1α,2α-Ethylene-5α-androstane-1′,3,17-trione (13).—17β-Hydroxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11c**, 45 mg) was dissolved in acetone (5 ml) and excess Jones reagent was added. After allowing the mixture to stand at 20° for 15 min, it was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, yielding a white solid (34 mg) which on crystallization from hexane–ethyl acetate gave 1′,3,17-trione (**13**): mp 207°; $[\alpha]_D$ +86° ($CHCl_3$); ν_{max} 1775, 1735, 1700 cm^{-1} ($CHCl_3$); nmr (100 Mc) 0.86 (s, 18-H), 0.89 (s, 19-H), 2.7–3.4 (m, three protons), 3.45–3.75 ppm (m, one proton). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.21; H, 8.41.

Registry No.—**2**, 24467-63-8; **3a**, 24515-46-6; **3b**, 24467-64-9; **3c**, 24467-65-0; **4**, 24467-66-1; **5**, 24467-67-2; **7a**, 24467-68-3; **7b**, 24467-69-4; **8a**, 24467-70-7; **8b**, 24467-71-8; **9**, 24515-47-7; **10**, 24523-22-6; **11a**, 24467-72-9; **11b**, 24467-73-0; **11c**, 24515-48-8; **12a**, 24467-74-1; **12b**, 24471-11-2; **13**, 24471-12-3.

Synthetic Approaches to Some of the *Lythraceae* Alkaloids[1]

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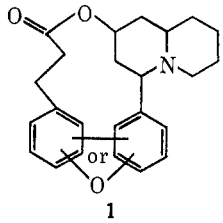
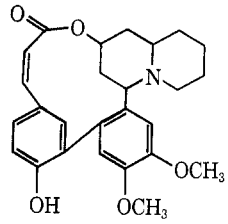
The uncoupled precursor (**20**) to dihydrolyfoline (**22**), a *Lythraceae* alkaloid was prepared by a biogenetic-type synthesis, based upon the assumption that the alkaloids arise from phenylpropane, acetate, and/or lysine sources. Condensation of the acryloylacetic ester (**12**) with Δ^1-piperideine (**7**) gave 1-carbethoxy-2-keto-4-(3-benzyloxy-4-methoxyphenyl)-*trans*-quinolizidine (**13**). Decarboxylation of **13** and reduction of the tetraphenylborate salt of the resulting ketone (**14**) with $NaBH_4$ gave a mixture of alcohols from which the axial isomer (**16**) was separated. Esterification of the alcohol (**16**) with *p*-benzyloxyhydrocinnamic acid and debenzylation yielded the desired compound (**20**). Preliminary attempts to couple **20** oxidatively to provide dihydrolyfoline (**22**) or another of the *Lythraceae* alkaloids have failed.

The alkaloids of the genera *Heimia* and *Decodon*, family *Lythraceae*, are a series of about 17 compounds corresponding to **1**. These alkaloids[2] contain a quinolizidine ring bearing phenyl and phenylpropionyloxy substituents. The two benzene rings are joined either by a biphenyl or a biphenyl–ether bridge. The structures of the alkaloids are based upon chemical correlations[3] with lythrine (**2**) and vertaline (**3**), whose structures were solved by X-ray analysis.[4]

Experimental data about the biosynthesis of these compounds was not available when this investigation was initiated.[5] Therefore, it was necessary for us to suggest a plausible route by which they might be formed *in vivo*. For the purpose of discussion, the molecules may be divided into cinnamate and 4-phenylquinolizidine portions. Considering the type and the oxygenation patterns of the phenyl–phenyl system, it seems logical to believe that these alkaloids are formed by an oxidative phenol coupling of the two portions.[6] Whether the phenyl–phenyl connection is made before or after the ester formation is debatable.



1



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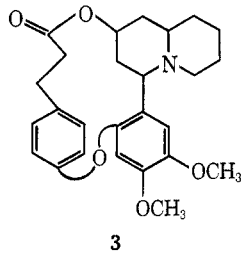


3

It has been suggested[7] without experimental data that the quinolizidine ring system (**5**) could arise from isopelletierine (**4**) and a suitably substituted benzaldehyde as shown in Scheme I. This approach was used[8] for the preparation of a mixture of *cis*- and *trans*-4-phenyl-2-ketoquinolizidines (**5** with no substituents) which was reduced to give a mixture of the epimeric alcohols. No reactions have been reported with oxygenated quinolizidines.

It would seem equally logical that the quinolizidine system might arise from a suitable phenyl–polyketide precursor such as **6** and Δ^1-piperideine (**7**). We would like to report the application of this approach in the synthesis of these alkaloids. The original plan was to prepare the uncoupled precursor (**20**) to the alkaloids and oxidize it to form the phenyl–phenyl connection to yield dihydrolyfoline (**22**). Compound **20** was prepared as

(1) This work was supported in part by Training Grant GM-1139 from the National Institutes of Health. It is based in part upon the Ph.D. Dissertation of J. P. R., University of Connecticut, 1969. The work was presented at the IUPAC 5th International Symposium on the Chemistry of Natural Products, London, and at the 1968 meeting of The American Society of Pharmacognosy, Iowa City, Iowa.

