Thalictrum Alkaloids. VIII.[1-3] The Isolation, Structural Elucidation, and Synthesis of Dehydrothalicarpine

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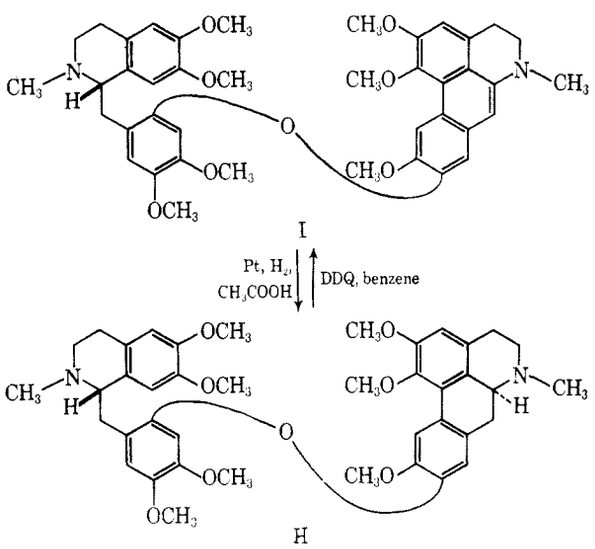
Evidence is presented for assignment of structure and configuration I to dehydrothalicarpine, a new dehydroaporphine alkaloid isolated from the roots of *Thalictrum dasycarpum* Fisch. and Lall. Elementary analysis of the alkaloid and its dimethiodide and spectral data supported a $C_{41}H_{46}N_2O_8$ molecular formula. Sodium–liquid ammonia cleavage yielded 6′-hydroxylaudanosine (III) and 2,10-dimethoxydehydroaporphine (IV). The 2,10-dimethoxydibenzo[*de*,*g*]quinolin-7-one (VII) and 1,2,10-trimethoxydibenzo[*de*,*g*]quinolin-7-one (VIII) structures were proposed for two minor products isolated from the sodium–liquid ammonia reaction mixture. Catalytic hydrogenation of dehydrothalicarpine (I) gave thalicarpine (II). A formal total synthesis was achieved by a route which involved oxidation of thalicarpine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to dehydrothalicarpine.

The genus *Thalictrum* has served as a uniquely profuse source of new and novel benzylisoquinoline and aporphine alkaloids. Thus, *Thalictrum* species have yielded, *inter alia*, the first benzylisoquinoline alkaloid with a C-5 oxygenated substituent,[4] the first dimeric benzylisoquinoline–aporphine alkaloid,[1b,c,5] the first bisbenzylisoquinoline with a C-5 oxygenated substituent,[6] and the first bisbenzylisoquinoline with a diphenyl ether terminus at C-5, which was also the first unsymmetrical bisbenzylisoquinoline recognized to contain a twenty-membered ring.[1a] We report herewith the isolation, structural elucidation, and synthesis of dehydrothalicarpine (I), the first naturally occurring dehydroaporphine alkaloid.[2,7]

In an earlier communication,[5] we reported the extraction of an alkaloid mixture from the roots of *Thalictrum dasycarpum* Fisch. and Lall from Wisconsin. Furthermore, the fractionation of the nonquaternary nonphenolic alkaloid fraction by chromatography on Florisil was described in detail, as was the procedure for isolation of thalicarpine (II) from the appropriate chromatographic fraction. The present report describes the isolation of thalidasine,[1a] argemonine, and dehydrothalicarpine (I) (mp 186–187°, $[\alpha]^{29}D$ +55°) from other chromatographic fractions of the nonquaternary nonphenolic alkaloid fraction.

The molecular formula $C_{41}H_{46}N_2O_8$ was assigned for dehydrothalicarpine on the basis of elemental analysis



of the alkaloid and its dimethiodide derivative. Analysis showed the presence of seven O-methyl groups. The nmr spectrum showed signals for six N-methyl protons, twenty-one O-methyl protons, eleven aliphatic protons, and eight aromatic protons. The signal for one N-methyl group appeared at an unusually low field (τ 7.01). The ultraviolet absorption spectrum showed maxima at 265 mμ (ϵ 49,940) and 331 mμ (ϵ 13,400), indicative of a more highly conjugated chromophore than that of thalicarpine. The latter structural feature was indicated also by the more intense absorption at 6.20 μ in the infrared spectrum of dehydrothalicarpine.

