The Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. 4,5-Dimethyl-3-pentadecylcatechol[1]

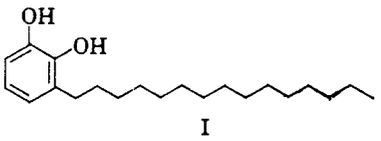
JOSEPH S. BYCK AND CHARLES R. DAWSON

Department of Chemistry, Columbia University, New York, New York 10027

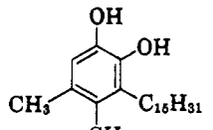
Received November 4, 1966

The allergenic components of poison ivy Urushiol have the carbon skeleton of 3-pentadecylcatechol. In order to evaluate the possible participation of the unsubstituted positions on the catechol ring in toxicity, sensitization, and allergenic response, two methods for the synthesis of 4,5-dimethyl-3-pentadecylcatechol have been examined. A successful synthesis from 3,4-xylenol is described and preliminary clinical results are reported.

It has been known for some years that poison ivy Urushiol, the dermatitis-producing material in the poison ivy plant, is an oil composed of four alkyl catechols differing only in degree of olefinic unsaturation.[2] Although it has been found that one of these, 3-pentadecylcatechol (I), can be used clinically as a substitute



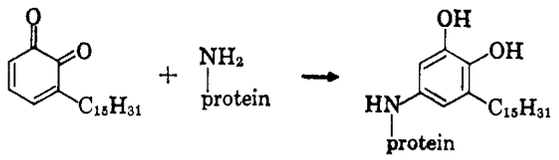
I



II

for the naturally occurring allergenic oil,[3] little is actually known about the physiological mode of activity of this compound. Studies by Keil, Wasserman, and Dawson[4] and by Kligman[5] on human subjects have demonstrated that the two vicinal hydroxyl groups and the alkyl side chain in the 3 position are important structural features related to the activity. However, much remains to be learned about the relationship between the chemical structure of this compound and its biological activity.

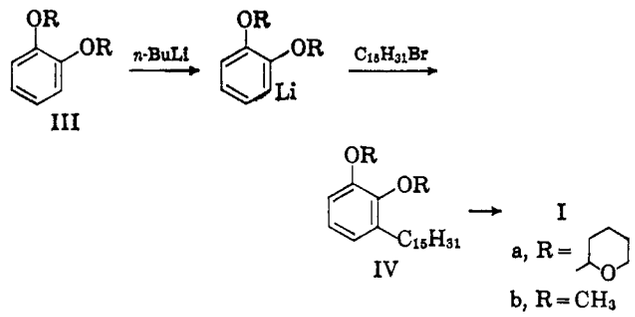
Any reaction pathway designed to explain the activity of such compounds must include an early reaction to account for the binding of the catechol to protein to form an antigen. Because of the well-known susceptibility of such catechols to oxidation leading to *o*-quinones, it has been suggested[6] that the protein binding may occur *via* a reaction of the type shown. Al-



though the *in vitro* formation of protein–allergen conjugates *via* the quinone has been experimentally demonstrated,[6] the possible involvement of such a reaction in the *in vivo* formation of antigen has not been investigated.

The initial phase of an investigation of the above hypothesis, now in progress in these laboratories, has been the synthesis and biological testing of 4,5-dimethyl-3-pentadecylcatechol (II). This compound differs from the naturally occurring 3-pentadecylcatechol only in that two methyl groups are substituted at the 4 and 5 positions of the aromatic ring, the normal sites of nucleophilic addition to the quinone. Such methyl substituents would be expected to greatly diminish the reaction between quinone and protein. Consequently, if the proposed pathway of antigen formation is involved *in vivo*, the catechol (II) should exhibit a marked reduction in allergenic activity.

As has been reported by a number of workers,[3b,c,4,7] the synthesis of 3-pentadecylcatechol can be conveniently accomplished starting from 2,3-dimethoxy benzaldehyde (*o*-veratraldehyde), which is readily available. The reaction of this aldehyde with tetradecylmagnesium bromide yields a carbinol which is easily converted to 3-pentadecylveratrole either by direct hydrogenolysis or by dehydration and subsequent catalytic reduction. The alkyl catechol (I) is then obtained by cleavage of the methoxyl groups. More recently, Hanafusa and Yukawa[8] published a three-step synthesis of 3-pentadecylcatechol directly from catechol. They reported having carried out the metalation of bistetrahydropyranylcatechol (IIIa) with butyllithium to obtain an aryllithium compound which was then allowed to react with 1-bromopentadecane in refluxing xylene. The product of this reaction was reported to be bistetrahydropyranyl-3-pentadecylcatechol (IVa) which was hydrolyzed without isolation to give compound I in 10–24% yield based on the quantity of alkyl halide used.



