those described above. After the theoretical amount of hydrogen had been taken up, the solution was filtered through a Jena glass funnel. Upon evaporation of the alcohol under reduced pressure, 9.5 g. of nearly colorless crystals, melting at 121–123°, were obtained. The solid was triturated with 25 cc. of methyl ethyl ketone to yield 7.5 g. of colorless crystals, m.p. 128–129°.

Anal. Calcd. for $C_{15}H_{28}O_8N_2$: C, 49.51; H, 7.74; N, 7.69. Found: C, 49.46; H, 7.72; N, 7.85.

Hydroxylysine Monohydrochloride (VII).—The crude aminoalcohol (VI) (19.2 g.) obtained by reduction of (V) and subsequent removal of solvent, was hydrolyzed by refluxing for 23 hours with 70 cc. of 20% HCl. The resulting brown solution was decolorized with Nuchar and then evaporated to about one-third its original volume in order to remove part of the hydrochloric acid. The solution was then diluted with an equal volume of water, and freshly prepared silver oxide was added to precipitate the chloride ion. After filtration, the excess silver ion was removed with hydrogen sulfide. The *p*H of the solution was then adjusted to 6.5–7.0 with hydrochloric acid and the solution evaporated under reduced pressure at room temperature to about 10 cc. The addition of absolute ethanol effected the precipitation of hydroxylysine monohydrochloride. After recrystallization from methanol–water, 6.2 g. (47%) of VII was obtained. After two or three recrystallizations from methanol–water, the material decomposed at 216–220°. Sheehan and Bolhofer reported the decomposition point of hydroxylysine hydrochloride as 215–220°.[5]

Anal. Calcd. for $C_6H_{15}O_3N_2Cl$: C, 36.27; H, 7.61; N, 14.10; Cl, 17.85. Found: C, 35.93; H, 7.63; N, 14.16; Cl, 17.88.

The dipicrate of (VII) was prepared by the addition of an equivalent amount of picric acid to the solution of (VII) obtained after the adjustment of *p*H as described above. In agreement with the results of Sheehan and Bolhofer,[5] the dipicrate was found to exist in two characteristic forms, one melting at 145–150°, and the other decomposing sharply at 195°.

Anal. Calcd. for $C_{18}H_{20}O_{17}N_8$: C, 34.85; H, 3.25; N, 18.06. Found (m.p. 145–150°): C, 34.50; H, 3.47; N, 17.81. Found (dec. 195°): C, 34.54; H, 3.56; N, 18.08.

A monopicrate was also obtained by the addition of very small amounts of picric acid to a solution of hydroxylysine hydrochloride. The deep yellow solid melted with decomposition at 227°.

Anal. Calcd. for $C_{12}H_{17}O_{10}N_5$: C, 36.83; H, 4.38; N, 17.90. Found: C, 37.43; H, 4.49; N, 18.03.

Acknowledgment.—The authors wish to thank the Research Corporation for a grant-in-aid supporting this project.

HOLLAND, MICHIGAN RECEIVED AUGUST 21, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF "ATANOR" CÍA. NACIONAL PARA LA INDUSTRIA QUÍMICA S.A.M.]

Cactus Alkaloids. I. *Trichocereus terscheckii* (Parmentier) Britton and Rose

BY L. RETI AND J. A. CASTRILLÓN

The dried branches of *Trichocereus terscheckii* (Parmentier) Britton & Rose contain 0.25 to 1.2% alkaloids. From this source trichocereine, a new vegetable base, and the already known mezcaline have been isolated and characterized. The ratio of trichocereine to mezcaline is 5:1. The chemical structure of trichocereine has been shown to be N-dimethylmezcaline by degradation, and its synthesis has been achieved by allowing 3,4,5-trimethoxy-β-phenylethyl chloride to react with dimethylamine.

