CHAPTER 26

Simple Isoquinoline Alkaloids

L. RETI

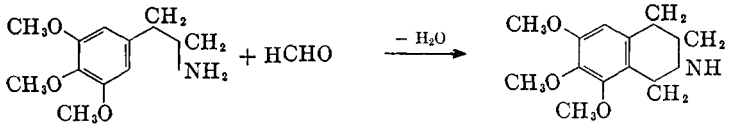
Buenos Aires, Argentina

I. Introduction

The large group of alkaloids of the isoquinoline type ranges in complexity from the simple isoquinolines, more exactly defined as simple tetrahydroisoquinolines, with only one aromatic nucleus, to the complicated structures of the bisbenzylisoquinolines.

According to suggestions first made by Pictet and Spengler (1) and later by Späth (2), the substituted β-phenethylamines may be considered as the precursors of the simple isoquinolines. For example, mescaline and formal-

dehyde would yield anhalinine:



The simultaneous occurrence of substituted phenethylamines and isoquinoline derivatives in the same species (*Anhalonium lewinii* Hennings) and the facility with which similar ring closures are performed *in vitro*, under conditions which can be considered as being comparable to physiological ones, make the above hypothesis seem reasonable.

Comparatively few simple isoquinoline alkaloids have been found to occur naturally. Until now such compounds have been encountered in three or four species of the Cactaceae, in a Chenopodiaceae [*Salsola arbuscula* Pall. (*S. richteri* Karel)], in three species belonging to the family of the Fumariaceae [*Corydalis pallida* (Thunb.) Pers., *C. aurea* Willd., *C. tuberosa* DC.] and in one Papaveraceae (*Papaver somniferum* L.). While no doubt exists as to the native occurrence of the anhalonium and salsola isoquinolines, hydrohydrastinine and hydrocotarnine may have been artifacts from the benzylisoquinoline alkaloids of *Corydalis tuberosa* and *Papaver somniferum*.

II. The Anhalonium Alkaloids

In chemical literature *Anhalonium lewinii*, *A. williamsii* Lem. and *A. jourdanianum* Lewin are mentioned as different species. However, botanists definitely recognize only one species (*Anhalonium williamsii* Britton and Rose; *Lophophora williamsii* (Lemaire) Coulter). It would be worth while to investigate, using fresh and well-identified material, whether only pellotine is present in *A. williamsii*, as stated by Heffter. Such findings may give support to a revision of the taxonomy of these cacti.

These small cacti grow from central Mexico to southern Texas and are the material of an illicit commerce, carried out by some Indian tribes. The globular plants are sliced into three or four sections and then dried in the sun; these dried pieces are the "mescal buttons" of the trade. The plant is also known as pellote, peyote, and peyotl; it is called challote in Starr County, Texas. Interest in the cactus alkaloids arose when the remarkable use by the Indian tribes and the strange pharmacological properties of this little cactus became known. (See Mescaline, Vol. III, pp. 331–334, and Cactus Alkaloids, Vol. IV, chap. 27).

Eleven bases have been isolated from *Anhalonium lewinii*; three phenethylamines: mescaline, *N*-methylmescaline, and *N*-acetylmescaline (see β-Phenethylamines Vol. III, chap. 22); and eight simple isoquinolines: anhalamine, anhalidine, anhalinine, anhalonidine, pellotine, *O*-methyl-*d*-

anhalonidine, anhalonine, and lophophorine. An extensive study on various varieties of pellote and their alkaloidal contents was published by Beccari (3).

The clarification of the structure and the syntheses of all of the *Anhalonium* alkaloids must be credited to Späth and his coworkers. The accomplishment is all the more remarkable since Späth had to contend with a scarcity of material; several fundamental structures were determined on very small samples, left over from Heffter's and Heyl's experiments.

III. Extraction and Separation of the Anhalonium Alkaloids

Extraction of the drug and isolation of the alkaloids from *A. lewinii* have been described by Heffter (4), Kauder (5), Tomaso (6), and Späth and Becke (7), as well as by Steiner-Bernier (8).

