THE RELATION OF CHEMICAL STRUCTURE IN CATECHOL COMPOUNDS AND DERIVATIVES TO POISON IVY HYPERSENSITIVENESS IN MAN AS SHOWN BY THE PATCH TEST

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(Received for publication, July 10, 1944)

In a previous study based on patch tests (1), a definite correlation was established in man between the responses to a poison ivy extract and 3-geranyl catechol. This substantiated the experimental results obtained by Landsteiner and Jacobs (2) in guinea pigs. These observations afforded biologic evidence that the active ingredient in poison ivy bears some relation to the catechol configuration with a long unsaturated side-chain in the 3-position (Fig. 1, formula 1).

In the present report a more detailed analysis of the effects of various catechol compounds applied to the skin will be given. An analogous study was reported by Toyama (3) in an investigation of urushiol and its derivatives on the skins of persons sensitive to Japan lac. Briefly, Toyama concluded that: (1) urushiol was the allergen in dermatitis due to Japan lac; (2) the dermatitis was caused by the catechol configuration with an unsaturated side-chain ($C_{15}H_{27}$) in the 3-position; (3) the intensity of the reaction was determined more by the presence of the hydroxyl groups; (4) compounds with longer alkyl chains were more harmful, the position of the alkyl group being almost wholly unrelated to the "toxicity."

Our present study provides additional substantiation of the view which postulates a close chemical and biologic relation between the active ingredients in poison ivy and Japan lac. The chemical and biologic literature refer briefly to the "vesicating" or "toxic" cutaneous effects of various compounds related to poison ivy "urushiol" and urushiol of Japan lac; among these are 3-methyl catechol, 3-*n*-propyl catechol, 3-allyl catechol, and 3-geranyl catechol (4). It may be noted that in nearly all such reports the fundamental distinction between primary irritation and true hypersensitiveness was apparently not considered. One of the main criticisms of such reports concerns the lack of adequate data on the concentrations used in determining whether a substance was harmful, and but little may be found on the nature of the reactions elicited. In this paper an attempt is made to bridge the gap.

Materials, Methods, and Manner of Evaluation

Patch tests were applied in the conventional manner to the skins of 50 patients who came to the Skin and Cancer clinic for various complaints which, except for one case, were unrelated to poison dermatitis. The tests were read at 48 hours and again at 96 hours as minimum readings, and in many cases observations were made for several weeks or more. The studies were carried out during the winter of 1943 and the spring of 1944. This group included a high percentage of persons who had no previous history of dermatitis due to poison ivy. This afforded a useful way of obtaining a large number of negatively reacting controls for purposes of evaluating the factors of primary irritation and of hypersensitiveness. As in a previous study, a few persons were found to be sensitive to poison ivy in the absence of a clinical history of dermatitis from this plant (1).

The substances investigated were various catechol compounds and derivatives, the formulas of which are given in Fig. 1. All were synthetic compounds (formulas 2 to 13), except "urushiol" dimethyl ether (formula 6) which was prepared by methylating the hydroxyl groups in the distilled oil obtained by alcoholic extraction of the poison ivy plant (5). The synthetic compounds were chemically pure,[1] whereas "urushiol" dimethyl ether may possibly have been contaminated by other ingredients (faint yellow color). These substances (formulas 2 to 13) were applied in the uniform concentration of 1 gm. per 100 cc. of acetone. Roughly computed, each patch contained about 0.5 mg. of substance in a 1 per cent solution in acetone. This relatively large concentration[2] was intentionally selected because it permitted better evaluation of the relation between chemical structure and hypersensitiveness to poison ivy, yet at the same time it was not fundamentally a primarily irritating strength. Quantitative tests, based on various dilutions, were not studied systematically.

