

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and Its Derived Compounds. XXVII.¹ Synthesis in the Syringyl Series^{2,3}

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Vanillin was converted to syringaldehyde by way of 5-iodovanillin in large-scale reactions. Electrolytic reduction of syringaldehyde yielded hydroxyvanillin which in turn yielded syringil upon oxidation with cupric hydroxide in acetic acid solution. Syringil was subjected to reduction under several reducing conditions to yield almost all of the possible monomolecular reduction products. Propiosyringone was reduced in alkaline solution with sodium amalgam to yield α,α' -diethylhydroxyvanillin.

During the past decade many sulfite pulp mills in the Middle West have ceased pulping the difficultly obtained conifers and are now pulping indigenous deciduous woods, especially quaking aspen (*Populus tremuloides*) and bigtooth aspen (*Populus grandidentata*). The spent liquor from the sulfite pulping of these deciduous woods offers a great potential source of syringyl compounds, the most important being syringaldehyde. A fundamental study of the chemical utilization of this spent liquor necessitated the production of large quantities of syringaldehyde and its conversion to a number of model compounds and anticipated reaction products. The present paper reports the large-scale synthesis of syringaldehyde from vanillin and a number of experiments in the bisyringyl series.

Several methods for the synthesis of syringaldehyde (I) from vanillin (II) in relatively small amounts have been reported recently,⁴⁻⁷ but, in most cases, the many steps involved precluded their use for large-scale laboratory preparations. Of these, only the procedure of Pepper and MacDonald,⁶ comprising the iodination of vanillin to 5-iodovanillin (III) and reaction of the latter compound with sodium methoxide under pressure in the presence of a copper catalyst, appeared adaptable to large-scale operation.

III was prepared in molar quantities by a modification of the method of Erdtman,⁸ and was obtained in yields of 95%.

(1) Paper XXVI of this series: I. A. Pearl, *J. Am. Chem. Soc.*, **77**, 2826 (1955).

(2) Presented before the Division of Organic Chemistry at the 131st Meeting of the AMERICAN CHEMICAL SOCIETY, Miami, Fla., April, 1957.

(3) A portion of this paper represents results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the league by The Institute of Paper Chemistry. Acknowledgment is made by the institute for permission on the part of the league to publish these results.

(4) R. A. McIvor and J. M. Pepper, *Can. J. Chem.*, **31**, 298 (1953).

(5) I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.*, **74**, 4262 (1952).

(6) J. M. Pepper and J. A. MacDonald, *Can. J. Chem.*, **31**, 476 (1953).

(7) K. Kratzl, T. Horejschi, and G. Billik, *Monatsh.*, **85**, 1165 (1954).

The results of Pepper and MacDonald⁶ on the conversion of III to I were repeated easily in the 13-g. amounts employed by these authors. However, attempts to scale up the reaction to 600-700 g. resulted in much lower yields of I with II as the unwanted by-product of the reaction. A desire to overcome the reducing action of the catalyst led to use of other copper catalysts, but in all cases, yields of I were lower than with the British Drug Houses precipitated copper powder employed by Pepper and MacDonald, and in many instances other by-products were noted in the reaction mixtures. Therefore, the British Drug Houses copper was used in large-scale experiments, and conditions were evolved for production of I in yields of 75-80% with II as the only by-product.

During the work-up of some of the experiments using Copper Brilliant 104⁹ fractions containing less than 65% I (as determined by paper chromatography) were upgraded before purification by crystallization. Solutions of reaction products in chloroform or mixtures of chloroform and Skellysolve C were saturated with dry ammonia gas. Both II and I precipitated as ammonium salts, but other by-products did not. The precipitate was filtered, washed with clean solvent, allowed to dry, stirred into absolute ethanol, and filtered to give a precipitate of pure ammonium syringaldehyde, which was acidified and crystallized from chloroform to give pure I. The ammoniated filtrate noted above was evaporated to dryness and recrystallized from Skellysolve C to give colorless crystals of an iodine-containing compound which appears to be 5-iodovanillyl methyl ether (IV). McIvor and Pepper⁴ obtained 5-bromovanillyl methyl ether from a similar reaction of 5-bromovanillin and sodium methoxide in methanol in the presence of a copper catalyst. Thus, Copper Brilliant 104 acted as both a reducing agent for the aldehyde group and a methylating agent in this reaction.