The total alkaloidal content and the relative amount of the individual alkaloids varies widely; Heffter's figures (%) are: mescaline 6.3; anhalonidine 5.3; anhalonine 3.0; lophophorine 0.5; anhalamine 0.1. Späth's yields, working with old material, are much lower. The other bases occur in very small quantities: anhalamine 0.1 %; anhalinine 0.01 %; anhalidine 0.001 %.

In Heffter's opinion (9), *A. lewinii* does not contain pellotine, the main alkaloid of *A. williamsii*. Kauder found pellotine in the "mescal buttons," but Heffter attributes this to contamination by *A. williamsii*. This opinion is shared by Lewin (10). Morphologically, these species are difficult to separate. Späth and Becke's extraction and isolation process is as follows:

> The drug is extracted with cold alcohol, and water is added to the sirup obtained by evaporating the extract *in vacuo*. The insoluble residue is treated with dilute hydrochloric acid. The solutions are united and filtered, and the filtrate is made alkaline with strong potassium hydroxide and extracted with ether. At this point the ether solution (*a*) contains the non-phenolic bases, while the aqueous solution (*b*) contains the phenolic alkaloids.
>
> (*a*) After evaporation of the solvent, the free bases are distilled *in vacuo* and the mescaline recovered as its crystalline sulfate. The regenerated bases from the mother liquor are redistilled *in vacuo* and treated with dilute hydrochloric acid when anhalonine hydrochloride crystallizes. The filtrate, after concentration, yields anhalinine hydrochloride. By a complicated treatment of the mother liquors, a further quantity of mescaline and a little lophophorine can be obtained.
>
> (*b*) The solution is acidified with hydrochloric acid, made alkaline again with excess potassium carbonate, and extracted exhaustively with ether. The residue from the extract is dissolved in dilute hydrochloric acid and anhalamine hydrochloride recovered. From the mother liquors anhalonidine hydrochloride is obtained by concentrating and adding alcohol. Pellotine may be recovered as picrate from the filtrate.

IV. The Anhalonium Isoquinolines

Table 1 includes all of the tetrahydroisoquinoline bases found in *Anhalonium lewinii*, and shows their structures and interrelations.

1. Anhalamine, $C_{11}H_{15}O_3N$

Anhalamine was first isolated by Kauder (5). According to Heffter (11) the drug contains 0.1 % anhalamine. The base crystallizes in microscopic needles, m.p. 189–191°; hydrochloride, from water with 2 H_2O, m.p. 258°; from alcohol with 1 H_2O; sulfate, colorless prisms, very soluble in water, less in alcohol; well-crystallized platinichloride and aurichloride; picrate, m.p. 237–240°; monobenzoyl derivative, m.p. 167.5°; dibenzoyl derivative, m.p. 128–129°; *N*-*m*-nitrobenzoyl derivative, m.p. 174–175°; *O*,*N*-dimethylanhalamine methiodide, m.p. 211.5–212.5°.

O-Methylanhalamine is termed anhalinine, and *N*-methylanhalamine is anhalidine.

2. Anhalinine, $C_{12}H_{17}O_3N$

Anhalinine was isolated by Späth and Becke (12) (yield, 0.01 %). Free base, m.p. 61–63°; hydrochloride, white crystals, m.p. 248–250°; picrate, m.p. 184–185°; aurichloride, m.p. 139–140°; platinichloride, m.p. 207–208°; *m*-nitrobenzoyl derivative, m.p. 147–148°; methiodide, m.p. 211.5–212.5°. *N*-methylanhalinine (= *O*-methylanhalidine) was prepared by Castrillon (63) by condensation of mescaline with formaldehyde by the Eschweiler-Clarke reaction. Hydrochloride, from abs. alcohol, m.p. 215–216°.

3. Anhalidine, $C_{12}H_{17}O_3N$

Anhalidine was found by Späth and Becke (13) (yield, 0.001 %). Free base, m.p. 131–133°; sublimes in high vacuum at 85–95°; *O*-methylanhalidine methiodide, m.p. 211.5–212.5°.