The most useful reaction in structural studies of dimeric alkaloids which possess diphenyl ether moieties has been cleavage by the action of metallic sodium in liquid ammonia.[8] Sodium–liquid ammonia cleavage of dehydrothalicarpine yielded a complex mixture of products. However, by a combination of thick layer and column chromatographic procedures, a phenolic base (III) and three nonphenolic bases (IV, VII and VIII) were isolated from the reaction mixture.[9]

The phenolic cleavage product was readily characterized as 6′-hydroxylaudanosine (III) by direct comparison of its hydroiodide salt with a sample obtained

(1) (a) Part VII: S. M. Kupchan, T.-H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Amer. Chem. Soc.*, **89**, 3075 (1967). (b) Part VI: M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Chem. Pharm. Bull.* (Tokyo), **15**, 959 (1967). (c) Part V: M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Tetrahedron Letters*, 4309 (1965).

(2) This work was presented, in part, at the Symposium on Selected Recent Advances in Natural Products Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April, 1965, Abstracts, p 31P. The name dehydrothalicarpine is adopted for the alkaloid earlier called thalictrucarpine.

(3) This investigation was supported by Public Health Service Research Grant HE-02952 from the National Heart Institute. T.-H. Yang thanks the National Council on Science Development, Republic of China, for partial financial support.

(4) (a) E. Fujita and T. Tomimatsu, *J. Pharm. Soc. Japan*, **79**, 1082 (1959); (b) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

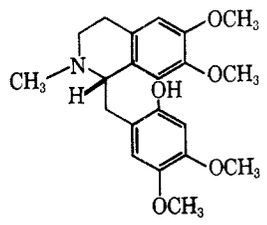
(5) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci*, **52**, 985 (1963).

(6) (a) J. Padilla and J. Herran, *Tetrahedron*, **18**, 527 (1962); (b) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *Chem. Commun.*, 7, (1966).

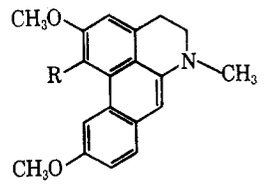
(7) H. B. Dutschewska and N. M. Mollov [*Chem. Ind.* (London), 770 (1966)] have reported their independent isolation and structural elucidation of dehydrothalicarpine from *Thalictrum minus ssp. elatum*. Direct comparison with our alkaloid of a sample of dehydrothalicarpine kindly provided by Dr. Mollov demonstrated the identity of the respective materials.

(8) M. Tomita, *Progr. Chem. Org. Nat. Prod.*, **9**, 175 (1952).

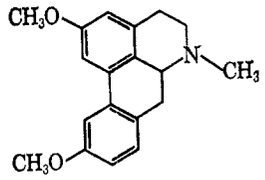
(9) It is noteworthy that no *d*-2,10-dimethoxyaporphine was detectable among the products obtained by sodium–liquid ammonia cleavage of dehydrothalicarpine, in contrast to the results reported in ref 7. The difference may be attributable to a difference in experimental procedures.



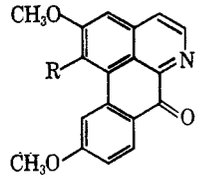
III



IV, R = H
V, R = OCH_3



VI



VII, R = H
VIII, R = OCH_3

earlier by sodium–liquid ammonia cleavage of thalicarpine.[1b,c,10]

The major nonphenolic base IV was characterized as 2,10-dimethoxydehydroaporphine on the basis of elemental analysis and characteristic and intense ultraviolet absorption.[11] The structural assignment was confirmed by catalytic reduction of IV to *dl*-2,10-dimethoxyaporphine, characterized by spectral and chromatographic comparison with a sample of *d*-2,10-dimethoxyaporphine (VI) obtained from thalicarpine.[1b,c,10]