(2) (a) J. P. Ferris, *J. Org. Chem.*, **27**, 2985 (1962); **28**, 817 (1963); (b) R. N. Blomster, A. E. Schwarting, and J. M. Bobbitt, *Lloydia*, **27**, 15 (1964); (c) H. Appel, A. Rother, and A. E. Schwarting, *ibid.* **28**, 84 (1965).

(3) (a) A. Rother H. Appel, J. M. Kiely, A. E. Schwarting, and J. M. Bobbitt, *ibid.*, **28**, 90 (1965); (b) J. P. Ferris, C. B. Boyce, R. C. Briner, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Tetrahedron Lett.*, 3641 (1966).

(4) (a) D. E. Zaccharias, C. A. Jeffrey, B. Douglas, J. A. Weisbach, J. L. Kirkpatrick, J. P. Ferris, C. B. Boyce, and R. C. Briner, *Experientia*, **21**, 247 (1965); (b) S. C. Chu, G. A. Jeffrey, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Chem. Ind.* (London), 1795 (1966); (c) J. P. Ferris, R. C. Briner, C. B. Boyce, and M. J. Wolf, *Tetrahedron Lett.*, 5125 (1966); (d) D. A. Hamilton and L. K. Steinrauf, *ibid.*, 5123 (1966).

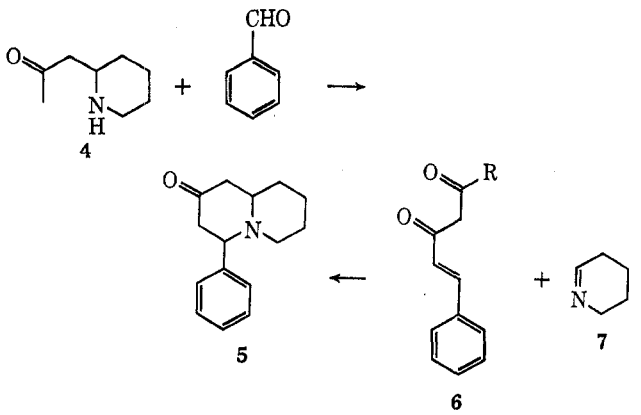
(5) Phenylalanine has since been shown to be a precursor of the phenylcinnamoyl moiety of one of the *Heimia* alkaloids. See A. Rother and A. E. Schwarting, *Chem. Commun.*, 1411 (1969).

(6) A. R. Battersby in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 119.

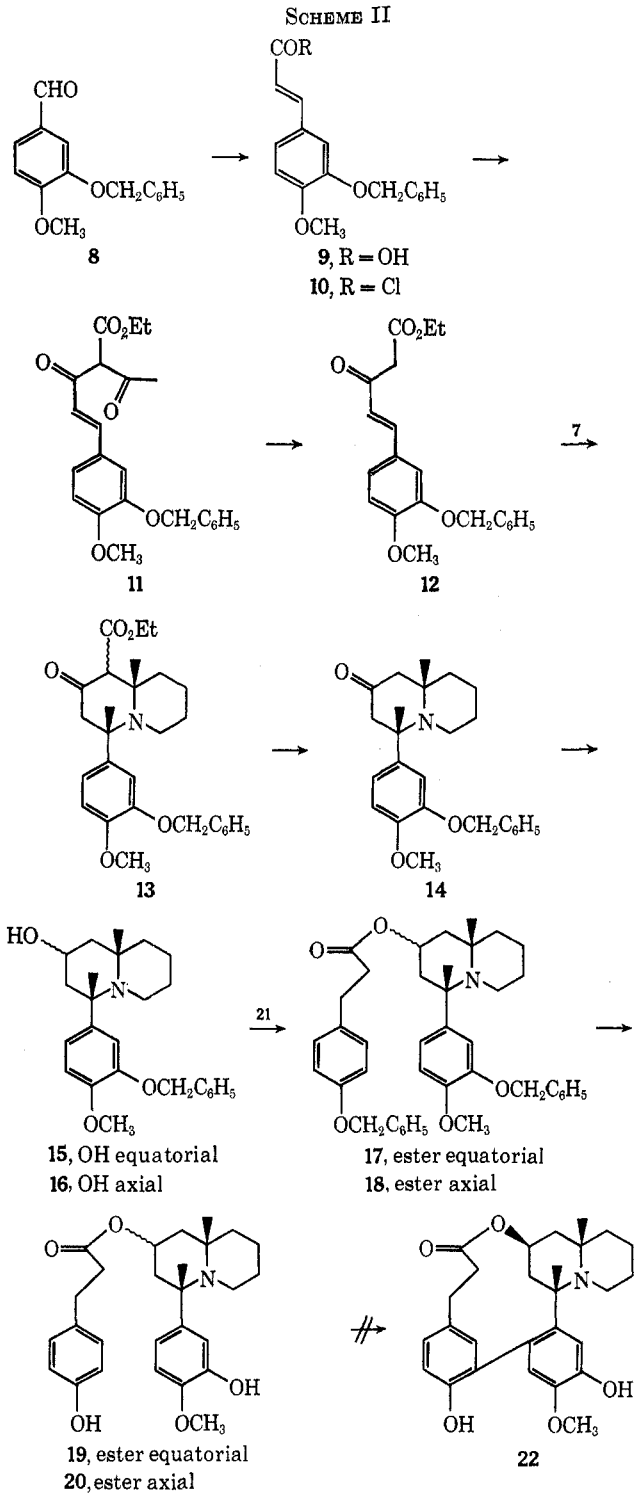
(7) J. P. Ferris, C. B. Boyce, and R. C. Briner, *Tetrahedron Lett.*, 5129 (1966).