An experiment employing Pale Gold Brilliant 111⁹ gave dehydrovanillin V as the chief by-product indicating a type of Ullman reaction under

(8) H. Erdtman, *Svensk Kem. Tidskr.*, **47**, 228 (1953).

(9) A copper pigment manufactured by Crescent Bronze Co., Chicago.

these conditions. Two other unidentified by-products were isolated in crystalline form. The data of a large number of preparative experiments led us to the conclusion that the transformation of III to I by reaction with sodium methoxide under pressure in the presence of a copper catalyst is a complex reaction, and that conditions of reactant ratios, temperature, and time are not alone in determining the course of the reaction. Changes in results obtained when all operating conditions were ostensibly alike indicated that the catalyst (which in this case was the copper plus any impurities in the reactants or in the stirring autoclave) determined the course of the reaction, and was responsible for completion of either the double decomposition to I or the reduction of II. The formation of the by-products would be still another reaction or reactions.

Electrolytic reduction of I in a manner already reported for II¹⁰ yielded the desired hydrosyringoin (VI), and oxidation with cupric hydroxide in glacial acetic acid gave syringil (VII). Reduction of VII under a variety of conditions employed earlier on vanillil¹¹ yielded most of the monomolecular reduction products of VII, although there appeared to be very little correlation between the reduction of vanillil and that of VII. The reduction products of VII were characterized by their methyl ethers and their acetates. 4,4'-Dihydroxy-3,3',5,5'-tetramethoxystilbene (VIII) and 1,2-bis(4-hydroxy-3,5-dimethoxyphenyl)ethanol (IX) could not be prepared directly from VII, but were readily prepared by reduction with sodium borohydride or sodium trimethoxyborohydride of deoxysyringoin (X), an intermediate easily prepared by reduction of VII with tin amalgam in ethanolic hydrochloric acid or with zinc in acetic acid. Bisyringyl (XI) and VIII were the only two reduction products of VII previously known.¹² All of the bis-syringyl compounds prepared in this study will be employed as intermediates in hardwood lignin model compound studies.

EXPERIMENTAL

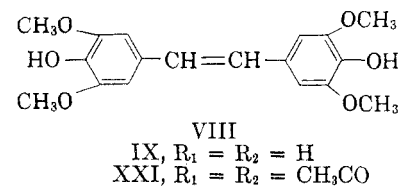
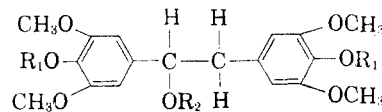
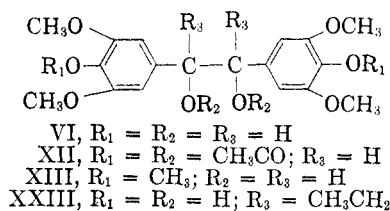
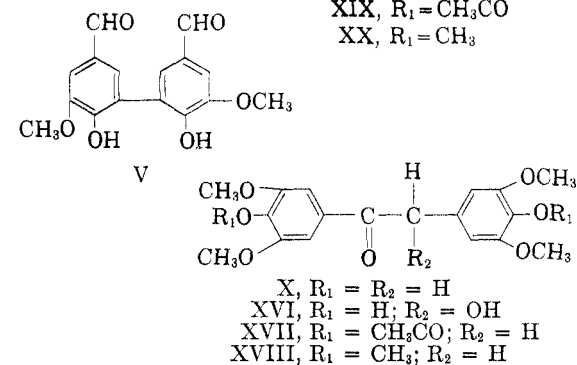
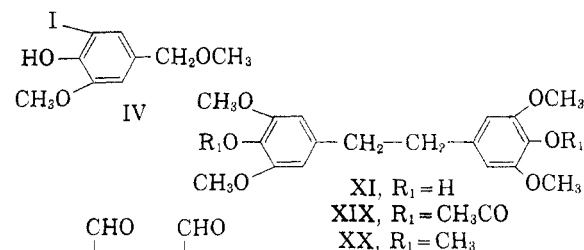
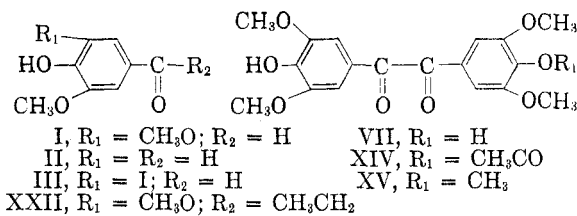
All melting points are uncorrected, and ultraviolet spectral data are for solutions in 95% ethanol (concentration, 0.02 g. per liter).

