Total Synthesis and Stereochemistry of *dl*-Elaeocarpidine[1]

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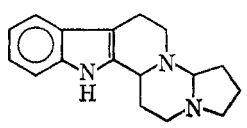
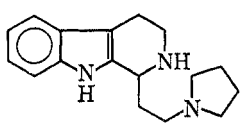
A total synthesis of the novel pentacyclic indole alkaloid elaeocarpidine (1) is described. The key amine lactam intermediate 6 undergoes reductive cyclization with lithium aluminum hydride to 1 and dihydroelaeocarpidine (2). In the presence of a secondary amine the lithium aluminum hydride reduction is directed almost entirely to cyclization to 1. The reductive cyclization gives only the naturally occurring epimer, which is suggested to be *cis* on the basis of spectral and chemical data.

Elaeocarpidine (1), an indole alkaloid of biogenetic interest, was recently isolated from *Elaeocarpus arch-boldianus* and postulated to have the pentacyclic structure shown.[2] This represents one of only a few indole alkaloids to contain three nitrogen atoms.[3] We now wish to report a simple three-step stereospecific total synthesis of *dl*-elaeocarpidine (1) and its hydrogenation product dihydroelaeocarpidine (2). The synthesis confirms the proposed structure for 1 and makes available large quantities of 1 and 2 for biological testing and further chemical studies.



1



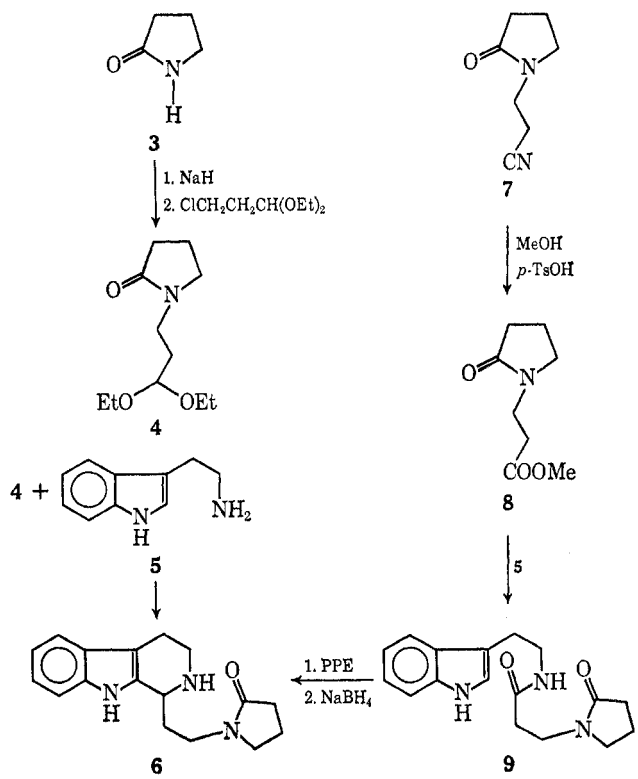
2

After our synthesis was completed, a brief report appeared describing a related preparation of elaeocarpidine and dihydroelaeocarpidine by Harley-Mason and Taylor.[4] Unfortunately, reaction yields and stereochemistry were not discussed in their preliminary publication[4] so a comparison with our synthesis is not presently possible.

Synthesis.—Our synthesis was formulated around two points: the ability of tryptamine (5) to condense with aldehydes to form tetrahydro-β-carbolines[5] and the property of lithium aluminum hydride to reduce tertiary amides to the carbinol amine–immonium salt stage.[6,7] Accordingly, our aim was directed toward the synthesis of 1-[2-(2-oxo-N-pyrrolidyl)ethyl]-1,2,-3,4-tetrahydro-β-carboline (6).

The synthesis of amine lactam 6 was readily accomplished by two routes, summarized in Scheme I. Treatment of 2-pyrrolidinone (3)[8] with sodium hydride in hexamethylphosphoramide–benzene followed by the addition of 3-chloro-1,1-diethoxypropane[8] gave N-(3,3-diethoxypropyl)pyrrolidin-2-one (4) as a labile yellow oil in 34% yield. Acid-promoted condensation of lactam acetal 4 with tryptamine (5)[8] gave the desired amine lactam 6 in 78% yield. In an alternate route

SCHEME I



to 6, methanolysis[9] of N-(2-cyanoethyl)pyrrolidin-2-one (7)[8] afforded N-(2-carbomethoxyethyl)pyrrolidin-2-one (8) in 52% yield. Condensation of lactam ester 8 with tryptamine gave N-[3-oxo-3-(N_b-tryptaminyl)-propyl]pyrrolidin-2-one (9) in 82% yield. Subsequent treatment of amide lactam 9 with polyphosphate ester (PPE)[10] followed by sodium borohydride gave amine lactam 6 in 40% yield, identical with that prepared by the first route.

With the desired intermediate (6) in hand, the task remaining was to construct the sensitive[2] N–C–N portion of elaeocarpidine by a suitable ring closure. As was mentioned earlier, it was believed that lithium aluminum hydride or lithium alkoxyaluminohydride[6] would convert the amide moiety in 6 to the corresponding immonium derivative which would be expected to undergo cyclization[11] to elaeocarpidine (1) and/or its

(1) The author wishes to thank the donors of The Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the Research Corporation for providing generous financial support.