The cutaneous reactions produced by these compounds were evaluated and checked in several ways: (1) by the simultaneous application of ground poison ivy leaves and, in a few cases, an acetone extract of the plant; (2) by the inclusion of a relatively large number of persons with no previous history of poison ivy dermatitis; (3) by the previous observations made with the use of an acetone extract of poison ivy and 3-geranyl catechol (1); (4) by the simultaneous use of other substances belonging in the Anacardiaceae family (7). The positive responses to the compounds were essentially the same as those exhibited by the ground leaves of poison ivy or the extract, save for intensity. These reactions were typically eczematous and similar in all respects to those shown by examples of contact dermatitis based on hypersensitiveness. In a few instances a mild degree of redness was found, particularly at the edges of the linen patch. These responses were probably instances of mild primary irritation and were considered as insignificant because they faded in the next 48 hours, often leaving faint pigmented areas, and because they differed entirely from the typical eczematous responses produced by poison ivy leaves or extract. In no instance did these erythemas become more pronounced on further observation.

A significant positive response showed varying grades of papulation, vesiculation, or bullous formation with outlying vesicles, and the vast majority exhibited typical vesicular or papulo-

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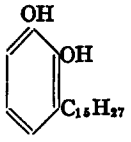
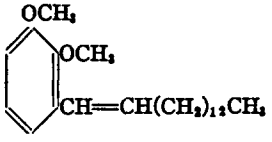
[1] All the synthetic catechols and derivatives (formulas 2 to 13) were solids which were recrystallized several times to a constant and sharp melting point (within a range of 1°). All gave elementary analysis which agreed within 0.3 per cent of the theoretically calculated values. The one exception (formula 13) was 3-geranyl catechol, an oily yellow-brown fluid, which had been synthesized by Kawai's method and had been furnished to us by Dr. Landsteiner (2).

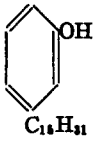
[2] However, quantitative studies now in progress with compounds of chemically related structure indicate that in some persons hypersensitiveness may be detected with the patch test using concentrations as low as 0.0001 per cent or less in acetone (7).

1 

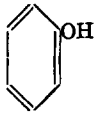
3-Pentadecadienyl catechol* (poison ivy "urushiol;" Japan lac urushiol)

5 

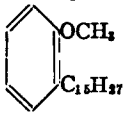
3-Pentadecenyl-1 -veratrole

10 

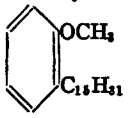
4-Pentadecyl catechol

2 

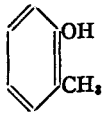
Catechol

6 

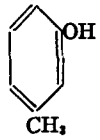
3-Pentadecadienyl veratrole ("urushiol" dimethyl ether; two double bonds, positions undetermined)

11 

3-Pentadecyl veratrole (hydrourushiol dimethyl ether)

3 

3-Methyl catechol

7 

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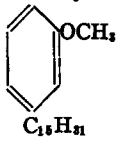
12 

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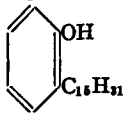
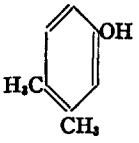
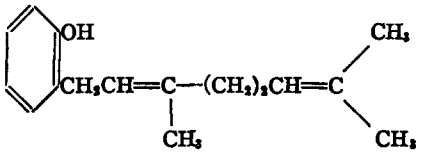
4 

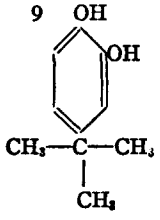
3-Pentadecyl catechol

8 

4,5-Dimethyl catechol

13 

3-Geranyl catechol

9 

4-Tertiary butyl catechol

FIG. 1

* It has been suggested that poison ivy "urushiol" is actually a mixture of several 3-pentadeca-catechols (8). The above formula is therefore an average representation of the side-chain, with varying degrees of unsaturation; the location of the double bonds has not yet been determined.