III

IV

It appeared that 4,5-dimethyl-3-pentadecylcatechol might be synthesized by either of these routes—from 5,6-dimethyl-*o*-veratraldehyde (V) in the first instance or from 4,5-dimethylcatechol by the Hanafusa and Yukawa procedure. Of the two, the latter procedure

(1) This investigation was supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health and by a predoctoral training grant (TI-GM-1130), National Institutes of General Medical Sciences, U. S. Public Health Service, to J. S. B. during 1963–1964.

(2) W. F. Symes and C. R. Dawson, *Nature*, **171**, 841 (1953); *J. Am. Chem. Soc.*, **76**, 2659 (1954).

(3) (a) H. Keil, D. Wasserman, and C. R. Dawson, *J. Allergy*, **16**, 275 (1945); (b) H. S. Mason, *J. Am. Chem. Soc.*, **67**, 1538 (1945); (c) C. R. Dawson, D. Wasserman, and H. Keil, *ibid.*, **68**, 534 (1946).

(4) H. Keil, D. Wasserman, and C. R. Dawson, *J. Exptl. Med.*, **80**, 275 (1944).

(5) A. M. Kligman, *Arch. Dermatol.*, **77**, 149 (1958).

(6) H. S. Mason and A. Lada, *J. Invest. Dermatol.*, **22**, 457 (1954).

(7) (a) H. S. Backer and N. H. Haack, *Rec. Trav. Chim.*, **57**, 225 (1938); (b) H. Keil, D. Wasserman, and C. R. Dawson, U. S. Patent 2,451,955 (Oct 19, 1948); (c) A. P. Kurtz and C. R. Dawson, unpublished results.

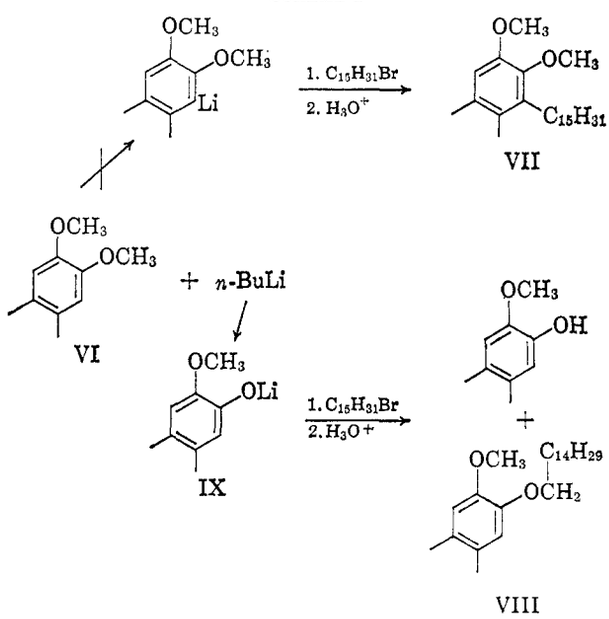
(8) T. Hanafusa and Y. Yukawa, *Chem. Ind.* (London), 23 (1961).

seemed more promising since the aldehyde (V) had never been prepared, whereas 4,5-dimethylcatechol has been synthesized in a variety of ways by Diepolder,[9] Loudon and Scott,[10] and Wood and Ingraham[11] and in this laboratory has also been prepared by pyridine hydrochloride ether cleavage of 4,5-dimethylveratrole which was prepared in three steps by the procedure of Bruce and Sutcliffe.[12] It was felt, however, that the route of Hanafusa and Yukawa would be satisfactory for the synthesis of II only if the conditions of the alkylation could be modified to give a substantially improved yield based on the starting catechol. Attempts in the present investigation to carry out the reaction in xylene as reported by Hanafusa and Yukawa, but using an excess of the alkyl halide rather than the catechol ether, failed to yield any 3-pentadecylcatechol. When diethylene glycol dimethyl ether (diglyme) was employed as the solvent in place of xylene, product was obtained, but the yield was still less than 10%, and no further modifications were found which improved the yield. From these results it was concluded that it would be difficult to utilize the sequence of reactions developed by Hanafusa and Yukawa as a general preparative method. This conclusion was later shared by the original authors.[13]