(2) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Commun.*, 410 (1968).

(3) R. H. F. Manske, Ed., "The Alkaloids," Vol. VIII, Academic Press Inc., New York, N. Y., 1965.

(4) J. Harley-Mason and C. G. Taylor, *Chem. Commun.*, 281 (1969).

(5) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).

(6) For the lithium aluminum hydride reduction of amides to aldehydes, see H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **86**, 1089 (1964).

(7) For the lithium aluminum hydride reduction of oxindoles to indoles, see P. L. Julian and H. C. Printy, *ibid.*, **71**, 3206 (1949).

(8) This material is commercially available from the Aldrich Chemical Co.

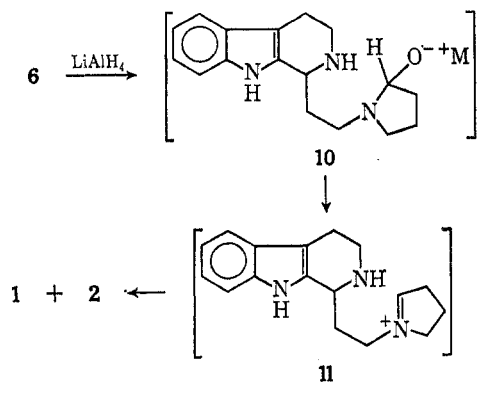
(9) F. L. James and W. H. Bryan, *J. Org. Chem.*, **23**, 1225 (1958).

(10) Y. Kanaoka, E. Sato, and O. Yonemitsu, *Tetrahedron*, **24**, 2591 (1968).

(11) More conventional amide cyclodehydrating reagents seemed unattractive since it was felt that they would preferentially interact with the more nucleophilic secondary amine center in **6**, rather than with the lactam group. Indeed, no cyclization could be detected when **6** was exposed to phosphorus oxychloride, PPE, phosphorus pentoxide, trimethyloxonium fluoroborate, acetic acid, sodium, sodium borohydride, and sodium hydroxide. Similar experiments with amide lactam **9** were unrewarding.

epimer prior to reduction to dihydroelaeocarpidine (2). This has been realized and is summarized in Scheme II.[12]

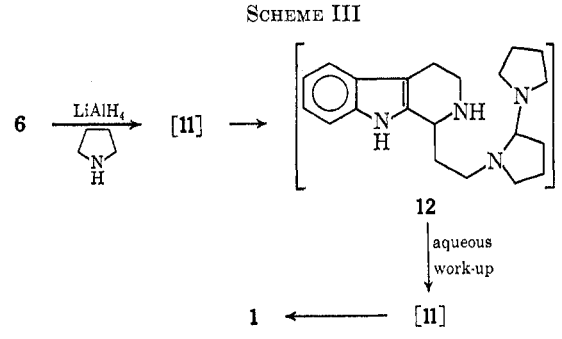
SCHEME II



Treatment of amine lactam 6 with excess lithium aluminum hydride in tetrahydrofuran or diethyl ether at room temperature gave a crystalline reaction product shown to be two compounds by tlc. These could be readily separated by crystallization or column chromatography to give two crystalline compounds. The less soluble compound (30% yield) was found to be completely identical with authentic elaeocarpidine (1). The second compound (60% yield) was completely identical with authentic dihydroelaeocarpidine (2). Both synthetic specimens gave practically superimposable infrared, ultraviolet, and mass spectra, as well as exhibiting identical tlc behavior with their natural counterparts. A careful search of the reaction mixture using tlc for the unnatural epimer (epielaeocarpidine) was unsuccessful. Even if epielaeocarpidine possessed identical tlc behavior as elaeocarpidine, the complete identity of the infrared spectra of natural with synthetic material, especially in the informative Bohlmann region (2840–2600 cm^{-1}), leaves no doubt that little if any epielaeocarpidine is formed in the cyclization reaction. It must therefore be concluded that elaeocarpidine is formed stereospecifically. Attempts to increase the 1:2 ratio by using limited amounts of hydride and/or low temperatures did not significantly alter the original experimental result. Likewise, treatment of amine lactam 6 with lithium diethoxyaluminohydride and lithium triethoxyaluminohydride invariably gave a mixture of 1 and 2. Control experiments showed no conversion of elaeocarpidine (1) to dihydroelaeocarpidine (2) under the reaction conditions. Since elaeocarpidine always directly crystallized from the crude reaction product in a nearly pure state, the reductive-cyclization reaction represents a very convenient source of elaeocarpidine. A single crystallization from benzene gave the pure product by tlc.