vesicular reactions that often increased in intensity in the following days and remained visible for several weeks. In order to provide a wider latitude in comparing the intensity of reactions, we used the following system of grading: 1 plus (a lasting erythema); 1 to 2 plus (erythema accompanied by edema or mild papulation); 2 plus (pronounced erythema with edema or a definite papular reaction); 2 to 3 plus (pronounced papular reaction with a few tiny vesicles); 3 plus (a moderate vesicular response); 3 to 4 plus (pronounced vesicular reaction with marked edema); 4 plus (widespread vesiculation); 4 to 5 plus (widespread vesiculation with small bullae); and 5 plus (large bullae with peripheral vesicles). This method of grading cutaneous reactions proved useful in making comparative observations. A significant positive reaction was considered as indicating present or past hypersensitiveness to poison ivy or a closely related allergen (1). Since none of the cases included in this study was suffering from poison ivy at the time of testing, with but one exception, and since a history of contact with related substances could not be obtained, it seems fair to conclude that in our study a positive reaction to poison ivy leaf or extract generally signified hypersensitiveness derived from past exposure to poison ivy. It is of fundamental interest to note that our observations in man are in essential agreement with the conclusions reached by Landsteiner and Jacobs in their studies on guinea pigs (2), although the clinical appearances and method of grading responses in guinea pigs were in many respects different from the criteria which we used. These data therefore seem to show a fundamental similarity.

RESULTS

A. General.—Of the 50 persons patch tested with these compounds, 21 gave positive reactions to the ground poison ivy leaves or the extract or both, whereas 29 showed completely negative responses. In this group, therefore, the incidence of persons sensitive to poison ivy as indicated by the patch test was 42 per cent. In every case showing negative reactions to poison ivy, all the synthetic catechol compounds gave uniformly negative responses. This provided additional evidence that the concentration used was not fundamentally a primarily irritating strength. As stated previously, a few instances revealed mild primary irritation, particularly at the edges of the linen patch, because in all probability the more rapid evaporation at the edges leads to greater concentrations at the periphery; the further course of these responses indicated their lack of significance.

B. Specific.—This section will concern the group of 21 cases which showed hypersensitiveness to poison ivy as indicated by the positive patch test to the poison ivy leaves or extract or both (Table I).

(1) Poison Ivy Leaves or Extract.—In the present study we were obliged, at first, to use coarsely ground poison ivy leaves for patch testing; in a few cases an acetone extract was also applied. In comparison with the acetone extract (1), the powdered leaves gave weaker reactions and, in addition, 5 out of the 19 cases, showed delayed responses occurring on the 3rd or 4th day after application of the patch. The delayed reactions indicated, in all likelihood, that the powdered leaves contained a relatively small percentage of active ingredient. Besides this, it was also found that the potency of various portions of this specimen varied considerably. For these reasons patients were observed at 48

hours and again in 96 hours after the patches were applied. This relatively large number of delayed reactions (5 out of 19) occurring on the 3rd or 4th day needs to be stressed, since conclusions based on observations limited to the first day or two may be fallacious. In general, the delayed responses were weaker than the positive reactions seen in 48 hours, the average of the former being about a 1 to 2 plus response; however, this rule was not invariably true. The

TABLE I

*Analyses of 21 Cases Sensitive to Poison Ivy**

Substance	No. of cases tested	No. of positive reactions	Positive	Average intensity of positive reactions	Other data
			per cent		
Rhus leaves (powdered)	19	19	100	++(+)	5 were delayed to 3rd or 4th day
Rhus extract (acetone)	4	4	100	+++	
	21‡	21‡			
3-Pentadecyl catechol	21	21	100	+++	One delayed reaction on 3rd or 4th day
4-Pentadecyl catechol	21	8	38	+(+)	3 delayed reactions on 3rd or 4th day
3-Methyl catechol	21	3	14	+(+)−++	One delayed reaction on 3rd or 4th day
3-Geranyl catechol	2	2	100	++++	
"Urushiol" dimethyl ether	13	3	23§	About ++(+)−+++	
3-Pentadecenyl-1′-veratrole	14	3	21	About ++(+)	

* See text for discussion of other catechols.