The second nonphenolic base VII was assigned the empirical formula $C_{18}H_{13}NO_3$ on the basis of elemental analysis, and the low hydrogen content indicated a highly unsaturated structure. The infrared spectrum showed a band at 6.02 μ, indicative of the presence of a conjugated ketone. The ultraviolet spectrum resembled those of liriodenine[12] and related dibenzo[*de*,*g*]quinolin-7-one derivatives.[13a] The nmr spectrum showed the presence of two methoxy groups and seven aromatic protons and the absence of N-methyl and aliphatic protons, and hence strongly supported structure VII. Similarly, the 1,2,10-trimethoxydibenzo[*de*,*g*]quinolin-7-one structure (VIII) was suggested for the third nonphenolic (red) base on the basis of elemental analysis and infrared, ultraviolet, and nmr spectral characteristics. In view of the ease of oxidation of aporphines to liriodenine-type derivatives,[13] it appears likely that compounds VII and VIII were formed during the work-up of the sodium–liquid ammonia cleavage reaction, by oxidation of the presumed dehydroaporphine precursors, IV and V.

The foregoing evidence led to the postulation that the alkaloid should be formulated as a dehydrothalicarpine. This postulation was confirmed by catalytic reduction of dehydrothalicarpine to yield thalicarpine. Assignment of the double bond to the 6a,7 position of the aporphine moiety was made on the basis of the intensity of the ultraviolet absorption and the characteristic downfield shifts observed in the nmr spectrum for the C-11 proton and N-methyl signals of the dehydroaporphine system. The signal for the C-11 proton in dehydrothalicarpine occurs at τ 0.75. It has been noted earlier that exceptionally low τ values are found for protons in the 11 position of aporphines if position 1 is substituted by a methoxyl group.[14] The lowfield shift was attributed to deshielding by the neighboring ring as well as anisotropy effects of the C–O single bond, as the hydrogen is held very close to the opposite oxygen atom. The deshielding has been shown to be increased in 6a,7-dehydroaporphines, with resultant shifts of the C-11 proton resonance to still lower fields.[15] The downfield shift of the signal for an N-methyl group adjacent to the 6a,7 double bond of a dehydroaporphine has been noted earlier.[16]

Oxidation of thalicarpine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and separation of the reaction mixture by partition chromatography[17] gave dehydrothalicarpine (47% yield). In view of the earlier synthesis of thalicarpine by condensation of L-6′-bromolaudanosine and L-N-methyllaurotetanine,[1b,c] the combined achievements constitute a direct formal total synthesis of dehydrothalicarpine.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Values of $[\alpha]D$ have been approximated to the nearest degree. Ultraviolet spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Beckman Models IR-5A and -9 recording spectrophotometers. Nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Paper chromatography was conducted by the descending technique on Whatman No. 4 paper. The paper was prewetted with McIlvain buffer of pH 5.4, and alkaloids were detected by spraying with a chloroform solution of bromophenol blue. The mobile phase consisted of petroleum ether (bp 65–68°)–butyl acetate–*n*-butyl alcohol (60:40:17 by volume).

Isolation of Dehydrothalicarpine (I).—The chromatographic separation on Florisil of the nonquaternary nonphenolic alkaloid fraction from *T. dasycarpum* roots has been described earlier.[5] The fractions eluted by 30 and 60% chloroform–benzene yielded thalicarpine. The fractions eluted with chloroform, 20% acetone–chloroform, and the initial fractions eluted with acetone were found to contain the same three principal components (R_f 0.20, 0.54, and 0.88, upon paper chromatography), and were combined. This alkaloid mixture (37 g) was rechromatographed on Florisil (1 kg) and eluted successively with benzene, 10 and 50% chloroform–benzene, chloroform, acetone, and finally, methanol. The fractions eluted with chloroform, enriched in the component of R_f 0.54, were combined in ethanol and treated with oxalic acid to yield, after recrystallization from ethanol, thalidasine oxalate[1a] (0.800 g), mp 160–162° and $[\alpha]^{26}D$ −53° (*c* 0.55, methanol).

Anal. Calcd for $C_{39}H_{44}N_2O_7 \cdot C_2H_2O_4 \cdot 2.5\ H_2O$: C, 62.50; H, 6.53; N, 3.56. Found: C, 62.46; H, 6.21; N, 3.19.

