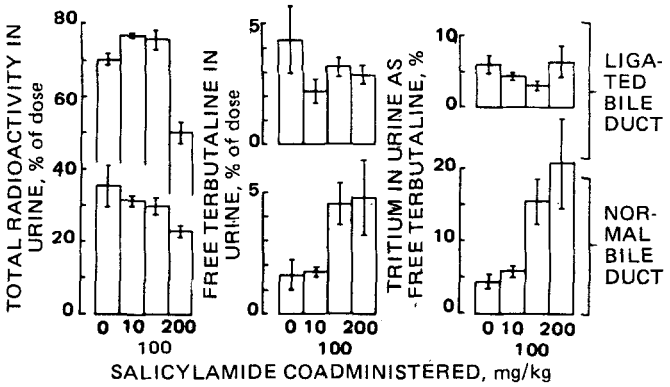


Figure 1—*Excretion of total radioactivity and free terbutaline in the 24-hr urine following oral administration of ^3H-terbutaline (1 mg/kg) coadministered with salicylamide to rats with either patent or ligated bile ducts. Values are the means ±1 SE for groups of three rats.*

that terbutaline in the intestinal wall and in the liver is not appreciably inhibited by coadministered salicylamide. A definitive explanation for the rise in the fraction of terbutaline excreted unchanged when salicylamide was coadministered to normal animals cannot be given. Nevertheless, the observation can be rationalized in terms of the reported finding (2) that unchanged terbutaline passing the gut and subsequently conjugated in the liver is preferentially excreted in the bile while the conjugate previously formed in the intestinal wall is preferentially excreted in urine. The simultaneous presence of salicylamide or its conjugate might influence the partitioning between bile and portal blood of terbutaline glucuronide formed in the liver and thereby influence the observed fraction of terbutaline excreted unchanged in the urine. Such a process would not influence the ratio of metabolites in bile duct-ligated animals since all conjugated drug, regardless of its site of formation, would be excreted in urine.

REFERENCES

(1) W. D. Conway, S. M. Singhvi, M. Gibaldi, and R. N. Boyes, *Xenobiotica*, **3**, 813 (1973).

(2) S. M. Singhvi, W. D. Conway, M. Gibaldi, and R. N. Boyes, *ibid.*, **4**, 563 (1974).

(3) G. Levy and J. A. Procknal, *J. Pharm. Sci.*, **57**, 1330 (1968).

(4) G. Levy and H. Yamada, *ibid.*, **60**, 215 (1971).

(5) C. F. George, E. W. Blackwell, and D. S. Davies, *J. Pharm. Pharmacol.*, **26**, 265 (1974).

(6) M. E. Connolly, D. S. Davies, C. T. Dollery, C. D. Morgan, J. W. Paterson, and M. Sandler, *Br. J. Pharmacol.*, **46**, 458 (1972).

(7) W. D. Conway, H. Minatoya, A. M. Lands, and J. M. Shekosky, *J. Pharm. Sci.*, **57**, 1135 (1968).

(8) W. D. Conway, V. K. Batra, and A. Abramovitz, *ibid.*, **62**, 1810 (1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 14, 1976, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260.*

Accepted for publication January 8, 1977.

Supported in part by a grant from Astra Pharmaceutical Products, Worcester, Mass., and by General Research Support Grant 5-S01RR-5454-10 from the National Institutes of Health, Bethesda, MD 20014.

* Present address: Drug Metabolism Laboratory, Squibb Institute for Medical Research, New Brunswick, NJ 08903.

‡ Present address: Wyeth Ltd., Toronto, Canada.

ˣ To whom inquiries should be directed.

Dehydrodiisoeugenol: A Naturally Occurring Lignan from *Aristolochia taliscana* (Aristolochiaceae)

F. IONESCU, S. D. JOLAD, and J. R. COLE ˣ

Abstract □ The ethanol–water extract of *Aristolochia taliscana* Hook and Arn (Aristolochiaceae) yielded a compound which was identified as dehydrodiisoeugenol by means of elemental analysis, IR, UV, NMR, and mass spectra, and direct comparison with a synthetic sample.

