

A STUDY OF 'CARPASEMINE' ISOLATED FROM CARICA PAPAYA SEEDS

BY T. B. PANSE AND A. S. PARANJPE

(Pharmacology Department, Seth G. S. Medical College, Parel, Bombay)

Received July 21, 1943

(Communicated by Dr. K. Venkataraman, F.A.Sc.)

THE seeds of *Carica papaya* are said to possess powerful anthelmintic and emmenagogue properties.¹ In order to verify these claims and other medicinal properties claimed for the seeds, a pharmacological study of the seeds was undertaken and as a part of the work the chemical analysis of seeds was first carried out.

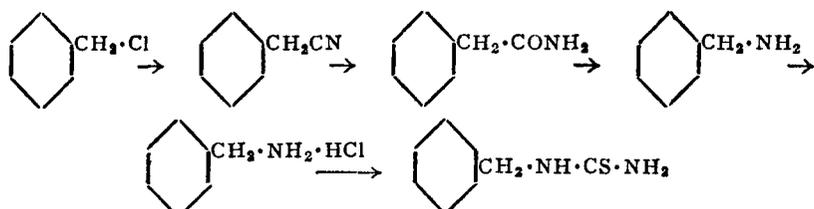
Reference to previous work on the subject showed that Greshoff² had isolated mainly from the leaves (and is also stated to have obtained from the fruit and seeds) of *Carica papaya* Linn., the alkaloid Carpaine, m.p. 121°. We have, however, isolated from the seeds a crystalline substance, melting at 165°. In a preliminary note³ on the substance it was provisionally named 'Carpasemine' because of its alkaloidal character, such as the presence of nitrogen in the molecule and positive results for tests with reagents for alkaloids.

A careful examination of the constituent elements in the substance showed that it contained sulphur (instead of O₂ as was assumed in our previous note) together with carbon, hydrogen and nitrogen. The results of the ultimate analysis of the substance as well as those of its molecular weight determination by cryoscopic method, indicated the molecular formula to be C₈H₁₀N₂S, for the substance. The substance gave an acetyl derivative, m.p. 131° and also formed a methiodide compound, m.p. 103°. However, it did not form salts with the common acids. On boiling the substance, m.p. 165°, with sodium hydroxide, an "oil" (A) and a product (B), m.p. 148-9° (in low yield), were obtained. Evolution of ammonia was noticed during the reaction. The "oil" (A) formed a hydrochloride, m.p. 245-6°. While the product (B) formed an acetyl derivative, m.p. 130° and was not found to contain sulphur. On oxidation, the product (B) yielded a compound, m.p. 205-7°, which is under investigation. During the oxidation a distinct smell of benzaldehyde was noticed. Direct oxidation of the original substance, m.p. 165°, however yielded benzoic acid.

The oxidation results indicated that the substance, m.p. 165°, contained a benzene ring with a side chain. Evolution of ammonia on boiling with sodium hydroxide, suggested it to be a substituted ammonia derivative, which could also form acetyl and methiodide compounds. While its weak

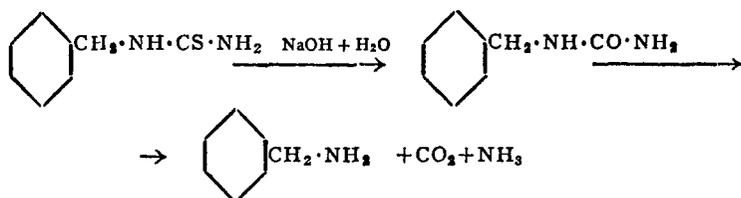
basic character together with the fact that it contained sulphur indicated it to be a phenyl derivative having probably as its side chain a heterocyclic ring containing S and N or a thiourea residue.

On referring to the literature, it was found that benzylthiourea (or benzylthiocarbamide) possessed properties similar to those enumerated for the substance, m.p. 165°. In order to confirm this assumption, a direct comparison of the natural product and synthetic benzylthiourea was considered necessary. The synthetic benzylthiourea was prepared by the scheme indicated below :—



The mixed melting point of the product, m.p. 165° isolated from the papaya seeds with the synthetic benzylthiourea (Salkowski)⁴ showed no depression and thus established the identity of the former with the latter. The identity was further confirmed by the mixed melting point of their acetyl derivatives.