Syringaldehyde I. A freshly prepared solution of 450 g. of sodium metal in 12,500 ml. of acetone-free methanol was alped in a 5-gallon stainless steel autoclave equipped with automatic temperature control and a stirring device, and treated with 650 g. of crude III⁸ and 125 g. of British Drug Houses precipitated copper. The autoclave was sealed and, while stirring, heated to 130° in 1 hr., maintained at 130° for 5 hr., and allowed to cool. The reaction mixture was filtered and the precipitate was washed with water. The water washings were acidified, and the precipitate was filtered to give fraction A-1. The filtrate was extracted with chloroform, and the chloroform was dried and distilled to give fraction A-2. The original methanolic filtrate was concentrated under reduced pressure until the heavy precipitate

(10) I. A. Pearl, *J. Am. Chem. Soc.*, **74**, 4260 (1952).

(11) I. A. Pearl, *J. Am. Chem. Soc.*, **74**, 4593 (1952).

(12) H. Richtzenhain, *Ber.*, **77**, 409 (1944).



prevented further distillation, and filtered. The precipitate was dissolved in water, acidified with hydrochloric acid, and extracted with chloroform. Drying and distillation of the chloroform gave fraction B. The methanolic filtrate was again concentrated and processed as before to give fraction C. The final methanolic filtrate was diluted with water and extracted with chloroform. This chloroform extract was dried and distilled to yield fraction D. The several fractions obtained were analyzed quantitatively by the procedure of Pepper and MacDonald.⁶ A typical experiment is illustrated by the data of Table I.

Extracts containing I in amounts of 65% or greater could be crystallized from chloroform or mixtures of chloroform and Skellysolve C to give crystals of pure I melting at 110°. Extracts containing less than 65% I (filtrates from the crystallization of pure I noted directly above are included

TABLE I
REACTION OF 5-IODOVANILLIN WITH SODIUM METHYLATE

Fraction	Syringaldehyde, g.	Vanillin, g.	5-Iodovanillin, g.
A-1	80		20
A-2	27		
B	154	17	
C	16	4	
D	65	36	
Total	342 (80%)	57 (16%)	20 (3%)

in this category) were upgraded before crystallization. Solutions containing I, II, and possibly by-products in chloroform or mixtures of chloroform and Skellysolve C were saturated with dry ammonia gas. Both I and II precipitated as ammonium salts, but by-product material remained in solution. The precipitate was filtered, washed with clean solvent, and air-dried. The dry mixture of ammonium salts was stirred into absolute ethanol and filtered. The precipitate consisted substantially of the ammonium salt of I, and the filtrate contained the ammonium salt of II with some I. The ammonium salt of I was dissolved in water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform was concentrated to a small volume and cooled to yield crystals of pure I melting at 110°. Hunter and Hibbert¹³ noted the difference in the solubilities in ethanol of the ammonium salts of I and II. I was compared with authentic I⁴ by mixed melting point.

In an experiment employing Copper Brilliant 104⁹ as a catalyst the ammoniated filtrate from the precipitation of I and II was evaporated to dryness at room temperature, and the residue was boiled with Skellysolve C and filtered hot. Cooling of the filtrate yielded colorless crystals melting at 93–94°. These crystals contained iodine, had a butyl alcohol–2% aqueous ammonia R_f at 20° of 0.85, and gave positive reactions with bisdiazotized benzidine and ferric chloride, but not with the Mäule or with 2,4-dinitrophenylhydrazine spray reagents. A configuration corresponding with the analytical data and with the observed chemical reactions is that of IV: λ_{\max} 215 m μ , ϵ 30000; λ_{\min} 290 m μ , ϵ 2620.

Anal. Calcd. for C₉H₁₁O₃I: C, 37.09; H, 3.77; CH₃O, 21.11. Found: C, 37.38; H, 3.89; CH₃O, 20.88.

