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# NECINES OF ALKALOIDS IN *HELIOTROPIUM* SPECIES FROM MEXICO AND THE U.S.A.*

JAMES L. CATALFAMO, MICHAEL W. FROHLICH, WILLIAM B. MARTIN JR† and HELENA BIRECKA‡

Department of Biological Sciences;† Department of Chemistry, Union College, Schenectady, NY 12308, U.S.A.

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**Key Word Index**—*Heliotropium*; Boraginaceae; amino alcohol; pyrrolizidine alkaloids; trachelanthamidine; lindelofidine; supinidine; retronecine; heliotridine.

**Abstract**—The qualitative and quantitative compositions of necines in plants of 20 *Heliotropium* species collected in Mexico and the U.S.A. and one species from Spain are reported. Trachelanthamidine, supinidine and retronecine were found in all species after hydrolysis of their alkaloids; lindelofidine was detected in most species, whereas heliotridine only in four. Trachelanthamidine, lindelofidine, and supinidine were dominant in four, two and one species, respectively; retronecine was dominant in 15 species, whereas heliotridine only in one. The dominant necine in *H. ternatum* was either retronecine or lindelofidine depending on the collection locality. Qualitative as well as quantitative differences depending on the collection locality were found in *H. curassavicum*. Plants from Oaxaca, Mexico, contained lindelofidine and a pyrrolizidine-diol as major necines, trachelanthamidine as minor, and traces of retronecine. Plants originating from two other localities contained trachelanthamidine (dominant), retronecine, and supinidine. The necine patterns found in the examined species differ significantly from those previously reported for 21 species mainly collected in Asia, the Middle East and Australia.

## INTRODUCTION

Information available in the literature on the occurrence of pyrrolizidine alkaloids (PA's) in the genus *Heliotropium* is summarized in Table 1 [1–32]. Most of the 21 species listed have been collected in Asia and only one, *H. arborescence*, originated from the American continent. Apparently very few of the species have been fully characterized with regard to the qualitative composition of their PA's, in particular their necines. However, as far as the data indicate, in most species heliotridine was the only or the major amino alcohol found; it was represented by heliotrine, lasiocarpine, or europine as the dominant PA. Retronecine has been reported to occur in six species, supinidine in three species and trachelanthamidine only in two species, namely in *H. curassavicum* and *H. strigosum*. Croallinecine recently identified in *H. ovalifolium* is the only triol necine ever detected in Boraginaceae.

In a preliminary study on 24 species, collected in Mexico and adjacent U.S.A. in 1978, unsaturated PA's were found in leaves of all species using TLC and Mattocks' methods for their qualitative and quantitative determinations [33]. Saturated pyrrolizidines could be detected in only nine species. In this study a re-examination of the aerial parts of 19 previously collected species at flowering and/or fruiting is presented. Additional material was examined, namely *H. polyphyllum* collected in Florida in 1980; *H. supinum* collected in Spain in 1851; samples of *H. curassavicum* and *H. spathulatum* collected in 1979, 1980 and 1981 in Mexico or the U.S.A.; and greenhouse grown *H. karwinskyi* and *H. ternatum* plants. Results obtained from *H. curassavicum* and *H. spathulatum* plants, grown in the greenhouse for preparative purposes, are also included.

## RESULTS AND DISCUSSION

The qualitative composition of the necines found in most of the 21 *Heliotropium* species (Table 2) is much more complex than that previously reported for any PA-bearing plant species [34] and, perhaps, it is even more complex than indicated. Some amino alcohols or PA's not extractable with chloroform from aqueous solutions after *N*-oxide reduction could have been lost during analysis, except for *H. indicum*, *H. curassavicum* and *H. spathulatum* plants. In these cases the chloroform extraction was followed by an extensive chloroform–ethanol extraction.

