green plants, form the principal tropophytes. The deciduous forests, which include the oaks, the beeches, the ashes, the maples, the walnuts, the chestnuts, cover a great part of eastern and western China, central Europe (England, France, Belgium, Germany) and eastern Australia, and are coincident with countries occupied by most civilized races of man, such as the Americans, Europeans, Chinese and Japanese. The cold temperate climatic conditions which have determined the distribution of the forest trees have been influential also in the development of the energetic races of mankind.

AMERICAN STYRAX.*

BY RAY E. SPOKES.

The name styrax is applied to an exudation obtained from several species of Liquidambar, belonging to the family of Styraceae, and growing in tropical and subtropical countries. There are two commercial varieties, one known as Levant styrax, and the other known as American styrax, or sweet gum, obtained from *Liquidambar styraciflua*. Styrax is official in nearly all the pharmacopoeias, and the tests and standards refer solely to the Levant variety, or balsam of European origin.

The balsam was discovered soon after the discovery of America, and, soon after the first settlement, vast shipments were sent from Mexico to Spain and other European countries, where it was used in medicines, ointments, incense, and perfumery. Shortly before the world war, the amount of material exported to the United States was limited, and interest was aroused in the American styrax, in order to meet the demands. This had been used for years by the aborigines in the western hemisphere, even prior to the discovery of America; the early settlers appreciated its value and considered it one of the great discoveries along with tobacco, cinchona, etc. As there was thought to be some difference in composition between the Levant and the American variety the shipments fell off; there continued a local use, however, not only by people of Central America and northern parts of South America, but by people of this country.

During 1918 Levant styrax was not obtainable; in 1916–1917, styrax was quoted at $6.00 to $7.00 per pound. It is said that American styrax can be gathered and sold, at a profit, at $1.50 a pound.[1] Owing to the limited supply of the European article, even at the present time, the American species must be recognized, and for this reason has received some attention of late. It is now extensively used in perfumery, for incense, and in tobacco. Many of the analyses have been made from the exudations of South American trees; the material for this study was collected from trees growing in the vicinity of Atlanta. The South American product is semi-liquid; the product obtained from southern United States is of a firmer consistency, resembling the European styrax.

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* The writer is indebted to Dr. Henry Kraemer, who has been deeply interested in the development of American styrax, and who assisted in obtaining the various samples.

[1] H. Kraemer, *Am. J. Pharm.*, 1918, 404.

Hanbury[1] states that a conventional distinction of confining the name styrax to the liquid drug and storax to the solid drug is adopted by some authors. Throughout this paper, the name styrax refers to the semi-liquid drug, unless otherwise noted. "Storax" is the English equivalent of the original Greek word. Tschirch[2] has worked out (1901) the chemical constituents of American styrax in a very interesting way, along lines similar to those followed by von Miller in his work on styrax. At that time the museum of the Pharmaceutical Society of Great Britain and the pharmacognosy collection of Berne possessed no authentic samples of American styrax. Tschirch, working on styrax from Mobile, Ala., and von Miller, working on styrax from Statesville, N. C., have isolated the following constituents: Styrol, free cinnamic acid, styracin, cinnamic acid-phenyl-propyl ester, vanillin, and styresinol, both free and as the cinnamic acid ester. Tschirch states that the ethyl ester of cinnamic acid exists only in the Levant species, but this may be due to some change in the method of collection. The first work attempted on the American variety, previous to this time, is found in the *Journal de Pharmacie* for June 1831. In that article, M. Bonastre furnished a description of a styrax product from America, and also gave some account of its constituents. Its acid, previous to this time, was thought to be benzoic, and it was only after Liebig detected cinnamic acid in Peru and Tolu balsams, that he suspected its presence in styrax. About this time M. Plantemeur and Fremy contributed some information of a general nature relative to the gum.

The valuation of styrax is rendered rather difficult, because the true composition of the constituents of the gum as they normally occur is not fully known; when this is determined, more frequent and successful use will be made. The quality of styrax has deteriorated markedly in the last few years. Requirements of the various pharmacopoeias have been compared, and it appears that the acid and saponification numbers are not sufficient criterions of quality. Since the consumption of a strictly U. S. P. product is comparatively small, interest in having the acid number changed in the pharmacopoeias, so that the American styrax may be included, is more academic than commercial, the bulk being used, as heretofore mentioned, for technical purposes.