The genus *Trichocereus* of the cactus family consists of 19 recognized species, confined to South America (N. L. Britton and J. N. Rose, "The Cactaceae." The Carnegie Institution of Washington, Washington, 1919–1923). So far only seven species have been chemically examined and all contain basic substances; the genus must, therefore be, considered as alkaloidiferous. *T. Candicans*[1] and *T. lamprochlorus*[2] contain candicine and hordenine (anhaline); *T. spachianus*,[3] candicine; *T. thelegonoides*, *T. thelegonus* and *T. huascha*,[4] alkaloids of still undetermined structure. A preliminary report on the bases of *T. terscheckii* was presented at the X International Congress of Chemistry in Rome 1938.[5] An exhaustive survey on Cactus alkaloids and some related compounds has been published recently.[6]

Trichocereus terscheckii grows in the high valleys of northwestern Argentia (provinces of La Rioja, Catamarca, Tucumán, Salta, etc.) and often forms the most conspicuous plant in the landscape. It is a very large cactus, 10 to 12 meters high, resembling the American saguaro (*Carnegiea gigantea*).

Various lots of plants have been examined, collected at blossom time (October–December) near Chilecito (La Rioja) and Andalgalá (Catamarca). The content of alkaloids varied between 0.25 and 1.2%, referred to the dry plant. Preliminary tests showed that no appreciable amount of phenolic bases could be expected and that two types of alkaloids were present: (a) soluble in ether, (b) insoluble in ether but soluble in chloroform. Two basic compounds have been isolated and characterized: mezcaline (chloroform soluble) and a new vegetable alkaloid which should be named trichocereine (ether soluble). Apparently there are also other bases in small amounts. In some lots with high alkaloidal content, no mezcaline could be detected. The ratio trichlocereine to mezcaline is 5:1. This is the first case where mezcaline, the active hallucinatory principle of the "mescal-buttons" (*Anhaloniumlewinii syn. Lophophora williamsii*) has been found in a different species.

Mezcaline has been identified as the main alkaloid of the ether-insoluble fraction, by comparing several derivatives of the base found in *T. terscheckii* with the synthetic substance. Trichocereine is a new natural phenylethylamine, found so far only in this species. The structure has been determined by analytical and synthetical methods. Trichocereine, $C_{13}H_{21}O_3N$, contains three methoxyl and two N-methyl groups. Trimethylgallic acid is formed in good yields on oxida-

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(1) L. Reti, *Rev. Soc. Argentina Biol.*, **9**, 344 (1933).

(2) L. Reti and R. I. Arnolt, *Actas y Trabajos del V° Congreso Nacional de Medicina, Roasario*, **3**, 39 (1935).

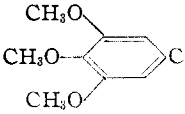
(3) S. A. Haagen-Smit and M. Olivier, private communication.

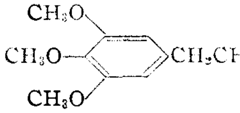
(4) S. A. Haagen-Smit and M. Olivier, private communication.

(5) L. Reti, *Atti Congr. Intern Chim 10th Congr. Rome*, 1938, **5**, 396 (1939).

(6) L. Reti, "Fortschritte der Chemie organischer Naturstoffe," Vol. VI, L. Zechmeister, Ed., Springer Verlag, Wien, 1950, p. 242.

tion with permanganate. Of the two alternate phenylethylamine structures which can be postulated from these data, the β-form is biologically plausible. Actually, the methiodide of trichocereine proved to be identical with dimethylmezcaline methiodide.[7] Trichocereine is therefore N-dimethylmezcaline.


Mezcaline


Trichocercine

Synthesis of trichocereine has been carried out by treating 3,4,5-trimethoxy-β-phenylethyl chloride with dimethylamine. Attempts to methylate mezcaline with methyl iodide or with formaldehyde–formic acid have failed.

The pharmacological action of trichocereine has been examined by Ludueña.[8] Ingestion of 0.55 g. had no apparent effects in a self experiment; especially no effects of a sensory nature were noted. This very low toxicity explains how men and animals on the deserts of Argentina's Northwest in time of drought may find relief by drinking the juice of the crushed plant. The alkaloids are located prevalently in the cortical parenchyma; a comparative estimation gave: green epidermis 0.29%; central parts 0.45% of total alkaloids.

Experimental

All melting points are corrected.

Extraction of the Alkaloids.—The plant (cut branches) was cleaned, the spines extracted with nippers and the material cut in thin slices was dried at 40–60°. The dry plant is easy to grind and can be stored. The fresh plant contains 92–95% water.

