SYNTHESIS OF VANILLIN FROM CRESOLS. I. SYNTHESIS OF HOMOPYROCATECHIN.

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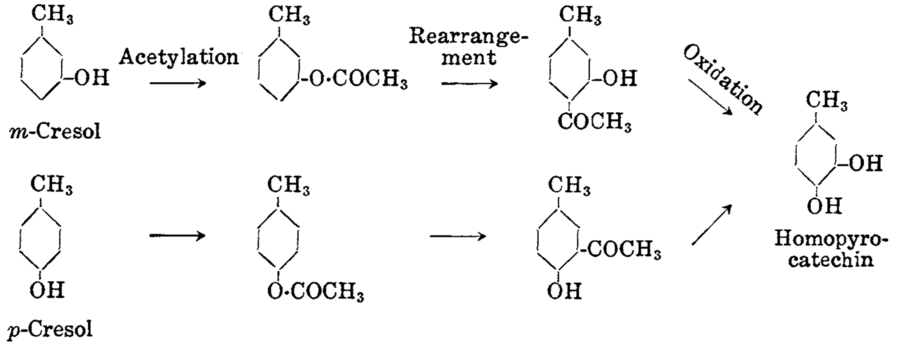
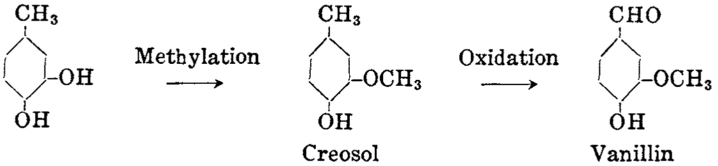
The pyrocatechin-derivatives play important rôles in nature as vanillin, adrenalin, urushiol, zingerone, capsaicin, etc. Our factory has succeeded in the industrial preparation of vanillin from safrol, one of the principal constituents of camphor oil, and is now pursuing further studies with a view to a more effective preparation of vanillin and related compounds. This paper concerns the synthesis of homopyrocatechin from cresols. Homopyrocatechin, which has been prepared by the demethylation of creosol, is an intermediate compound of importance for many useful pyrocatechin-derivatives. Our scheme for the synthesis is as follows :



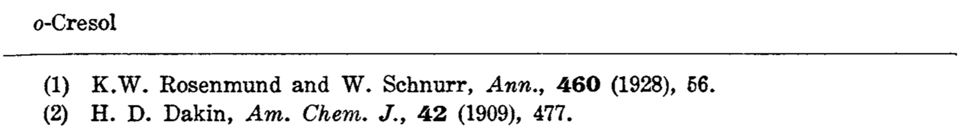
And in addition, the methylation and subsequent oxidation of homopyrocatechin into creosol and vanillin are reported preliminarily.



Through Fries rearrangement of *m*-cresol acetate with aluminium chloride, the acetyl group was rearranged to ortho and para positions to the hydroxyl group.(1) But the ratio of quantities of ortho and para products can be controlled to a certain extent by the conditions. On rearranging at 160°, we obtained 22 g. of *o*-substituted compound and only 2 g. of *p*-substituted. The separation of these is simple, for only the *o*-compound distils with steam. The oxidation of the rearranged *m*-cresyl-methylketone to homopyrocatechin was carried out by the Dakin-process(2) with an alkaline hydrogen peroxide solution.

The case of *p*-cresol, a synthesis completely analogous to the former, is in fact simpler, for the product in Fries rearrangement is an *o*-compound and nothing more.

From *o*-cresol, we cannot obtain homopyrocatechin by similar reactions, as the following formulas show :



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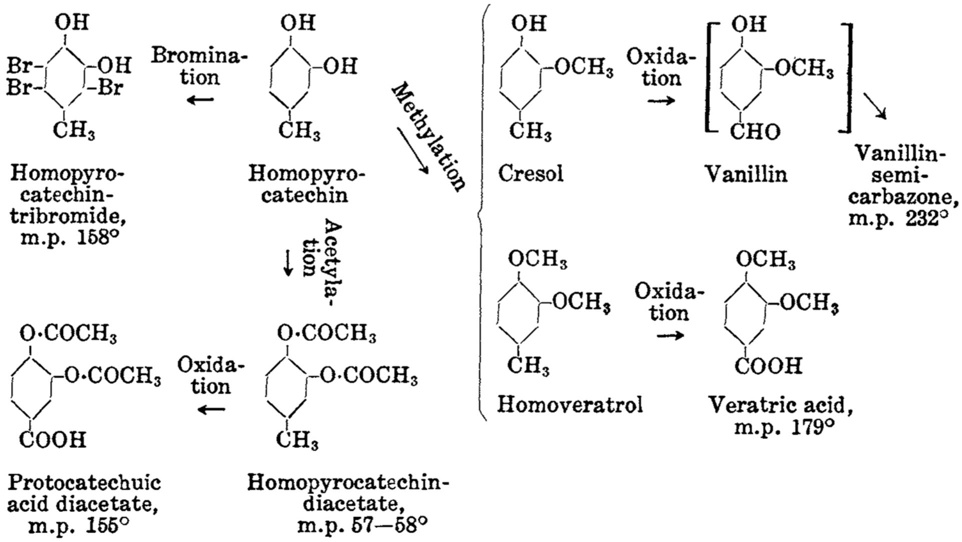
(1) K.W. Rosenmund and W. Schnurr, *Ann.*, **460** (1928), 56.

(2) H. D. Dakin, *Am. Chem. J.*, **42** (1909), 477.

But fortunately, the *o*-cresyl-methylketone would not give a definite oxidation-product by the Dakin-process, as proved experimentally in our laboratory.(3) And the industrial separation of *o*-cresol from the raw cresol-mixture is possible.(4) So in the preparation of homopyrocatechin according to our method, it is not necessary to use pure cresol, but it is enough that the cresol-mixture is somewhat free from the ortho component.

