pseudo*Carpaine, a New Alkaloid from* Carica papaya *L.*

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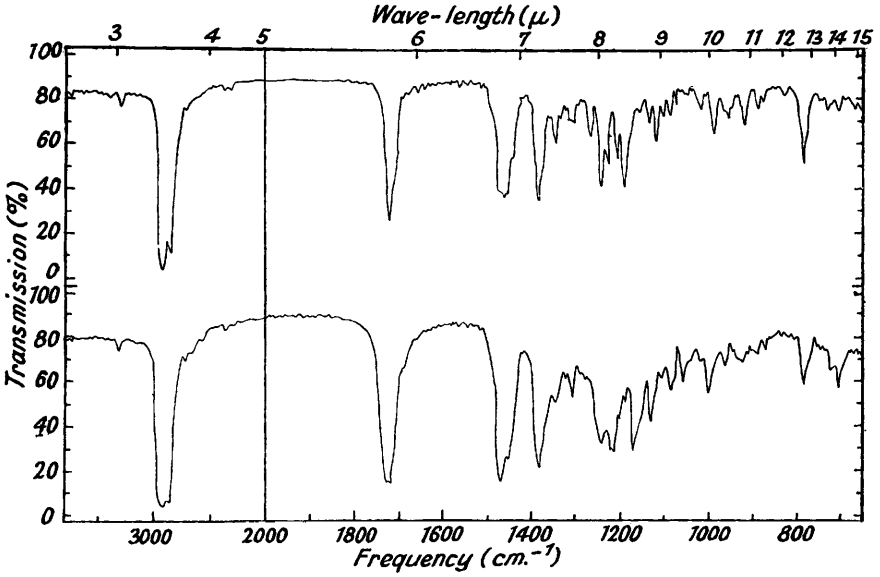
The leaves of *Carica papaya* L. are shown to contain a new alkaloid, *pseudo*carpaine, isomeric with carpaine. Evidence is presented that *pseudo*-carpaine differs from carpaine only in the configuration at the " alcoholic " carbon atom.

The alkaloid carpaine, first isolated by Greshoff (*Ber.*, 1890, **23**, 3537) from the leaves of *Carica papaya* L., is the only alkaloid reported from this source. Recently, we had occasion to process a fair amount of papaya leaves for isolation of carpaine. Previous

Infra-red absorption spectra of carpaine (top) and pseudo*carpaine (bottom), in Nujol mull.*

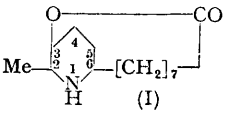


workers (Barger, Girardet, and Robinson, *Helv. Chim. Acta*, 1933, **16**, 90; Barger, Robinson, and Work, *J.*, 1937, 711; Rapaport and Baldridge, *J. Amer. Chem. Soc.*, 1951, **73**, 343), except Greshoff (*loc. cit.*), had isolated carpaine in yields ranging from 0·018 to 0·04% : we have obtained it in 0·11% yield. In addition, we isolated, in 0·01% yield, an alkaloid to which we assign the name *pseudo*carpaine. The new alkaloid has the same molecular formula as carpaine, $C_{14}H_{25}O_2N$, but differs from it in melting point, rotation,

and solubility characteristics. The infra-red absorption spectra are very similar (see Figure), notable differences being found only in the 7—15 μ region.

Dehydrogenation of *pseudo*carpaine in *p*-cymene with palladised charcoal yielded 2 mols. of hydrogen and deoxycarpyrinic acid, identical with that obtained from carpaine (Rapaport and Baldridge, *J. Amer. Chem. Soc.*, 1952, **74**, 5365) under the same conditions. Hydrolysis of *pseudo*carpaine with concentrated hydrochloric acid gave an amino-acid in quantitative yield; this material, isolated as the hydrochloride, did not melt sharply and attempts to obtain sharp-melting fractions from what was evidently a mixture, by repeated crystallisations, did not succeed. The product was esterified by the Fischer procedure. Crystallisation of the ester hydrochloride yielded a first fraction (*ca.* 50%), consisting of ethyl carpamate hydrochloride, and a second fraction of ethyl *pseudo*carpamate hydrochloride. Dehydrogenation of the latter ester yielded ethyl carpyrinate (Govindachari and Narasimhan, *J.*, 1953, 2635). Reduction of *pseudo*carpaine with lithium aluminium hydride yielded *pseudo*carpamodiol, $C_{14}H_{29}O_2N$, isomeric with carpamodiol obtained by reduction of carpaine with the same reagent (Govindachari and Narasimhan, *loc. cit.*).