It appears that the cinnamic acid content does not add or detract from the therapeutic value, as the presence of the acid may indicate an ester decomposition, and one might assume that the lower the cinnamic acid content, existing as true acid, the higher the percent of aromatic constituents. The samples used were of average quality, some were lighter and less firm than others, but all softened in the hand, became elastic, and melted to a clear, yellow fluid at 50°. It will be noted that the saponification number ran just within the U. S. P. requirements, about constant at 170°. The total cinnamic acid content was determined by the bromine absorption method which after trying several methods is, in the writer's opinion, the best and most accurate. This method was first suggested by Lemke and von Itallie,[3] and depends upon the following reactions:

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[1] Hanbury, "Science Papers."

[2] Tschirch and von Itallie, *Arch. der Pharm.* 238 532, 1901.

[3] Schweiz: *Apoth.-Ztg.* 1918, 286.

$$3C_6H_5CH:CH.COOH + KBrO_3 + 5KBr + 3H_2SO_4 = C_6H_5CHBr.CHBrCOOH + K_2SO_4 + H_2O.$$

$$KBrO_3 + 5KBr + 3H_2SO_4 = 3H_2SO_4 + 6Br + 3H_2O.$$

$$1Na_2S_2O_3 = 1\,I = 1Br \begin{array}{l} \nearrow \dfrac{KBrO_3}{6} \\ \searrow \dfrac{C_6H_5CH:CH.COOH}{2} \end{array}$$

1 Cc. $\frac{N}{10}$ thiosulphate, or 1 Cc. $\frac{N}{10}$ bromate = 0.0074 Gm. cinnamic acid.

The details for carrying out this method are to be found in the reference below. The U. S. P. method, in which the weighed sample is shaken out for a period of two hours with petroleum benzin-alcohol-potash mixture and then titrated, does not appear to be adequate. The bromine method gives very constant results, although a method as outlined by C. A. Hill and T. T. Cocking is equally as good.[1] All my samples were strained:

	(a). %.	(b). %.	(c). %.	U. S. P. Standard.
Incineration residue	1.4	1.4	1.4	not more than 1%
Acid value	35	39	37	not more than 86
				not less than 56
Undissolved residue	3.0	3.5	3.6	not more than 2.5%
Cinnamic acid (free)	12.07	13.84	13.75	*Saponification value*
Resin esters	34.1	35.5	.....	not more than 230
Styrol	1.1	1.6	.....	not less than 170

In estimating the esters in American styrax, results seem to vary as much as four percent, when analyzing aliquot portions of the same sample, under slightly varying conditions. Like results were obtained in determining the composition of formates and acetates by A. Behal.[2] It is altogether possible that, under a reflux condenser, the esters of styrax in the presence of alcoholic potash are decomposed with the result that a certain amount of the esters of an alcohol of lower molecular weight and also an alcohol of higher molecular weight is split off. Behal points out that in heating benzoates of phenol, p-chlorphenol, eugenol, etc., with semi-normal alcoholic potash solution a certain amount of ethyl benzoate forms which is sweet-smelling in contrast to the benzyl benzoate that has but little odor. Results similar to these occur with cinnamyl cinnamate; the reaction becomes more pronounced when a large amount of alcoholic potash is used. I determined the acid content in as many as fifteen samples of American styrax by placing them in a 125 Cc. combustion bottle in an autoclave, and hydrolyzing them for a period of two hours at 50 pounds' pressure. The results, although running from one to two percent higher than in instances where reflux condensers were used, were entirely satisfactory and the method is to be recommended. Nievierre points out that heating under pressure gives high results not due to any possible action of the alkali on the ester, but probably to the influence of such other bodies as aldehydes. Tschirch and von Itallie have isolated an aldehyde from American styrax in a rather impure state, and have identified it as vanillin. This body

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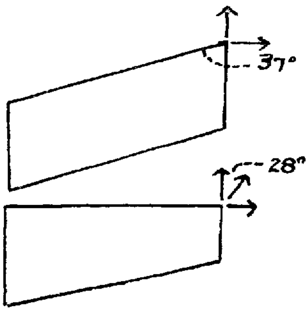
[1] Schimmel and Co. Report for 1912.