Keyphrases □ *Aristolochia taliscana*—ethanol–water extract of aboveground parts, dehydrodiisoeugenol isolated and identified □ Dehydrodiisoeugenol—isolated from ethanol–water extract of aboveground parts of *Aristolochia taliscana* □ Lignans—dehydrodiisoeugenol isolated from ethanol–water extract of aboveground parts of *Aristolochia taliscana*

During the search for tumor inhibitory constituents from plants, it was found that the ethanol–water extract of stems, leaves, flowers, and fruits of *Aristolochia taliscana* Hook and Arn (Aristolochiaceae)[1] contained a crystalline substance that did not show tumor inhibition activity against the P-388 lymphocytic leukemia test system[2] (3PS). However, to determine the nature of the potentially active constituents in the ethanol–water extract of this plant, it was decided to characterize the isolated compound. The plant was collected in Nayarit, Mexico, in June 1970.

RESULTS AND DISCUSSION

Elemental analysis and molecular weight determination of the compound, mp 130°, by mass spectrometry indicated the molecular formula $C_{20}H_{22}O_4$. IR, UV, NMR, and mass spectral data revealed that the compound corresponded to dehydrodiisoeugenol (I), an oxidation coupling product of *trans*-isoeugenol (1). This structure was verified by direct comparison of UV and IR spectra, co-TLC, and mixed melting point with a synthetic sample[3].

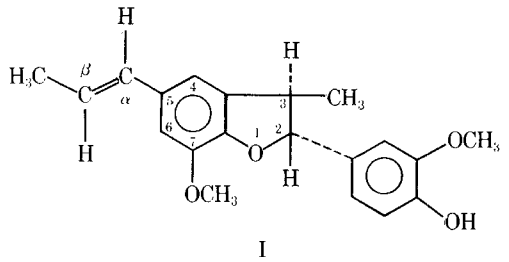
Dehydrodiisoeugenol, licarin A, was previously isolated for the first time from the trunk wood of *Licaria aritu* Ducke (Lauraceae) and characterized by IR, UV, optical rotatory dispersion, NMR, and mass spectral methods (2). Except for its melting point (114–116°) and optical activity, other data (UV, IR, and NMR) reported for licarin A[4] were identical with the dehydrodiisoeugenol isolated from *A. taliscana*.

[1] Identification was confirmed by Robert Barr, College of Pharmacy, and Dr. Charles Mason, Botany Department, University of Arizona, Tucson, Ariz., where a reference specimen was also deposited.

[2] Data from the Drug Evaluation Branch, Drug Research and Development, Chemotherapy, National Cancer Institute, Bethesda, MD 20014.

[3] Prepared in accordance with the procedure given in Ref. 1.

[4] Courtesy of Dr. O. R. Gottlieb, Laboratoio de Produtos Naturais da Fundacao de Amparo a Pesquisa do Estado de San Paulo, Instituto do Quimica, Universidade do Sao Paulo, Brazil.



I

EXPERIMENTAL[5]

Air-dried stems, leaves, flowers, and fruits of *A. taliscana* (5.5 kg) were ground in a Wiley mill and macerated with ethanol–water (1:1 v.v). The aqueous ethanol extract was filtered and air dried, and the residue (1 kg) was repeatedly extracted with methanol until the methanol was clear. The combined methanol filtrate was air dried, and the residue was exhaustively extracted with ether. The combined ether extract, after removal of the solvent under vacuum, was subjected to three-funnel partition between benzene–methanol–water (8:5:1 v/v) (each phase was 1600 ml).

The lower phases were combined and air dried, and the residue (28 g) was chromatographed on an aluminum oxide (Grade III; 1 kg) column using hexane with increasing concentrations of acetone (0.1–0.5%) as the eluent. Fifty 250-ml fractions were collected. Based on TLC analysis, fractions 9–34 were combined to give a residue. Treatment with petroleum ether yielded a colorless material, which was filtered and then crystallized from methanol as colorless needles. The melting point, 130°, was undepressed by admixture with a synthetic sample.