Carpaine yields on hydrolysis a single product, carpamic acid, in quantitative yield. Rapaport, Baldridge, and Volcheck (*J. Amer. Chem. Soc.*, 1953, **75**, 5290) have shown conclusively that carpaine has structure (I). Hydrolysis of *pseudo*carpaine to both *pseudo*carpamic and carpamic acid shows that *pseudo*carpaine is diastereoisomeric with carpaine, differing only in configuration at $C_{(3)}$. It may be that carpaine undergoes hydrolysis solely by acyl–oxygen fission, whereas *pseudo*carpaine undergoes hydrolysis at least partly by alkyl–oxygen fission with formation of $C_{(3)}$-epimers, steric factors being responsible for this difference.



(I)

Reduction with lithium aluminium hydride yields a single product in each case as expected, there being no change in the configuration at $C_{(3)}$ during lactone cleavage by this reagent.

Experimental

Isolation of the Crude Alkaloids.—Papaya leaves were collected from the districts of Mangalore and Salem in Madras State and from the environs of Madras City. The highest alkaloid content (0·2%) was present in leaves collected from Malaya, though *pseudo*carpaine was present in all the sources.

The leaves were extracted by the following procedure which is considerably simpler than Rapaport and Baldridge's (*loc. cit.*). The dried, powdered leaves (14 kg.; from Malaya) were covered with 90% alcohol containing 1% acetic acid. After 3 days, the extract was drawn off. The material was extracted twice more. The combined alcoholic extracts were concentrated to a small volume, initially at ordinary pressure and later under reduced pressure. The residue was treated with water (3 l.), and acidified with acetic acid. The mixture was shaken intermittently during 2 days and the aqueous layer was poured off from the non-basic resinous material. The residue was again treated with further quantities of dilute acetic acid till it was free from alkaloidal material. The combined aqueous extracts were concentrated to about 2 l. *in vacuo*, cooled, and filtered from a small quantity of resin. The clear aqueous solution was repeatedly extracted with ether. The aqueous solution was then cooled well and basified with aqueous ammonia. The liberated base was thoroughly extracted with ether and, after drying (Na_2SO_4), and evaporation of the ethereal extract, the total alkaloids (28 g.) were obtained as a sticky light brown solid.

Separation of the Alkaloids.—The crude alkaloidal material (28 g.) was dissolved in the minimum amount of acetone and cooled at 0° overnight. The crystals that had separated were filtered off and constituted pure carpaine (12 g.), m. p. 121°. The filtrate was mixed with benzene and washed with water repeatedly. It was then extracted several times with dilute acetic acid. The acid extract was shaken with benzene to remove non-basic material, and rendered alkaline with sodium carbonate. The liberated base was extracted with benzene. Removal of the solvent after drying yielded 10·8 g. of a sticky oil. This was chromatographed in benzene on alumina (200 g.), the following fractions (total, 7·38 g.) being obtained: (i) by benzene (5 l.), a solid (3·6 g.; 3·1 g. thereof had m. p. 80—100°); (ii) by benzene + 1% of alcohol (5 l.), an oil (3·3 g.); and (iii) by benzene + 2·5% of alcohol (3·5 l.), an oil (0·48 g.). Fraction (i), after one crystallisation from acetone, gave pure carpaine (2·1 g.), m. p. 121°;

$[\alpha]_D^{28}$ +21·4° (*c*, 1·08 in EtOH). Fraction (ii), dissolved in absolute ether, was saturated with dry hydrogen chloride. The hydrochloride (2·1 g.) which was precipitated melted at 270—280°. Crystallisation from absolute alcohol yielded pure pseudo*carpaine hydrochloride* (1·4 g.), m. p. 295° (Found: C, 61·0; H, 9·5; N, 5·0. $C_{14}H_{26}O_2NCl$ requires C, 61·0; H, 9·4; N, 5·1%). A further crop of this hydrochloride (0·25 g.) was obtained from the mother-liquor after addition of absolute ether to turbidity. *pseudo*Carpaine hydrochloride was much less soluble in absolute alcohol than carpaine hydrochloride.

pseudo*Carpaine*, obtained by basification of an aqueous solution of the hydrochloride and extraction with ether, crystallised from light petroleum (b. p. 50—55°) and melted at 65—68°, $[\alpha]_D^{28}$ +4·95° (*c*, 1·62 in EtOH) (Found: C, 70·4; H, 10·4; N, 5·7. $C_{14}H_{25}O_2N$ requires C, 70·3; H, 10·5; N, 5·7%).