‡ Two cases were tested with both powdered leaves and extract.

§ The percentage of positives was increased when additional cases were tested (Table II).

reactions which were positive at 48 hours averaged about a 2 to 3 plus, with more intense responses to the acetone extract of poison ivy.

As stated previously, those cases which on extended observation showed negative reactions to poison ivy leaves or extract gave also negative responses to the various synthetic catechol compounds. In only one exceptional case was a mild follicular papular reaction seen with 4-methyl catechol, but this corresponded in no way with the significant positive responses exhibited by other catechol compounds nor did it bear any relation to hypersensitiveness to poison ivy. This observation may, therefore, be considered as without real significance in the problem at hand.

Finally, it may be noted that no direct comparison can be made between the reactions to poison ivy leaves or extract and the various catechol compounds since the percentage of active ingredient in the natural product or its extract was unknown.

(*2*) *3-Pentadecyl Catechol* (*Formula 4*).—In every person shown to be hypersensitive to poison ivy, 3-pentadecyl catechol likewise gave positive responses. These reactions, with one exception, were always more intense than those exhibited by the powdered leaves, the average being about a 3 plus vesicular reaction. The responses were about equal to those shown by the acetone extract of poison ivy. In most cases the responses to 3-pentadecyl catechol became more intense in subsequent periods of observation, and in a large number the sites were still visible several weeks later. In only one case was a genuine delayed reaction seen, this occurring on the 3rd or 4th day.

These results indicate definitely the occurrence of a group reaction between 3-pentadecyl catechol and the active ingredient in poison ivy.

(*3*) *4-Pentadecyl Catechol* (*Formula 10*).—Of the 21 cases showing positive reactions to both poison ivy and 3-pentadecyl catechol, eight gave positive responses to 4-pentadecyl catechol. In the latter group five showed mild positive reactions in 48 hours, the maximum being a 1 to 2 plus response. In the remaining three, delayed reactions of mild grade occurred on the 3rd or 4th day after the patches were applied. In all instances the reactions to 4-pentadecyl catechol were much weaker than those shown by 3-pentadecyl catechol.

The occurrence of group reactions between the active ingredient in poison ivy and 4-pentadecyl catechol is therefore demonstrated, although to a much lesser degree than that shown by 3-pentadecyl catechol.

(*4*) *3-Methyl Catechol* (*Formula 3*).—Only three cases showed positive reactions to 3-methyl catechol. In two of these instances the patients were also hypersensitive to 3-pentadecyl catechol but did not react to any compound containing the alkyl group in the 4-position. In the third case the patient was intensely hypersensitive to poison ivy and other catechol compounds; here the positive reactions to both 3-methyl catechol and 4-pentadecyl catechol were delayed to the 4th day, whereas 3-pentadecyl catechol elicited a positive response in 48 hours. In all three, the reactions to 3-methyl catechol were far weaker than those to 3-pentadecyl catechol but somewhat stronger than those to 4-pentadecyl catechol in two of the three cases.

These results show that in occasional instances of intense hypersensitiveness to poison ivy, the group reactions extend to include 3-methyl catechol. In one of the three examples, the group reactivity seemed to implicate only the 3-position.

(*5*) *3-Geranyl Catechol* (*Formula 13*).—In a previous report (1) 3-geranyl catechol was found to elicit practically constant group reactions in cases sensitive to poison ivy. In a comparative study of the cutaneous effects of 3-geranyl

catechol (1 per cent in acetone) and of a potent acetone extract of poison ivy, the former gave more intense reactions than the latter in the vast majority of instances. In the present group of 21 cases two instances were patch tested with 3-geranyl catechol; this compound produced more intense responses than any of the other substances listed in Fig. 1. It may be noted that 3-geranyl catechol has a side-chain in the 3-position, which is not only fairly long (10 carbon atoms) but also unsaturated (two double bonds).