The residue from the Skellysolve boiling was washed successively with boiling benzene, ethanol, and toluene to leave colorless crystals melting at 278–279°. These crystals possess the syringyl group as indicated by the positive Mäule reaction and lack of reaction with bisdiazotized benzidine. Analysis indicates a compound with the formula C₂₂H₂₄O₉ with two methoxyl groups, but as yet no structure has been assigned. The ultraviolet absorption spectrum indicated the following maxima: λ_{\max} 215 m μ , ϵ 42200; λ_{\min} 286 m μ , ϵ 6260.

Anal. Calcd. for C₂₂H₂₄O₉: C, 61.10; H, 5.59; CH₃O, 14.35. Found: C, 60.90, 60.92; H, 5.63, 5.53; CH₃O, 14.3, 14.5.

The boiling benzene washings from the above experiment were diluted with petroleum ether (b.r. 65–110°), and the yellow precipitate was recrystallized from benzene–Skellysolve C to give yellow crystals melting at 137–141°. Recrystallization did not raise its melting point. Acetylation with acetic anhydride in pyridine and recrystallization of the acetate from ethanol gave bright yellow crystals melting at 145–146°.

Analysis indicated C, 61.56; H, 5.26; and CH₃O, 21.5, but no structure has been assigned to the product.

An experiment using Pale Gold Brilliant 111⁹ yielded over

3% of by-product in fraction D. The dry fraction was covered with ether and filtered. The insoluble material was washed with ether and recrystallized from acetic acid to give dehydrodivanillin melting at 302–304° and not depressing the melting point of authentic V.¹⁴

Hydrosyringoin (VI). A warm (60°) mixture of 100 g. of I and 64 g. of sodium hydroxide in 1600 ml. of water was placed in the cathode compartment of the electrolysis cell described earlier.¹⁰ The anode compartment was filled with a solution of 16 g. of sodium hydroxide in 400 ml. of water. A current of 3.6 amperes was maintained across the cell for 7.5 hr. at which time the temperature had dropped to 25°. During the last hour of electrolysis a precipitate separated in the cathode compartment. The catholyte was filtered, and the precipitate was washed thoroughly with water. The combined filtrate and washings were acidified with sulfur dioxide. The resulting white precipitate was filtered, washed with water, and air-dried to give 70 g. of crude VI melting at 245–251°. Recrystallizations from acetic acid gave colorless crystals melting at 265–266°: λ_{\max} 250 m μ , ϵ 20150; λ_{\min} 369 m μ , ϵ 35100.

Anal. Calcd. for C₁₅H₂₂O₈: C, 59.01; H, 6.05. Found: C, 58.85; H, 6.12.

The tetraacetate XII was prepared with acetic anhydride in pyridine and was obtained as white crystals from ethanol melting at 203–204°: λ_{\max} 274 m μ , ϵ 2960; λ_{\min} 360 m μ , ϵ 160.

Anal. Calcd. for C₂₆H₃₀O₁₂: C, 58.42; H, 5.66. Found: C, 58.49; H, 5.68.

Methylation of VI with dimethyl sulfate in alkaline solution and recrystallization first from ethanol and then from methanol yielded 3,3',4,4',5,5'-hexamethoxyhydrobenzoin XIII melting at 215–216° and identical with authentic XIII.¹⁵

Syringil (VII). A mixture of 184 g. (0.5 mole) of hydrosyringoin, 234 g. (2.4 moles) of commercial copper hydrate powder, and 3000 ml. of glacial acetic acid was boiled under reflux with stirring for 6 hr. and allowed to cool. The mixture was diluted with water and filtered. The precipitate was leached thoroughly with dilute sodium hydroxide solution and then with water. The combined washings and leachings were acidified with dilute sulfuric acid, and the precipitate was filtered, washed, and air-dried to yield 101 g. of crude VII melting at 194–197°. Recrystallization from acetic acid yielded fluffy yellow needles melting at 198–199° which proved to be the dihydrate of VII.

Anal. Calcd. for C₁₈H₂₂O₁₀: C, 54.27; H, 5.57. Found: C, 54.30; H, 5.57.

Pure VII was obtained by boiling crude VII in xylene under a water-separator, filtering, and allowing to cool. These crystals melted at 198° and their ultraviolet absorption spectrum was identical with that of the dihydrate and indicated the following maximum: λ_{\max} 330 m μ , ϵ 21270.

Anal. Calcd. for C₁₈H₁₈O₈: C, 59.66; H, 5.01. Found: C, 59.69; H, 4.98.

Bland¹⁶ reported a melting point of 198° for VII prepared by essentially the same procedure,¹⁰ but recorded no intermediates.