The mother liquor alkaloids after separation of thalicarpine and thalidasine oxalate were pooled with the remaining alkaloid fractions from both chromatographic separations on Florisil. The alkaloid mixture (25 g, shown by paper chromatography to contain two major components, of R_f 0.20 and 0.88) was chromatographed on alumina (400 g, Woelm "neutral" alumina, deactivated by intimate admixture with 12.5 ml of 10% acetic acid solution). The column was developed by successive elution

(10) S. M. Kupchan and N. Yokoyama, *J. Amer. Chem. Soc.*, **86**, 2177 (1964).

(11) *Cf.*, *e.g.*, M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

(12) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, **25**, 1389 (1960).

(13) (a) M. Tomita, T.-H. Yang, H. Furukawa, and H.-M. Yang, *J. Pharm. Soc. Japan*, **82**, 1574 (1962); (b) T.-H. Yang, *ibid.*, **82**, 798 (1962).

(14) W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 4778 (1964).

(15) N. M. Mollov and H. B. Dutschewska, *Compt. Rend. Acad. Bulgare Sci.*, **19**, 495 (1966).

(16) N. M. Mollov and H. B. Dutschewska, *Tetrahedron Lett.*, 853 (1966).

(17) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatog.*, **9**, 71 (1962).

with methylene chloride, 5, 10, 20, 30, and 40% chloroform–methylene chloride, and 50% methanol–chloroform. The first methylene chloride eluate (1.5 l.) was evaporated to dryness and the oily residue (15 g) was treated with warm acetone and filtered to remove insoluble fatty substances. The acetone-soluble alkaloids (13 g) were rechromatographed on deactivated alumina (400 g) with methylene chloride. The third, fourth, and fifth 500-ml eluates showed similar paper chromatographic patterns and were combined and evaporated to dryness. The alkaloidal residue (7.5 g) was crystallized from acetone and recrystallized several times from ethyl acetate to yield dehydrothalicarpine (1.02 g), mp 182–183°. Recrystallization from methanol gave crystals with mp 186–187°; $[\alpha]^{29}D$ +55° (*c* 0.44, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3.55, 3.62, 6.20, 6.83, 8.00, 8.90 μ; λ_{max}^{EtOH} 265 mμ (ε 49,940), 331 (13,400); nmr signals at τ 7.58, 7.01 (6 H, two NCH_3), 6.74, 6.44, 6.22, 6.05, 5.99, 5.92 (21 H, seven OCH_3), and 3.77, 3.63, 3.48, 3.31, 3.18, 3.01, and 0.75 (8 H, aromatic *H*).

Anal. Calcd for $C_{41}H_{46}N_2O_8$: C, 70.87; H, 6.67; N, 4.03; 7(OCH_3), 31.27. Found: C, 70.59; H, 6.65; N, 4.11; OCH_3, 31.47.

The **dimethiodide** was prepared by refluxing a solution of dehydrothalicarpine (0.056 g) in methanol (1.5 ml) and methyl iodide (1.5 ml) for 6 hr. Evaporation of the solvents and crystallization of the residue from methanol gave dehydrothalicarpine dimethiodide (67 mg), mp 167–171°.

Anal. Calcd for $C_{41}H_{46}N_2O_8 \cdot 2CH_3I \cdot H_2O$: C, 51.81; H, 5.46; N, 2.81; I, 25.47. Found: C, 51.75; H, 5.36; N, 2.82; I, 25.66.

The chloroform–methylene chloride and chloroform–methanol eluates were combined and evaporated to dryness. The residue was rechromatographed on alumina (G., E. Merck, 40 g)–Celite (10 g) with 50% ethyl acetate–petroleum ether. The first and second 125-ml eluates were combined and evaporated to dryness, and the semisolid residue (6.74 g) was crystallized from ethyl acetate to yield thalicarpine (1.08 g). Fractional crystallization of the mother liquor alkaloids from ethyl acetate–ether gave colorless crystals (0.37 g), mp 156–157° and $[\alpha]^{26}D$ −200° (*c* 0.98, MeOH). The resemblance of the physical and spectroscopic properties of the alkaloid to those reported for argemonine[18] led to direct comparison and demonstration of identity (by mixture melting point determination, mixed tlpc and infrared and nmr spectral studies) with an authentic sample of argemonine.