(*6*) *Remaining Catechol Compounds* (*Formulas 2, 7, 8, and 9*).—Of the 21 cases sensitive to poison ivy and 3-pentadecyl catechol, only one showed a delayed mild papular reaction to 4-tertiary butyl catechol; this patient likewise exhibited an essentially delayed vesicular response to 4-pentadecyl catechol (case 39).[3]

In no instance was there a positive response to 4,5-dimethyl catechol.

Only one case in the group of 21 gave a mild papular response to 4-methyl catechol (case 9).

In three instances (cases 9, 15, and 39) very mild or delayed reactions were encountered with catechol.

It may be concluded, then, that no group sensitivity was demonstrated with 4,5-dimethyl catechol. Slight, but probably insignificant, responses were encountered with catechol, 4-methyl catechol, and 4-tertiary butyl catechol; the mildness of the reactions elicited by these substances needs to be stressed, and in some instances it was difficult to differentiate them from primary irritation of a mild grade. The degree of group reactivity displayed by these substances was therefore regarded by us as insignificant. In no instances were these responses definitely vesicular.[4]

(*7*) *Veratrole Derivatives.*—These substances were derived from catechol compounds by replacing the two hydroxyl groups with methoxy radicals (—OCH_3). Two such derivatives were studied simultaneously with the other synthetic catechol compounds, and subsequently, two others were included in an additional comparative investigation of veratrole compounds.

(*a*) *3-Pentadecenyl-1′-Veratrole* (*Formula 5*).—This substance was tested in 14 of the 21 cases sensitive to poison ivy. In three cases which showed intense hypersensitiveness to poison ivy, the reactions to 3-pentadecenyl-1′-veratrole were positive (2 plus, 3 to 4 plus, and a delayed 2 to 3 plus in cases 15, 20, and 39 respectively).

In general then, "group" reactivity to this compound is demonstrated in cases illustrating intense hypersensitiveness to poison ivy. The response in

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[3] This was the 39th patient tested chronologically in the group of 50 cases.

[4] However, in a subsequent case (not included in the above statistics) a delayed widespread papular edematous reaction was produced by 4-tertiary butyl catechol; the significance of this reaction is unclear at present.

all cases was somewhat less pronounced than those exhibited by 3-pentadecyl catechol in the same patient.

(*b*) *"Urushiol" Dimethyl Ether or 3-Pentadecadienyl Veratrole (Formula 6).*— This substance, the only non-synthetic compound used in our study, was patch tested in 13 cases, and positive responses were obtained in three patients (cases 2, 15, and 39). Two of these three cases showed positive reactions to 3-pentadecenyl-1′-veratrole (cases 15 and 39), the responses to "urushiol" dimethyl ether being slightly more intense than those given by the latter substance.

The conclusion which holds for 3-pentadecenyl-1′-veratrole also applies therefore to "urushiol" dimethyl ether, the latter giving slightly more intense "group" reactions.

TABLE II

Comparison of Reactions of Veratrole Compounds in Additional Group of 20 Cases Sensitive to Poison Ivy, of Which 6 Had Active Lesions of Poison Ivy

Substance	No. of cases tested	No. of positive reactions	Positive	Average intensity of positive reactions
			per cent	
Rhus powdered leaf	7 } 20	7 } 20	100	<++(+)
Rhus acetone extract	13 }	13 }	100	>+++
"Urushiol" dimethyl ether	20	8	40*	About ++(+)
Hydrourushiol dimethyl ether	20	2	10	About ++
4-Pentadecyl veratrole	12	0	0	

* When the cases tested with urushiol dimethyl ether as recorded in Tables I and II were added together, the total number of cases tested was 33 and of these eleven were positive (33 per cent).

At this point it seemed advisable to study the comparative effects of a number of veratrole derivatives. This was done in a further series of 20 cases sensitive to poison ivy, among which were six patients with active lesions of poison ivy dermatitis. For our present purposes we wish to present data on the cutaneous effects of "urushiol" dimethyl ether (3-pentadecadienyl veratrole), hydrourushiol dimethyl ether (3-pentadecyl veratrole), and 4-pentadecyl veratrole. (Table II.)