Although it had not been possible to accomplish the desired synthesis by metalation of bistetrahydropyranylcatechol, it was hoped that a similar approach might be successful if the corresponding dimethyl ether was used. As was noted above, 4,5-dimethylveratrole (VI) can easily be synthesized for use as starting material in the preparation of 4,5-dimethyl-3-pentadecylcatechol by such a route. An analogous synthesis had been accomplished by Barnes and Bush,[14] who converted 1,7-dimethoxynaphthalene to 6-methyl-1,7-dimethoxynaphthalene *via* metalation with butyllithium and subsequent alkylation. In the current investigation, the preparation of 3-pentadecylveratrole (IVb) in such a manner from veratrole (IIIb) was first attempted as a model for the synthesis of the analogous dimethyl compound. It was found that metalation of veratrole by butyllithium, followed by reaction of the resulting veratryllithium with 1-bromopentadecane, produced 3-pentadecylveratrole in 45–60% yield. Use of xylene or diglyme as solvent during the alkylation resulted in approximately the same yield, but the reaction proceeded more rapidly in diglyme to give maximum yield after only 6 hr instead of 24 hr when xylene was used.

Although synthesis of 3-pentadecyl veratrole by this route appeared to be most satisfactory, attempts to alkylate 4,5-dimethyl veratrole in the same way were not successful. The product of the reaction at first appeared to be the desired compound (VII), but further investigation established that it was actually 2-pentadecyloxy-4,5-dimethyl anisole (VIII). This structure is consistent with the observed nmr spectrum of the compound since the integration of the peaks at τ 6.41 (OCH) and 3.65 (aromatic hydrogens) were found to be in the ratio 5:2, not 6:1 as would be expected for structure VII. Furthermore, ether cleavage of the alkylation product by means of refluxing pyridine hydrochloride gave 4,5-dimethylcatechol (in satisfactory yield) and no 4,5-dimethyl-3-pentadecylcatechol. This result is also consistent with formation of VIII instead of VII. Since the presence of the two methyl groups on the ring is the only change in the molecule and must be responsible for the altered course of the reaction to give VIII, this unexpected result is probably best explained in the following manner. Apparently the methyl group *ortho* to the 3 position produced considerable steric hindrance to metalation at that site so that the butyllithium reacted instead with one of the methoxyls which resulted in cleavage of a methyl ether linkage to give IX, the lithium salt of 4,5-dimethylguaiacol (see Scheme I). A portion of this

SCHEME I



lithium phenoxide must then have reacted with alkyl halide to yield VIII, while the remainder was later hydrolyzed to 4,5-dimethyl guaiacol, which was isolated as a second product of the reaction. It seemed that cleavage to the guaiacol might be minimized, thus permitting the reaction to follow the desired course, if a lower boiling solvent were employed in the alkylation step in place of diglyme (bp 160.5–162.0°). Both ethyl ether (bp 34.6°) and dimethoxyethane (bp 83°) were tried, but neither was successful. Although no appreciable amounts of 4,5-dimethylguaiacol or of VIII were formed in either case, it appeared that little metalation of the aromatic ring took place either, since much of the starting material was recovered unchanged.

Once it seemed unlikely that 4,5-dimethyl-3-pentadecylcatechol could easily be synthesized from an ether of 4,5-dimethylcatechol by a direct alkylation route employing metalation by butyllithium as proposed, the synthesis of 5,6-dimethyl-*o*-veratraldehyde (V) was undertaken since the conversion of that compound to II should clearly be possible by the other well-established route previously described. The simplest way by which compound V might have been prepared was the direct formylation of 4,5-dimethylveratrole (VI). Since VI is a symmetrical compound, only one monoformylation product would have been possible.

(9) B. Diepolder, *Ber.*, **44**, 2501 (1911).
(10) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).
(11) B. L. B. Wood and L. L. Ingraham, *Arch. Biochem. Biophys.*, **98**, 479 (1962).
(12) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 3820 (1956).
(13) T. Hanafusa, private communication.
(14) R. A. Barnes and W. M. Bush, *J. Am. Chem. Soc.*, **81**, 4705 (1959).