Acetylation yielded the diacetate of VII (XIV) as light yellow needles from ethanol melting at 192–193°: λ_{\max} 215 m μ , ϵ 42200; λ_{\min} 297 m μ , ϵ 18500.

Anal. Calcd. for C₂₂H₂₂O₈: C, 59.19; H, 4.97; CH₃O, 27.8. Found: C, 59.16; H, 4.94; CH₃O, 27.8.

Methylation of VII and recrystallization from either methanol or ethanol yielded 3,3',4,4',5,5'-hexamethoxybenzil (XV) melting at 192–193° and identical with authentic XV.¹⁶

Syringoin (XVI). A solution of 5 g. of VII in 350 ml. of warm *N* sodium hydroxide was treated with sodium hydro-sulfite powder and heated on the steam bath until almost

(14) K. Elbs and H. Lerch, *J. prakt. Chem.*, **93**, 1 (1916).

(15) M. Marx, *Ann.*, **263**, 249 (1891).

(16) D. E. Bland, *Australian J. Appl. Sci.*, **6**, 511 (1955).

(13) M. J. Hunter and H. Hibbert, *J. Am. Chem. Soc.*, **61**, 2190 (1939).

neutral in reaction. The mixture was made alkaline with sodium hydroxide and cooled. The cool mixture was filtered, and the precipitate was dissolved in boiling water and acidified with dilute sulfuric acid. The precipitate was filtered, washed with water, and recrystallized twice from ethanol to give 3 g. of pure XVI melting at 165–166°: λ_{\max} 310 $m\mu$, ϵ 13170.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 59.33; H, 5.53. Found: C, 59.21; H, 5.49.

Methylation with dimethyl sulfate in alkaline solution yielded XV instead of the desired 3,3',4,4',5,5'-hexamethoxybenzoin just as vanilloin yielded veratril under the same conditions.¹¹

Syringoin was also prepared by the reduction of VII with iron and acetic acid.

Deoxyisyringoin (X). One hundred grams of tin amalgam¹⁷ was covered with 800 ml. of ethanol, treated with 25 g. of VII, and heated to boiling under reflux on the steam bath. The boiling solution was treated portionwise with 200 ml. of concentrated hydrochloric acid through the reflux condenser, and boiling was continued 6 hr. The warm mixture was filtered, and the filtrate was diluted with water and concentrated in a rotating evaporator. The concentrated solution deposited a crystalline precipitate which was filtered and recrystallized from ethanol to yield 22 g. of X as colorless crystals melting at 185–186°: λ_{\max} 306 $m\mu$, ϵ 12080.

Anal. Calcd. for $C_{13}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.09; H, 5.79.

Acetylation gave the diacetate (XVII) as colorless crystals from toluene melting at 200–201°: λ_{\max} 300 $m\mu$, ϵ 21750.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 60.82; H, 5.58.

Methylation yielded 3,3',4,4',5,5'-hexamethoxydesoxybenzoin (XVIII) melting at 165–166°, not depressing the melting point of XVIII prepared by reduction of XV with zinc and acetic acid,¹⁵ and having the following maximum in its ultraviolet absorption spectrum: λ_{\max} 283 $m\mu$, ϵ 11070.

Anal. Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.75; H, 6.35.

X was also prepared by reduction of VII with zinc in acetic acid and as a by-product in the reduction of VII with sodium hydrosulfite in alkaline solution.

Bisyringyl (XI). A boiling mixture of 5 g. of VII, 300 ml. of 95% ethanol, and 10 g. of zinc dust was removed from the hot plate and treated gradually with 40 ml. of concentrated hydrochloric acid. The colorless solution was filtered immediately and concentrated under reduced pressure with gradual addition of water. Finally, the concentrated mixture was diluted to one liter with water and allowed to cool. The white precipitate was filtered and recrystallized from ethanol to give 4 g. of XI melting at 176–177°: λ_{\max} 215 $m\mu$, ϵ 35400; λ_{\max} 274 $m\mu$, ϵ 2875; λ_{\max} 335 $m\mu$, ϵ 435.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.67; H, 6.63.

Acetylation yielded the diacetate of XI melting at 165–166° (from ethanol): λ_{\max} 271 $m\mu$, ϵ 2460.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.08; H, 6.17.