4. Anhalonidine, $C_{12}H_{17}O_3N$

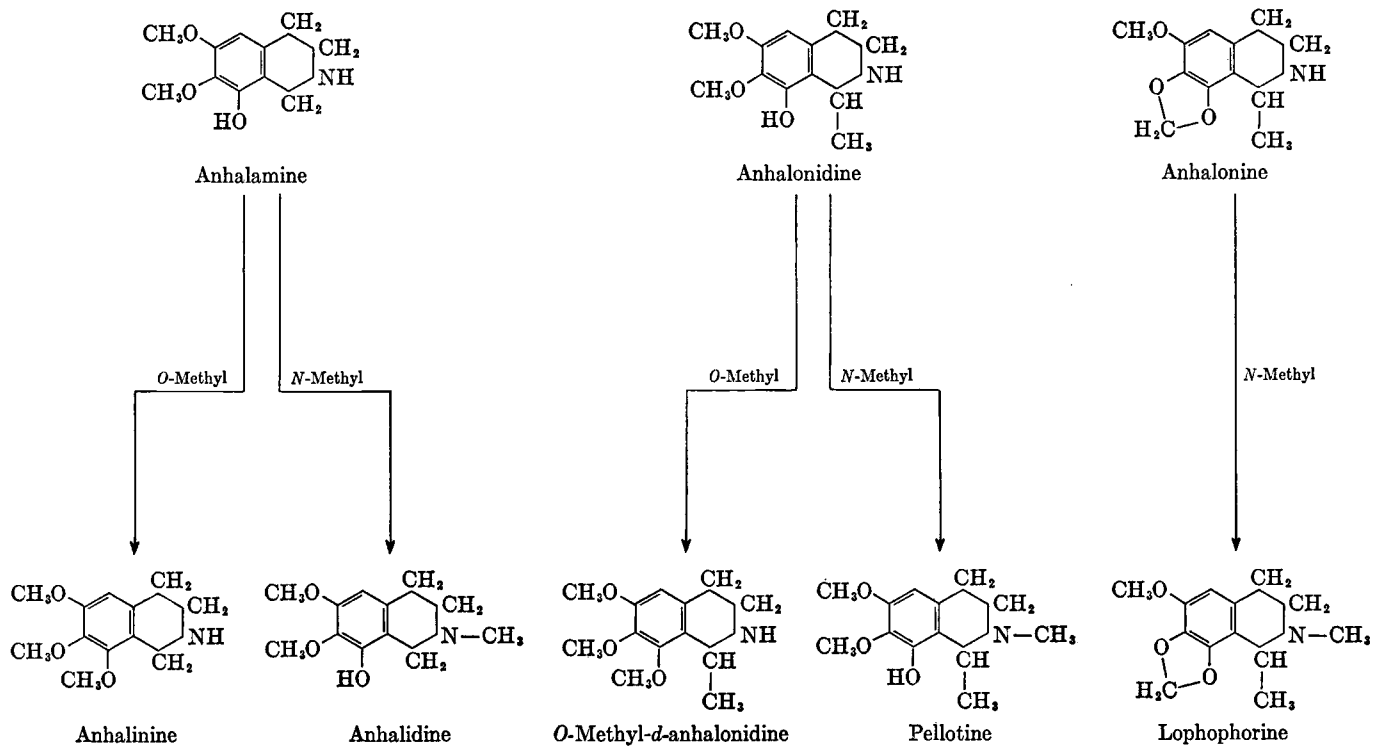
Anhalonidine was discovered by Heffter (4). According to this author pellote contains as much as 5 % of the alkaloid. The free base crystallizes in small octahedra, m.p. 160–161°; picrate, m.p. 201–208°; *N*-benzoyl derivative, m.p. 189°; dibenzoyl derivative, m.p. 125–126°; *N*-*m*-nitrobenzoyl derivative, m.p. 207–208°; *N*-methylanhalonidine hydroiodide (pellotine hydroiodide), m.p. 125–130°; *N*-methylanhalonidine methiodide (pellotine methiodide), m.p. 199°.

5. Pellotine (*N*-Methylanhalonidine), $C_{13}H_{19}O_3N$

Pellotine was isolated by Heffter (9) from *Anhalonium williamsii* (0.74 % of the fresh plant) and was found later by Kauder (5) in *A. lewinii*. The

TABLE 1

TETRAHYDROISOQUINOLINE ALKALOIDS ISOLATED FROM ANHALONIUM LEWINII



base is only slightly soluble in water; crystallizes from alcohol, m.p. 111–112°; the salts have a bitter taste; hydriodide, m.p. 125–130°; picrate, m.p. 167–169°; aurichloride, m.p. 147–148°; methiodide, m.p. 199°; *O*-methylpellotine methiodide, m.p. 226–227°.