Of the 21 species 18 definitely revealed the presence of at least four and some of them five amino alcohols. The necines, obtained after hydrolysis or in a free form, were identified on the basis of their mass spectra, $R_T$ and $R_f$ values, and in some cases also on the basis of their optical rotation (underlined values in Table 2). All species contained retronecine; heliotridine was found only in four. The former was the dominant necine in 15 species, whereas the latter only in one, namely *H. glabriusculum*. Supinidine was found in all species, in most cases in relatively very

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*Part 3 in the series "Aminoalcohols of Pyrrolizidine Alkaloids in *Heliotropium* Species". For Part 2 see ref. [35].

‡To whom requests for reprints should be addressed.

Table 1. Amino alcohols of pyrrolizidine alkaloids in *Heliotropium* (literature review)

| Section | Species* | Sample origin | Developmental stage† | Organ‡ | Alkaloid content (% dry wt) | Number of alkaloids |  | Amino alcohols‖ |  |  |  | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Identified§ | Unidentified | T | S | H | R |  |
| *Heliotropium* | *acutiflorum* Kar. et Kir. | Kirgizya | fl | ae | 2.1 | 1 (h) | 1 | — | — | + | — | [1] |
| *Heliophytum* | *amplexicaule* Vahl | — | — | ae | — | 1 (i) | — | — | — | — | + | [2] |
| *Odontotropium* | *arbainense* Fresen. | Israel | — | — | — | 3 (eu) | — | — | — | + | — | [3] |
| *Heliothamnus* | *arborescens* L.<br>= *peruvianum* L. | Peru | — | — | — | 1 (1a) | 2 | — | — | + | — | [4] |
| *Radula* | *arguzioides* Kar. et Kir. | Kazachstan | fl; fr | ae | 2.0; 0.8 | 1 (h) | — | — | — | + | — | [5] |
|  |  |  |  | rt | 0.2; 0.8 |  |  |  |  |  |  |  |
|  |  | Uzbekistan | fl; fr | ae | 0.7; 0.4 | 1 (t) | — | — | — | — | + | [6] |
|  |  |  |  | rt | 0.3; 0.5 |  |  |  |  |  |  |  |
| *Halmyrophila* | *curassavicum* L. | India, Delhi | — | wh | > 0.13 | 3 (h) | 3 | — | — | + | — | [7] |
|  |  | India, Madras | fr | ae | 0.8 | 3 (cu) | — | +¶ | — | — | — | [8] |
|  |  |  |  | rt | 0.4 |  |  |  |  |  |  |  |
| *Catimas* | *dasycarpum* Ledeb. | Kazachstan | fl; fr | ae | 0.5; 0.3 | 1 (h) | 2 | — | — | + | — | [9] |
|  |  | Uzbekistan | fl | ae | 4.9 | 1 (h) | 6 | — | — | + | — | [6] |
|  |  |  |  | rt | 0.8 |  |  |  |  |  |  |  |