The powdered material (10 kg.) was exhaustively extracted in a percolator with hot, acidulated 96% ethanol, the extract filtered and concentrated *in vacuo* to 500 ml. Water was added (2500 ml.) and concentrated again to approx. 2300 ml. This solution was filtered to separate oils, resins, chlorophyll, etc., and washed twice with 500 ml. of chloroform. The aqueous solution was neutralized with solid potassium carbonate, and an excess of 20 g. was added. A precipitate containing only calcium carbonate was eliminated, and the solution extracted 4 times with the same vol. (2300 ml.) of chloroform. The combined extracts, after having been dried with anhydrous sodium sulfate were concentrated to 780 ml. and filtered. The solution was extracted twice with 150 ml. of 5% hydrochloric acid and once with 100 ml. of water. The aqueous solution was repeatedly washed with ether and filtered. This is the purified aqueous solution of total alkaloids.

This solution was alkalinized again with dry potassium carbonate and extracted 5 times with 500 ml. of ether. This extract, containing the ether soluble alkaloids, was concentrated to 500 ml.; it is called A (trichocereine).

After ether extraction, the aqueous solution was extracted three times with 500 ml. of chloroform, and the extract concentrated to 200 ml.; this is sol B (mezcaline).

Trichocereine Hydrochloride.—Sol A was again purified by extraction with 5% hydrochloric acid, alkalinization, extraction with ether etc. The ether extract was concentrated to 200 ml. and the basic residue was found to be 19.8 g. The solution was neutralized with absolute alcoholic hydrochloric acid (25%) using congo red as indicator. The crude trichocereine hydrochloride which separated was filtered and dried. It weighed 20 g. The salt, after recrystallization from absolute alcohol melted at 205°. Repeated recrystallization did not raise the m.p.

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.61; H, 8.04; N, 5.08; CH_3 (O), 16.35; CH_3 (N), 10.90; Cl, 12.86. Found: C, 56.71; H, 7.88; N, 5.30; CH_3 (O), 15.96; CH_3 (N), 10.86; Cl, 12.40.

Trichocereine.—The pure base regenerated from hydrochloride is a colorless oil of basic reaction; it distils *in vacuo* without decomposition and is soluble in water, alcohol, methanol, ether, chloroform and acetone. The salts crystallize well.

Trichocereine Picrate.—0.32 g. of the base in 2 ml. of alcohol was mixed with a solution of 0.32 g. of picric acid in 2 ml. of hot alcohol. The precipitate was washed with alcohol and repeatedly recrystallized from acetone; fine yellow needles were obtained m.p. 171–172°.

Anal. Calcd. for $C_{13}H_{21}O_3N \cdot C_6H_3O_7N_3$: N, 11.96. Found: N, 12.27.

Trichocereine Picrolonate.—0.25 g. of trichocereine hydrochloride in 2 ml. of alcohol was mixed with a warm solution of 0.26 g. of picrolonic acid in 4 ml. of alcohol. Allowing the solution to cool, the picrolonate separated spontaneously. It was repeatedly recrystallized from alcohol–acetone giving canary-yellow prisms, m.p. 166°. If the melted salt is heated again it melts at 175°.

Anal. Calcd. for $C_{13}H_{21}O_3N–C_{10}H_8O_5N_4$: N, 13.91. Found: N, 13.60.

Trichocereine chloroplatinate precipitates from a diluted solution of the hydrochloride by adding a 1:10 solution of platinum chloride. Recrystallized from water, orange colored crystals are obtained; m.p. 184–185°, with decomposition.

Anal. Calcd. for $2C_{13}H_{21}O_3N \cdot Cl_6PtH_2$: Pt, 21.98. Found: Pt, 22.08.

Trichocereine chloroaurate was obtained the same way with gold chloride 1:10; burnt siena colored crystals, m.p. 136–139° with decomposition.

Anal. Calcd. for $C_{13}H_{21}O_3N \cdot Cl_4AuH$: Au, 34.04; C, 26.93; H, 3.83. Found: Au, 34.6; C, 26.73; H, 3.78.

Trichocereine Methiodide.—The free base (0.48 g.) was dissolved in 1 ml. of acetone and 0.3 ml. of methyl iodide added. The reaction is exothermic and was complete after 24 hours standing. The product was washed with acetone and recrystallized from water. Short colorless needles, slightly soluble in cold, soluble in hot water, were obtained; m.p. 226–228°. Dimethylmezcaline methiodide obtained from synthetical mezcaline melted at 226–228°, and no depression was observed in the m.p. of a mixture of synthetic and natural salts.