Späth and Kesztler (14) prepared the optically active forms of pellotine and studied their racemization to determine whether the compound is present in the plant in the inactive form or is racemized when manipulated or during the aging of the drugs. By means of *d*-tartaric acid a fraction with $[\alpha]_D^{17}$ −15.2° was obtained from racemic pellotine. Considering the ease with which this base undergoes racemization, the authors suppose that optically active pellotine is present in the plant. Nakada and Nishihara (51) prepared 6,7,8-trimethoxy-1-methyl-3,4-dihydro-isoquinoline, from which the methyl ether of pellotine was obtained.

6. *O*-Methyl-*d*-anhalonidine, $C_{13}H_{19}O_3N$

Späth and Bruck (15) found very small quantities of a new isoquinoline alkaloid in the mother liquors from the crystallization of the non-phenolic bases of *A. lewinii*. Its structure was established by analytical and synthetic methods. It is an oil, b.p. 140° (0.05 mm.); optically active, $[\alpha]_D^{16}$ +20.7° (methanol). It yields a characteristic 2,4,6-trinitrobenzoyl derivative, m.p. 259–260°, $[\alpha]_D^{14}$ +39.7° (methanol). The *dl*-form had been synthesized by Späth (2) as early as 1921.

7. Anhalonine, $C_{12}H_{15}O_3N$

Anhalonine was discovered by Lewin (16, 17, 10). According to Heffter (4) the drug contains about 3% anhalonine. The base crystallizes from light petroleum in needles, m.p. 85.5°, $[\alpha]_D$ −56.3° (chloroform); hydrochloride, $[\alpha]_D^{17}$ −41.9°; *N*-methylanhalonine methiodide (lophophorine methiodide), m.p. 223°. Heated to its melting point the quaternary iodide is racemized and then melts at 242–243°.

Späth and Kesztler (18) prepared optically active forms of synthetic anhalonine base, with the following properties: *l*-anhalonine, m.p. 85–86°, $[\alpha]_D^{25}$ −56.3° (chloroform); *d*-anhalonine, m.p. 84.5–85.5°, $[\alpha]_D^{25}$ +56.7°. The synthetic *l*-form, when methylated with formaldehyde and formic acid, gave an *N*-methyl derivative, $[\alpha]_D^{25}$ −47.3° (chloroform), identical with natural lophophorine; picrate, m.p. 162–163°.

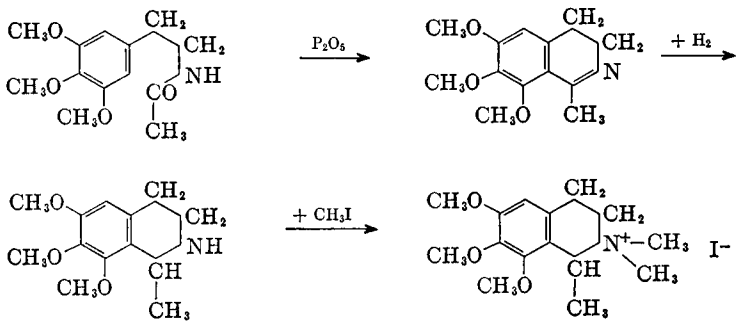
8. Lophophorine (*N*-Methyl-*l*-anhalonine), $C_{13}H_{17}O_3N$

Lophophorine was detected by Heffter (4) (yield 0.5%). It is an oily base, $[\alpha]_D$ −47° (chloroform); hydrochloride, $[\alpha]_D^{17}$ −9.47°; picrate, m.p. 162–163°; methiodide, m.p. 223°; trinitro-*m*-cresolate of the quaternary compound, m.p. 171–172°; picrate of the quaternary compound, m.p. 211–212°.

