium sulfate and the tetrahydrofuran was removed under vacuum. Distillation at reduced pressure gave 4.62 g. of recovered N-methylcarpamdiol and 8.32 g. of N-methylcarpamol, b.p. 119° (0.4 mm.), $n^{25}D$ 1.4713.

(12) All melting points were taken on a calibrated Kofler hot stage. All distillations were done through a 2-ft. Podbielniak column and the boiling points are uncorrected. Optical rotations were taken with a Rudolph photoelectric polarimeter, Model 200. Molecular weights were made with a Mechrolab, Inc., vapor pressure osmometer, Model 301A.

(13) H. Rapoport and H. D. Baldridge, Jr., *J. Am. Chem. Soc.*, **73**, 343 (1951).

Anal. Calcd. for $C_{15}H_{31}NO$: C, 74.62; H, 12.94. Found: C, 74.47; H, 12.68.

Methiodide of N-Methylcarpamol (5).—A solution of 8.0 g. of N-methylcarpamol and 6.5 g. of methyl iodide in 75 ml. of methanol was heated at reflux overnight. Removal of the volatile material under vacuum gave 13 g. of waxy hygroscopic solid which was not further purified but was used directly in the following reactions.

(*R*)-(−)-3-Tetradecanol from Carpaine (6).—The methiodide of N-methylcarpamol was converted to 3-hydroxytetradecane without attempting to separate or purify any of the reaction products until the final step. The methiodide of N-methylcarpamol from the preceding preparation was dissolved in 150 ml. of water and stirred overnight with silver hydroxide (from 11.2 g. of silver nitrate[14]). The mixture was filtered and the solid was washed with 50 ml. of hot water. The aqueous solutions were combined and evaporated under vacuum. The resulting sirup was distilled at 170° at 2 mm. The distillate was taken up in ether and dried. Removal of the ether gave a liquid which was reduced in 100 ml. of glacial acetic acid with 0.25 g. of platinum and hydrogen at 60 p.s.i. Filtration and evaporation under vacuum followed by basification with dilute potassium carbonate and ether extraction gave an ether solution which was dried and evaporated to yield 5.90 g. of a liquid.

The above liquid (5.90 g.) was converted to the methiodide using 3.6 g. of methyl iodide in 100 ml. of methanol. The methiodide was treated with silver hydroxide and distilled as before. The distillate was taken up in ether, washed with dilute hydrochloric acid, and dried. Removal of the ether gave 2.5 g. of liquid. A sample of 1.0 g. of this liquid in 50 ml. of methanol was reduced with 0.2 g. of 10% palladium on carbon and hydrogen at 30 p.s.i. Filtration and removal of the methanol under vacuum gave 1.0 g. of liquid which would not crystallize. A 0.7-g. sample of this liquid was chromatographed on 20 g. of Woelm grade I neutral alumina. Elution with 100 ml. of ether gave a liquid which was not investigated. Elution with an additional 1 l. of ether gave 0.26 g. of (*R*)-(−)-3-tetradecanol, m.p. 39.5–40°, $[\alpha]^{25}D$ −6.2° (*c* 3.11 g./100 ml., absolute ethanol) (lit.[15] m.p. 38°, $[\alpha]^{20}D$ −6.25°).

Anal. Calcd. for $C_{14}H_{30}O$: C, 78.43; H, 14.11. Found: C, 78.33; H, 13.89.

This compound was shown to be identical in chromatographic behavior with a sample of racemic 3-tetradecanol.

1-Dimethylamino-2-butanol.—The procedure used was similar to that of Hill.[16] A solution of 21.6 g. (0.30 mole) of 1,2-epoxybutane and 40 ml. of anhydrous dimethylamine in a sealed heavy-wall Pyrex tube was heated at 105° for 48 hr. The tube was cooled and opened and the mixture was distilled to give 31.3 g. (89%) of 1-dimethylamino-2-butanol, b.p. 142–143° (754 mm.), $n^{25}D$ 1.4227 [lit.[17] b.p. 142–144° (760 mm.)].

(*R*)-(−)-1-Dimethylamino-2-butanol.—A solution of 8.8 g. of racemic 1-dimethylamino-2-butanol in 20 ml. of absolute ethanol was added to a warm solution of 27.0 g. of dibenzoyl-(*R*)-(+)-tartaric acid[18] in 60 ml. of absolute ethanol. The solution was cooled to room temperature. After crystallization had taken place the mixture was cooled to 10° and filtered to yield 21.0 g. of an air-dried salt, m.p. 95–100°. Recrystallization of this salt from 100 ml. of absolute ethanol gave 14.0 g. of solid, m.p. 109–112°. Further crystallizations did not change the melting point or the optical rotation of this salt. This salt was not analyzed but is apparently an ethanol solvate because liberation of the amino alcohol below gave a considerable quantity of ethanol.

The optically active amino alcohol was liberated from the dibenzoyl-(*R*)-(+)-tartrate salt as follows. A mixture of 48.0 g. of the recrystallized salt, 100 ml. of 10% aqueous hydrochloric acid, and enough ether to dissolve the dibenzoyl (*R*)-(+)-tartaric acid was shaken until all solids dissolved. The ether layer was separated and washed with 20 ml. of water. The aqueous solutions were combined and cooled in ice while 16.0 g. of sodium hydroxide was added. The basic solution was saturated with sodium chloride and extracted repeatedly with ether. The ether solutions were combined, dried, and evaporated. Distillation of the resulting liquid gave 9.9 g. of (*R*)-(−)-1-dimethylamino-2-butanol, b.p. 140–144° (756 mm.), $[\alpha]^{25}D$ −21.9° (*c* 4.18 g./100 ml., absolute ethanol).