(8) T. Matsunaga, I. Kavasaki, and T. Kaneko, *ibid.*, 2471 (1967).

SCHEME I



SCHEME II



described in Scheme II, but the oxidation has not yet been successful.

Benzylisovanillin (**8**)[9] was allowed to react with malonic acid to yield the cinnamic acid (**9**).[10] Although the melting point of **9** was not in agreement with the literature, the structure was shown to be correct by nmr, microanalysis, titration, and reduction to the known 3-hydroxy-4-methoxyhydrocinnamic acid.[11] The acid chloride (**10**) was prepared with thionyl chloride in xylene and allowed to react with sodium ethylacetoacetate to yield **11**. A modification of the procedure of English and Lapides[12] was used. Compound **11** is yellow and its ir spectrum contains only a single carbonyl peak, both properties probably due to its highly enolic character (positive $FeCl_3$ test). The ester (**11**) was deacylated with ammonia in xylene to yield **12** by a modification of the procedure of Guha and Nasipuri.[13] Like **11**, **12** probably exists largely in the enolic form. The nmr spectra of compounds **8** to **12** were in agreement with the structures.

Δ^1-Piperideine (**7**) is a difficult compound to prepare. It may exist in any one of three trimeric forms,[14] α-, β-, and isotripiperideine. Only the α and β forms depolymerize to form **7**. The mixture of isomers prepared according to the literature[14] yielded the α form only when seeded with an authentic sample;[15] otherwise, the useless iso form crystallized.

The condensation of **7** with **12** to form the quinolizidine **13** is somewhat similar to the methods used by Lions and Willison to prepare indolizidines,[16] and by Anet, Hughes, and Ritchie[17] for the preparation of quinolizidines. In both cases, the portion similar to **12** was formed in the reaction mixture from ethyl acetonedicarboxylate and an aldehyde, and in neither case was the reaction very satisfactory. A more recent example[18] involves the condensation of α,β-unsaturated ketones with unsaturated λ-carbolines to yield indoloquinolizidones.

The condensation of **7** and **12** was found to take place in neutral solution (in contrast to the previous work which required slightly acidic media[16-18]) to give **13** in high yield (84%). The stereochemistry of **13** is based upon the reasoning that a structure with the benzene ring in the equatorial position would be the most stable and on the presence of Bohlmann bands[19] in its ir spectrum. These bands are said to be due to an interaction between the electron pair on the nitrogen and the axial

(9) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).
(10) R. Robinson and S. Sugasawa, *ibid.*, 3163 (1931).
(11) M. B. Moore, H. B. Wright, M. Vernsten, M. Freifelder, and B. K. Richards, *J. Amer. Chem. Soc.*, **76**, 3656 (1954).
(12) J. English, Jr., and L. J. Lapides, *ibid.*, **65**, 2466 (1943).
(13) M. Guha and D. Nasipuri, *Org. Syn.*, **42**, 41 (1962).
(14) C. Schöpf, G. Berry, F. Braun, H. Hinkel, and R. Rakahl, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).
(15) M. M. El-Olemy and A. E. Schwarting, *J. Org. Chem.*, **34**, 1352 (1969).
(16) F. Lions and A. M. Willison, *J. Proc. Roy. Soc. N. S. W.*, **73**, 240 (1940).
(17) E. F. L. J. Anet, G. H. Hughes, and A. Ritchie, *Aust. J. Sci. Res.*, **3A**, 635 (1950).
(18) C. Szantay, L. Töke, K. Hantz, and G. Kalaus, *J. Org. Chem.*, **32**, 432 (1967).
(19) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

hydrogens α to the nitrogen.[20] The ir spectrum of **13** showed two carbonyl groups, and the nmr and mass spectra could be correlated with the structure. All of the compounds after **13** are racemic.