V. Structure and Synthesis of the Anhalonium Alkaloids

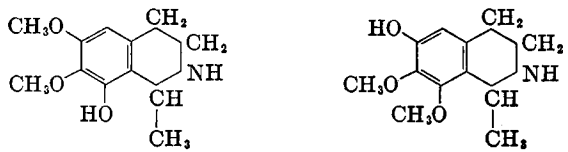
1. Anhalonidine and Pellotine

Degradation experiments disproved Späth's first assumption that the other bases in "mescal buttons," were structurally similar to the then known mescaline. Späth, therefore, gathered experimental evidence for their structure, mainly of synthetic nature, working on the hypothesis that their structures were of the isoquinolinic pattern (2). Starting from *N*-acetylmescaline the following route was followed:



The quaternary iodide obtained was shown to be identical with *O*-methylpellotine methiodide. Pellotine and anhalonidine yield, on complete methylation, the same product, and, since anhalonidine is a secondary base, pellotine must be *N*-methylanhalonidine.

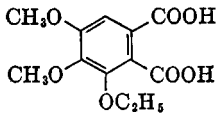
In a further study Späth (19) described the synthesis of anhalonidine and pellotine. Treatment of the *O*,*N*-diacetyl derivative of the 5-hydroxy-3,4-dimethyoxyphenethylamine with phosphorus pentoxide, and reduction of the resultant dihydroisoquinoline followed by hydrolysis of the *O*-acetyl group afforded anhalonidine. However, the position of the free hydroxyl group in anhalonidine (and pellotine) had still to be determined; two different structures were possible, since the ring closure might have taken place either in the ortho (I) or para position (II) to the hydroxy group:



I II

The correct anhalonidine structure (I) was proved by Späth and Passl

(20) as follows: Pellotine was converted into its *O*-ethyl ether, which on oxidation with permanganate yielded known 4,5-dimethoxy-3-ethoxyphthalic acid (III). This was confirmed using a different analytical method by Späth and Boschan (21), and by a new synthesis of pellotine (22).



III

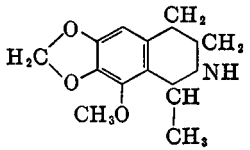
2. Anhalamine, Anhalidine, and Anhalinine

Anhalamine differs from anhalonidine by containing a —CH_2 less; Späth (2) therefore inferred that the former was a simple isoquinoline. *O*-methylanhalamine, later found to be a natural constituent of "mescal buttons" and called anhalinine (12), was obtained *in vitro* by condensing mescaline with formaldehyde. Späth and Röder (23) synthesized anhalamine by condensation of 5-benzyloxy-3,4-dimethoxyphenethylamine with formaldehyde, and further operations. The position of the free hydroxyl, however, still remained uncertain. The decision was made by Späth and Becke (24) who showed that *O*,*N*-diethylanhalamine, upon oxidation with permanganate, yielded the same 4,5-dimethoxy-3-ethoxyphthalic acid as was obtained by Späth and Passl (20) in the case of pellotine. All known phenolic tetrahydroisoquinolines which occur in the "mescal buttons" contain, therefore, the free hydroxyl in the 8-position.

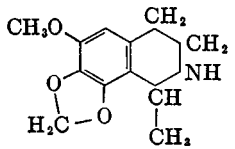
Anhalidine is *N*-methylanhalamine (13).

3. Anhalonine and Lophophorine

It was demonstrated by Späth and Gangl (25) that, contrary to the belief of Heffter, lophophorine is *N*-methylanhalonine. They showed that both alkaloids contain a methylenedioxy group, and starting from the assumption of a methylisoquinoline structure and considering a biochemical relationship with the other *Anhalonium* bases of known constitution, the structures IV and V were considered for anhalonine:



IV



V

Compound IV was then prepared by the action of methyl magnesium iodide on cotarnine iodide by Freund and Reitz's method (26). The qua-

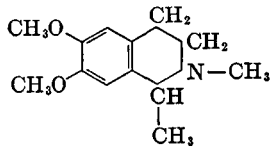
ternary iodide of this tetrahydroisoquinoline base was found to be different from lophophorine methiodide. Compound V was similarly synthesized by condensing (in the presence of phosphorus pentoxide) acetylhomomyristicylamine to a dihydroisoquinoline, which was then reduced to the tetrahydro derivative. The quaternary iodide of V proved to be identical with inactive lophophorine methiodide. Eventually, structure V for lophophorine was confirmed by Späth and Becke (12) by the isolation of isocotarnic acid (3,4-methylenedioxy-5-methoxyphthalic acid) from the oxidation products of the quaternary base corresponding to anhalonine.