|  |  | Kirgizya | — | ae | 1.9 | 1 (h) | — | — | — | + | — | [10] |
| *Heliotropium* | *eichwaldii* Steud. | India | fl | wh | — | 3 (h) | — | — | — | + | — | [11] |
|  |  | Armenia | fl | — | 0.5 | 2 (1a) | — | — | — | + | — | [12] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *europaeum* L. | Australia | — | ae | 0.6–3.1 | 7 (h) | — | — | + | + | — | [13–16] |
| | | Caucasus | fl | wh | 0.8 | 2 (h) | 2 | — | — | + | — | [9] |
| *Tiaridium* | *indicum* L. | Ghana | — | ae | 0.1–0.4 | 3 (i) | — | — | — | — | + | [17, 18] |
| | | Australia | — | — | 0.4 | | | | | | | |
| | | Bangladesh | — | — | — | 6 (i) | 1 | — | + | + | + | [19] |
| *Heliotropium* | *lasiocarpum* Fisch et Mey. | Uzbekistan | fr | ae | 0.4–1.1 | 2 (h) | — | — | — | + | — | [6] |
| | = *ellipticum* Ledeb. | Uzbekistan | — | — | — | 2 (h) | — | — | — | + | — | [20, 21] |
| | | Tadzhikistan | fl; fr | ae | 0.6; 0.2 | 2 (h) | 3 | — | — | + | — | [22] |
| | | Kazachstan | fl | wh | 1.2 | 2 (h) | — | — | — | + | — | [9] |
| | | Kazachstan | fl | ae | 0.8 | 2 (h) | 4 | — | — | + | — | [9] |
| *Catimas* | *maris-mortui* Zohary | Israel | — | — | — | 2 (eu) | — | — | — | + | — | [3, 23] |
| *Heliotropium* | *olgae* Bunge | Kirgizya | fl | ae | 0.5 | 1 (h) | — | — | — | + | — | [9] |
| | | Kirgizya | — | wh | 1.2 | 3 (h) | — | — | — | + | + | [24] |
| | | Uzbekistan | fl | ae | 0.8 | 1 (h) | 3 | — | — | + | — | [25] |
| | | | | rt | 0.3 | | | | | | | |
| *Orthostachys* | *ovalifolium* Forsk | India | — | wh | 0.05 | | 2 | — | — | — | +** | [40] |
| *Catimas* | *popovii* H. Riedl | Afganistan | — | sd | 0.7–1.5 | 1 (h) | 1 | — | — | + | — | [26] |
| *Messerschmidia* | *ramosissimum* Sieb. | Saudi Arabia | — | wh | 0.6 | 1 (h) | 2 | — | — | + | — | [27] |
| | = *persicum* L. = *undulatum* Vahl | Pakistan | — | ae | — | 1 (h) | — | — | — | + | — | [28] |
| *Heliotropium* | *rotundifolium* Sieb. | Israel | — | ae | — | 1 (eu) | — | — | — | + | — | [23] |
| *Coeloma*? | *steudneri* Vatke | East Africa | — | ae | — | 1 (ly) | — | — | — | — | + | [29] |
| *Orthostachys* | *strigosum* Willd. | — | — | wh | — | 2 (st) | 3 | + | — | — | — | [30] |
| *Piptoclaina* | *supinum* L. | Australia | — | wh | — | 6 (su) | — | — | + | + | — | [31] |
| *Catimas* | *transoxanum* Bunge | Kirgizya | fl | ae | 1.7 | 1 (h) | 1 | — | — | + | — | [1] |