In this group of 20 cases "urushiol" dimethyl ether elicited eight positive reactions, ranging from 1 to 2 plus to 3 plus. In all instances the response was weaker than that produced by an acetone extract of poison ivy but about equal to the reactions elicited by the powdered leaves. Adding these cases to those in the first group of 13 cases (Table I), the incidence of positive responses to this substance is 11 out of 33 cases hypersensitive to poison ivy.

(*c*) *Hydrourushiol Dimethyl Ether (3-Pentadecyl Veratrole) (Formula 11).*— In the same group of 20 cases used in the comparative study of veratrole

compounds, only two showed positive reactions to hydrourushiol dimethyl ether (2 to 3 plus and 1 to 2 plus). In both instances the reactions to "urushiol" dimethyl ether were more intense (3 plus and 2 to 3 plus respectively).

It may be concluded, then, that "group" reactivity to hydrourushiol dimethyl ether (3-pentadecyl veratrole) occurs but that it can be demonstrated only in an occasional instance.

(*d*) *4-Pentadecyl Veratrole* (*Formula 12*).—In this group of 20 cases twelve were tested with this substance; all gave negative responses. This indicates the absence of group reactivity on the part of this substance.

DISCUSSION

1. Relation to the Position and Length of the Side-Chain in Catechol Compounds.—Our results indicate that group reactions between the active ingredient in poison ivy and the various catechol compounds were observed in their most intense form with those containing an alkyl chain in the 3-position of the catechol nucleus. This was true of 3-pentadecyl catechol, which showed a constant group relation, and held to a much lesser degree for 3-methyl catechol. The data appear to show that in the 3-position, the longer alkyl chain was far more effective in producing positive reactions than the short chain. It is likely, therefore, that in passing from the short methyl group through the long straight-chain pentadecyl radical, the incidence of positive responses and their intensity would increase in a definite way. On the other hand, group reactions were not limited to the 3-position, for positive responses were obtained with 4-pentadecyl catechol, and these were more frequent than those exhibited by the compound having a short methyl radical in the 3-position. Among the compounds with an alkyl group in the 4-position, only the long-chain 4-pentadecyl catechol was effective in eliciting positive reactions, whereas the short side-chain compounds were generally ineffective or entirely negative. It is of interest that Landsteiner and Jacobs (2) in their experiments on guinea pigs were able to demonstrate mild group reactions between 4-tetradecyl catechol and urushiol. In one instance observed by us the hypersensitiveness displayed by the patient seemed to be restricted to catechol compounds with an alkyl chain in the 3-position. From these data we can conclude that the position of the side-chain is, contrary to Toyama's views, definitely related to the degree of "toxicity." A compound, such as 4,5-dimethyl catechol gave uniformly negative reactions. We have no data with respect to long-chain compounds in other positions in the catechol configuration.

2. Relation to the Degree of Unsaturation in Catechol Compounds.—Whereas 3-pentadecyl catechol gave uniformly positive group reactions in persons sensitive to poison ivy, the same was true of 3-geranyl catechol (1) which elicited even more intense responses. This was observed even though the geranyl side-chain is shorter than the pentadecyl radical, but, on the other hand,

3-geranyl catechol has two unsaturated bonds in its geranyl radical. It is likely, therefore, that the degree of unsaturation plays an important part in determining the grade of response to these catechol derivatives. Similar results were obtained in the case of the veratrole derivatives; thus, "urushiol" dimethyl ether gave more frequent and intense reactions than did 3-pentadecenyl-1′-veratrole, and the latter was more effective than hydrourushiol dimethyl ether. The point has often been stressed that contact dermatitis due to plants and trees is caused by unsaturated compounds. Although it is true that in nature unsaturated compounds exist in abundance, and whereas our data indicate the relatively greater reactivity of unsaturated compounds as compared with related saturated compounds, it may be pointed out that a high degree of group sensitivity was also exhibited by a saturated substance with a long-chain in the 3-position, namely, 3-pentadecyl catechol. It is of practical interest, therefore, that saturating the double bonds in the side-chain does not eliminate group hypersensitiveness in persons originally sensitized by the unsaturated compound, particularly when this involves a long side-chain with 15 carbon atoms. It will be interesting, also, to study the sensitizing ability of these long-chained saturated catechol derivatives in persons who are not sensitive to poison ivy.