Späth and Kesztler (18) achieved the synthesis of anhalonine and lophophorine. Synthetic *dl*-anhalonine (25) was resolved into its optical antipodes by fractional crystallization of the *l*-tartrate. The *l*-form obtained proved to be identical with natural anhalonidine, and lophophorine was obtained by methylation of this substance with formaldehyde and formic acid.

VI. Other Natural Simple Isoquinolines

1. Carnegine, $C_{13}H_{19}O_2N$

Heyl (27) in 1901 isolated from the Mexican cactus *Cereus pecten-aboriginum* Engelm. an alkaloid as its crystalline hydrochloride (yield, 0.65%) and termed it pectenine. The same author (28) found (1928) in the American cactus *Carnegiea gigantea* Britton and Rose a base with the composition $C_{13}H_{19}O_2N$. This alkaloid was named carnegine, and several of its crystalline derivatives were characterized. In 1929 Späth (29) established the structure of carnegine and described its synthesis. Finally, a few months later, Späth and Kuffner (30) reported that carnegine and pectenine were identical.

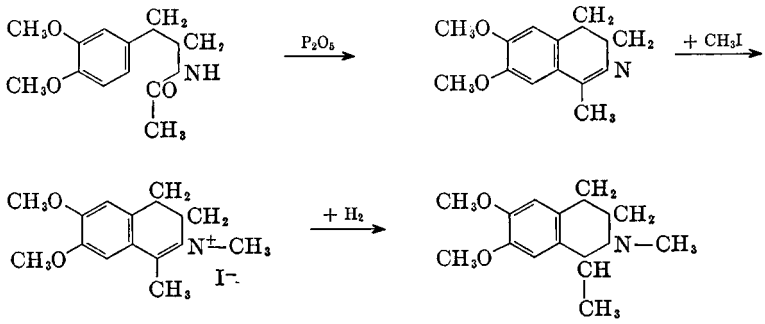


Carnegine

Carnegine is an optically inactive colorless sirup, b.p. 170° (1 mm.). The salts are crystalline: hydrochloride, m.p. 210–211°; hydrobromide, m.p. 228°; picrate, m.p. 212–213°; methiodide, m.p. 210-211°; and trinitro-*m*-cresolate, m.p. 169–170°.

Späth synthesized carnegine, without having carried out cleavage experiments, making use only of the empirical formula as well as the presence of two methoxyl groups, and being guided by the evident structural relationships with the *Anhalonium* bases. Starting from *N*-acetylhomoveratryl-

amine, the following route was followed:



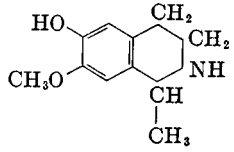
The derivatives of the synthetic oily base were identical with those of naturally occurring carnegine and pectenine. Furthermore, the possible alternate structure (the product of ring closure in *o*-position to one of the methoxy groups) was excluded by the observation that permanganate oxidation of the dihydro compound gave *m*-hemipinic and not hemipinic acid.

Schöpf and Bayerle (31) obtained "norcarnegine" under mild ("physiological") conditions (pH 5, at 25°) by condensing hydroxytyramine with acetaldehyde.

Nakada and Nishihara (51) synthesized carnegine by suspending veratrylacetoxime in toluene and treating with $POCl_3$, obtaining 1-methyl-6,7-dimethoxy-3,4-dihydro-isoquinoline. Catalytic reduction of the methyl methosulfate of this compound yielded carnegine.

2. Salsoline, $C_{11}H_{15}O_2N$ and Salsolidine, $C_{12}H_{17}O_2N$

These alkaloids are not cactus alkaloids, but their structure reveals a surprising analogy with carnegine. Actually, carnegine is *O*,*N*-dimethylsalsoline.



Salsoline

Salsoline and salsolidine (*O*-methylsalsoline) have been found by Orekhov and Proskurnina (32–35, 36, 37) in the desert plant *Salsola arbuscula* (*S. richteri*) belonging to the family Chenopodiaceae. A third alkaloid, of unknown constitution (salsamine), occurs in traces in the drug.