Methylation and recrystallization of the product from dilute ethanol gave 3,3',4,4',5,5'-hexamethoxybibenzyl (XX) melting at 136–137° which agrees with the m.p. 138–139° reported for XX by Richtzenhain¹² who prepared XI by dehydrogenation of 4-methyl-2,6-dimethoxyphenol. Richtzenhain reported melting points of 179° and 157–158° for XI and XIX, respectively.

Hydroisyringoin (VI) by reduction of VII. Reduction of VII with Raney nickel alloy in alkaline solution¹¹ or with excess sodium trimethoxyborohydride in aqueous alkaline solution

yielded VI, identical with that prepared by electrolytic reduction of I.

Unsuccessful reductions of VII. Attempted reductions of VII with zinc in ethanolic acetic acid¹¹ and with sodium trimethoxyborohydride in tetrahydrofuran yielded only the starting material.

1,2-Bis(4-hydroxy-3,5-dimethoxyphenyl)ethanol (IX). A solution of 10.5 g. (0.03 mole) of X in 500 ml. of absolute methanol was cooled under tap water and treated portionwise with 3.5 g. (0.09 mole) of sodium borohydride. After addition was complete, the mixture was allowed to stand 2 hr. During this time the solution turned green in color, and colorless crystals separated from solution after 30 min. The reaction mixture was concentrated almost to dryness in a rotating evaporator, and the yellowish residue was covered with 500 ml. of water, and filtered. The yellowish crystals melted at 227–228° and amounted to 7 g. Recrystallization from ethanol yielded very light pink crystals of IX melting at 231–232°: λ_{\max} 273 $m\mu$, ϵ 2660.

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.60; H, 6.32.

Reduction of 10 g. of X in 250 ml. of dilute sodium hydroxide solution with 10 g. of powdered sodium trimethoxyborohydride for 30 min. and acidification with carbon dioxide of the filtered reaction mixture gave crude IX which was recrystallized from benzene to give crystals melting at 231–232° which did not depress the melting point of IX prepared above.

Acetylation of IX gave the triacetate, 3,3',5,5'-tetramethoxy- α ,4,4'-triacetoxibenzyl (XXI) melting at 175–176° (from ethanol): λ_{\max} 270 $m\mu$, ϵ 1547.

Anal. Calcd. for $C_{24}H_{28}O_{10}$: C, 60.50; H, 5.92. Found: C, 60.51; H, 6.20.

4,4'-Dihydroxy-3,3',5,5'-tetramethoxystilbene (VIII). Treatment of IX or X in warm methanol with excess sodium borohydride caused dehydration of IX to form VIII. The resulting warm methanol solution was evaporated to dryness in a rotating evaporator, and the residue was recrystallized from acetic acid to yield light pink crystals of VIII melting at 246–247°: λ_{\max} 328 $m\mu$, ϵ 14170.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C 64.90; H, 6.11.

Richtzenhain¹² reported 242° as the melting point of VIII and also reported that the compound turned pink in air.

Propiosyringone (XXII). Propiosyringone was prepared by the rearrangement of the propionate of pyrogallol 1,3-dimethyl ether with aluminum chloride in nitrobenzene solution in accordance with the procedure of Hunter, Cramer, and Hibbert¹³ and was obtained in 30% yield as crystals melting at 109–110°.

α,α' -Diethylhydroisyringoin (XXIII). A suspension of 35 g. of XXII in 500 ml. of water was treated with 250 g. of 3% sodium amalgam, and the warm mixture was stirred for 7 hr. After 2 hr., the foamy mixture became clear and dark in color. After standing overnight, the mixture was filtered, and the clear filtrate was acidified with sulfur dioxide and filtered. The precipitate was covered with benzene and boiled under a water separator until all water was removed. Cooling of the benzene yielded a granular precipitate. This was filtered to give 13.8 g. of product melting at 118–120° which, when crystallized from dilute ethanol, yielded colorless needles melting at 104–105° with gas evolution. These crystals appear to be the dihydrate of XXIII.

Anal. Calcd. for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47. Found: C, 58.02; H, 7.19.

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APPLETON, WIS.

(17) I. A. Pearl and W. M. Dehn, *J. Am. Chem. Soc.*, **60**, 57 (1938).

(18) M. J. Hunter, A. B. Cramer, and H. Hibbert, *J. Am. Chem. Soc.*, **61**, 516 (1939).