3. Effect of Methylating the Hydroxyl Groups in Catechol Compounds.— The reactions elicited by the veratrole compounds, in which the hydroxyl groups of the catechol substances were replaced by methoxy radicals, showed definitely that the incidence of positive group reactions was much decreased but not entirely eliminated when the long-chain substituent was in the 3-position, although the reactivity was abolished when this substituent occupied the 4-position. Whereas Toyama claimed that hydrourushiol dimethyl ether was entirely harmless in persons sensitive to Japan lac, we obtained positive results in two out of 20 persons sensitive to poison ivy. A comparative study of the veratrole compounds bearing a long side-chain in the 3-position showed that more pronounced reactions were elicited by the compound with two unsaturated bonds ("urushiol" dimethyl ether) than the one with a single unsaturated bond (3-pentadecenyl-1′-veratrole), and the least effective was the substance with the side-chain fully saturated (hydrourushiol dimethyl ether).

It should be pointed out that patients showing a positive response to compounds in the veratrole series were generally highly sensitive to poison ivy and substances in the catechol series. This introduces a possible complication in drawing conclusions with respect to group reactivity, since the patch test technique permits detection of hypersensitiveness within a range of concentration that may be beyond the limits of chemical analysis. For this reason in considering the group reactivity in the veratrole series, three possibilities come to mind: (*a*) The skin may be capable of demethylating the veratrole compounds to a catechol configuration. In this connection it should be noted that hydrourushiol dimethyl ether, which elicited an occasional positive reaction,

was found to be relatively easy to demethylate chemically, whereas 4-pentadecyl veratrole, which gave uniformly negative responses, was demethylated only with difficulty.[5] (*b*) The veratrole compound may be contaminated by traces of catechol substance. Although this does not seem likely, further work with quantitative patch testing is needed to eliminate decisively this explanation. (*c*) The veratrole compounds elicit positive responses due to true group reactions.

4. Miscellaneous Points.—Catechol itself is very soluble in water, whereas the introduction of alkyl side-chains decreases water solubility and increases the solubility in fat solvents. 3-pentadecyl catechol, for example, is insoluble in water and quite soluble in fat solvents, and the same is true of the oil obtained from poison ivy. It therefore seems reasonable to believe that the active ingredient in poison ivy may be carried into the epidermis *via* the lipid components of the skin. The introduction of one or more double bonds in the 3-position should enhance both lipid solubility and water solubility, the latter undoubtedly to a much lesser extent. The increase in fat solubility may be attributed to the similar unsaturated nature of many fats themselves, and an enhanced water miscibility would be expected because of the polar character of the double bond. In any event, the active ingredient in poison ivy appears to be a catechol derivative with a long unsaturated side-chain in the 3-position (see footnote to Fig. 1). A consideration of the arrangement of polar and non-polar groups in poison ivy "urushiol" suggests the property of concentrating at the interface of water and oil. In this connection it is of interest, therefore, that 3-pentadecyl catechol, which is highly effective in eliciting group reactions, is readily emulsified, whereas the short-chain 3-methyl catechol, a much less active substance, is much less readily emulsified. It is likely that physical factors of this type are important in influencing the degree of contact with the skin.

Once having penetrated the layers of the epidermis, the fate of these catechol compounds with long side-chains is unknown as yet. The available evidence indicates that after a short period of contact with skin, the active ingredient in poison ivy is no longer demonstrable in its original form (1, 6). It is possible that the hydroxyl groups are oxidized to a quinone configuration or the compounds may in some way, unknown at present, combine with native protein in the manner suggested by Landsteiner's theory of haptens.