Saponification and decarboxylation of **13** to yield **14** took place in dilute base, rather than in the usual base followed by acid reaction. Attempts to carry out the normal saponification and acid decarboxylation gave **14** in low yield. It was found that the yields were quite independent of the time that the acidic mixture was heated but somewhat dependent upon the time of base treatment. A systematic study of yield *vs.* concentration of KOH in ethanol–water (1:1) showed that a maximum yield (55%) could be obtained in 0.5% base. Yields fell off sharply below 0.25% and above 1% KOH. When the base required for the saponification was subtracted from the total base present, the KOH concentration dropped to 0.1%. Thus, the reaction takes place in an extremely dilute basic medium. The necessity of using dilute base for the saponification can be rationalized by the reversible character of the reaction used to form **13**, but the dependence of the decarboxylation upon base concentration is not entirely clear. It is interesting to note that all attempts to decarboxylate the ester of 4-phenyl-2-ketoquinolizidine-1,3-dicarboxylate failed.[17] The structure of **14** was in complete agreement with its ir, nmr, and mass spectra.

The reduction of **14** to the epimeric alcohols **15** and **16** also required extensive exploratory work. The reduction of such 2-ketoquinolizidines usually[8,21] leads to the formation of a mixture of epimers in which the equatorial isomer predominates by about 10:1. Unfortunately, for our purposes it was necessary to produce the axial isomer **16**. Catalytic hydrogenation gave poor overall yields of alcohol with platinum, palladium on carbon, and ruthenium on carbon (reported[21] to give the highest yields of axial alcohols). Reductions with $NaBH_4$ and $LiAlH_4$ gave good overall yields, but, as expected,[21] the equatorial isomer was the major component. For tenuous theoretical reasons, it was decided to carry out the reductions with $NaBH_4$ on complexed forms of the quinolizidine. Consequently, the reactions were carried out on complexes prepared in methanol with $AlCl_3$, $AlBr_3$, AlI_3, and sodium tetraphenylborate.[22] The axial:equatorial ratios, as estimated from comparative tlc follow: uncomplexed, 1:10, $AlCl_3$, decomposed; $AlBr_3$, 1:4; AlI_3, 3:7; and sodium tetraphenylborate, 1:1. The borate reaction was carried out in quantity and 40% of the axial isomer was isolated. The overall yields of the alcohol mixture were excellent. Several explanations are possible for this shift in the ratios, but none is especially satisfying, and none has been proved. There does appear to be a steric effect. It is possible that complexing destroys the original stereospecific reduction, thus producing a more random isomer distribution.

The structures of the two epimers, **15** and **16**, are based upon the following: first, the well-known fact that the equatorial isomer predominates[8,21,23] under normal hydride reductions; second, the chemical shift of the carbinol carbon proton of the alcohols. These have been assigned[8,24] as τ 6.02 and 6.53 for the axial and equatorial compounds, respectively. The values for **16** and **15** were τ 5.88 and 6.49. Both structures were in accord with their ir, nmr, and mass spectra in all respects. The axial isomer only was crystalline.

The two alcohols, **15** and **16**, were separately converted to their respective esters **17** and **18**, by transesterification[25] with methyl-*p*-benzyloxyhydrocinnamate (**21**) in xylene and methoxide. Compound **21** was prepared from *p*-benzyloxyhydrocinnamic acid[26] through the acid chloride. It was later learned that the esters **17** and **18** were easier to separate than the alcohols **15** and **16**. In the preparative procedures, the alcohol mixture was transesterified, and the epimeric esters were separated by column chromatography. Only the axial isomer **18** could be crystallized. The structures of these compounds were in accord with their spectra.

Debenzylation of **17** and **18** with hydrogen and palladium on carbon took place quantitatively to yield the diphenols, **19** and **20**. Neither of these compounds could be crystallized. The structures were in accord with their spectra.

Attempts to couple the diphenols oxidatively to any of the desired products (**1**) using $FeCl_3$,[27] $K_3Fe(CN)_6$,[27] electrolytic oxidation,[28] and catalytic oxygenation[29] failed to yield any recognizable products.

Experimental Section[30]

3-Benzyloxy-4-methoxycinnamic Acid (**9**).—A solution of malonic acid (24 g, 0.231 mol), benzylisovanillin[9] (**8**) (25 g, 0.103 mol), and piperidine (1 ml) in 55 ml of dry pyridine was stirred at 90° for 3 hr, and then at reflux for 2 hr. While hot, the solution was poured onto 200 ml of water and ice. After 1 hr, the precipitated solid was collected by filtration, washed (H_2O), air-dried, and crystallized from absolute ethanol to give 25.3 g (86%) of **9** as fine white needles: mp 214–216° (lit.[10] mp 179–180°); nmr (NaOD) τ 3.33 (m, 10, aromatic and vinylic), 6.62 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67; neut equiv, 284. Found: C, 72.39; H, 5.89; neut equiv, 290.