The formylation was attempted by a Gatterman aldehyde synthesis and also using phosphorus oxychloride and N-methylformanilide (Vilsmeir reaction[15]). Although veratrole can be converted to 3,4-dimethoxybenzaldehyde by either of these reactions, all attempts at the formylation of VI, which requires *ortho* rather than *para* substitution, failed to produce any product. Since 4,5-dimethylveratrole cannot be successfully metalated by butyllithium for the reason elaborated above, it was also not possible to accomplish the formylation by treating dimethylveratryllithium with dimethylformamide or any of several similar compounds which have been used in the preparation of substituted benzaldehydes in such a manner.

Having thus failed to find a convenient procedure for the direct formylation of 4,5-dimethylveratrole, the synthesis of 4,5-dimethylguaiacol (X) was carried out since it was anticipated that the presence of a free phenolic hydroxyl might facilitate formylation. One way to obtain compound X was by cleavage of one of the methoxyl groups of 4,5-dimethylveratrole. Birch[16] had reported that, in the absence of a proton source, sodium in liquid ammonia could be used to cleave aryl methyl ethers. Although most substituted anisoles gave less than 20% yield of cleavage product, Birch found that conversion of veratrole to guaiacol proceeded in 89% yield. A comparable yield was obtained when the veratrole to guaiacol reaction was repeated as a preliminary experiment of the current investigation. However, the cleavage of 4,5-dimethylguaiacol by the same procedure occurred in only 65% yield resulting in an over-all yield of the guaiacol of less than 50%.

A second route used to obtain the guaiacol involved the introduction of a hydroxyl group into 3,4-dimethylanisole, which had been prepared in good yield by methylation of 3,4-xylenol. The procedure used was similar to the conversion of 2,2′-dimethoxybiphenyl into 2,2′-dimethoxy-3,3′-dihydroxybiphenyl which had been accomplished by Gilman, Swiss, and Cheney.[17] The initial step in the synthesis of 4,5-dimethylguaiacol was metalation of the anisole (XI) under a nitrogen atmosphere by butyllithium. The product of the metalation was then allowed to react with butyl Grignard reagent, after which oxidation was accomplished by passage of dry oxygen over the rapidly stirred reaction mixture to give a salt of 4,5-dimethylguaiacol. This was then treated with dilute acid to give the desired product (X), which was the only major product as no appreciable quantity of 5,6-dimethylguaiacol, the product from metalation at the more hindered *ortho* position, was isolated. The conversion of 3,4-dimethylanisole to 4,5-dimethylguaiacol was accomplished in about 60% yield to give an over-all yield of 52%, which is only a slight improvement over the first route described. The use of butyl Grignard reagent is not essential in this sequence since it was possible to oxidize the lithiated anisole directly. However, when the Grignard reagent was omitted from the reaction sequence, the yield of the guaiacol was diminished by over 50%.

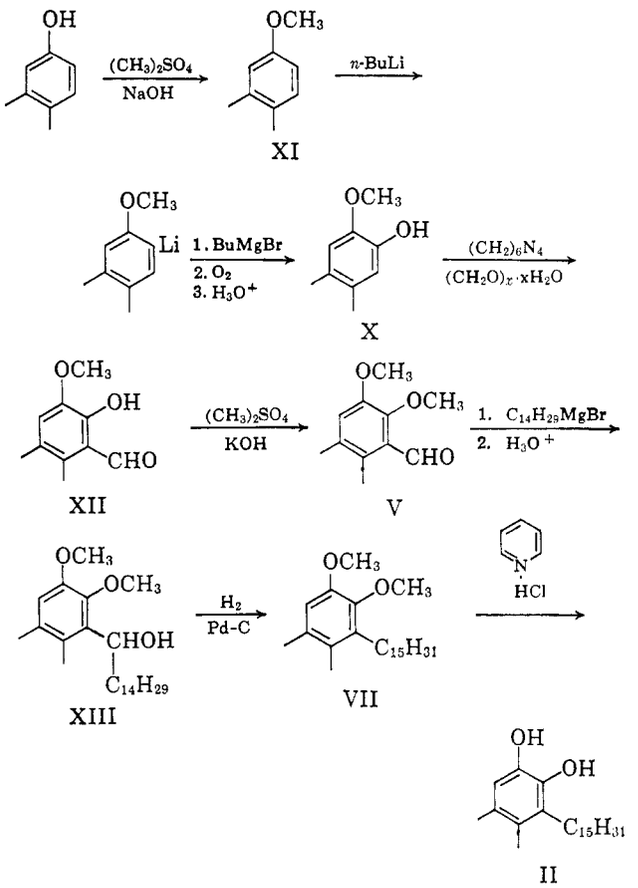
(15) (a) A. H. Sommers, R. J. Michaels, and A. W. Weston, *J. Am. Chem. Soc.*, **74**, 5546 (1952); (b) L. Mangoni, *Ann. Chim.* (Rome), **48**, 930 (1958).