Finally, it must be stressed that the data recorded hold only for group reactions to catechol compounds and derivatives. There is evidence, which will be published in another paper (7), that the group reactivity extends to other phenolic derivatives.

[5] This suggestion is also in line with the observation that the dimethyl ether of 5-pentadecyl resorcinol, which is extremely difficult to demethylate chemically, has been found, thus far, to be inactive in patch tests in a concentration of 1 per cent in acetone, whereas the free resorcinol compound gave positive responses in a large percentage of cases under similar conditions (7).

SUMMARY AND CONCLUSIONS

1. Additional evidence is presented in support of the view which postulates a close chemical and biologic relation between the active ingredients in poison ivy and Japan lac.

2. Biologic evidence, based on the use of the patch test in man, is presented in support of the view that the active ingredient in poison ivy is a catechol derivative with a long, unsaturated side-chain in the 3-position.

3. Of the catechol compounds and derivatives studied, group reactions in patients sensitive to poison ivy leaves or extract were exhibited by the following compounds: 3-pentadecyl catechol (100 per cent of 21 cases), 4-pentadecyl catechol (38 per cent of 21 cases), "urushiol" dimethyl ether (33 per cent of 33 cases), 3-pentadecenyl-1′-veratrole (21 per cent of 14 cases), 3-methyl catechol (14 per cent of 21 cases), and hydrourushiol dimethyl ether (10 per cent of 20 cases). It has been found that 3-geranyl catechol shows a practically constant group reactivity in persons sensitive to poison ivy.

4. The uniformly positive group reaction to 3-pentadecyl catechol is notable since this substance possesses a saturated side-chain, whereas the active ingredient in poison ivy is known to have an unsaturated side-chain.

5. The group reactivity was not restricted to the 3-position, for in some instances 4-pentadecyl catechol also gave group reactions which, however, were less intense and less frequent than those shown by 3-pentadecyl catechol. This indicates that in some cases a long side-chain in the 4 position may be effective in producing group specific reactions.

6. Only an occasional person showed sensitiveness to 3-methyl catechol (short side-chain), and in one instance the group reactivity appeared to be specific for the 3-position.

7. The position of the side-chain in the catechol configuration has some bearing on the degree and incidence of group reactions in persons hypersensitive to poison ivy.

8. Evidence is presented to indicate that the introduction of double bonds in the alkyl side-chain increases the incidence and intensity of group reactions.

9. Methylating the hydroxyl groups in the catechol configuration diminishes strongly the incidence of group reactivity but does not eliminate it entirely in persons hypersensitive to poison ivy. Thus, "urushiol" dimethyl ether (3-pentadecadienyl veratrole) gave group reactions in 33 per cent of 33 persons.

10. Methylating the hydroxyl groups as well as saturating the double bonds in the alkyl side-chain still further diminishes the group reactions but an occasional person hypersensitive to poison ivy may still show positive reaction to such a substance as 3-pentadecyl veratrole (hydrourushiol dimethyl ether). In this respect our results are not in full agreement with those recorded by Toyama who stated that hydrourushiol dimethyl ether is entirely harmless.

11. The significance of the group reactivity displayed by certain veratrole compounds is discussed, and several possible explanations of their behavior are advanced.

12. The group reactions discussed in this paper relate only to various catechol and veratrole compounds. Preliminary studies by us indicate that this sensitiveness extends to other phenolic derivatives.

13. Among the veratrole compounds showing positive reactions, the order of frequency and intensity was: (1) "urushiol" dimethyl ether (average of two double bonds); (2) 3-pentadecenyl-1′-veratrole (one double bond); (3) hydrourushiol dimethyl ether (saturated side-chain). It may be noted that 4-pentadecyl veratrole was inactive.

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