Anal. Calcd. for $C_{13}H_{21}O_3NI \cdot CH_3$: C, 44.10; H, 6.34. Found: C, 44.50; H, 6.32.

Picrate of the Quaternary N-Methyltrichocereine.—Trichocereine methiodide (0.06 g.) was heated with 1 ml. of water, and 2.5 ml. of sodium picrate in 2% solution added. Recrystallized from hot water the substance melted at 165°. The product obtained from synthetical mezcaline melted at 165°, alone or after mixture with that derived from trichocereine.

Anal. Calcd. for $C_{14}H_{24}O_3N \cdot C_6H_2O_7N_3$: C, 49.79; H, 5.43; N, 11.61. Found: C, 49.49; H, 5.48; N, 11.66.

Oxidation of Trichocereine.—Trichocereine chlorohydrate (2.5 g.) dissolved in 250 ml. of water was added to 150 ml. of 4% $KMnO_4$ solution. Oxidation occurred spontaneously. After heating to boiling the solution was filtered. The filtrate was oxidized again with 50 ml. of the $KMnO_4$ solution and concentrated to 100 ml. Hydrochloric acid precipitated a white crystalline substance (0.65 g.), which when recrystallized from hot water melted at 169°. Synthetic 3,4,5-trimethylgallic acid melted at the same temperature alone or mixed with the acid obtained from trichocereine.

Synthesis of Trichocereine.—Direct methylation with methyl iodide or dimethyl sulfate has been attempted but it was not possible to isolate the tertiary base from the reaction mixture. Methylation with formaldehyde and formic acid led to isoquinoline derivatives. Synthetic trichocereine was finally obtained through the following steps:

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(7) E. Späth, *Monatsh.*, **40**, 129 (1919).

(8) F. P. Ludueña, *Compt. rend. soc. biol.*, **121**, 368 (1936).

(1) conversion of mezcaline to 3,4,5-trimethoxyphenylethyl chloride; (2) reaction of the chloride with dimethylamine.

Mezcaline hydrochloride (1.3 g.) was dissolved in 5 ml. of 10% hydrochloric acid, and 0.71 g. of sodium nitrite dissolved in 1.1 ml. of water added. A vigorous reaction followed, which was completed by heating in the water-bath.

The reaction mixture was extracted with ether, and the crude chloride was obtained by evaporation of the dried extract.

The crude chloride was heated in a sealed tube with 5 ml. of a 14% solution of dimethylamine in alcohol, during 6 hours at 100°. The reaction mixture was evaporated, dissolved in diluted hydrochloric acid, filtered, alkalinized with K_2CO_3 and extracted with ether. The residue of this ether extract was neutralized with hydrochloric acid, and recrystallized from alcohol. White crystals were obtained, m.p. 204–205°. No m.p. depression was observed when mixed with natural trichocereine chloride.

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.61; H, 8.04. Found: C, 56.77; H, 8.13.

The picrate, picrolonate and methiodide obtained from the synthetic chlorhydrate did not depress the melting points of the derivatives of the natural base.

Mezcaline Hydrochloride.—The chloroform solution B was extracted twice with 40 ml. of 5% hydrochloric acid and once with 20 ml. of water. The aqueous extract was then washed with 20 ml. of chloroform and 20 ml. of ether. After alkalinization with K_2CO_3, the solution was extracted with chloroform and the extract evaporated to dryness. It weighed 4 g. After neutralization with alcoholic hydrochloric acid, the crude hydrochloride was dissolved in 30 ml. of abs. alcohol and the filtered solution overlayed with 30 ml. of ether. The hydrochloride crystallized. Recrystallized from alcohol, the pure salt melted at 181–182°.

Anal. Calcd. for $C_{11}H_{18}O_3NCl$: C, 53.32; H, 7.32; N, 5.65; Cl, 14.32. Found: C, 52.84; H, 7.24; N, 5.64; Cl, 13.91.

Several derivatives of this substance were prepared and the m.p. compared with those of the corresponding compounds obtained starting from synthetic mezcaline. In all cases a perfect concordance was observed between both series, alone or after admixture.