Compound **9** was catalytically hydrogenated over Pd–C to yield 3-hydroxy-4-methoxyhydrocinnamic acid, mp 146° (lit.[11] mp 146°).

Ethyl 2-Acetyl-3-keto-5-(3-benzyloxy-4-methoxyphenyl)-4-pentenoate (**11**).—A mixture of **9** (19 g, 0.067 mol, dried at 110° for 12 hr) and $SOCl_2$ (15.8 g, 0.134 mol) in 100 ml of dry xylene

(20) H. P. Hamlow and S. Okuda, *Tetrahedron Lett.*, 2553 (1964).

(21) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

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(23) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 30.

(24) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

(25) R. E. Counsell and T. O. Soine, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 289 (1960).

(26) D. G. Doherty, *J. Amer. Chem. Soc.*, **77**, 4887 (1955).

(27) H. Musso in ref 7, p 1.

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(30) The melting points are corrected. Spectra were determined as follows: ir on Perkin-Elmer instruments (Models 137B and 21); nmr spectra on a Varian A-60 instrument against a tetramethylsilane standard; mass spectra on an AEI Model AS-12 instrument at 70 eV. Chromatography was carried out on thin (0.25-mm) and thick (1-mm) layers of silica gel GF_{254} and PF_{254} and on aluminum oxide GF_{254} (Brinkmann Instruments Westbury, N. Y.). Dragendorff's reagent-1, (J. M. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Co., New York, N. Y., 1963, p 93), aqueous 1% $FeCl_3$, and methanolic 2,4-DNPH solution (A. I. Vogel, "Practical Organic Chemistry including Qualitative Organic Analysis," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 1051) were used as spray reagents. All of the reactions were monitored by tlc. Column chromatography was carried out on silica gel M (Hermann Brothers, Cologne, Germany) and on aluminum oxide, Woelm (Alupharm Chemicals, New Orleans).

was heated at reflux until the acid dissolved and for 0.5 hr more. The solution was evaporated to dryness under vacuum and the residue was taken up in 200 ml of dry xylene.[31] The solution of **10** was added over 30 min to a suspension of sodium ethyl acetoacetate, prepared from 1.54 g (0.067 mol) of sodium sand in 200 ml of xylene and 8.7 g (0.067 mol) of ethyl acetoacetate. The resulting orange-yellow mixture was stirred at room temperature for 16 hr, filtered to remove a fine white precipitate of NaCl, and evaporated, under vacuum, to a brown oil. The oil crystallized when cooled over ice and recrystallized from absolute ethanol to give 21.3 g (81%) of yellow needles, mp 110.5–111.5°.

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 70.04; H, 6.14.

Ethyl 3-Keto-5-(3-benzyloxy-4-methoxyphenyl)-4-pentenoate (12).—Anhydrous ammonia was allowed to bubble through an ice-cold solution of 19.65 g (0.046 mol) of **12** in 500 ml of dry xylene for 1 hr. The turbid mixture was allowed to come to room temperature and was stirred for 16 hr. The mixture was filtered and evaporated, under vacuum, to a brown, viscous oil which crystallized when placed in the cold. Recrystallization from 250 ml of absolute ethanol gave 14.6 g (83%) of light yellow **12**, mp 84–88.5°. Compound **12** was used for the next step without further purification.

1-Carbethoxy-2-keto-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidine (13).—α-Tripiperideine (**7**) was prepared by the method of Schöpf and coworkers[14] and was seeded with an authentic sample.[15] The acryloylacetic ester **12** (1.5 g, 0.0042 mol) and α-tripiperideine (0.35 g, 0.0043 mol) were stirred in 200 ml of 95% ethanol for 48 hr. Tlc (silica gel GF, benzene–ethyl acetate 5:1) showed the reaction to be complete in about 24 hr. Column chromatography gave 1.56 g of **13** (84% yield). In later experiments the product was crystallized directly from the reaction medium. Crystallization from absolute ethanol yielded the analytical sample: mp 116–116.5°; ir (KBr) μ 3.543 (Bohlmann band), 5.73, 5.762 (C=O); nmr ($CDCl_3$) τ 2.90 (m, 8, aromatic), 4.89 (s, 2, $OCH_2C_6H_5$), 5.78 (q, 2, OCH_2CH_3), 6.18 (s, 3, OCH_3), 6.68 (m, 2), 7.38 (m, 4), 8.47 (m, 10, OCH_2CH_3 and quinolizidine protons); ir ($CHCl_3$) μ 3.55, 3.70, (Bohlmann bands); mass spectrum *m/e* (relative intensity) 437 (8), 364 (12), 300, (13), 240 (19), 110 (15), 91 (100), 84 (48), 82 (27). The compound decomposed slightly when placed on a thin layer of silica gel G and warmed.

Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.09; H, 7.19; N, 3.25.

2-Keto-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidine (14).—The quinolizidine ester, **13**, (8.75 g, 0.02 mol) was suspended in 310 ml of 0.5% KOH in aqueous ethanol (1:1) and stirred at reflux for 17 hr. The hot solution was adjusted to pH 2–4 with 5% H_2SO_4 and the solution was allowed to cool for 20 min. A large excess of NH_4OH was added, and the mixture was extracted with $CHCl_3$ (three 100-ml portions). The $CHCl_3$ extracts were combined, dried (Na_2SO_4), filtered, and evaporated to a residue under vacuum. The resulting brown oil was taken up in hot methanol (50 ml). After 24 hr 1.5 g of **14** had crystallized. When the mother liquor was chromatographed on silica gel using benzene–ethylacetate (5:1) as developer, an additional amount (2.34 g, total yield 53%) of **14** was obtained. Crystallization from methanol gave the analytical sample, mp 169–170°: ir (KBr) μ 3.495, 3.566 (Bohlmann bands), 5.764 (C=O); nmr ($CDCl_3$) τ 2.90 (m, 8, aromatic), 4.90 (s, 2, $OCH_2C_6H_5$), 6.19 (s, 3, OCH_3), 6.59 (m, 3), 7.67 (s, 4), 8.50 (m, 7, quinolizidine); mass spectrum *m/e* (relative intensity) 365 (26), 274 (24), 250 (14), 191 (32), 110 (18), 91 (100), 84 (43), 82 (32).

Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.41; H, 7.39; N, 3.79.

Epimeric 2-Hydroxy-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (15 and 16).—The tetraphenylborate salt of **14** was prepared by adding 1.132 g (0.0033 mol) of sodium tetraphenylboron in 100 ml of H_2O to a solution of 1.093 g (0.003 mol) of **14** in 100 ml of H_2O adjusted to pH 2 with concentrated HCl. The precipitated salt was collected and washed with H_2O to remove excess HCl.

The salt was dissolved in 100 ml of absolute methanol and cooled to ice temperature. Sodium borohydride (0.266 g, 0.006 mol) in 25 ml of cold methanol was added over 5 min to the stirred solution. After 20 min, a second portion (0.226 g) of sodium borohydride was added and the reaction was stirred for an additional 0.5 hr more. Tlc (silica gel GF, benzene–methanol 10:1 and 5:1) monitoring of the reaction showed the necessity of adding the second portion of borohydride, and also that the reaction was finally about 80% complete. The reaction mixture was then passed (500 ml in 16 hr) through a column (1.5 × 20 cm) of Dowex 1-X8-OH (previously washed with and suspended in ethanol). The column was washed with ethanol until no more Dragendorff-positive material was eluted. The ethanol was evaporated under vacuum to a dark oil which was chromatographed over 120 g of silica gel (previously dried at 110°) using benzene–methanol (10:1) as developer. Fractions of 15 ml were collected at a flow rate of 0.5 ml/min. Fractions 6–28 yielded 0.266 g of starting material **14**. Fractions 32–63 contained 0.488 g of the equatorial epimer **15**. Fractions 64–76 contained 0.050 g of a mixture of **15** and **16**, and 77–132 contained 0.323 g of the axial epimer **16**. The overall recovery from the column was 103%, and the yields of pure **15** and **16** were 59 and 39%, respectively, after correcting for recovered starting material.

The axial isomer **16** showed the following spectroscopic properties: ir (KBr and $CHCl_3$) μ 2.78, 2.98 (OH), 3.504, 3.559 (Bohlmann bands); nmr ($CDCl_3$) τ 2.78 (m, 8, aromatic), 4.83 (s, 2, $OCH_2C_6H_5$), 6.19 (s, 3, OCH_3), 5.88 (s, 1, carbinol proton), 7.23 (m, 2), 8.39 (m, quinolizidine); mass spectrum *m/e* (relative intensity) 367 (36), 276 (37), 154 (38), 110 (22), 91 (100), 84 (27), 82 (20). The compound crystallized from chloroform–ether to yield an analytical sample, mp 126–127°.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.44; H, 7.93; N, 3.87.

The equatorial alcohol **15** did not crystallize but showed spectral properties virtually identical with those of **16** except for the nmr peak of the carbinol proton which appeared at τ 6.49.