Sodium–Liquid Ammonia Cleavage of Dehydrothalicarpine (I).—A three-necked, 1-l. flask equipped with a mechanical stirrer, a dropping funnel with a nitrogen gas inlet, and a nitrogen gas outlet on a dewar-type condenser was placed in an acetone–Dry Ice bath (bath temperature, −76°). Metallic sodium (1.7 g) was added in small portions with vigorous stirring until the blue color persisted for more than 15 min. Dehydrothalicarpine (0.96 g) was dissolved in 25 ml of dried toluene and placed in the dropping funnel. The reaction was carried out, under a nitrogen atmosphere, by adding small portions of the toluene solution and metallic sodium to the reaction vessel alternately so that the blue color of the reaction mixture was maintained. The reaction was stopped 30 min after all the toluene solution had been added to the mixture; the mixture maintained its blue color. About 0.9 g of metallic sodium had been consumed in the reaction. The reaction mixture was allowed to stand overnight in a hood to evaporate the ammonia. The residual toluene solution was washed with water (50 ml) and transferred with ether to a separatory funnel. The aqueous layer was extracted successively with ether (850 ml) until the extract gave a negative test to Dragendorff's reagent. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness, to yield 830 mg of light brown oil (fraction A). The alkaline aqueous extract was treated with ammonium chloride (20 g) and extracted with chloroform (200 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness, to leave 62 mg of residue (fraction B).

Fraction A (830 mg) was subjected to thick layer chromatography on silica gel $HF_{254+366}$ (14 plates, 20 × 20 cm, 1-mm thick) with 10% methanol–chloroform. The band of highest mobility gave (upon elution with 25% methanol–chloroform) a green residue (493 mg). This material was subjected to thick layer chromatography on alumina G (five plates, 20 × 20 cm, 0.5 mm thick) with 1% methanol–chloroform, to yield fractions C (higher R_f, green 180 mg) and D (lower R_f, yellow, 44 mg). The band of second-highest mobility in the silica gel $HF_{254+366}$ separation gave fraction E (red, 19 mg) and the band of third highest mobility gave fraction F (168 mg).

2,10-Dimethoxydehydroaporphine (IV).—Fraction C (180 mg) was chromatographed on Woelm neutral alumina (10 g) in chloroform. The first chloroform eluate (200 ml) yielded a green residue (90 mg). This was dissolved in a small volume of ethanol–ether and treated with 10% hydrogen chloride in methanol to complete precipitation. The precipitate (65 mg) was collected, washed with ether, and recrystallized from ethanol–1-propanol to yield 2,10-dimethoxydehydroaporphine hydrochloride as microneedles, mp 127–131°.

Anal. Calcd for $C_{19}H_{19}NO_2 \cdot HCl \cdot {}^1/_3C_3H_7OH$: C, 68.41; H, 6.72. Found: C, 68.69; H, 6.87.

The free base, liberated from the hydrochloride salt by treatment with ammonium hydroxide, resisted attempts at crystallization: λ_{max}^{MeOH} 245 mμ (ε 40,640), 259 (sh), (34,640), 293 (15,140), 324 (6360), 386 (1430). Upon addition of acid, the maxima shifted to 240, 253, 261, 285, 303, and 314 mμ.

Further elution of the alumina column with chloroform yielded a yellow residue (13 mg, fraction G), which showed a tlc pattern resembling that of fraction D.

In a subsequent experiment, direct chromatography of fraction A (800 mg) on Woelm neutral alumina (200 g) in chloroform gave a first eluate (275 mg) which was converted directly into IV hydrochloride (161 mg), mp 127–131°.

Catalytic Reduction of 2,10-Dimethoxydehydroaporphine (IV). *dl*-2,10-Dimethoxyaporphine (VI).—A suspension of platinum oxide (21 mg) in glacial acetic acid (3 ml) was saturated with hydrogen and 2,10-dimethoxydehydroaporphine hydrochloride (21.3 mg) in acetic acid (1 ml) was added. The mixture was subjected to catalytic hydrogenation at 26° and atmospheric pressure. The reaction was stopped after 17 hr (hydrogen consumption, 1.44 ml) and the mixture was filtered. The catalyst was washed with a small amount of water. The filtrate was combined with the washing and evaporated to dryness under reduced pressure to yield a yellowish oil. The reaction product was dissolved in dilute hydrochloric acid solution and washed with ether. The acidic layer was made alkaline with 2% sodium hydroxide and extracted with ether. The ethereal extract was dried over anhydrous sodium carbonate and evaporated to dryness, to leave a yellowish oil (12.8 mg). The oily residue was dissolved in a small amount of dilute hydrochloric acid and filtered. Potassium iodide (100 mg) was added with stirring to the acidic solution to complete precipitation. The precipitate was collected, washed with a small amount of water and dried in a vacuum desiccator. The dried precipitate was crystallized from methanol to yield plates (8.7 mg, hydroiodide salt), mp 226–228° dec and $[\alpha]^{27}D$ ±0° (*c* 0.06, methanol).

