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CONSTITUENTS OF *HOLACANTHA EMORYI*[1]

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Abstract—*Holacantha emoryi* Gray, fam. Simaroubaceae, contains glaucarubol, a compound characteristic of the family. Ellagic acid, betulin and (−)-syringaresinol were also isolated.

INTRODUCTION

Holacantha emoryi Gray (crucifixion thorn) is a xerophytic shrub common to the southwestern deserts of Arizona and California. Although the view has been offered[2] that *Holacantha* should be separately classified as a monotypic family, the weight of opinion appears to place it in the family Simaroubaceae.[3] That *Holacantha* and *Castela* are closely allied but differ significantly from other members of the family has been noted,[4] and it is further stated that *Holacantha* is related to and probably derived from *Castela*.[3]

Castela nicholsoni Hook. contains the typically simaroubaceous lactones chapparin (I),[5] glaucarubolone (II),[6] and glaucarubol (III).[7] The latter, heretofore known in nature only as the α-methyl-α-hydroxybutyryl ester, glaucarubin (IV), occurs in *Simarouba glauca*[8] and *Perriera madagascariensis*.[9]

RESULTS AND DISCUSSION

The occurrence of glaucarubol (III) in nature has now been established by its discovery in *Castela nicholsoni*[7] and in *Holacantha emoryi*. The compound obtained from *H. emoryi* (0·03 per cent yield) was identified by direct comparison of its pentaacetate with an authentic specimen[10] and by the comparison of its spectral properties with those described.[11]

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[3] A. CRONQUIST, *Brittonia* **5**, 128 (1944); P. A. MUNZ, *A California Flora*, University of California Press, Berkeley (1959).

[4] I. E. WEBBER, *Am. J. Botany* **23**, 577 (1936).

[5] (a) T. A. GEISSMAN and K. R. CHANDORKAR, *J. Org. Chem.* **26**, 1217 (1961); (b) T. A. GEISSMAN and G. A. ELLESTAD, *Tetrahedron Letters* 1083 (1962); (c) T. A. DAVIDSON, T. R. HOLLANDS and P. DE MAYO, *Tetrahedron Letters* 1089 (1962).

[6] J. POLONSKY and N. BOURGUIGNON-ZYLBER, *Bull. Soc. Chim. Fr.* 2793 (1965).

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[9] N. BOURGUIGNON and J. POLONSKY, *Bull. Soc. Chim. Biol.* **46**, 1145 (1964).

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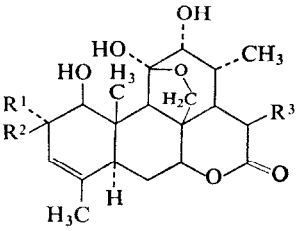
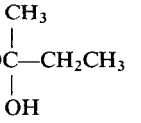
[11] J. POLONSKY, C. FOUQUEY and A. GAUDEMER, *Bull. Soc. Chim. Fr.* 1827 (1964). The compound described by Polonsky *et al.*, was reported to have m.p. 130–135°, while ours and that received from Dr. Ham had m.p. 200–201°. Since the analytical values and NMR spectra of our and the French compounds were the same in all respects, it appears that the two materials represent different crystal forms, and not different degrees of acetylation.



(I) Chapparin, $R^1 = OH$; R^2, $R^3 = H$
(II) Glaucarubolone, R^1, $R^2 = O$; $R^3 = OH$
(III) Glaucarubol, $R^1 = R^3 = OH$; $R^2 = H$



(IV) Glaucarubin, $R^1 = OH$; $R^2 = H$; $R^3 =$ OCOC(CH$_3$)(OH)—CH$_2$CH$_3$

A second compound isolated from *H. emoryi* has been found to be the levorotatory form of syringaresinol, a compound previously found in several plant species as the (±)- and (+)-forms, and as what appears to be an impure (−)-form. (−)-Syringaresinol from *H. emoryi*, m.p. 184–187°, $[\alpha]_D^{25}$ −32·5°, showed identical behavior on TLC (R_f and color reactions) as (+)-syringaresinol and (±)-syringaresinol,[12] and its i.r. spectrum (in KBr) was identical

TABLE 1.