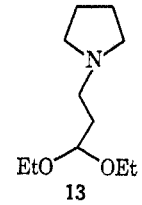
The success of the reductive-cyclization reaction (Scheme II) leading to elaeocarpidine suggested that perhaps the intermediate[13] immonium salt 11 could be more efficiently trapped by an external secondary amine present in large excess.[14] This intermolecular "protection" of the C–N double bond in 11 should prevent overreduction by hydride to dihydroelaeocarpidine (2). Aqueous work-up would be expected to regenerate 11 which should cyclize to elaeocarpidine without the interfering presence of lithium aluminum hydride. Indeed, this proposal has been realized and is summarized in Scheme III. Treatment of amine

SCHEME III



lactam 6 in pyrrolidine–tetrahydrofuran (1:1) at 0° with excess lithium aluminum hydride in small portions over several hours followed by the usual work-up gave elaeocarpidine in 52% yield along with unchanged lactam 6. More importantly, dihydroelaeocarpidine (2) was found to be totally absent from the reaction product.[15]

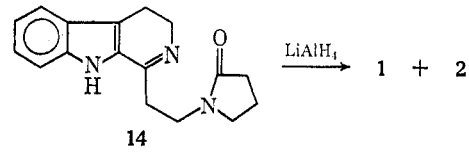
The structure of dihydroelaeocarpidine (2) was further established by independent synthesis. Thus, 3-(N-succinimido)propionaldehyde[16] was converted to N-(3,3-diethoxypropyl)pyrrolidine (13) in 29% overall



13

yield by lithium aluminum hydride reduction of the derived diethyl acetal. Subsequent acid-catalyzed condensation of 13 with tryptamine (5) gave dihydroelaeocarpidine (2) in 48% yield.

The lithium aluminum hydride reductive cyclization of 1-[2-(2-oxo-N-pyrrolidyl)ethyl]-3,4-dihydro-β-carboline (14) was also examined. Imine lactam 14 was readily prepared by treating amide lactam 9 with PPE as previously described but omitting the sodium borohydride reduction step. Treatment of 14 with lithium aluminum hydride gave elaeocarpidine (1) and



14

(12) For simplicity, the acidic hydrogens of 6 are left intact in Scheme II. Probably the indole NH is removed by lithium aluminum hydride and possibly the secondary amine proton is also: J. A. Krynitsky, J. E. Johnson, and H. J. Carhart, *J. Amer. Chem. Soc.*, **70**, 486 (1948).

(13) The intermediate in the cyclization reaction could also be the carbinolamine derivative 10 but, although we as yet have no evidence on this point, we favor a reduction–cyclization competition arising from 11.

(14) The author is indebted to Professor Heinz G. Viehe for this suggestion.

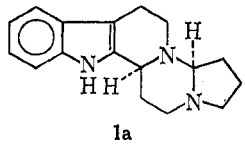
(15) Optimum conditions for this reaction have not been explored as yet, but morpholine behaves similarly. No attempt has yet been made to isolate the intermediate aminal 12. It seems possible[14] that this reaction (6 → 12) may represent a new general enamine synthesis. A study of the scope of this reaction and its implications will be reported separately.

(16) O. A. Moe and D. T. Warner, *J. Amer. Chem. Soc.*, **71**, 1251 (1949).

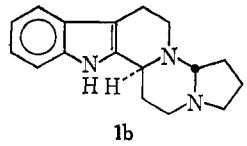
dihydroelaeocarpidine (2) in approximately the same ratio as was obtained from amine lactam 6. No other compound could be detected by tlc. The structure of 14 was confirmed by its conversion to amine lactam 6 with sodium borohydride in nearly quantitative yield.

Two points remain to be settled: the reason for the stereospecificity of the reductive cyclization of amine lactam 6 and the stereochemistry of elaeocarpidine.

An examination of Dreiding models of immonium salt 11, the presumed intermediate in the reductive-cyclization reaction, reveals that if attack occurs by the piperidine nitrogen from an equatorial position it will occur on the top face (as drawn in 11) of the immonium derivative leading to a *cis* arrangement of methine hydrogens in elaeocarpidine (1a). The equatorial nucleophile can come very close to the electrophilic carbon atom without evident strain or other interactions. On the other hand, if attack occurs *via* the axial position of the piperidine nitrogen, models predict that it will occur on the bottom face of the five-membered ring leading to a *trans* arrangement of methine hydrogens in elaeocarpidine (1b). Thus, it appears from



1a

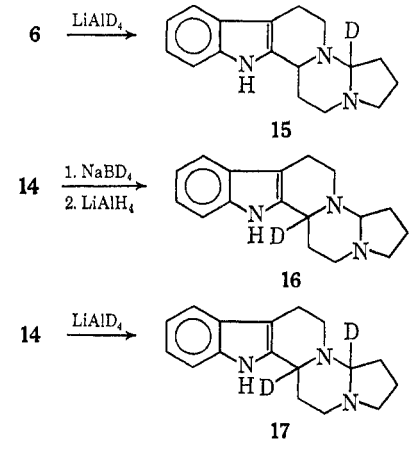


1b

these arguments[17] that the stereospecificity of the ring closure can be rationalized, but, because the attacking conformation of the piperidine ring is unknown, the stereochemistry of elaeocarpidine cannot be predicted with certainty.

Stereochemistry.—For each of the two possible configurations of elaeocarpidine (1a or 1b) there are several conformations available due to nitrogen inversion and ring flipping in the molecule.[18] To establish which conformation(s), and hence configuration, exists for elaeocarpidine, an examination of the nmr and infrared spectra of elaeocarpidine and the deuterated elaeocarpidines 15, 16, and 17 was made. The preparation of 15, 16, and 17 is outlined. The structure of each deuterated alkaloid follows directly from the method of preparation, from spectral and tlc comparison with undeuterated elaeocarpidine, and from mass spectral data.