(16) A. J. Birch, *J. Chem. Soc.*, 102 (1947).

(17) H. Gilman, J. Swiss, and L. C. Cheney, *J. Am. Chem. Soc.*, **62**, 1963 (1940).

Formylation of the guaiacol (X) to give 5,6-dimethyl-*o*-vanillin (XII) was first attempted by a Reimer–Tieman reaction, but no aldehyde product could be isolated. The compound (XII) was finally obtained in moderate yield using a mixture of hexamethylenetetramine and paraformaldehyde as the formylating reagent.[18] This compound was then easily methylated using dimethyl sulfate in aqueous base to give 5,6-dimethyl-*o*-veratraldehyde (V), the desired synthetic intermediate for use in the preparation of 4,5-dimethyl-3-pentadecylcatechol (II, see Scheme II). As had been anticipated, the conversion of V to II was accomplished without difficulty by essentially the same route currently employed in this laboratory for the synthesis of 3-pentadecylcatechol. The reaction of V with tetradecylmagnesium bromide produced the carbinol (XIII) which was converted directly to 4,5-dimethyl-3-pentadecylveratrole (VII) by hydrogenolysis over palladium-on-charcoal catalyst. The final step was cleavage of the methyl ether protecting groups using refluxing pyridine hydrochloride[7c] to give 4,5-dimethyl-3-pentadecylcatechol (II). The three-step conversion of 5,6-dimethyl-*o*-veratraldehyde to 4,5-dimethyl-3-pentadecylcatechol was accomplished in about 47% yield. The over-all yield of this synthesis starting from the 3,4-xylenol was quite satisfactory (approximately 13%), considering the number of steps involved.

SCHEME II



(18) British Patent 794,885 (to Farbenfabriken Bayer A.-G.) (May 14, 1958); *Chem. Abstr.*, **53**, 320 (1959).

Preliminary findings from studies on guinea pigs now in progress[19] have indicated that 4,5-dimethyl-3-pentadecylcatechol is significantly less active as a dermititant than 3-pentadecylcatechol. On animals sensitized to 3-pentadecylcatechol a response to the 4,5-dimethyl compound required ten times as large a dose as was needed for a similar response with 3-pentadecylcatechol. When evaluated as a sensitizing agent, the blocked compound failed to induce any observable sensitization in over half of the subjects tested. When observable sensitization did occur, the magnitude of the allergic response, as measured in terms of the minimum reactive dose, was about 100-fold less than in parallel cases involving 3-pentadecylcatechol.

Experimental Section[20]

3-Pentadecylveratrole (IVb).—To 0.3 mole of butyllithium in 150 ml of anhydrous ether prepared by the procedure of Gilman and co-workers[21] was added a solution of 20.8 g (0.15 mole) of veratrole (Eastman) in 200 ml of ether, and the mixture was refluxed under a nitrogen atmosphere for 18 hr to produce a white suspension. After cooling with an ice bath, 42.5 g of 1-bromopentadecane (0.15 mole) was added in 350 ml of anhydrous diethylene glycol dimethyl ether (diglyme). Ether was then removed by distillation and the resulting, turbid, yellow solution was refluxed under nitrogen. In about 2 hr the reaction mixture had become clear. After 6 hr of reflux, the solution was cooled and 200 ml of ether was added, followed by 150 ml of 10% aqueous hydrochloric acid. The two clear layers were separated and the aqueous phase was extracted with 200 ml of ether, which was combined with the original organic layer. This solution was washed with three 100-ml portions of 10% aqueous sodium hydroxide and then with three 100-ml portions of water. After drying with magnesium sulfate, the solvent was removed and the residual oil was distilled at 0.3 to 0.4 mm. A clear, almost colorless oil was obtained boiling at 171–177° which cooled to a white solid, mp 36.8–38.2° (lit.[7b] mp 36.5–37.5° for 3-pentadecylveratrole). The infrared and nmr spectra of this compound were indistinguishable from those of authentic 3-pentadecylveratrole prepared from *o*-veratraldehyde. The yield was 26.6 g (51%).