Name	m.p.	Rotation (chloroform)	Di-O-methyl-derivatives m.p.	Di-O-methyl-derivatives Rotation (chloroform)	Reference
(±)-Syringaresinol	175–176°	—			13
(±)-Syringaresinol	174°	0	107–108°	0	14
(±)-Syringaresinol	amorphous				15
Lirioresinol A	210–211°	+127	118–120°	+119	16
Lirioresinol B	172–177°	+ 62·2	121–123°	+ 46·2	16
Lirioresinol C	185–186°	+ 48·9			16
Compound A	180–181°				17
Compound C	235–236°				17
Compound D	168–172°	+ 3·93			17
	189–190°	− 9·31			18
	183–184°	+ 4·2			18
(±)-Syringaresinol	170–171°	0			19
(−)-Syringaresinol	170–172°	− 21·5			20
(−)-Lirioresinol C	177–183°	− 34·8			21
Compound from *Holacantha*	184–187°	− 32·5	123·5–125°	− 41·7	—

[12] We are grateful to Professor K. Freudenberg for a specimen of (±)-syringaresinol; to Professor P. R. Jefferies for (+)-syringaresinol dimethyl ether; and to Dr. E. E. Dickey for (+)-syringaresinol (lirioresinol C), (+)-episyringaresinol (lirioresinol A), and (+)-syringaresinol dimethyl ether (lirioresinol B dimethyl ether).

[13] K. FREUDENBERG, R. KRAFT and W. HEIMBERGER, *Chem. Ber.* **84**, 472 (1951).
[14] K. FREUDENBERG and H. DIETRICH, *Chem. Ber.* **86**, 4 (1953).
[15] K. FREUDENBERG and H. SCHRAUBE, *Chem. Ber.* **88**, 16 (1955).
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[17] I. A. PEARL, D. L. BEYER and E. E. DICKEY, *J. Org. Chem.* **23**, 705 (1958).
[18] I. A. PEARL and D. L. BEYER, *J. Org. Chem.* **26**, 546 (1961).
[19] H. NIMZ and H. GABER, *Chem. Ber.* **98**, 538 (1965).
[20] L. A. ELYAKOVA, A. K. DZIZENK, and G. B. ELYAKOV *Dokl. Akad. Nauk SSSR* **165**, 562 (1965); *Chem. Abstr.* **64** 8290 (1966).
[21] R. R. ARNDT, S. H. BROWN, N. C. LING, P. ROLLER, C. DJERASSI, S. M. FERREIRA, F. B. GILBERT, E. C. MIRANDA, S. E. FLORES, A. P. DUARTE and E. P. CARRAZZONI, *Phytochem.* **6**, 1653 (1967).

in all respects with that of (+)-syringaresinol (lirioresinol C). Its NMR spectrum, the fragmentation pattern in the mass spectrometer, its elemental composition, and the corresponding data for its dimethyl ether and diacetate were all in agreement with the structure V.

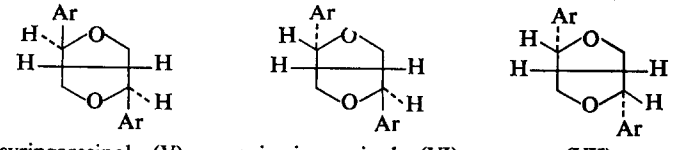
Other investigations of syringaresinols have led to the description of numerous substances bearing various names and showing a wide variation in rotations and melting points. These are summarized in Table 1. Corresponding dimethyl ethers are also found in nature (Table 2),

TABLE 2.

Name	m.p.	Rotation (chloroform)	Reference
Lirioresinol B dimethyl ether	122–123°	+ 45·8	22
Lirioresinol B dimethyl ether	121–122°	+ 46·0	21
Lirioresinol B dimethyl ether	119–122·5°	—	23
Lirioresinol C dimethyl ether*	145–147·5°	+284	23

* Not the dimethyl ether of Dickey's lirioresinol C[16].

and, in contrast to the phenols, appear to be more readily obtainable in pure form. Freudenberg and Sidhu[24] have proposed that the name "lirioresinol" be abandoned and that these compounds be called syringaresinols. The stereochemistry of these compounds has been deduced by comparisons of molecular rotations with those of lignans of known absolute configuration[24, 25] and by other studies,[22, 26] and are as follows:



syringaresinol (V) episyringaresinol (VI) (VII)

Ar = syringyl

A syringaresinol possessing the quasi-diaxial conformation (VII) has recently been isolated from *Marcopiper excelsum* (Piperaceae). Although named "lirioresinol C dimethyl ether", it is not the ether of the compound earlier called lirioresinol C.