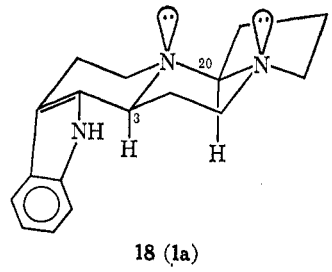
The infrared spectrum of elaeocarpidine (1) shows several intense bands in the 2845–2660-cm^{-1} region commonly known as Bohlmann bands,[19] which are characteristic of conformations having two or more protons in a 1,2-*trans*-diaxial arrangement with a nitrogen lone pair. The infrared spectra of 15, 16, and 17



also show intense Bohlmann bands in the 2800–2700-cm^{-1} region. These observations strongly imply that at least the lone pair on N_c is flanked by two protons in a *trans*-diaxial arrangement. The conformations which satisfy this criterion are the *trans-anti-trans* (1a), the *cis-syn-trans* (1a), and the *cis-anti-trans* (1b).[20]

The infrared spectra of the deuterated elaeocarpidines is also informative in the C–D stretching region. Compound 15 shows a band at 1930 cm^{-1}, 16 shows a band at 1990 cm^{-1}, and 17 shows two bands, at 1990 and 1935 cm^{-1}. Since it is established[19] that C–D bonds that are 1,2 *cis* to a nitrogen lone pair appear at higher frequency than those that are 1,2 *trans* diaxial (~2150 *vs.* 2000 cm^{-1} for methylene and methine groups), it is very tempting to conclude that the C_7–H(D) and C_{20}–H(D) bonds in 15, 16, and 17 (and by analogy 1) are *trans*-diaxially situated to the nitrogen lone pairs. Furthermore, the unusually low frequency value of 1930 cm^{-1} for 15 is fully consistent with the C_{20}D(H) being *trans* diaxial to both nitrogen lone pairs, resulting in a very efficient interaction.[19,21] The only conformation which has C_{20}H *trans* diaxial to both lone pairs and C_7H *trans* diaxial to one lone pair is the *trans-anti-trans* (18).

An nmr examination of elaeocarpidine (1) likewise supports the *trans-anti-trans* conformation (*cis* con-



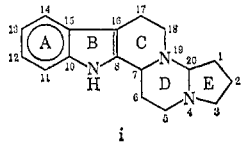
18 (1a)

figuration) arrived at from infrared-based conclusions.

The 60-MHz nmr spectrum of elaeocarpidine in $DCCl_3$ shows no saturated C–H absorption below 3.5 ppm. Similarly, at 100 MHz no methylene or methine absorption appears downfield from the main saturated C–H absorption band. This observation supports the infrared-based conclusion that the C_7H in 1 is *trans* to the adjacent nitrogen lone pair. This follows since

(17) Similar considerations have led to an elegant structure proof and synthesis of cernuine and related lycopodium alkaloids: W. A. Ayer and K. Piers, *Can. J. Chem.*, **45**, 451 (1967), and accompanying papers.

(18) The numbering system used for elaeocarpidine follows the general system adopted for most indole alkaloids and is shown in i.



i

(19) J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968), and references therein.

(20) The *trans-syn-trans* conformation, having a boat D ring, would not show intense Bohlmann bands.

(21) (a) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); (b) M. J. T. Robinson, *ibid.*, 1153 (1968).

it is well established that when a 1,2-*cis* proton lone-pair relationship exists, the absorption for this proton appears at very low field (3.6–4.5 ppm) relative to the 1,2-*trans* diaxial arrangement (1.7–3.2 ppm) in indolo-[2,3-*a*]quinolizidines.[22,23]

In summary, on the basis of infrared and nmr evidence, it must be concluded that the preferred conformation of elaeocarpidine (**1**) is *trans-anti-trans* (**18**) and, therefore, **1** exists as the *cis* configuration **1a**.

Chemical observations also tend to support the more stable *cis* configuration for **1**, although in a negative sense. Attempts to epimerize **1** to epielaeocarpidine (**1b**) using sodium methoxide–methanol, potassium *t*-butoxide–hexamethylphosphoramide, pivalic acid–toluene, hydrobromic acid–acetic acid, and *p*-toluenesulfonic acid–benzene–ethanol were uniformly unsuccessful and led to recovered elaeocarpidine and, in some cases, dihydroelaeocarpidine and amine lactam **6**. Similarly, oxidation of elaeocarpidine with mercuric acetate followed by reduction with sodium borohydride or zinc gave no epielaeocarpidine as judged by tlc.

Finally, studies on other ring systems tend to support the stereochemistry for elaeocarpidine arrived at in the present paper. Quinolizidine and indolizidine both predominate with the *trans* ring fusion having free energy differences of 2.1–4.4 and 1.9 kcal/mol, respectively.[24] In contrast, the pyrrolizidine system exists in the *cis*-fused form since the *trans* is appreciably strained.[25]

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Unless otherwise stated, proton magnetic resonance spectra were recorded on a Varian HA60-IL spectrometer using tetramethylsilane as an internal standard. Woelm alumina was used for column chromatography and silica gel G was used for thin layer chromatography. The tlc solvent system found to be most satisfactory was methanol–triethylamine (~95:5). Other solvent systems used, when comparing authentic material with synthetic material, were ethyl acetate–triethylamine (~95:5), methylene chloride–triethylamine (~95:5), and chloroform–methanol (~90:10). The developing agent was 3% ceric sulfate–10% sulfuric acid solution which was followed by a 5-min heat treatment at 102°. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