2-Pentadecyloxy-4,5-dimethylanisole (VIII).—To 0.5 mole of freshly prepared butyllithium under an inert atmosphere of nitrogen was added 58.1 g of 4,5-dimethylveratrole (0.35 mole), prepared by the method of Bruce and Sutcliffe,[12] in 350 ml of anhydrous ether. The mixture was heated at reflux overnight, during which time a greenish yellow color developed. After 20 hr, heating was discontinued and 102 g of 1-bromopentadecane (0.35 mole) was added in 750 ml of diglyme. The reaction mixture was again heated and, after all the ethyl ether had been removed by distillation, was refluxed for 6 hr. The flask was then cooled and 400 ml of ether was added, followed by 300 ml of 10% aqueous hydrochloric acid. The two phases were separated, the aqueous phase was extracted with 200 ml of ether, and the combined ethereal solution was washed with two 250-ml portions of water, followed by three 250-ml portions of 10% aqueous sodium hydroxide, and again with three 250-ml portions of water until the washings were neutral. The ether solution was dried over magnesium sulfate and the solvent was stripped to give an oil which was distilled at 0.2 mm. The main fraction, collected at 202–210°, was 29.3 g of a colorless oil which cooled to give a white solid (mp 42.5–44.0°) concluded to be 2-pentadecyloxy-4,5-dimethylanisole (VIII) on the basis of cleavage experiments (see text) and nmr analysis. The nmr spectrum showed a singlet peak at τ 3.65, a multiplet at 6.41, and a singlet a 7.98, in addition to a broad peak for the side chain.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.34; H, 11.65.

The combined aqueous washings were acidified with hydrochloric acid and were extracted with three 250-ml portions of ether. After drying the combined ether solution, the solvent was removed and the residual oil was distilled to give 10.3 g of 4,5-dimethylguaiacol.

4,5-Dimethylguaiacol (X). A. By Ether Cleavage of 4,5-Dimethylveratrole.—To about 150 ml of liquid ammonia in a 500-ml, three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a cold-finger condenser filled with Dry Ice–acetone was added 8.3 g of sodium metal to produce a dark blue solution. After all the sodium had dissolved, 16.6 g of 4,5-dimethylveratrole in 25 ml of anhydrous ether was introduced slowly and the mixture was stirred rapidly for 15 min. Stirring was then stopped, a dewar flask was placed around the reaction vessel, and the ammonia was permitted to evaporate slowly overnight. When this had been accomplished, 100 g of ice was added and the reaction mixture was heated on the steam bath until all solid had dissolved. The ether which had not evaporated during heating was separated, and the aqueous solution was washed with three additional 100-ml portions of ether and then was acidified. The acidic solution was extracted with three 200-ml portions of ether, the combined ether solution was treated with charcoal and dried over magnesium sulfate, and the solvent was removed to give 9.9 g (65%) of 4,5-dimethylguaiacol, mp 66–68° (lit.[12] mp 68.5°).

B. By Hydroxylation of 3,4-Dimethylanisole.—To 1.2 moles of butyllithium under an inert atmosphere of nitrogen was added 54.4 g (0.4 mole) of 3,4-dimethylanisole (prepared from 3,4-xylenol in 88.5% yield) in 200 ml of anhydrous ether and the reaction mixture was refluxed overnight for 18 hr. Reflux was then discontinued, the flask was cooled in an ice bath, and 0.8 mole of freshly prepared butylmagnesium bromide was added. After the cooled reaction mixture had been stirred under nitrogen for 15 min, a rapid stream of dry oxygen was passed through the reaction vessel. An exothermic reaction took place which caused rapid refluxing. After 2 hr the oxygen flow was discontinued and hydrolysis of the viscous grey mixture which had formed during the oxidation was carried out by addition of 200 g of ice, followed by 500 ml of 25% aqueous hydrochloric acid. After separating the phases, the aqueous layer was extracted with 250 ml of ether. This was added to the original ether layer and the combined solution was washed with eight 200-ml portions of 1 *N* sodium hydroxide. The basic solution was acidified with hydrochloric acid and then extracted with six 200-ml portions of ether. After drying and stripping the solvent, 35.6 g of 4,5-dimethylguaiacol (59%) was obtained by distillation at 235–241°. The distillate, on cooling, gave transparent plates, mp 67.0–68.0°.