The plant yields by extraction with dichloroethane 0.32 % of salsoline. The alkaloid isolated from old plants is optically inactive, but, if a recent

crop is extracted, a mixture of *dl*- and *d*-salsoline results. Salsolidine occurs in the plant likewise as a mixture of the *dl*- and *l*-forms (37). The properties of these natural alkaloids are, therefore, somewhat different from those of the synthetic forms. The optically active bases are stable with respect to racemizing agents, and thus racemization must have taken place in the plant tissue itself and not in the course of extraction and isolation. According to Proskurnina and Merlis (52), *d*-salsoline is extremely resistant to racemization by alcoholic KOH.

Konovalova, Platonova and Konovalova (53), isolated salsoline and salsolidine from infusions of *Salsola arbuscula* (*S. richteri*) by adsorption on bentonite.

Natural salsoline melts at 218–221°; hydrochloride, 1.5 H_2O, m.p. 141–152°; *O*,*N*-dibenzoyl derivative, m.p. 166–168°; *N*-benzoyl derivative, m.p. 172–174°. Resolution of salsoline through its bitartrate (36) yields the pure *d*-form, m.p. 215–216°; hydrochloride, m.p. 171–172°, $[\alpha]_D$ +40.1°, and the pure *l*-form, m.p. 215–216°; hydrochloride, m.p. 171–173°, $[\alpha]_D$ −39.2°.

Natural salsolidine (*O*-methyl-*l*-salsoline) (36), m.p. 69–70°, $[\alpha]_D$ −53°; *hydrochloride, m.p. 229–231°, $[\alpha]_D$ −26.2°; picrate, m.p. 194–195°; picrolonate*, m.p. 220–221°.

Synthetic salsolidine (Späth and Dengel, 38): *dl*-base, m.p. 53–53.5°; hydrochloride, m.p. 196–197°; picrate, m.p. 201–201.5°; picrolonate 241°. Free *l*-base, m.p. 47.5–48.5° $[\alpha]_D^{16}$ −59.7° (alcohol); hydrochloride, m.p. 235–236°, $[\alpha]_D^{18}$ −24.8°. Free *d*-base, m.p. 47.5–48.5°; $[\alpha]_D^{16}$ +59.90° (alcohol); hydrochloride, m.p. 235–236°, $[\alpha]_D^{17}$ +25.3°. The optically active picrates, m.p. 193–194°; picrolonates, m.p. 235–236°.

Proskurnina and Orekhov (37) explained these differences by showing that *d*- and *l*-salsolidine occur in two forms (m.p. 41–45° and 71–73°), produced, respectively, by distillation in vacuum and crystallization from water; both forms gave identical HCl salts, m.p. 233–235°.

The third alkaloid, salsamine, is not found in all samples; base, m.p. 155–157°; picrate, m.p. 213–214°; picrolonate, m.p. 220–221°.

Methods applicable to the determination of salsoline include a colorimetric method introduced by Bezuglyĭ (54), volumetric titration with diazotized *p*-nitraniline, salsolidine not interfering, as proposed by Konovalova and Zaĭtseva (55), and electrolytic separation of the alkaloid, according to Babich (56).

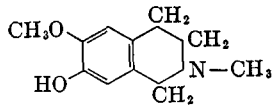
Salsoline, when methylated with diazomethane, yields *O*-methylsalsoline, the *l*-form of which is salsolidine. *O*,*N*-dimethylsalsoline is carnegine. *O*-Methylsalsoline, oxidized with permanganate, yields *m*-hemipinic acid. The position of the hydroxyl group was established by Späth, Orekhov and Kuffner (39) by synthesis, starting from isovanillin. Salsolidine was synthesized by Späth and Dengel (38).

A synthesis of salsoline, under "physiological conditions" was achieved

by Kovàcs and Fodor (57) by condensing 3-hydroxy-4-methoxy-phenethylamine with acetaldehyde, following Schöpf and Bayerle's (31) method.

3. Corypalline, $C_{11}H_{15}O_2N$

Corypalline was found by Manske (40) in *Corydalis pallida* and in the seeds of *C. aurea*. The base melts at 168°; picrate, m.p. 178°.