[2] *Bull. Soc. Chim.*, 1914, 565.

gave with phloroglycin hydrochloride the characteristic vanillin reaction, and with hydrochloric acid and pyrogallol the blue-violet reaction.

After the removal of sodium cinnamate by steam distillation of styrax and the subsequent treatment with caustic soda, the resinous mass contains styracin, or cinnamyl cinnamate. I obtained this by dissolving the resinous mass mentioned above in twenty parts of boiling alcohol, filtering, and recovering about two-thirds of the alcohol used by distillation. After cooling the residue, the styracin precipitates in a more or less impure state, and is very often gummy. To purify, the mass was washed with cold alcohol, and recrystallized from ether, when it formed pure white needle-shaped crystals, m. pt. 38°. It is distinguished from cinnamic acid by its action toward sodium hydroxide, its easy crystallization, and by the formation of the dibromide $C_6H_5CH:CHCO_2CH_2CHBr$, by brominating the ether solution of styracin until it is no longer decolorized. The white powder is then washed with ether, and recrystallized from hot alcohol.

If styracin be distilled with strong caustic soda solution, cinnamic alcohol passes over, leaving in the retort basic cinnamate of soda, which yields upon treatment with HCl, rhomboidal prisms of cinnamic acid. I have found additional help in the differentiation between styracin and cinnamic acid in the observation of their respective sublimates. Wherry[1] has published an article showing the application of the optical methods to the identification of organic compounds. Sublimates of both styracin and cinnamic acid were obtained according to the method of Tunmann in subliming similar organic compounds. The material is placed on an asbestos slab, first being placed upon a small piece of a recipient. At a distance of two or three centimeters from the asbestos slab is a wooden stick, 3–4 mm. high and 6–8 mm. long. A recipient for the sublimate is placed over the sublimate in such a way that one end rests upon the asbestos slab, and the other upon the wooden stick, care being taken that the recipient does not touch the lower piece of glass. Styracin does not sublime as readily as the cinnamic acid, the latter readily separates out in large rapidly growing crystals. Tunmann has found that silver nitrate dissolves the cinnamic acid crystals and causes them to lose their magnificent colors under polarized light.



Cinnamic Acid

Character mineral.........	+
Character zone...........	+
Biaxial..................	+
Extension................	parallel

Styracin

Character mineral.........	+
Character zone...........	—
Biaxial..................	+
Extension................	inclined

The remaining mass after the removal of the esters and acid was shown by Tschirch and von Itallie to contain styresinol, a cinnamic acid ester formation similar to that found in Asiatic styrax. Styrax often deposits resin when rubbed

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[1] "Optical Methods in Identification of Organic Compounds" (pamphlet).

upon the skin, even when mixed with oil. I obtained this styresinol by digesting a quantity of styrax for twenty-four hours at 30° with a one percent solution of caustic soda. The substance was light yellow, amorphous and melted between 154° and 161°. I could not obtain this in crystalline form. As styrax does not owe its efficacy to storesin, the resin of styrax, this may be removed by treatment with petroleum ether. Tschirch and von Itallie determined the formula of styresinol, which they report as a white amorphous powder, $C_{16}H_{22}O_2$. I was not able to obtain this in a seemingly pure state.

The volatile oil (1.5–2.0%) obtained by steam distillation has been identified as styrol $C_6H_5CH:CH_2$, a phenyl substitution product of ethylene, and identical to that obtained from the Oriental species. B. pt. 145°; sp. gr. 0.070; dextrorotatory 16° 30″. Meta styrol, solid, is not obtainable by prolonged heating in a sealed tube of the styrol from American styrax. This is easily obtained from the synthetic styrol. The optical rotation of the purified balsam was also determined. Two solutions, one an ethereal solution made from 10 Gm. balsam, 10 Gm. NaOH solution, and shaking with 50 Gm. ether; the other an alcoholic solution prepared by distillation of the ether from the above, and dissolving the residue in four times its quantity of alcohol. Specific rotation in each case was found to be (20°) 6° 20″.