Dehydrogenation of pseudo*Carpaine.*—A solution of *pseudo*carpaine (200 mg.) in *p*-cymene was dehydrogenated by Rapaport and Baldridge's procedure (*loc. cit.*); 180 mg. of deoxycarpyrinic acid hydrochloride were obtained. Crystallisation from acetone gave colourless crystals, m. p. 74—76° (Found: C, 58·0; H, 8·2; N, 4·8. $C_{14}H_{22}O_2NCl,H_2O$ requires C, 58·0; H, 8·3; N, 4·8%).

Dehydrogenation of carpaine yielded the same hydrochloride, m. p. 74—76° alone or mixed with the above product.

Rapaport and Baldridge have isolated deoxycarpyrinic acid hydrochloride in the anhydrous form, m. p. 96—97°. Our product has the same ultra-violet absorption spectrum as that reported for deoxycarpyrinic acid hydrochloride by these authors.

Hydrolysis of pseudo*Carpaine.*—*pseudo*Carpaine hydrochloride (500 mg.) in concentrated hydrochloric acid (25 ml.) was refluxed for 4 hr. The solution was then evaporated to dryness *in vacuo*. The residue, thoroughly dried and crystallised from absolute alcohol–ether, furnished a hydrochloride (390 mg.), m. p. 133—145°; repeated crystallisation yielded material melting in the same range.

Esterification of the Hydrolysis Product.—A solution of the foregoing hydrochloride (390 mg.) in absolute alcohol (50 ml.) was saturated at 0° with dry hydrogen chloride. After being kept for 2 days, the solution was concentrated to 5 ml. Absolute ether was added to incipient turbidity. Overnight, a colourless crystalline hydrochloride (150 mg.) separated, melting at 160—170°, which on one crystallisation from alcohol–ether furnished ethyl carpamate hydrochloride, m. p. and mixed m. p. 173° (Found: C, 59·3; H, 9·4; N, 4·5. $C_{16}H_{32}O_3NCl$ requires C, 59·7; H, 10·0; N, 4·4%). The mother-liquor was evaporated to dryness and the resulting material, after decolorisation with charcoal, was crystallised from absolute alcohol–ether (180 mg.; m. p. 110—120°). One recrystallisation from absolute alcohol–ether furnished *ethyl* pseudo*carpamate hydrochloride*, m. p. 122—124° (Found: C, 60·0; H, 10·4; N, 4·3. $C_{16}H_{32}O_3NCl$ requires C, 59·7; H, 10·0; N, 4·4%).

Dehydrogenation of Ethyl pseudo*Carpamate.*—Ethyl *pseudo*carpamate (200 mg.) was dehydrogenated in *p*-cymene with 30% palladised charcoal (100 mg.). In 1 hr. hydrogen corresponding to 3 mols. was evolved. The dehydrogenation product isolated in the usual way melted at 78—80° and did not depress the melting point of ethyl carpyrinate.

pseudo*Carpamodiol.*—*pseudo*Carpaine (600 mg.) was reduced with lithium aluminium hydride, and the product was isolated as in the case of carpaine (Govindachari and Narasimhan *loc. cit.*). The oil (600 mg.) obtained initially gradually set to a solid. Two crystallisations from absolute ether gave pseudo*carpamodiol*, m. p. 78—80° $[\alpha]_D^{28}$ −13·53° (*c*, 2·18 in EtOH) (Found: C, 69·0; H, 12·0; N, 5·7. $C_{14}H_{29}O_2N$ requires C, 69·1; H, 12·0; N, 5·8%). Carpamodiol (Govindachari and Narasimhan, *loc. cit.*) had $[\alpha]_D^{28}$ −1·11° (*c*, 2·2 in EtOH).

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