*In addition to the reported species, PA's were found in *H. biannulatiforme* M. Pop. (0.3%) collected in Turkmenia [32] and *H. bucharicum* B. Fedtsch. (0.3%), collected in Uzbekistan [9]. In the latter seven PA's were found, one of which, named bucharine, had a formula $C_{15}H_{27}NO_4$.

†Flowering, fl; fruiting, fr.

‡Aerial parts, ae; roots, rt; whole plant, wh; seeds, sd.

§In parentheses the dominant PA is indicated: heliotrine, h; indicine, i; europine, eu; lasiocarpine, la; trichodesmine, t; curassavine, cu; lycopsamine, ly; strigosine, st; supinine, su.

||Trachelanthamidine, T: supinidine, S; heliotridine, H; retronecine, R.

¶A free amino alcohol, MW 157, with a mass spectrum suggesting a pyrrolizidine-2,9-diol has been detected in addition to the free and ester-bound trachelanthamidine.

**A new alkaloid, heliofoline, which is a monoester of croalbinecine, has been identified in addition to free retronecine.

Table 2. Amino alcohols of alkaloids in *Heliotropium* species from Mexico and the U.S.A.

| Section and subsection | Species* | Alkaloid content (% dry wt)† | Amino alcohols‡ (% total) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $M^{+}$ 157 base peak | |
| | | | T | L | S | R | H | 82 | 83 |
| *Orthostachys* | | | | | | | | | |
| *Ebracteata* | *fallax* Johnston (2135) | 0.01 | 60 | 40 | trace | trace | — | — | — |
| | *procumbens* Mill (1538 or 1850) (g) | 0.02 | 12 | ? | 3 | 84 | — | — | — |
| | *queretaroanum* Johnston (2159) | 0.02 | + + | ? | + | + | — | — | — |
| | *torreyi* Johnston (2161) | 0.02 | 28 | 12 | 2 | 58 | — | — | — |
| *Bracteata* | *confertifolium* (Torr.) Gray (2166) | 0.05 | 1 | trace | trace | 99 | — | — | — |
| | *convolvulaceum* (Nutt.) Gray (2113) | 0.09 | 8 | 11 | trace | 74 | 7 | — | — |
| | *foliosissimum* McBride (2150) | 0.18 | 3 | 1 | trace | 96 | — | — | — |
| | *fruticosum* L. (2117) | 0.02 | 21 | 1 | 2 | 76 | — | — | — |
| | *gregii Torr.* (2168) | 0.41 | $\underline{85}$ | ? | trace | 15 | — | — | — |
| | sp. *huehuetoca* (2154) | 0.07 | 13 | 2 | 4 | 81 | — | — | — |
| | *karwinskyi* (2162) | 0.13 | 5 | trace | $\underline{65}$ | 30 | — | — | — |
| | *karwinskyi* (2162) (g) | 0.72 | $\underline{13}$ | trace | $\underline{51}$ | 30 | — | — | — |
| | *tenellum* (Nutt.) Torr. (2171a) | 0.01 | 19 | 5 | 10 | 66 | — | — | — |
| | *ternatum* Vahl (2161.2) | 0.10 | 14 | 8 | 2 | 76 | — | — | — |
| | *ternatum* Vahl (1980) | 0.95 | 16 | 52 | 3 | 29 | — | — | — |
| | *ternatum* Vahl (1980) (g) | 0.90 | $\underline{12}$ | $\underline{75}$ | trace | 13 | — | — | — |
| | *ternatum* Vahl (1980) (g) | 0.19 | 20 | 58 | trace | 22 | — | — | — |
| | *polyphyllum* Lehm. (Florida)§ | 0.43 | 1 | trace | trace | 99 | — | — | — |
| *Axillaria* | *axillare* Greenman (2156) | 0.32 | 9 | 1 | trace | 89 | 1 | — | — |
| | *pringlei* Robins (2147) | 0.02 | 18 | 2 | 3 | 77 | — | — | — |
| *Coeloma* | *glabriusculum* Gray (2170.5) | 0.11 | 13 | — | 26 | 1 | 60 | — | — |
| *Piptoclaina* | *supinum* L. (Spain)‖ | 0.49 | 5 | trace | 3 | 65 | 27 | — | — |
| *Tiaridium* | *indicum* L. (2112) | 0.18 | 3 | trace | 1 | 95 | — | — | 1 |
| *Halmyrophila* | *curassavicum* L. (2138) | 0.23 | 9 | $\underline{49}$ | — | trace | — | 42 | — |
| | *curassavicum* L. (2303)¶ | 0.41 | $\underline{87}$ | ? | 2 | 10 | — | — | — |
| | *curassavicum* L. (1502) (g) | | | | | | | | |
| | aerial parts | 2.43 | $\underline{61}$ | ? | 7 | 32 | — | — | — |
| | roots | 3.21 | $\underline{70}$ | ? | 8 | 22 | — | — | — |
| | *spathulatum* Rydb. (2202)** | | | | | | | | |
| | aerial parts | 0.13 | 10 | trace | 5 | 85 | — | — | — |
| | roots | 0.67 | 13 | trace | 4 | 83 | — | — | — |
| | *spathulatum* Rydb. (2255)†† | | | | | | | | |
| | aerial parts | 0.08 | 12 | trace | 6 | 82 | — | — | — |
| | roots | 5.58 | $\underline{11}$ | trace | 8 | 81 | — | — | — |
| | *spathulatum* Rydb. (2175) (g) | | | | | | | | |
| | aerial parts | 1.84 | $\underline{32}$ | trace | 15 | 53 | — | — | — |
| | roots | 4.89 | $\underline{15}$ | trace | 12 | 73 | — | — | — |

*College Herbarium; g, greenhouse grown plants harvested at flowering and/or fruiting.

†Calculated as monocrotaline, MW 325.