It is known that substituted thioureas when boiled with aqueous alkali decompose into a substituted amine, carbon dioxide, hydrogen-sulphide and ammonia. In view of this fact, the "oil" (A) obtained on boiling the substance, m.p. 165° with alkali, was suspected to be benzylamine. The surmise proved to be correct as the mixed melting point determination of the hydrochloride of (A) and the hydrochloride of benzylamine showed no lowering. The other product (B) obtained on boiling the substance m.p. 165° with alkali, appeared from its properties to be benzylurea (or benzylcarbamide). It was subsequently identified to be benzylurea by a mixed melting point with synthetic benzylurea (Paterno and Spica).⁵ The action of 20% aqueous sodium hydroxide solution on benzylthiourea may, on the basis of the results obtained above, be represented as follows :—



The course of the reaction also explains the low yield of the intermediate product, benzylurea, in view of the possibility of its further hydrolysis into benzylamine, carbon dioxide and ammonia.

The pharmacological study of benzylthiourea or 'carpasemine' is in progress and the results of the investigation will be published elsewhere in due course.

Experimental

Isolation of the substance, m.p. 165°, from Carica papaya Seeds.—Dried papaya seed powder (100 gm.) was digested in Prollius's fluid (approx. 550 c.c.) with occasional shaking during forty-eight hours. The liquor was then filtered off and the seed powder discarded. The filtrate was allowed to evaporate at the room temperature, when an oil together with some solid was obtained as a residue. The solid after separation from the oil was crystallised from boiling water. The repeated crystallisations of the solid resulted in the formation of beautiful bunches of colourless crystals, m.p. 165°, yield 0.35% of the seed powder. It may be mentioned here, that the yield of the substance was seriously hampered when the seeds were powdered long before the extraction. Analysis (Found: C, 57.95, H, 6.44, N, 16.3, S 19.3%, $C_8H_{10}N_2S$ requires C, 57.8, H, 6.0, N, 16.9, S, 19.3%). The molecular weight of the substance (determined by the cryoscopic method, using nitrobenzene as solvent) was found to be 163 which indicated the molecular formula $C_8H_{10}N_2S$ for the substance. The substance is bitter to taste. It is insoluble in cold water, petroleum ether and benzene but fairly soluble in alcohol and acetone. A mixed melting point of the substance with benzylthiourea (Salkowski,⁴ m.p. 164°) showed no depression.

Acetyl derivative of the product, m.p. 165°—was prepared with sodium acetate and acetic anhydride as usual. The acetate crystallised from 40% alcohol into prisms, m.p. 131°. Analysis (Found: N, 13.2%; $C_{10}H_{12}N_2OS$ requires N, 13.46%). The mixed melting point of this acetate with the acetate of benzylthiourea (Werner,⁶ m.p. 129–30°) showed no depression.

Methiodide of the product, m.p. 165°.—Equimolecular quantities of methyl iodide and the product, m.p. 165°, were added to methyl alcohol and refluxed on a water-bath for four hours. Alcohol was then distilled off and a sticky residue was obtained. The residue, which solidified on keeping, was crystallised from benzene into fine hexagonal crystals, m.p. 103–5°. Analysis (Found: N, 9.1%, $C_9H_{13}N_2SI$ requires N, 9.0%). The product was fairly soluble in water.

Oxidation of the product, m.p. 165°.—0.5 Gm. of the product, m.p. 165°, was dissolved in warm water and (30 c.c) of potassium permanganate solution (2%) was added to it in dropwise manner. After the reaction was over the manganese dioxide precipitate was filtered off. The excess of potassium permanganate in the filtrate was then destroyed with a few drops of alcohol and manganese dioxide precipitate again filtered. The resulting clear filtrate,

on cooling was extracted with ether, which on dehydration with anhydrous sodium sulphate followed by evaporation yielded a solid, m.p. 120°. It was identified as benzoic acid.

The action of alkali on the product, m.p. 165°.—0.5 Gm. of the product, m.p. 165°, was refluxed with 20% aqueous sodium hydroxide solution (75 c.c.) for four hours. During the reaction a distinct smell of ammonia was perceptible. The alkaline reaction mixture on cooling, was extracted with ether. Dehydration of the ethereal layer with anhydrous calcium chloride followed by evaporation gave a crystalline solid and an oil. The solid was separated from the oil and crystallised from benzene into light lustrous needles, m.p. 148–9°. Yield 7%. Analysis (Found: C, 64.52; H, 6.75; N, 18.57%; $C_8H_{10}N_2O$ requires C, 64.00, H, 6.4, N, 18.66%). A mixed melting point of the product, m.p. 148–9°, with benzylcarbamide (Paterno and Spica,⁵ m.p. 147°) prepared from benzylamine and potassium cyanate showed no depression.