Anal. Calcd for $C_{19}H_{21}NO_2 \cdot HI$: C, 53.91; H, 5.24. Found: C, 54.06; H, 5.06.

The ultraviolet absorption spectrum of the sample was identical with that of the hydroiodide of authentic *d*-2,10-dimethoxyaporphine obtained from sodium–liquid ammonia cleavage product of thalicarpine.[10] Liberation of the free base was effected by treatment of the hydroiodide salt in water with ammonium hydroxide and extraction with ether. Evaporation of the ether solution left a slightly yellowish residue. The infrared spectrum in chloroform and the mobility upon thin layer chromatography were identical with those of the authentic *d*-2,10-dimethoxyaporphine.

2,10-Dimethoxydibenzo[*de*,*g*]quinolin-7-one (VII).—Fractions D and G were combined (57 mg) and chromatographed on Woelm neutral alumina (5 g) in chloroform. Elution with chloroform (100 ml) gave a yellow residue (25 mg) which was crystallized first from chloroform–ether, and, then from acetone, to give yellow needles (VII, 13 mg): mp 218–220°; λ_{max}^{MeOH} 236 mμ (ε 25,470), 266 (24,500), 273 (sh) (22,330), 284 (18,830), 312 (6500), 345 (10,330) and 376 (9000); λ_{max}^{Nujol} 6.02 μ (conjugated ketone); nmr signals at τ 6.04 (6 H, two OCH_3) and 1.55–3.12 (7 H, aromatic *H*).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50. Found: C, 74.07; H, 4.65.

In a subsequent qualitative experiment, tlc analysis indicated that oxidation of crude 2,10-dimethoxydehydroaporphine (IV) with activated manganese dioxide in chloroform solution yielded a two mixture enriched in VII.

(18) M. J. Martell, Jr., T. O. Soine, and L. B. Kier, *J. Amer. Chem. Soc.*, **85**, 1022 (1963), and earlier papers in the series. We thank Professor T. O. Soine cordially for an authentic sample of argemonine.

1,2,10-Trimethoxydibenzo[*de,g*]quinolin-7-one (VIII).—Fraction E (19 mg) was subjected to thick layer chromatography on silica gel H_{254} (one plate, 20 × 20 cm, 0.5 mm thick) with 10% ethanol–chloroform. The principal band was transferred to a column and washed with chloroform. The chloroform eluate yielded a red solid residue (11 mg) which was recrystallized from acetone–ethanol to yield red microneedles (VIII, 5 mg): mp 256–258°; λ_{max}^{MeOH} 234 mμ (ε 33,330), 246.5 (41,050), 322 (7420), 470 (5830); λ_{max}^{KBr} 5.99 μ (conjugated ketone); nmr signals at τ 6.27 (3 H, OCH_3), 5.97 (6 H, two OCH_3), 1.75–2.82 (6 H, aromatic *H*).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71. Found: C, 70.95; H, 4.76.

6′-Hydroxylaudanosine (III).—Fraction F (312 mg) was dissolved in 10% acetic acid (5 ml) and the solution was filtered. The filtrate was treated with aqueous potassium iodide to complete precipitation. The precipitate was collected, washed with water, and recrystallized from ethanol to yield needles (118 mg), mp 184–186°. The melting point was not depressed by admixture with an authentic sample of 6′-hydroxylaudanosine hydroiodide, and the ultraviolet and infrared (Nujol) spectra and tlc mobility were identical with those of the authentic sample.[10]

Fraction B, shown by tlc to contain III as a major component, yielded 25 mg of III hydriodide.