A comparison of the values for rotation and melting point of the compounds listed in the tables indicates that many of the syringaresinols may have been sterically inhomogeneous, perhaps because of the occurrence in natural sources of both enantiomers in varying ratios.

[22] P. R. JEFFERIES, J. R. KNOX and D. E. WHITE, *Australian J. Chem.* **14**, 175 (1961).
[23] L. H. BRIGGS, R. C. CAMBIE and R. A. F. COUCH, *J. Chem. Soc.* (C) 3042 (1968).
[24] K. FREUDENBERG and G. S. SIDHU, *Chem. Ber.* **94**, 851 (1961).
[25] K. FREUDENBERG and K. WEINGES, *Tetrahedron* **15**, 115 (1961).
[26] E. N. MASLEN, C. NOCHOLDS and M. PATON, *Australian J. Chem.* **15**, 161 (1962).

It appears that the dimethyl ethers are relatively easier to obtain in pure form, and that the enantiomers with m.p. 123–125° and $[\alpha]_D \pm 42$–46° represent the authentic compounds. A summary of a revised nomenclature based upon the suggestions of Freudenberg and Sidhu and upon observations made in this study is given in Table 3.

TABLE 3.

Name	Formerly called
(+)-Syringaresinol	Lirioresinol B; lirioresinol C[16]
(−)-Syringaresinol[20]	(−)-Lirioresinol C[21]
(+)-Episyringaresinol	Lirioresinol A[16]
(−)-Episyringaresinol[20]	—

Besides glaucarubol and (−)-syringaresinol, ellagic acid and betulin were isolated from *H. emoryi* in the course of this study.

EXPERIMENTAL

Melting points were taken in capillaries and are corrected. Spectral measurements were made with Beckman IR4 (i.r.), Varian A-60D (NMR), AEI-MS9 (m.s.) spectrometers, and a Cary 60 spectropolarimeter with circular dichroism accessory, model 6002.

Extraction of Holacantha emoryi

Seeds of *H. emoryi* (7·86 kg), collected 25 miles southwest of El Centro, California, in April, 1968, were powdered and defatted with pentane (giving 706 g (9 per cent) of oily extract). The plant material was dried and allowed to stand for 3 days after the addition of 15 l. H_2O and then extracted exhaustively with $CHCl_3$ and MeOH. After removal of the solvents the residual syrup was diluted with an equal volume of MeOH. A precipitate (ellagic acid; identified by comparison with an authentic specimen) was removed and the filtrate evaporated. Extraction of the residue with $CHCl_3$ (A) and then with $CHCl_3$–EtOH, 3:1 (B), gave extracts that were examined separately.

Isolation of (−)-*Syringaresinol* (*V*)

The $CHCl_3$ extract (A) was washed with 2 N $NaHCO_3$, dried, and chromatographed on silica gel. Fractions containing syringaresinol (TLC) were combined and evaporated to give 1·5 g of the crude lignan. After repeated recrystallization from acetone–Et_2O, this afforded 250 mg of (−)-syringaresinol, m.p. 184–187°; $[\alpha]_D^{24} -32{\cdot}5°$ ($c = 0{\cdot}46$, $CHCl_3$). (Calc. for $C_{22}H_{26}O_8$: C, 63·15; H, 6·26. Found: C, 63·37; H, 6·44 per cent.)

The NMR spectrum showed, besides signals for the MeO— groups at δ3·88, the aromatic protons at δ6·57, and the —OH groups at δ5·57, a doublet for Ar—CH(—O)— at 4·73, a multiplet between about δ3·75 and 4·40 for the four protons of $—CH_2O—$, and a narrow multiplet at 3·10 for the protons at the ring junction. The mass spectrum showed the molecular ion at *m/e* 418 and prominent fragments at *m/e* 167 corresponding to the 4-hydroxy-3,5-dimethoxybenzyl ion and at *m/e* 181 for the syringoyl ion.