N-(3,3-Diethoxypropyl)pyrrolidin-2-one (4).—To a suspension of 11.5 g (56.8%, 0.27 mol) of sodium hydride, which had been washed several times with dry light petroleum ether to remove the mineral oil coat, in 400 ml of dry benzene and 800 ml of dry hexamethylphosphoramide under nitrogen at 25° was added dropwise 22.9 g (0.27 mol) of 2-pyrrolidinone[8] (**3**) with stirring. The mixture was then heated at 70° for 0.5 hr. After cooling the mixture to 5–10°, 45 g (0.27 mol) of 3-chloro-1,1-diethoxypropane[8] was added over a 0.5-hr period. After standing overnight (10 hr) the mixture was refluxed for 1 hr. Stirring under nitrogen was maintained throughout all of these operations. Most of the solvent was removed *in vacuo* and the remaining mixture was poured onto ice water and extracted with benzene. The organic layer was washed with cold distilled water, dried (Na_2SO_4), and concentrated *in vacuo* to give 20 g (34%) of a yellow oil. This material slowly darkened on standing and was used immediately after preparation, without further purification.

Pertinent spectral data for **4** are as follows: ir ($CHCl_3$) 2990, 1678, 1494, 1462, 1441, 1421, 1288, 1261, 1123, 1053 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (t, 6, J = 7 Hz), 2.00 (m, 6), 3.49 (m, 8), and 4.48 (t, 1, J = 5.5 Hz).

N-(2-Carbomethoxyethyl)pyrrolidin-2-one (8).—This was prepared using a slightly modified procedure of James and Bryan.[9] A mixture of 50 g (0.361 mol) of N-(2-cyanoethyl)pyrrolidin-2-one[8] (**7**), 68.8 g (0.361 mol) of *p*-toluenesulfonic acid monohydrate, and 115 g (3.6 mol) of methanol was stirred at reflux for 20 hr. A precipitate of presumably ammonium *p*-toluenesulfonate forms after 3 hr. During the final stage of reflux 125 ml of methanol was removed by distillation. To the cooled reaction mixture was added water and then solid sodium carbonate until the mixture was slightly basic. This was extracted with chloroform, which was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a red oil. Distillation under reduced pressure gave 32.3 g (52%) of **8** as a colorless oil, bp 102–104° (0.2 mm).

Pertinent spectral data for **8** are as follows: ir ($CHCl_3$) 2980, 1730, 1669, 1483, 1450, 1426, 1412, and 1282 cm^{-1}; nmr ($CDCl_3$) δ 2.28 (m, 6), 3.51 (m, 4), and 3.68 (s, 3); mass spectra (70 eV) *m/e* 171, 138 (nitrile impurity), 112, 111, 98, 84, 70, 56, 55, 54, 42, and 41.

1-[2-(2-Oxo-N-pyrrolidyl)ethyl]-1,2,3,4-tetrahydro-β-carboline (6).—A mixture of 23 g (0.117 mol) of tryptamine hydrochloride[8] (**5**), 25.2 g (0.117 mol) of lactam acetal **4**, and 200 ml of water was refluxed for 1 hr under nitrogen with stirring. At this time an additional 0.117 mol of hydrochloric acid (10 ml of 12 *N* HCl–20 ml of water) was added and heating continued for 0.5 hr. The dark amber solution was allowed to cool, washed with ether (discarded), made basic with aqueous sodium hydroxide, and extracted with chloroform–methanol. The organic layer was washed with water, dried (K_2CO_3), and concentrated *in vacuo* to give 38 g of an amber foam. Chromatography over activity III basic alumina gave, with benzene–chloroform elution, 25.9 g (78%) of a viscous yellow syrup which slowly crystallized on standing. Tlc showed one major spot (90%) and several tiny impurity spots. Crystallization from methylene chloride–ether gave tiny colorless crystals of **6**, mp 132–134°.

Pertinent spectral data for **6** are as follows: ir ($CHCl_3$) 3550, 3310, 2960, 1670, 1494, 1467, and 1452 cm^{-1}; mass spectra (70 eV) *m/e* 283, 197, 185, and 171. *Anal.* Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 71.76; H, 7.49; N, 14.98.

N-[3-Oxo-3-(N$_b$-tryptaminyl)propyl]pyrrolidin-2-one (9).—A mixture of 4.0 g (0.025 mol) of tryptamine (**5**) and 4.28 g (0.025 mol) of **8** was heated with stirring under nitrogen at 130–160° for 1 hr and at 160–170° for 5 hr. The reaction can be conveniently followed by tlc. The amber red syrup was allowed to cool to about 50°, diluted with benzene, and chromatographed over activity III neutral alumina. Elution with benzene–chloroform (increasing concentrations of the latter) gave a yellow syrup which crystallized on standing. Crystallization from methanol–ether gave 3.64 g (49%) (two crops) of **9** as tiny needles, mp 118–119°. The mother liquors could be rechromatographed to give additional pure material as judged by tlc.

In subsequent preparations of **9** the crude reaction mixture was diluted with methanol and ether, seeded with pure **9**, and allowed to stand at 5°. In this fashion there was obtained directly pure **9** in 66% yield. An additional 16% could be obtained by chromatography of the mother liquors.