‡Trachelanthamidine, T; lindelofidine, L; supinidine, S; retronecine, R; heliotridine, H; lines under the values indicate that the optical rotation of the necine was determined.

§Plants at flowering, collected by Darren Saunders in December 1980 (collection No. 3).

‖Plant material (aerial parts) removed from a specimen (Union College Herbarium) collected by E. Bourgeau in October 1851 between Murcia and Alkezar, Spain.

¶Collected at flowering and fruiting in Tamalipas, Mexico, in August 1981.

**Plants at the vegetative stage, collected in Guyamas, Sonora, Mexico, in December 1979.

††Dormant plants collected in Laguna Hills, California, in December 1980.

small amounts, except for the field collected and greenhouse grown *H. karwinskyi* plants in which it was the dominant necine and identified as (−)-supinidine.

Lindelofidine as a dominant amino alcohol was found in the field collected (Yucatan), as well as greenhouse grown, *H. ternatum* (1980). It was also found in plants of the same species collected at a different location (San Luis Potosi); however, in these plants retronecine was the dominant amino alcohol. As a major necine lindelofidine was also found in *H. curassavicum* (2138) plants collected in Oaxaca, Mexico. However, it could not be detected in any other *H. curassavicum* plants either collected in Tamalipas or in greenhouse grown plants originating from seeds collected in Baja California Sur. The same is true for *H. gregii*, *H. queretaroanum* and *H. procumbens*. However, if lindelofidine occurred in amounts below 1% of trachelanthamidine, it could not be clearly separated from the latter either by GC/MS or TLC. In the case of *H. procumbens* the limiting factor was the amount of available plant material. However, none of the mentioned obstacles occurred in the case of *H. glabriusculum* in which lindelofidine was not detected. In the remaining species the necine has been found in relatively small amounts with the exception of *H. fallax*.

As the mass spectrum and $R_T$ value of lindelofidine are identical with, and its $R_f$ value not very different from, those of (−)-isoretronecanol, there is no absolute certainty that the amino alcohol, described here as lindelofidine and occurring in relatively small amounts, was not in fact, isoretronecanol. However, the latter has not been reported to occur in any genus of Boraginaceae, Compositae, or Leguminosae.

All analysed species showed the presence of trachelanthamidine. The optical rotation measurements taken for the necine, isolated from *H. curassavicum*, *H. spathulatum*, *H. ternatum*, *H. karwinskyi* and *H. gregii*, indicated in all cases (−)-trachelanthamidine. However, in other species the occurrence of (+)-trachelanthamidine (laburnine) is not excluded. Trachelanthamidine was the dominant necine in four species and the major or minor necine in the remaining species. In a free form trachelanthamidine, as well as retronecine, were found in PA extracts of *H. curassavicum* and *H. spathulatum* plants prior to hydrolysis.

Three species here examined have been tested previously, namely *H. supinum*, from Australia, *H. indicum* from Ghana, Australia and Bangladesh, and *H. curassavicum* from India. None of the species showed the same qualitative composition of their necines as previously reported. The major necine in *H. supinum* from Spain was retronecine not reported to be even present in plants from Australia. Neither was trachelanthamidine or lindelofidine found in the latter. Plants of *H. indicum*, whether collected in their natural habitat or grown in the greenhouse [35], contained retronecine as the dominant necine and small amounts of trachelanthamidine, lindelofidine and supinidine; the first two minor necines have not been previously reported to occur in this species. In the field collected plants an additional base (in a free form) was detected in the chloroform–ethanol extract. GC/MS showed $M^+$ 157 and base peak 83. The mass spectrum of the base suggests a pyrrolizidine-diol, but not a pyrrolizidine-7,9-diol. The spectrum is not identical with that reported for a free base isolated from *H. curassavicum* and supposedly representing a pyrrolizidine-2,9-diol. [8]. It also differs from the mass spectrum of macronecine [36]. The base could not be detected in greenhouse grown *H. indicum* plants of the same origin.