The IR (KBr: λ_{max} 3450, 3040, 2970, 2930, 2880, 2850, and 955 cm^{-1}), UV [CH_3OH: λ_{max} 243 (log ϵ 4.55) and 276 (4.35) nm], NMR [$CDCl_3$: δ 1.35 (3H, d), 1.83 (3H, d), 3.12–3.73 (1H, m), 3.38 or 3.85 (3H, s), 3.38 or 3.85 (3H, s), 5.07 (1H, d), 5.67 (1H, s), 6.01–6.27 (1H, m), 6.01–6.27 (1H, m), and 6.73–6.93 (5H, m) ppm], and mass [*m/e* 326 (M^+, base), 311, 283, 202, 189, 163, 151, 149, and 137] spectra are in accord with Structure I. This compound was optically inactive, $[\alpha]_D^{24} \pm 0°$.

Anal.—Calc. for $C_{20}H_{22}O_4$: C, 73.68; H, 6.80; mol. wt., 326. Found: C, 73.70; H, 6.91; *m/e* 326 (M^+).

[5] Carbon and hydrogen analyses were carried out by Chemalytics, Inc., Tempe, Ariz. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. UV and IR spectra were run on a Beckman KB spectrophotometer and a Beckman IR-33, respectively. NMR and mass spectra were run using a Varian T-60 spectrometer and a Hitachi Perkin-Elmer double-focusing spectrometer (model RMU-6E), respectively. Optical rotations were run in chloroform using a Cary 60 spectropolarimeter.

REFERENCES

(1) B. Leopold, *Acta Chem. Scand.*, **4**, 1531 (1950).

(2) C. J. Aiba, R. G. Campos Correa, and O. R. Gottlieb, *Phytochemistry*, **12**, 1163 (1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 24, 1976, from the *Division of Pharmaceutical Chemistry, College of Pharmacy, University of Arizona, Tucson, AZ 85721.*

Accepted for publication December 15, 1976.

Supported in part by Contract N01-CM-3-3750 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014, and the Elsa U. Pardee Foundation, Midland, Mich.

[x] To whom inquiries should be directed.

Rapid GLC Determination of Propranolol in Human Plasma Samples

ROBERT E. KATES [x] and CATHERINE L. JONES *

Abstract □ A rapid GLC method for measuring plasma propranolol levels is reported. 4-Methylpropranolol was utilized as an internal standard. Pentafluoropropionate derivatives of propranolol and the internal standard eluted rapidly and gave good sensitivity under the conditions employed. The advantage of this procedure over previously reported methods is the speed of analysis, which is facilitated by rapid elution of contaminant peaks.

Keyphrases □ Propranolol—GLC analysis, human plasma □ GLC—analysis, propranolol in human plasma □ Cardiac depressants—propranolol, GLC analysis in human plasma

Recent studies demonstrated that the effect of propranolol is plasma level related (1, 2). The accurate measurement of plasma propranolol levels has become essential for studies involving the mechanism of action of this agent; in some institutions, the monitoring of plasma propranolol levels is being used to aid patient therapy. Because of the increasing demand for rapid and accurate analysis of propranolol in plasma samples, previously reported procedures are being modified to increase efficiency and new procedures are being offered as improved alternatives.

The fluorometric method for measuring propranolol in biological fluids recently was reported to be limited with respect to both specificity and sensitivity (3). Three GLC procedures were proposed, two utilizing trifluoroacetyl derivatives (4, 5) and one utilizing a difluorobutyrate derivative (6); each employs a different internal standard. These three methods have their subtle differences and each, in order of publication, offers an advantage over the previous method. When analyzing large numbers of samples, however, these methods share one common disadvantage: the slow elution of contaminant peaks, which limits the frequency with which samples can be injected. Because of this limitation, an alternative procedure was developed, affording a greater efficiency by facilitating the more rapid analysis of large numbers of samples.

EXPERIMENTAL

Reagents—Glass-distilled[1] benzene, ethyl acetate, and cyclohexane were used, and 5 *N* NaOH, 0.2 *N* H_2SO_4, and 0.05 *M*, pH 11.5 phosphate buffer were prepared with double-distilled water and extracted twice with benzene. GLC grade pyridine[2] was diluted to 1.5% in ethyl acetate.

[1] Burdick & Jackson Laboratories, Muskegon, Mich.

[2] Pierce Chemical Co., Rockford, Ill.