Catalytic Reduction of Dehydrothalicarpine (I).—A suspension of platinum oxide (50 mg) in glacial acetic acid (15 ml) was saturated with hydrogen, and dehydrothalicarpine (50 mg) in acetic acid (2 ml) was added. The mixture was subjected to catalytic hydrogenation at 26° and atmospheric pressure. The reaction was terminated after 18 hr (hydrogen consumption, 10.0 ml) and the mixture was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in 2.5% hydrochloric acid (10 ml). The solution was made alkaline with dilute ammonium hydroxide and extracted with chloroform. The chloroform was dried over anhydrous sodium sulfate and evaporated to dryness (residue, 41 mg). The residue was dissolved in the upper phase of the system Skellysolve B–ethylene chloride–methanol–water (10:2:2:0.16) and chromatographed on a column of Celite 545 impregnated with chlorophenol red and lower phase of the solvent system.[17] The fractions containing thalicarpine (tlc) were combined and crystallized from ether to yield thalicarpine (II, 17 mg), mp 156–158°, $[\alpha]^{29}D$ +133° (*c* 0.31, methanol). The melting point was not depressed by admixture with an authentic sample of thalicarpine, and the infrared spectrum and mixed tlc were identical with those of the authentic sample.

Oxidation of Thalicarpine (II) with DDQ.—To a stirred solution of thalicarpine (II, 1.00 g) in benzene (65 ml) was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (320 mg) in benzene (10 ml), and the solution was heated in an oil bath at 62° for 5 hr. A black powdery solid (855 mg) was separated by filtration, and the benzene solution was extracted with 2.5% hydrochloric acid. The solution was made alkaline with 10% ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure to dryness (residue, 502 mg). The residue was subjected to partition chromatography as described for thalicarpine above, and two bands were separated. The first band eluted corresponded to dehydrothalicarpine (364 mg) and the second to thalicarpine (26 mg). Crystallization of the first band from acetone yielded dehydrothalicarpine (338 mg), mp 180–183°, characterized by mixture melting point determination, mixed tlc, and ir, uv, and nmr spectral comparison with the authentic sample. The black solid (855 mg) separated from the original reaction mixture was shaken for 3 hr with 2.5% sodium hydroxide solution (25 ml) and benzene (100 ml). The benzene layer was filtered through a bed of anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The residue (460 mg) was subjected to partition chromatography, as described above, to yield 23 mg of dehydrothalicarpine, mp 180–183°, and 206 mg of thalicarpine, mp 150–155°. The yield of dehydrothalicarpine, based on unrecovered starting material, was 47%.

Registry No.—I, 7224-94-4; I dimethiodide, 15569-53-6; IV, 15562-38-6; IV hydrochloride, 15562-39-7; (±)-VI hydroiodide, 15562-40-0; thalidasine oxalate, 11040-48-5; VII, 15562-41-1; VIII, 15562-42-2.

The Alkaloids of *Tabernaemontana riedelii* and *T. rigida*

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The alkaloids of two Amazonian species of *Tabernaemontana* have been studied; each species yielded indole alkaloids of only one structural type. Thus, *T. riedelii* contained the new alkaloids (+)-8-oxominovincine and (+)-minovincine, as well as a mixture of (±)- and (+)-vincadifformine. *T. rigida* contained (±)-vincamine, (+)-vincamine, (+)-apovincamine, and a substance believed to be a mixture of (±)- and (−)-14-epivincamine.

The genus *Tabernaemontana* of the family Apocynaceae has been the subject of continued controversy with regard to problems of botanical classification. Even recent authorites such as Markgraf[3] and Woodson[4] have disagreed on the question of whether a considerable number of *Tabernaemontana* species should be retained within the genus or should be reclassified as members of related genera. At the present time, we are engaged in a broad study of the alkaloids of the genus *Tabernaemontana*, in the expectation that the results will have chemotaxonomic value in a future reclassification of the genus.

Indole alkaloids have been isolated and identified from a number of *Tabernaemontana* species.[5] These include *Tabernaemontana australis*,[6] *T. psychotrifolia*,[6] *T. oppositifolia*,[6] *T. alba*,[7] *T. pachysiphon*,[8] *T. pandacaqui*,[9] *T. mucronata*,[10] *T. laurifolia*,[11] *T. heyneana*,[12]

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(5) The related genera *Voacanga*, *Ervatamia*, *Gabunia*, and *Conopharyngia* are not included in this listing.

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