Methyl *p*-Benzyloxyhydrocinnamate (21).—Dry *p*-benzyloxyhydrocinnamic acid [mp 123–125° (lit.[26] mp 123–124°), 10 g, 0.039 mol] was heated at reflux with 9.2 g (0.078 mol) of $SOCl_2$ in 150 ml of dry benzene for 16 hr. The benzene was removed under vacuum, and the resulting syrup was dissolved in 200 ml of petroleum ether (bp 65–110°). This solution was combined and stirred with 50 ml of dry methanol. From this two phase system, the product began to crystallize after 15 min. After 7 hr, the solution was cooled, and the product (8.85 g, 84%) was collected and washed with cold petroleum ether. The compound showed the predicted spectral properties and melted at 81–82°.[32]

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.21; H, 6.66.

Epimeric 2-(*p*-Benzyloxyhydrocinnamoyloxy)-4-(3-benzyloxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (17 and 18).—The two compounds were made in the following way. The alcohols **15** or **16** (0.642 g, 1.75 mmol) and 0.472 g (1.75 mmol) of **21** were dissolved in 125 ml of xylene and heated at reflux under a Dean-Stark separator for 1 hr. NaOMe (0.095 g, 1.75 mmol) suspended in xylene was added to the mixture and heating was continued for 21 hr. The reaction was monitored by tlc (silica gel GF, benzene–ethyl acetate 3:1). The reaction mixture was cooled and extracted three times with H_2O. The xylene was removed under vacuum and the brown residue was purified by column chromatography (40 g of silica gel in a 1.5 × 36 cm column, developed at 0.5 ml/min with benzene–ethyl acetate 5:1). Evaporation of the appropriate fractions yielded 0.750 g (70%) of **17** or 0.762 g (72%) of **18**.

Crystallization of the axial epimer **18** from acetone–methanol yielded an analytical sample: mp 109–110°; ir (KBr) μ 3.50, 3.578 (Bohlmann bands), 5.748 (C=O); nmr (CCl_4) τ 2.97 (m, 17, aromatic), 5.09 (d, 4, $OCH_2C_6H_5$), 6.31 (s, 3, OCH_3), 7.28 (m, 5), 8.64 (m, 11, quinolizidine); mass spectrum *m/e* (relative intensity) 605 (9), 604 (18), 514 (10), 513 (26), 350 (17), 349 (14), 348 (25), 267 (3), 258 (15), 136 (32), 91 (100), 84 (16), 82 (10).

Anal. Calcd for $C_{39}H_{43}NO_5$: C, 77.33; H, 7.15; N, 2.31. Found: C, 77.06; H, 7.29; N, 2.30.

The equatorial epimer **17** did not crystallize, but the spectral properties were qualitatively the same as those of **18**.

Anal. Found: C, 76.96; H, 7.22; N, 2.17.

(31) The acid chloride, **10**, was isolated, and melted at 100–113°. However, because it was extremely sensitive to moisture, it was not further characterized.

(32) This compound was previously prepared [I. T. Strukov, *Zh. Obshch. Khim.*, **29**, 2914 (1959); *Chem. Abstr.*, **54**, 12110 (1959)] but was not crystallized.

Epimeric 2-(*p*-Hydroxylhydrocinnamoyloxy)-4-(3-hydroxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (19 and 20).—The appropriate benzyl ether (17 or 18, 0.3 g) in absolute ethanol were hydrogenated over 0.06 g of 5% Pd–C. The theoretical amount of hydrogen was taken up in 4 hr. Removal of the catalyst and the solvent gave the two phenols, 19 or 20 in essentially quantitative yields. Neither crystallized and both were characterized as glasses.

The axial epimer 20 showed a softening point of 70–85° and had the following spectral properties: ir (KBr) μ 3.00 (OH), 3.59, 3.64 (Bohlmann bands), 5.82 (C=O); nmr ($CDCl_3$) τ 3.33 (m, 7, aromatic), 5.0 (s, phenolic), 6.24 (s, 3, OCH_3), 7.20 (m, 7), 8.59 (m, quinolizidine); mass spectrum *m/e* (relative intensity) 426 (28), 425 (100), 424 (17), 260 (70), 259 (50), 258 (67), 177 (72), 150 (20), 137 (22), 136 (65), 117 (33), 110 (15), 107 (63), 84 (71), 55 (22); uv (ethanol) the spectrum was shifted to a higher wave length upon NaOH addition.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.03; H, 7.32; N, 2.91.

The equatorial isomer 19 had spectral properties qualitatively similar to those of 20. It liquified at 65–75°.

Anal. Found: C, 69.91; H, 7.35; N, 2.89.

Registry No.—**9**, 24807-37-2; **11**, 24807-38-3; **12**, 24807-39-4; **13**, 24806-75-5; **14**, 24806-76-6; **15**, 24806-77-7; **16**, 24806-78-8; **17**, 24806-79-9; **18**, 24806-80-2; **19**, 24806-81-3; **20**, 24806-82-4; **21**, 24807-40-7.

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Chemistry of *Ottonia vahlii* Kth. II.[1] Constitution of the Nonvolatile Component[2]

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The nonvolatile principle (piperovatine) of the leaves, roots, and stems of *Ottonia vahlii* Kth., has been shown, by spectral study and synthesis, to be N-isobutyl-6-*p*-methoxyphenylsorbamide (1).