(−)-*Syringaresinol Diacetate*

Prepared in the usual way (acetic anhydride-pyridine, room temperature), the acetate had m.p. 185–186°; $[\alpha]_D^{24} -5{\cdot}2°$ ($c = 0{\cdot}52$, $CHCl_3$). (Calc. for $C_{26}H_{30}O_{10}$: C, 62·14; H, 6·02. Found: C, 62·15; H, 6·06 per cent.)

The mass spectrum showed *m/e* 502 (M^+) and principal peaks at 460 ($M—CH_2CO$), 418 (460 $—CH_2CO$), 210, 209, 193, 181, 167, 161, 154 and 151. Its NMR spectrum showed the expected features for the structure assigned; it was essentially identical with that of the phenol except for the absence of the signal for —OH and the appearance of that for the acetyl methyl groups (δ2·32).

(−)-*Syringaresinol Dimethyl Ether*

Methylation of (−)-syringaresinol with Me_2SO_4 and alkali in the manner previously described[14] yielded the methyl ether, m.p. 123·5–125°, $[\alpha]_D^{23} -41{\cdot}7°$ ($c = 0{\cdot}46$, $CHCl_3$). (Calc. for $C_{24}H_{30}O_8$: C, 64·56; H, 6·77. Found: C, 64·68; H, 6·92 per cent.)

The circular dichroism curve showed a negative maximum at 274 nm, $[\theta] = -3020$ (MeOH). The mass spectrum showed peaks at *m/e* 446 (M^+), 414, 347, 265, 250, 235, 223, 207, 195 and 181. The NMR spectrum showed the expected features (six methyoxl groups, no phenolic hydroxyl).

Glaucarubol (III)

A proportion of the $CHCl_3$–EtOH extract (B) was evaoprated and the residue extracted with hot ethyl acetate. An insoluble residue (2·3 g) was warmed with H_2O, when most of it dissolved leaving glaucarubol as an insoluble residue. Recrystallized from MeOH, this afforded 380 mg of glaucarubol, m.p. 291° d. (reported,[11] 290–292° d.), $[\alpha]_D^{25}$ 38·2° (*c* = 0·54, pyridine) (reported,[11] 38°, c = 0·8, pyridine). (Calc. for $C_{20}H_{28}O_8$: C, 60·59; H, 7·12. Found: C, 60·72; H, 7·13 per cent.)

The mass spectrum showed the molecular ion at *m/e* 396. Glaucarubol gives the characteristic[5] deep purple color with conc. H_2SO_4.

Glaucarubol Pentaacetate

Acetylation of glaucarubol with acetic anhydride–pyridine (90 min, steam bath) yielded the pentaacetate which, after chromatography (silica gel) and crystallization from ether–hexane, formed colorless needles, m.p. 200–201°. Mixed with an authentic specimen[8] (m.p. 199–200°), the m.p. was unchanged. (Calc. for $C_{30}H_{38}O_{13}$: C, 59·40; H, 6·31. Found: C, 59·30; H, 6·51 per cent.)

The mass spectrum showed the highest *m/e* value at 546 (M-60). No hydroxyl absorption was found in the i.r. spectrum.

The NMR spectrum was identical with that published by Polonsky *et al.* It showed the following signals: δ1·03 (d, *J* = 6, C-13 methyl); 1·43 (s, C-10 methyl); 1·70 (s, br, C-4 methyl); 1·82, 1·98, 2·10, 2·16 and 2·24 (all s, acetoxymethyl); 3·34 (s, C-9 H); 3·84 (d, *J* = 13) and 4·65 (d, *J* = 13), —CH_2OAc; 4·65 (t, C-7 H); 5·05 (C-12 H); 5·10 (C-1 H); 5·4 (C-2 H, C-3 H); 6·22 (d, *J* = 11, C-15 H).

Comparison of glaucarubol pentaacetate from *H. emoryi* with that from *Castela nicholsoni*[7] showed their identity.

Acknowledgements—The plant material was collected by Mr. R. .J Barr, Tucson, Arizona. Preliminary studies on *H. emoryi* were carried out in this laboratory by Drs. R. S. Rosich and F. P. Toribio. These studies were supported by a research grant AI-7435 from the U.S. Public Health Service, and one of us (L. B. de Silva) wishes to acknowledge the support provided by a Fulbright Fellowship (1968–9). Elemental analyses are by Miss Heather King. The spectropolarimeter and the mass spectrometer were obtained with funds provided by the National Science Foundation in grants GP-1682 and GP-3672, respectively.