The populations of *H. curassavicum* examined here add to the complexity of the necine qualitative composition reported previously for this species. The greenhouse grown plants, originating from Baja California Sur, and those collected in Tamalipas showed an identical composition with trachelanthamidine as the dominant amino alcohol in both cases. However, plants collected in Oaxaca revealed a quite different necine pattern; trachelanthamidine was a minor necine, retronecine was found in traces only, and supinidine was not detected at all. Instead, the plants contained two major necines; one was identified as lindelofidine and the other, extracted together with retronecine after PA hydrolysis, showed $R_f$ 0.11 (TLC), $M^+$ 157; and base peak 82. Its mass spectrum suggests a pyrrolizidine-7, 9-diol [36–38].

Results presented previously [35] showed no differences in the qualitative pattern of necines either depending on the organ or developmental stage of the plants when grown in the greenhouse. Neither were any qualitative differences found between greenhouse grown and field collected plants of *H. ternatum*, *H. karwinskyi* and *H. spathulatum*. In all these species only quantitative differences were observed, namely a higher share of unsaturated bases in the field collected plants as compared with those in the greenhouse. The qualitative and quantitative patterns of field collected and greenhouse grown plants of *H. indicum* are also similar, except for the puzzling minor base with $M^+$ 157 (the field collected plants showed signs of significant injury apparently caused by insects). Thus, the observed significant qualitative differences in the necine composition between populations of the same species but different localities may be treated as real. Perhaps, the most striking example is *H. curassavicum*. Obviously, even in this case there is always a possibility that trace amounts of a necine could remain undetected.

At the same time the necine qualitative patterns in the 21 species examined belonging to six different *Heliotropium* sections are very similar although not identical. The possibility of detecting monoalcohols even in traces in the presence of high amounts of diols was facilitated in this study by their fractional extraction after PA hydrolysis. It is quite probable that the species presented in Table 1 had, in fact, a much more complex necine pattern than detected.

In *H. spathulatum* plants, (−)-trachelanthamidine seems to be the first synthesized necine [39]. One wonders whether this may be the case also in other *Heliotropium* species and what may be the status of lindelofidine in this respect or in the interconversion pattern(s) of the necines.

## EXPERIMENTAL

*Plant material.* (A) *Field collected plants.* Most of the analysed aerial parts of plants, at the stage of flowering and/or fruiting, were collected in Mexico and adjacent U.S.A. in the summer of 1978. The description of the species and their habitats has been previously reported [33]. In addition, *H. supinum* L., *H. polyphyllum* Lehm., *H. curassavicum* L. and *H. spathulatum* Rydb. collected in various localities were also analysed. (B) *Greenhouse grown plants.* The following species were grown during summer 1980: *H. ternatum* Vahl (1980) from seeds collected in Yucatan; *H. spathulatum* Rydb. (2175) from roots collected in California; and *H. curassavicum* L. (1502) from roots of plants grown from seeds that were collected in Baja California Sur. The plants were sampled at the stage of flowering and/or fruiting.

*Analyses.* Extraction of PA's, *N*-oxide reduction, purification, hydrolysis, and necine extraction were as previously described [34]. Conditions of TLC and GC/MS were also similar. When determined using the polarimeter Auto Pol II, $[\alpha]_D^{20}$ of lindelofidine was +77° (EtOH; *c* 0.75); the optical rotations of trachelanthamidine and supinidine were similar to those previously reported [34].

MS of heliotridine ($R_T$ 10.1 min): $M^+$ 155(20), 111(52), 94(20), 93(10), 80(100), 68(19), 67(12), 55(8), 53(26): MS of the base from the field collected *H. indicum* plants ($R_T$ 5.9 min): $M^+$ 157(20), 140(9), 126(8), 104(18), 98(8), 83(100), 70(13), 55(53). MS of the base from *H. curassavicum* (2138) plants ($R_T$ 9.2 min): $M^+$ 157(14), 113(15), 82(100), 80(7), 68(6), 67(3), 55(12), 53(5). The MS of trachelanthamidine, lindelofidine, supinidine, and retronecine were identical with those previously reported [35].

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