Pertinent spectral data for **9** are as follows: ir ($CHCl_3$) 3590, 3370, 3030, 1671, 1517, 1481, and 1285 cm^{-1}; mass spectra (70 eV) *m/e* 299, 157, 144, 143, 140, 130, and 98. *Anal.* Calcd for $C_{17}H_{21}N_3O_2$: C, 68.21; H, 7.07; N, 14.04. Found: C, 68.35; H, 7.05; N, 14.08.

Amine Lactam 6 from Amide Lactam 9.—A mixture of 1.3 g (4.35 mmol) of amide lactam **9** and 6 g of polyphosphate ester (PPE) in 15 ml of dry chloroform was refluxed under nitrogen with stirring for 4.5 hr then at room temperature for 8 hr. The dark green mixture was poured into water, made basic with 10% sodium carbonate solution, diluted with ethanol, and treated with 5 g of sodium borohydride at 0° for 1 hr and 25° for 20 hr. Ether extraction gave, after water washing, drying (K_2CO_3), and concentration *in vacuo*, 0.72 g of a yellow-orange foam. Chro-

(22) (a) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961); (b) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961); (c) E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962); (d) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963); (e) H. Zinnes, R. A. Comes, and S. Shavel, Jr., *ibid.*, **30**, 105 (1965); and (f) C. M. Lee, W. F. Trager, and A. H. Beckett, *Tetrahedron*, **23**, 375 (1967).

(23) Conformations having C$_{20}$H *cis* to both of the lone pairs can also be excluded since the proton absorption would also be at low fields (below 3.5 ppm). This is especially significant since models indicate that the *trans-syn-cis* conformation would appear to be the most favorable one for the *trans*-configuration **1b**.

(24) H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968).

(25) I. M. Skvortsov and J. A. Elvidge, *J. Chem. Soc., B*, 1589 (1968).

matography over activity III basic alumina gave, with benzene–chloroform elution, 0.51 g (41%) of **6** as a yellow oil which slowly crystallized. This material was identical (infrared, tlc behavior) with that obtained earlier.

Elaeocarpidine (1) and Dihydroelaeocarpidine (2).—To a solution of 4.2 g (14.8 mmol) of amine lactam **6** in 140 ml of dry tetrahydrofuran at 0° under nitrogen with stirring was added in one portion 1.5 g (40 mmol) of lithium aluminum hydride. The mixture was stirred at 0° for 1 hr, then at 25° for 18 hr. To the ice-cold mixture was added successively ice water (dropwise), 6 *N* sodium hydroxide, water, and ether. The organic extract was washed with water, dried (K_2CO_3), and concentrated *in vacuo* to give 4.0 g of a yellow syrup which partially crystallized. Trituration with hot benzene and collection of the resulting white solid afforded 0.675 g (17%) of nearly pure elaeocarpidine contaminated with only a small amount of dihydroelaeocarpidine as indicated by tlc. Crystallization from benzene–methanol gave pure elaeocarpidine, mp 226–227° (slight sintering and darkening at 222°). This synthetic material was completely identical with authentic elaeocarpidine [infrared, mass spectral analysis, tlc (four solvent systems: spot shape, color, and mobility as well as spot enhancement), and ultraviolet]. The unnatural epimer could not be detected by tlc in either the synthetic or natural elaeocarpidine.

On standing, the mother liquor from above deposited 1.19 g (30%) of practically pure dihydroelaeocarpidine, mp 119–122°, which was contaminated with but a trace (tlc) of elaeocarpidine. Crystallization from methanol–ether gave pure dihydroelaeocarpidine, mp 123–124°. This material was identical with authentic dihydroelaeocarpidine (by same criteria used to compare elaeocarpidine).

Chromatography of the mother liquors from above over activity III "super 200" basic alumina gave, with benzene–chloroform elution (increasing concentrations of the latter), 1.25 g (31%) of dihydroelaeocarpidine (pure by tlc) and 0.39 g (10%) of elaeocarpidine, slightly contaminated (tlc) by a small amount of dihydroelaeocarpidine.

Pertinent spectral data for these compounds are as follows.

Elaeocarpidine: ir ($CHCl_3$) 3525, 2950, 2845, 1450, 1372, 1356, 1300, and 1170 cm^{-1}; mass spectrum (70 eV) *m/e* 267, 266, 239, 225, and 160. *Anal.* Calcd for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.50; H, 7.86; N, 15.86.

Dihydroelaeocarpidine: ir ($CHCl_3$) 3535, 2940, 2835, 1492, and 1448 cm^{-1}; mass spectrum (70 eV) *m/e* 269, 239, 225, 198, 185, 184, and 171. *Anal.* Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 75.86; H, 8.66; N, 15.83.

Treatment of 1 with Lithium Aluminum Hydride.—A mixture of elaeocarpidine (**1**) and dihydroelaeocarpidine (**2**) (0.70 g; ~50:50) was refluxed with lithium aluminum hydride (0.10 g) in tetrahydrofuran under nitrogen. Aliquots were periodically removed, processed, and examined by tlc. No change in the 1/2 ratio was observed. After 15 hr the reaction mixture was worked up to give 0.5 g of product which showed the same elaeocarpidine/dihydroelaeocarpidine ratio as was present at the beginning of the reaction. No other spots were present on the tlc chromatogram.