In an earlier communication[1] we identified the volatile constituent of the shrub *Ottonia vahlii* [syn. *Piper ovatum* (Vahl)], native to the West Indies, as 1-butyl-3,4-methylenedioxybenzene. In this paper we are concerned with the chemical structure of the nonvolatile component of the same plant.

The sole chemical studies of this shrub were published over 70 years ago.[5] The isolation from the leaves of a crystalline "alkaloid," mp 123°, was described; it was named piperovatine, assigned a molecular formula $C_{16}H_{21}NO_2$, and found to be neutral in reaction and to have marked physiological properties. It proved to be a temporary nerve depressant, a heart poison, a local anesthetic, and a powerful sialagogue when applied to the tongue.

We have isolated from the leaves, roots, and stems of this plant what appears to be the same compound by a simplified mode of extraction. Some difficulty was experienced with its purification, owing to the fact that, as noted by the earlier workers, crystallization attempts were attended by a strong tendency towards gel formation in a variety of solvents. Eventually a combination of high-vacuum sublimation followed by crystallization from a critical volume of ether yielded a crystalline product of maximum mp 121°. A sample of the earlier workers' product was not available for comparison, but there seems little doubt, from the physical and physiological properties of our material, that it is identical with piperovatine.

Elemental analysis and molecular-weight determination by mass spectrometry necessitated an alteration of the molecular formula to $C_{17}H_{23}NO_2$, containing one methoxyl group. The presence of the latter was confirmed, and its aromatic character was revealed by nmr spectroscopy (singlet, 3.82 ppm, 3 H). The neutral character of the product suggested it might be amidic. This was confirmed by its ir spectrum (in CCl_4): maxima at 3460 (free NH), 3380 (H-bonded NH), and 1673 cm^{-1} suggested the carbonyl group is conjugated with two double bonds. Bands at 1461 and 1438, and 1178 and 1171 are assigned to a $>C(CH_3)_2$ group, at 1243 to an aromatic OCH_3 group, and at 991 cm^{-1} to a *trans,-trans* CH=CH—CH=CH system conjugated with the amide carbonyl group.[6] The uv spectrum (λ_{max}^{EtOH} 262 mμ, ϵ 26,500) confirms the presence of a diene system conjugated with the amidic carbonyl group and further supports the belief that the double bonds are both *trans* in geometry [compare sorbic acid, λ_{max}^{EtOH} 263 mμ, ϵ 25,800).[7] The nmr spectrum revealed the following features in the molecule: (a) a *para*-disubstituted benzene ring (A_2B_2 pattern, centered at 6.90, 4 H); (b) olefinic protons (4 H) attached to a conjugated diene system [multiplicity of signals in the range 5.6–6.4; of these a doublet centered at 5.87 (J = 15 Hz) is assigned to an α proton *trans* to the β proton on the α,β C=C bond (compare sorbic acid[8])]; (c) an aromatic methoxyl group singlet at 3.82, 3 H); (d) a benzylic CH_2 group (doublet, J = 5 Hz, centered at 3.45, 2 H); (e) an apparent triplet centered at 3.20, J = 5 Hz (2 H), assigned to a $-NHCH_2CH<$ grouping, is in reality a quartet in which the two innermost signals overlap ($J_{CH-NH} = J_{CH-CH}$). On deuteration these signals collapse to a doublet centered at 3.12 (J = 7 Hz) [several model compounds containing the grouping $R\cdot C(O)\cdot NH\cdot CH_2CH<\begin{matrix}R'\\R''\end{matrix}$, were synthesized;

(1) Part I: A. R. Pinder and S. J. Price, *J. Chem. Soc. C*, 2597 (1967).

(2) Presented at the Annual Meeting of the South Carolina Academy of Science, Columbia, S. C., April 1968; at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, and at The Third National Products Symposium, Kingston, Jamaica, W. I., Jan 1970.

(3) Submitted by S. J. Price in partial fulfillment of the requirements for the Degree of M.S., Clemson University, May 1969.

(4) To whom inquiries should be addressed.

(5) W. R. Dunstan and H. Garnett, *J. Chem. Soc.*, **67**, 94 (1895). See also T. A. Henry, "The Plant Alkaloids," 4th ed, Churchill, London, 1949 p 2.

(6) For examples, see J. L. H. Allan, G. D. Meakins, and M. C. Whiting, *J. Chem. Soc.*, 1874 (1955).

(7) (a) U. Eisner, J. A. Elvidge, and R. P. Linstead, *ibid.*, 1372 (1953); (b) see also A. I. Scott, "Interpretation of the UV Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 81.

(8) Varian Associates NMR Spectral Catalog, Vol. 2, spectrum no. 462.