A summary of the results are given in Table I.

TABLE I

Substance	Synth. mezcaline. m.p., °C.	Mezcaline from *T. terscheckii*. m.p., °C.	Mixture. m.p., °C.
Hydrochloride	181–182	181–182	181
Picrate	216–218	219	218–219
Chloroplatinate	187–188	188	188
Methiodide	226–228	226–228	227
Picrate of the quaternary cmpd.	165	165	165

BUENOS AIRES, ARGENTINA RECEIVED SEPTEMBER 8, 1950

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Papilionaceous Alkaloids. X. Identity of Hexalupine with *d*-Thermopsine(1,2)

BY LÉO MARION, WILLIAM F. COCKBURN(3) AND JAMES F. COUCH(4)

Hexalupine has been shown to be identical with *d*-thermopsine by means of their infrared spectra, and the melting points of several of their derivatives.

The alkaloid hexalupine occurs in *Lupinus corymbosus*, Heller.(5) As the physical constants of this compound differ very little from those of *d*-thermopsine,(6) a comparison of the two bases and several of their derivatives was made.

Hexalupine was found to be separable by careful vacuum distillation, into a colorless crystalline solid and a small amount of oily impurity whose nature has not yet been established. Reanalysis of the purified alkaloid showed the formula to be $C_{15}H_{20}ON_2$, without the third of a molecule of water of crystallization reported previously,(5) while measurement of the optical rotation gave $[\alpha]^{28}D$ + 152.4° (*c*, 4.62 in ethanol), as compared with +154.4° (*c* 0.8 in ethanol) for *d*-thermopsine.(6) The melting points of the free base, picrate, perchlorate and chloroplatinate were almost identical with those of the corresponding derivatives of *d*-thermopsine, and admixture caused no depression.

Final confirmation was obtained by comparison of the infrared spectra of the two bases, taken in carbon disulfide solution, with a rock-salt prism. As can be seen from the figure, the two curves are identical.

It has been shown recently that thermopsine is a stereoisomer of anagyrine giving rise to α-isosparteine when fully reduced catalytically.(7)

Acknowledgment.—The infrared spectra were taken by Dr. R. N. Jones and Mr. R. Lauzon, of these laboratories, whose courtesy is gratefully acknowledged.

Experimental

Purification of the Alkaloid.—Hexalupine dihydrochloride(5) was decomposed with sodium hydroxide, the free base extracted with ether and distilled in a Späth bulb at 150° (0.2 mm.). A small amount of impurity was obtained as two distinct oily fractions, one colorless, the other yellow, while the bulk of the material sublimed as colorless stubby prisms m.p. 207–209° (cor.). This melting point was not altered by admixture with pure *d*-thermopsine, m.p. 207–209° (cor.); $[\alpha]^{28}D$ +152.4° (*c* 4.62 in ethanol).

Anal. Calcd. for $C_{15}H_{20}ON_2$: C, 73.72; H, 8.23; N, 11.47. Found: C, 73.91, 73.74; H, 8.07, 8.22; N, 11.47.

Picrate.—Treatment of a methanolic solution of hexalupine with an equivalent amount of picric acid in methanol gave a yellow crystalline precipitate, which could be recrystallized from methanol in rectangular efflorescent plates, m.p. 248° (uncor.) with decomposition. This melting point was not depressed by admixture with *d*-thermopsine picrate m.p. 249° (uncor.).

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot C_6H_3N_3O_7$: C, 53.27; H, 4.90; N, 14.79. Found: C, 53.55, 53.65; H, 4.78, 4.90; N, 14.07.

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(1) For Part IX see *Can. J. Chem.*, **29**, 22 (1951).

(2) Published as National Research Council Bull. No. 2352.

(3) National Research Council of Canada Postdoctorate Fellow.

(4) Eastern Regional Research Laboratory, Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, Philadelphia 18, Penna.

(5) J. F. Couch, THIS JOURNAL, **56**, 155 (1934).

(6) L. Marion, F. Turcotte and J. Ouellet, *Can. J. Chem.*, **29**, 22 (1951).

(7) W. F. Cockburn and L. Marion, *ibid.*, **29**, 13 (1951).