Methiodide of (*R*)-(−)-1-Dimethylamino-2-butanol.—A solution of 28.3 g. (0.199 mole) of methyl iodide in 100 ml. of methyl alcohol was added slowly to a stirred solution of 23.0 g. (0.196 mole) of (*R*)-(−)-1-dimethylamino-2-butanol in 100 ml. of methyl alcohol. The reaction was kept at 0° during the addition of the methyl iodide and for an additional 1.5 hr. and was then heated at reflux for 5 hr. The methanol was removed under vacuum to give 50.0 g. (99%) of solid, m.p. 157–160°. This methiodide was used directly without further purification. An analytical sample was recrystallized from ethanol–ether: m.p. 161–162°, $[\alpha]^{25}D$ −21.4° (*c* 5.10 g./100 ml., absolute ethanol).

Anal. Calcd. for $C_7H_{18}INO$: C, 32.44; H, 7.00; N, 5.41. Found: C, 32.31; H, 6.88; N, 5.39.

(*R*)-(+)-1,2-Epoxybutane.—A mixture of silver hydroxide (from 93.0 g. of silver nitrate[14]), the methiodide of (*R*)-(−)-1-dimethylamino-2-butanol [from 31.0 g. (0.264 mole) of amino alcohol], and 200 ml. of water was stirred for 5 hr. at room temperature. The mixture was filtered and the solids were washed with 125 ml. of water. The aqueous solutions were combined and evaporated under vacuum at 50–55°. The resulting sirup was distilled at 130° at 30 mm. using a Dry Ice trap to collect the distillate. The epoxide was partially separated from the water in the distillate by distillation at 25° and 30 mm. using a Dry Ice trap to condense the epoxide. This epoxide was dried over magnesium sulfate and distilled to yield a forerun of trimethylamine followed by 6.8 g. (36%) of pure (*R*)-(+)-1,2-epoxybutane, b.p. 60–62.5° (755 mm.), $[\alpha]^{25}D$ +8.2° (*c* 4.99 g./100 ml., dioxane) [lit.[9c] $[\alpha]^{25}D$ +8.75 (neat)].

(*S*)-(+)-2-Butanol.—An ether solution of (*R*)-(+)-1,2-epoxybutane was reduced with lithium aluminum hydride in the usual way to give (*S*)-(+)-2-butanol, b.p. 98–100° (760 mm.), $[\alpha]^{25}D$ +12.1° (*c* 4.23 g./100 ml., absolute ethanol) [lit.[15] b.p. 99° (758 mm.), $[\alpha]^{20}D$ +11.0°]. The *S* configuration is known to correspond to the dextrorotatory enantiomer of 2-butanol.[9]

(*R*)-(−)-3-Tetradecanol.—A mixture of 2.0 g. (large excess) of lithium metal chips, 8.3 g. (0.0376 moles) of *n*-decyl bromide, and 30 ml. of anhydrous ether was stirred and heated at reflux under nitrogen for 1.3 hr. The excess lithium was removed and 2.7 g. (0.0375 mole) of (*R*)-(+)-1,2-epoxybutane in 30 ml. of ether was added slowly. The mixture was heated at reflux for 2.3 hr. and was then cooled in an ice bath while 50 ml. of cold water was added. The ether layer was separated, washed with 25 ml. of water, and dried over magnesium sulfate. The ether was removed on a steam bath to give 7.2 g. of liquid. This liquid was chromatographed over 200 g. of Woelm grade I neutral alumina. Elution with 425 ml. of ether gave 5.5 g. of a liquid which was not further investigated. Next, elution with 350 ml. of 5% methanol in ether gave 1.4 g. (17%) of (*R*)-(−)-3-tetradecanol, m.p. 30–38°, $[\alpha]^{25}D$ −4.0° (*c* 4.88 g./100 ml., absolute ethanol).

Anal. Calcd. for $C_{14}H_{30}O$: C, 78.43; H, 14.11. Found: C, 78.24; H, 13.89.

(*S*)-(+)-3-Tetradecanol.—The same procedure was used as above except that (*S*)-(−)-1,2-epoxybutane was used[19] to give (*S*)-(+)-3-tetradecanol, m.p. 32–38°, $[\alpha]^{25}D$ +5.1° (*c* 3.61 g./100 ml., absolute ethanol).

Anal. Calcd. for $C_{14}H_{30}O$: C, 78.43; H, 14.11. Found: C, 78.53; H, 13.92.

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(15) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1923 (1913).
(16) R. K. Hill, *J. Am. Chem. Soc.*, **80**, 1611 (1958).
(17) R. T. Major and H. T. Bonnett, *ibid.*, **58**, 22 (1936).
(18) C. L. Butler and L. H. Cretcher, *ibid.*, **55**, 2605 (1933).
(19) The (*S*)-(−)-1,2-epoxybutane was prepared by a series of reactions identical with those shown in Chart II except that dibenzoyl-(*S*)-(−)-tartaric acid was used as the resolving agent.