5,6-Dimethyl-*o*-vanillin (XII).—A mixture of 15.2 g of 4,5-dimethylguaiacol, 6.1 g of hexamethylenetetramine, and 6.1 g of paraformaldehyde was melted and heated to 110°. Glacial acetic acid (24.5 ml) was then added to the molten mixture to give a red-orange solution. Heating was continued and 12.2 ml of a 1:1 mixture of sulfuric acid and water was added slowly. After all the acid had been added, the solution was refluxed for 1 hr and then poured into 250 ml of water–ice slurry. Steam distillation yielded 9.3 g (52%) 5,6-dimethyl-*o*-vanillin which separated from the steam distillate as yellow plates, mp 95.0–96.5°, recrystallized from petroleum ether. The significant absorptions in the infrared were a weak hydroxyl peak at 2.75 and a carbonyl absorption at 6.05 μ.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.67; H, 6.83.

5,6-Dimethyl-*o*-veratraldehyde (V).—To a rapidly stirred melt of 14.5 g of 5,6-dimethyl-*o*-vanillin was added simultaneously over 30 min 7.4 g of potassium hydroxide in 15 ml of water and 10 ml of dimethyl sulfate. When the addition had been completed, the mixture was refluxed for 2 hr. After that time 50 ml of water was added, causing an oil to separate which became a cream-colored solid on cooling. The yield was 15.4 g (98.5%) of 5,6-dimethyl-*o*-veratraldehyde, mp 52.0–54.0°, recrystallized from hexane. The infrared spectrum showed a new methoxyl peak at 9.25 μ. The hydroxyl peak at 2.75 μ was no longer present and the carbonyl peak was shifted to 5.90 μ.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.27. Found: C, 68.02; H, 7.24.

(19) Biological studies will be reported subsequently by Dr. Harold Baer and associates of the Division of Biologic Standards of the National Institutes of Health.

(20) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 Infracord and were measured in carbon tetrachloride solution unless otherwise specified. Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard and carbon tetrachloride as solvent. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(21) H. Gilman, J. A. Beel, C. G. Branner, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

4,5-Dimethyl-3-(1'-hydroxy)pentadecylveratrole (XIII).—To a solution of tetradecyl Grignard reagent prepared in the customary manner from 2.4 g of magesium metal (0.1 g-atom) and 25.5 g of 1-bromotetradecane (0.092 mole) in 85 ml of anhydrous ether was added 15.4 g of 5,6-dimethyl-*o*-veratraldehyde (0.08 mole) in 100 ml of ether. When the initial exothermic reaction had subsided, the mixture was heated at reflux for 20 hr. Hydrolysis was then accomplished by addition of 100 ml of 10% aqueous sulfuric acid and the phases were separated. After extracting with 100 ml of ether, the ethereal solutions were combined and washed with two 50-ml portions of 10% sodium bicarbonate, followed by four 50-ml portions of water. The ether solution was dried over magnesium sulfate and the solvent was removed to give a yellow oil which was dissolved in 50 ml of boiling ethanol. On cooling, 3.2 g of octacosane precipitated and was removed by filtration. The resulting solution was evaporated to give 25.7 g of crude 4,5-dimethyl-3-(1'-hydroxy)-pentadecylveratrole, which was used without further purification.

4,5-Dimethyl-3-pentadecylveratrole (VII).—The crude carbinol (XIII) from the previous reaction was dissolved in 150 ml of ethyl acetate containing 20 drops of sulfuric acid and the solution was hydrogenated in a Parr pressure reaction apparatus for 23 hr over 2.5 g of 10% palladium-on-carbon catalyst at an intial hydrogen pressure of 60.5 psi and about 60°. The catalyst was then removed by filtration and the solution was diluted with 100 ml of ether and then washed with 50 ml of 10% sodium bicarbonate, followed by four 50-ml portions of water. The residual oil obtained after drying the solution and removal of solvent was distilled at 0.4 mm to give 14.3 g of 4,5-dimethyl-3-pentadecylveratrole as a colorless oil (bp 215–235°) which became a white solid on cooling, mp 41.5–43°. The significant peaks in the nmr were singlets at τ 3.42 and 6.10 and a pair of singlets at 7.64 and 7.72 in the ratio 1:6:6.

Anal. Calcd for $C_{25}H_{44}O_2$: C, 79.73; H, 11.78. Found: C, 80.00; H, 11.81.