A white amorphous body, styrogenin, is reported by some investigators to be present in styrax, but taking up their procedure with American styrax, I was not able to isolate any such body. The leaves of the American species possess a turpentine-like odor when bruised and yield when distilled a very small but varying portion of greenish yellow oil; sp. gr. 0.87, and having a rotatory power of 38° 45″. This oil consists of a terpene, borneol, and borneol acetate.

The balsam is as difficult to collect as is our Canada balsam, which is probably the greatest cause for a somewhat constant decrease in its use during the past years. The tree is one of the most ornamental of the American forests; the leaves are deeply lobed, fragrant, and turn deep crimson in the autumn. The bark develops an excrescence, this latter forms a pocket which secretes the balsam. Very often these pockets occur near the ground; when they occur near the top of the trunk, the balsam is collected with much more difficulty. To some extent, the trees in the South have been girdled in the spring, and the large yellow drops, first forming, harden and the balsam may be gathered. Trees thus killed often go to waste. In some cases young trees, which yield more balsam, are used, and the larger trees, suitable for timber, are thus saved. It has been suggested that a system of rotation be thus established.

In the early spring, the trees are wounded by making shallow cuts in the branches, and these develop into resin pockets, with deposits of from one to four pounds. The previous summer's bark is easily removed. Often a cut is made in the excrescence and the balsam collected in the same manner as in the rubber industry, the balsam being led to a suitable container by means of a gutter. The balsam is skimmed off the top, and that still remaining in the bark is then extracted by placing the bark in horse-hair bags and pressing. The dried bark may then be used for fumigation.

American styrax is widely distributed from Connecticut to southeastern Missouri, south to Tampa Bay, Florida, through Arkansas and Oklahoma to

Texas, and then south to Mexico. There are some trees further north, but these are said to possess a lower balsamic content. The trees of the American species measure when well matured from five to twelve feet at the base, and often attain a height of 150 feet. The wood is exceedingly hard, and straight, close-grained, but not very strong. The roots spread widely and rapidly, and deeply under the ground. The sapwood has upwards of sixty layers of annual growth.

Among the common names for American styrax are sweet gum, gum wax, liquidambar, and copalm balm. Levant styrax has lately been quoted at $8.00 a pound, and very little on the market; American styrax is not quoted regularly; it should even now be produced at a figure less than half of this. In contrast to the Levant species the American variety seems to be exempt from insect injury. The outlook for larger use of American styrax seems encouraging.

STUDIES ON THE PHARMACOLOGY OF DIGITALIS BODIES.

I. THE ACTIVITY OF THE DIGITALIS GLUCOSIDES.

BY THOMAS S. GITHENS.*

In 1910 I began studies in this laboratory with a view to making a preparation of digitalis which would avoid as far as possible the irritating and nauseating properties of the crude drug, while retaining its entire physiologic and therapeutic powers. Experiments were made with the two usual methods of preparing digitalis glucosides; namely, the precipitation of inert matters by lead acetate; leaving the active glucosides in solution; and the precipitation of the glucosides by tannic acid followed by their further purification. It was, however, found that both of these methods destroyed a large proportion of the active constituents and that the glucosides which remained were altered in some obscure manner, so that they no longer represented the drug properly. An attempt was therefore made to separate and purify the active constituents without the use of powerful chemical agents.

In order to understand the problem presented it is advisable to describe briefly the chief constituents of digitalis, active and inert. Digitalis contains at least four active glucosides, of which only two are of importance; namely, digitoxin and digitalein. Gitalin, described by Kraft[1] as the chief active principle, was established by later work of Kiliani[2] to be a mixture of glucosides, altered by chemical manipulation. Digitoxin and digitalein resemble each other closely in physiologic and therapeutic action, but differ widely in solubility, absorbability and in power to resist destructive agencies. Digitoxin is freely soluble in alcohol, even more soluble in chloroform, but insoluble in pure water. It is, however, soluble in a solution of the saponin which is present in digitalis leaf and it is therefore extracted from the leaf by water. Digitalein is insoluble in chloroform and ether, freely soluble in water, and sparingly soluble in alcohol. It is well extracted from the drug by alcohol, only if the drug be powdered. Its solubility in alcohol is

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[1] F. Kraft: *Arch. der Pharm.* 250, 118, 1912.

[2] H. Kiliani: *Ibid.*, 252, 13, 1914.