Acetate of the product, m.p. 148–9°—was prepared with sodium acetate and acetic anhydride as usual. The acetate was crystallised from boiling water and was found to melt at 130°. Analysis (Found: C, 62.95, H, 6.42, N, 14.55%; $C_{10}H_{12}O_2N_2$ requires C, 63.0, H, 6.25, N, 14.6%).

Oxidation of the product, m.p. 148–9°.—0.225 Gm. of the product m.p. 148–9°, was dissolved in warm water and 15 c.c. of potassium permanganate solution (2%) was added to it in a dropwise manner. During oxidation bitter almond-oil-like smell was noted. After the reaction was complete, the manganese dioxide precipitate was filtered off. The excess of potassium permanganate in the filtrate was destroyed with a few drops of alcohol and the precipitate of the manganese dioxide again filtered off. The resulting clear filtrate was concentrated on a water bath and on cooling, deposited beautiful hexagonal crystals, m.p. 205–7°. The product is under further investigation.

Hydrochloride of the oil obtained in the alkali boiling of the product, m.p. 165°.—A few drops of the oil were treated with conc. hydrochloric acid when a solid was thrown down immediately. The solid crystallised from alcohol into thin rectangular plates melting at 245–6°. The hydrochloride did not show any lowering in the melting point when admixed with benzylamine hydrochloride (Curtius and Lederer,⁷ m.p. 246°).

Synthesis of Benzylthiourea.—To a warm solution of sodium cyanide (52 gms.) in water (45 c.c.) was slowly added benzyl chloride (103 gm.) diluted with equal volume of alcohol. The reaction was completed by heating on a water-bath for three hours. Sodium chloride was removed by filtration and alcohol distilled off from the filtrate. Benzyl cyanide separated as an oil from the residual aqueous portion and purified by distillation under reduced pressure 10 mm. had a b.p. 115–20°. (Cannizzaro,⁸ b.p. 115–20°.) Yield

80 gm. benzyl cyanide (10 gm.) prepared as above was mixed and shaken with sulphuric acid (15 gms. D. 1.82) care being taken that the temperature is not raised above 65–70°. After the heat of the reaction was over, the mass was poured in water. The resulting precipitate of phenylacetamide was purified by treatment with sodium bicarbonate solution, followed by washing with water and crystallisation from hot water, m.p. 155° (Purgotti,⁹ m.p. 155–6°). To 135 gm. of phenyl acetamide (1/10 mol.) prepared as above was added bromine (8.0 gm. 1/10 mol.) dissolved in 4 molecular proportions of potassium hydroxide in 16 parts of water. The solution was heated rapidly and as soon as a clear solution was formed, it was distilled off to obtain benzylamine as an oil in the distillate, b.p. 185° (Hoogewerff and van Dorp,¹⁰ b.p. 185°). The benzylamine by treatment with hydrochloric acid was converted into its hydrochloride, m.p. 245° (Curtius,⁷ m.p. 246°). The hydrochloride on heating with equimolecular quantity of potassium sulphocyanide at a temperature of 120° for fourteen hours, yielded a brownish residue which after washing with cold water, was crystallised from boiling water into colourless needles. The benzylthiourea melted at 164° (Salkowski,⁴ m.p. 164°). Yield 80%.

Summary

From the seeds of *Carica papaya* a substance, m.p. 165° ($C_8H_{10}N_2S$) has been isolated for the first time and named 'Carpasemine' to indicate its source. The chemical properties of 'Carpasemine' together with its degradation products have been studied and some new derivatives have been prepared from it. 'Carpasemine' has been identified to be benzylthiourea or benzylthiocarbamide by mixed melting point with the synthetically prepared benzylthiourea. The identity has also been confirmed through the mixed melting point of their derivatives.

The present investigation forms a part of the Indigenous Drugs Inquiry financed by the Indian Research Fund Association, to which our thanks are due.

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