Elaeocarpidine (1) from 6 in the Presence of Pyrrolidine.—To a solution of 2.25 g of amine lactam **6** in 50 ml of dry tetrahydrofuran and 50 ml of dry pyrrolidine under nitrogen at 0° was added 2 g of lithium aluminum hydride in spatula-tip portions over 10 hr. The usual work-up gave 1.1 g (52%) of nearly pure elaeocarpidine (tlc) contaminated with a small amount of **6**. No dihydroelaeocarpidine (**2**) could be detected by tlc.

N-(3,3-Diethoxypropyl)pyrrolidine (13).—A mixture of 33 g (0.201 mol) of 3-(N-succinimido)propionaldehyde, 150 ml of dry ethanol, 5 g of anhydrous calcium chloride, and 6 drops of concentrated hydrochloric acid was allowed to stand at 25° for 5.5 days. Fresh calcium chloride was added periodically so that it was always present in solid form. The mixture was made slightly basic with sodium ethoxide and the ethanol was removed *in vacuo*. The solid residue was added in portions to a suspension of 40 g of lithium aluminum hydride in 1 l. of dry tetrahydrofuran. After addition, the mixture was refluxed under nitrogen for 24 hr. The excess lithium aluminum hydride was destroyed by cautious addition of ice water to the ice-cold reaction mixture. This was followed by the addition of 6 *N* sodium hydroxide and extraction with ether. The organic layer was washed with cold distilled water, dried (K_2CO_3), and concentrated *in vacuo* to give 13 g of a yellow oil. Distillation under reduced pressure gave 11.7 g (29%) of pure **13** as a colorless oil, bp 101–103° (8–9 mm).

Pertinent spectral data for **13** are as follows: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz), 1.82 (m, 6), 2.50 (m, 6), 3.57 (m, 4), and 4.57 ppm (t, 1, J = 5.5 Hz); ir ($CHCl_3$) 2940, 1450, 1388, 1368, and 1344 cm^{-1}; mass spectrum (70 eV) *m/e* 201, 172, 157, 128, 126, 98, 84, 70, 57, 55, and 42. *Anal.* Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.44; H, 11.39; N, 7.07.

Dihydroelaeocarpidine (2) from Amine Acetal 13. To a mixture of 9.75 g (0.0496 mol) of tryptamine hydrochloride in 50 ml of water at 75° under nitrogen with stirring was added dropwise 9.9 g (0.0493 mol) of **13**. The mixture was heated at 80–90° for 0.5 hr, an additional 0.049 mol of hydrochloric acid (4 ml of 12 *N* HCl) was added, and the mixture was refluxed for an additional 1 hr. The cooled mixture was filtered and the residue was washed with aqueous hydrochloric acid. The combined acid extract was washed with ether (discarded), made basic with aqueous sodium hydroxide, and extracted with chloroform. This afforded after the usual manipulation 10.2 g (77%) of an amber syrup. Chromatography over activity III basic alumina gave, with benzene–chloroform elution, 6.3 g (48%) of dihydroelaeocarpidine (**2**) as an oil which slowly crystallized (nearly pure by tlc). Crystallization from methanol–ether–petroleum ether (bp 20–40°) gave prism clusters, mp 123–124°. This material was identical with that obtained by lithium aluminum hydride reduction of lactam acetal **6** as well as with authentic material (infrared and tlc behavior).

1-[2-(2-Oxo-N-pyrrolidyl)ethyl]-3,4-dihydro-β-carboline (14).—A mixture of 5.1 g (17 mmol) of amide lactam **9**, 25 g of PPE, and 60 ml of dry chloroform was refluxed under nitrogen for 4 hr. The dark mixture was poured into water, made basic with sodium hydroxide, and extracted with methylene chloride. This afforded 1.37 g of an amber foam showing on tlc a spot different from amine lactam **6** and amide lactam **9**. Chromatography over activity III neutral alumina gave, with benzene–chloroform elution, 0.5 g (10%) of **14**, mp 145–148°, showing the expected long-wavelength uv absorption at 236 and 316 mμ. This material (pure by tlc) was used directly in the reductive cyclization.

Interestingly, sodium borohydride reduction of the aqueous basic layer gave 2 g (41%) of amine lactam **6**, indicating incomplete extraction of **14** into the organic layer.

Pertinent spectral data for **14** are as follows: ir ($CHCl_3$) 3260, 2960, 1667, 1629, 1550, 1495, 1470, 1448, 1317, and 1288 cm^{-1}.

Imine lactam **14** could not be satisfactorily crystallized and was characterized by sodium borohydride reduction to **6** in quantitative yield.

Preparation of 15.—A mixture of 0.9 g of amine lactam **6**, 0.35 g of lithium aluminum deuteride, and 35 ml of dry tetrahydrofuran was stirred under N_2 for 30 min at 0°, 5 hr at 25°, and 1 hr at reflux. The usual work-up gave 0.64 g of an oil which crystallized on standing. Tlc showed two spots of equal intensity having same characteristics as **1** and **2**. A single crystallization from benzene gave pure (tlc) **15**, mp 214–222°.

Pertinent spectral data for **15** are as follows: ir ($CHCl_3$) 3525, 2945, 2845, 2790, 2731, 1930, 1449, 1373, 1296, 1279, and 1177 cm^{-1}; mass spectrum (70 eV) *m/e* 268, 240, 226, and 171.