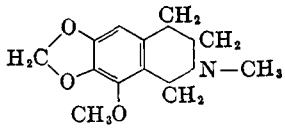


Corypalline

On methylation it yields 2-methyl-6,7-dimethoxytetrahydroisoquinoline (m.p. 82°), and upon ethylation, 2-methyl-6-methoxy-7-ethoxytetrahydroisoquinoline (m.p. 65°). The synthesis of corypalline was accomplished by a route parallel to that used by Späth, Orekhov, and Kuffner (39) in their synthesis of salsoline.

4. Hydrohydrastinine, $C_{11}H_{13}O_2N$

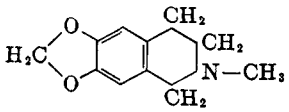
Hydrohydrastinine, m.p. 66°, is a degradation product of hydrastine or of cotarnine, but, according to Späth and Julian (41), it also occurs in *Corydalis tuberosa*.



Hydrocotarine

5. Hydrocotarnine, $C_{12}H_{15}O_3N$

Hydrocotarnine is a well-known hydrolytic product of narcotine. Hesse (42) found it in opium, both as a free base and in the form of salts; color-



Hydrohydrastinine

less plates, from light petroleum, m.p. 55.5–56.5°; hydrobromide, m.p. 236–237°, sparingly soluble in water.

Hydrohydrastinine and hydrocotarnine may be obtained from cotarnine by reduction, according to Clayson (58).

Rodionov and Chentsova (59) mention the formation of hydrocotarnine and hydrohydrastinine by reaction of cotarnine and hydrastinine with caustic alkali, either *per se* or in a crossed Cannizzaro reaction with formaldehyde.

Several derivatives of hydrocotarnine have been prepared by Semonsky (60).

The preparation of hydrastinine, hydrohydrastinine and hydrocotarnine, starting from narcotine and cotarnine has been described by Pyman and Remfry (43), Tanaka, Midzuno and Okami (44) and Topchiev (45). See Narcotine and Cotarnine under Phthalideisoquinoline Alkaloids, Vol. IV, chap. 32.

VII. Pharmacology

A chapter on the pharmacology of the cactus alkaloids has been written by Joachimoglu and Keeser (46) in Heffter's pharmacological handbook.

1. Anhalonine

Anhalonine was examined by Heffter (47); 5–10 mg., when injected in the frog, produced an increase in the reflex excitability after a phase of paresis. In the rabbit similar symptoms are observed but general hyperexcitability predominantes.

2. Anhalonidine

Doses of 20–25 mg. of the hydrochloride produced narcosis in the frog followed by increased excitability. Doses of 30–50 mg. provoked a curarizing effect. Large doses caused complete paralysis. No significant symptoms have been observed in mammals (47).

3. Pellotine

In doses of 5–10 mg. pellotine caused temporary convulsions in frogs, and the same effects were observed in dogs and cats (47). Several authors, cited by Joachimoglu and Keeser (46), believe that pellotine could be used in man as a relatively safe narcotic.

4. Lophophorine

Lophophorine is the most toxic of the bases obtained from *Anhalonium lewinii* (47); 0.25–1 mg. of injected hydrochloride provokes a long-lasting tetany in the frog. Although the animal recovers, the increased excitability may last for several days. There is no action on the isolated frog's heart. In rabbits 7 mg. of lophophorine per kilogram of body weight produced hyperexcitability and accelerated respiration; 12.5 mg. per kilogram provoke tetany; and 15–20 mg. per kilogram is the lethal dose. Intravenous

injection of 2.5 mg. caused an increase in blood pressure; larger doses, a fall. There is no effect on the heart.

5. Carnegine

Its pharmacological action is very similar to that of the isoquinoline bases obtained from *Anhalonium lewinii* (27, 48). The lethal dose in the frog is 3–4 mg.; the injection of 2–3 mg. of hydrochloride produces increased reflex excitability and convulsions; larger doses cause paresis. Carnegine provokes convulsions also in warm-blooded animals.

6. Salsoline

According to Gvishiani (49), salsoline resembles papaverine in its effects on blood circulation, and hydrastinine in its action on smooth muscles. Its use in the treatment of hypertension has been reported by Wastl (50).

Several *N*-derivatives of salsoline and salsolidine were prepared by Proskurnina and Merlis (52, 61) and found to lack the pharmacologic action of the parent substances.

Like other blood pressure reducing substances, salsoline has been found to display antihistaminic activity (62).

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