4,5-Dimethyl-3-pentadecylcatechol (II).—A solution of 10.4 g of 4,5-dimethyl-3-pentadecylveratrole in 50 g of pyridine was heated at reflux and a rapid stream of hydrogen chloride gas was passed through the reaction mixture. After about 45 min the solution stopped refluxing and the temperature of the reaction mixture rose slowly to about 225°. At that temperature refluxing began again with considerable frothing and the temperature was then maintained at 215–225° for 4.5 hr with continuous passage of hydrogen chloride. At the end of that time the contents of the flask were allowed to cool to 100°, and 50 ml of water was added, and after further cooling, 100 ml of ether was added as well. The phases were then separated, the water layer was extracted with two 100-ml portions of ether, and the combined ether solution was washed with three 100-ml portions of water and dried over magnesium sulfate. Removal of the solvent gave a tan solid which was recrystallized from hexane to yield 9.5 g (99%) 4,5-dimethyl-3-pentadecylcatechol as a white, noncrystalline solid, mp 77.0–78.2°. The hydroxyl peaks of the catechol appeared in the infrared in chloroform solution at 2.78 and 3.05 μ. A peak for methoxyl no longer was evident at ~9.3 μ.

Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.26; H, 11.57. Found: C, 79.46; H, 11.60.

Registry No.—II, 7771-22-4; IVb, 7461-75-8; VIII, 7771-24-6; X, 7771-25-7; XII, 7732-10-7; V, 7732-11-8; XIII, 7771-26-8; VII, 7771-27-9.

Small-Ring Compounds. XV. The Dehydration of *trans*-$\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-1,2-cyclopropanedimethanol

TATSUYA SHONO, TAMOTSU YOSHIMURA, AND RYOHEI ODA

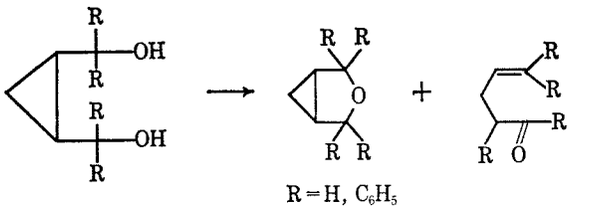
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

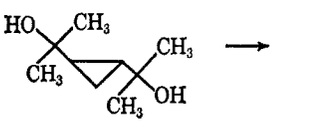
Received November 1, 1966

The dehydration of *trans*-$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,2-cyclopropanedimethanol (1), catalyzed by *p*-toluenesulfonic acid yielded six products: two cyclic ethers (4 and 7), three unsaturated hydroxy compounds (2, 5, and 8), and one unsaturated ketone (9). The reaction routes were discussed on the basis of the structures of the products and the results of the gas chromatographic analysis.

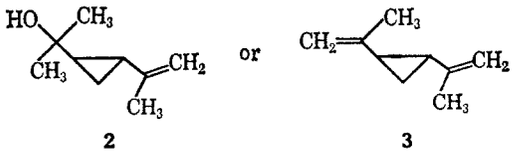
The possibility of conjugative interaction of the cyclopropane ring with an adjacent unsaturated group or an carbonium ion has been of interest to many workers.[1] Especially, recent nuclear magnetic resonance (nmr),[2] electron diffraction,[3] or solvolysis studies[4] have strongly suggested the existence of such interaction. If such a prediction is correct, the solvolytic behavior of cyclopropylcarbinyl compounds bearing an unsaturated group on their 2 position might be affected by the substituent. In the present study, the syntheses of some cyclopropane derivatives having an unsaturated substituent were attempted for the purpose of the investigation of the above-mentioned effect.

In the previous paper[5] in this series, a study was made of the dehydration of some *cis*-1,2-cyclopropanedimethanol derivatives to a cyclic ether and a rearranged product. On the other hand, the dehydration of *trans*-$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,2-cyclopropanedimethanol (1), synthesized from dimethyl *trans*-1,2-cyclopropanedicarboxylate by the Grignard method, might be expected to give *trans*-2-isopropenyl-α,α-dimethylcyclopropanemethanol (2) or *trans*-1,2-diisopropenylcyclopropane (3).





1



2 3

(1) For a summary of leading references, see P. von R. Schleyer and G. W. VanDine, *J. Am. Chem. Soc.*, **88**, 2321 (1966).

(2) G. L. Closs and H. B. Klinger, *ibid.*, **87**, 3265 (1965).

(3) L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647 (1965).

(4) H. C. Brown and J. D. Cleveland, *J. Am. Chem. Soc.*, **88**, 2051 (1966).

(5) T. Shono, A. Oku, T. Morikawa, M. Kimura, and R. Oda, *Bull. Chem. Soc. Japan*, **38**, 940 (1965).