Preparation of 16.—A mixture of 3.3 g of imine lactam **14**, 1 g of sodium borodeuteride, and 50 ml of methanol-O-*d* was stirred at 0° for 1 hr and then at 25° for 15 hr. The solution was diluted with water and extracted with methylene chloride. The usual manipulation gave 3.3 g of an amber foam. This was treated directly in the usual fashion with 1 g of lithium aluminum hydride in 60 ml of dry tetrahydrofuran at 0° for 30 min, at 25° for 18 hr, and at reflux for 1 hr. Work-up gave a yellow oil which crystallized slowly. Tlc showed two spots having the same characteristics as **1** and **2**. Crystallization from benzene afforded pure (tlc) **16**, mp 222–225°.

Pertinent spectral data for **16** are as follows: ir ($CHCl_3$) 3490, 2935, 2845, 2795, 2730, 1990, 1449, 1352, 1290, and 1267 cm^{-1}; mass spectrum (70 eV) *m/e* 268, 241, 240, 227, and 226.

Preparation of 17.—A mixture of 1.3 g of imine lactam **14**, 0.53 g of lithium aluminum deuteride, and 50 ml of dry tetrahydrofuran was stirred under nitrogen for 1 hr at 0°, 5 hr at 25°, and 3 hr at reflux. The usual work-up gave 1.1 g of an amber oil which crystallized on standing. Tlc showed two spots having the same characteristics as **1** and **2**. A single crystallization from benzene gave pure (tlc) **17**, mp 221–225°.

Pertinent spectral data for **17** are as follows: ir ($CHCl_3$) 3525, 2950, 2845, 2795, 2725, 1990, 1935, 1457, 1370, 1326, 1298, 1282, 1163, and 1124 cm^{-1}; mass spectrum (70 eV) *m/e* 269, 241, and 227.

Registry No.—**1**, 24343-81-5; **2**, 24298-76-8; **4**, 24299-76-1; **6**, 24298-77-9; **8**, 24299-77-2; **9**, 24343-82-6; **13**, 24299-78-3 **14**, 24299-79-4; **15**, 24298-78-0; **16**, 24298-79-1; **17**, 24343-83-7.

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4-Carbomethoxy-5α-androstane Derivatives. Synthesis of (−)-Sandaracopimaric Acid

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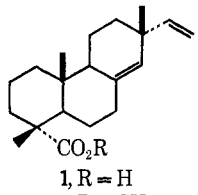
Novel steroidal β-keto esters **4** and **6** were prepared by direct carbonation of 17β-acetoxy-5α-androst-1-en-3-one (**3**) or by the reductive carbomethoxylation of testosterone acetate, respectively. Methylation of **6** affords selectively **7**, the expected product of stereoelectronically controlled axial alkylation. A reversal in the predicted stereochemical course of alkylation was observed with **4**, which afforded **11** as its exclusive methylation product. The configurations at C-4 in **7** and **11** were established through the corresponding 3-deoxy esters **9** and **10**. Ester **9** was converted by a series of reactions into (−)-sandaracopimaric acid (**1**).

Considerable support for the stereochemistry of the isomeric pimaric acids was provided by the syntheses of racemic pimaradiene and sandaracopimaradiene.[1] The stereochemical ambiguity at C-13[2] of the synthetic hydrocarbons was subsequently resolved by the conversion of testosterone into (−)-sandaracopimaradiene by three independent routes.[3] The synthesis of a pimaric acid-type natural product possessing a carboxyl group at C-4, however, has not been described in the literature. In this paper[4] we report the first synthesis of (−)-sandaracopimaric acid[5] (**1**) a diterpenoid resin acid isolated from *Callitris quadrivalvis*, starting from testosterone acetate. The present work provides a direct confirmation of the assigned structure **1** and absolute stereochemistry for the natural acid.



1, R = H
2, R = CH_3

Sandaracopimaric acid (**1**) has the same absolute stereochemistry at carbons 5, 9, 10, and 13 as steroids of the 5α series. Hence, the only stereochemical prerequisite for the conversion of a 5α steroid into **1** is the construction of the abietic acid type[6] of substitution pattern at C-4 of the steroid. Such a substitution pattern or the epimeric podocarpic acid type[6] of arrangement has been attained by a variety of approaches[7] in the syntheses of other resin acids from bi- and tricyclic intermediates. Among these approaches, the most direct method has been the selective methylation of β-keto esters.[8-10] We utilized this approach in preparing the epimeric keto esters **7** and **8**. Our interest in this area evolved from a program involving the preparation of novel 4-substituted androstane and pregnane derivatives for biological studies.

4-Carbomethoxy-5α-androstanes.—By analogy with the tricyclic series,[8] keto esters **4** and **6** would be the substrates of choice since methylation of either of these compounds would be expected to proceed by β attack, thereby providing the desired abietic acid type[6] of stereochemistry at C-4. Two methods were used for the introduction of the carbomethoxy group at C-4 of the appropriate steroid substrate. Using the direct carbonation procedure,[11,12] 17β-acetoxy-5α-androst-1-en-3-one[13] (**3**) was treated with an excess of tritylsodium followed by the introduction of carbon dioxide and conversion of the resulting acid into its methyl ester by reaction with diazomethane. Tlc indicated that the product was a complex mixture of keto esters and starting enone **3** in which the 17-acetate group had partially hydrolyzed and also had partially undergone carbona-

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