For the exact identification of the prepared homopyrocatechin, the following derivatives are synthesized:



Of these derivatives, creosol which is obtained from wood-tar, was noted recently as a new material for the vanillin-preparation.(5) And although the oxidation method still remains a subject for future study we have oxidized it preliminarily with ethyl nitrite and obtained vanillin, identifying it as its semicarbazone.

Experimental.

1. **Acetylation of Cresols.** (A) *m-Cresol.* (i) To a solution of *m*-cresol (108 g.), water (70 c.c.), and potassium hydroxide (70 g.), acetic anhydride (110 g.) was added slowly. After washed with 10%-solution of potassium hydroxide, the produced acetate was distilled. Yield, 80% of the theoretical. B.p. 210–215°, n_D^{10} 1.5059, d_4^{15} 1.051. (ii) To a mixture of *m*-cresol (108 g.) and acetic anhydride (130 g.), one drop of conc. sulphuric acid was added.

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(3) K. Ono and T. Oyamada, not yet published.

(4) For example, see S. Masai, *J. Soc. Chem. Ind., Japan,* **38** (1935), 217 B.

(5) H. Schulz, *Chem. Ztg.,* **59** (1935), 113.

The temperature was raised, for example, up to 95°. Yield was theoretical. B.p. 210–211°, n_D^{26} 1.4978, d_{26} 1.043.

(B) *p-Cresol.* From 250 g. of *p*-cresol, 300 g. of acetic anhydride, and one drop of conc. sulphuric acid, 280 g. of *p*-cresyl acetate was obtained. B.p. 209–211°, d_{26} 1.043, n_D^{26} 1.4972.

2. **Fries Rearrangement of Acetates.** (A) *m-Cresyl acetate.* To the ice-cooled *m*-cresyl acetate (29 g.), powdered aluminium chloride (30 g.) was added in portions and the mixture heated in an oil-bath at 130°. A violent evolution of HCl gas occurred. Temperature of the oil-bath was raised to 160° during 1.5 hours, and the reaction was then stopped. After cooling, the product was decomposed with ice-water and conc. hydrochloric acid (20 c.c.) and distilled with steam. From the distillate *m*-cresyl-*o*-methylketone was extracted with ether. After redistillation, it weighed 22 g. B.p. 230–235°, n_D^{27} 1.5511, d_{28} 1.081. From the residue of the steam distillation the para product crystallized out. It weighed 2.3 g. and melted at 124–126° after recrystallisation from water.

(B) *p-Cresyl acetate.* Similarly, *p*-cresyl acetate (50 g.) and aluminium chloride (60 g.) gave *p*-cresyl-*o*-methylketone (35 g.), melting at 50° and of somewhat yellowish colour. Recovered acetate weighed 8 g.

3. **Dakin-Oxidation.** (A) *m-Cresyl-o-methylketone.* A solution of *m*-cresyl-*o*-methylketone (22 g.) and sodium hydroxide (7 g.) in water (200 c.c.) was treated with 3% hydrogen peroxide solution at ordinary temperature. As seen from next case, the quantities of NaOH and H_2O_2 (both 1 mole) were insufficient. After standing a whole night, the product was extracted with ether. From the ethereal solution, unchanged *m*-cresyl-*o*-methylketone (15 g.) was recovered by steam distillation. The residue was extracted with ether. After drying the ethereal solution and distilling off the ether, a reddish black oil remained and it yielded a red oil (2.5 g.) boiling at 250-255°. When it was cooled, it solidified. This was the homopyrocatechin somewhat decomposed during the distillation under ordinary pressure.

(B) *p-Cresyl-o-methylketone.* To a solution of *p*-cresyl-*o*-methylketone (11 g.) and sodium hydroxide (7 g., double the theoretical quantity) in water (350 c.c.) was added a 3% hydrogen peroxide solution (260 g., 1.6 times the required quantity). After standing for 3.5 hours, the mixture was acidified with acetic acid and the unchanged *p*-cresyl-*o*-methylketone was distilled off with steam. It weighed 2 g. By extraction and redistillation there was obtained a somewhat yellowish, viscid, oily homopyrocatechin, boiling at 122° (6 mm.), 117° (4 mm.) or 114° (3 mm.). In the receiver, the oil solidified into a white, mass, but when left in the air, it became a red liquid again. (Found: C, 67.17; H, 6.76. Calc. for $C_7H_8O_2$: C, 67.74; H, 6.50%.)

(C) *Homopyrocatechin-tetrabromide.* A bromide was prepared according to H. Cousin.(6) To a solution of homopyrocatechin in glacial acetic acid was dropped a solution of bromine in the same solvent. Hydrogen bromide was evolved. After 1.5 hours, water was added. The separated substance was recrystallized repeatedly from dil. acetic acid. Somewhat orange coloured needles were obtained, m.p. 158° (Cousin gives m.p. 162–163°). (Found: C, 22.75, 23.73; H, 1.88 Calc. for $C_7H_5O_2Br_3$: C, 23.27; H, 1.38%.)

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(6) H. Cousin, *Ann. chim.*, (7), **13** (1898), 480.

(D) *Homopyrocatechin-diacetate.* After heating at 140–150° a mixture of homopyrocatechin (3 g.), acetic anhydride (10 g.), and anhydrous sodium acetate (2 g.) for four hours, the contents were extracted with ether, the ethereal solution washed with 10% KOH and fractionated under ordinary pressure. The obtained diacetate was a somewhat yellowish oil, boiling at 274–275°(7) and having the following constants: n_D^{28} 1.4932, d_4^{28} 1.1314 and M.R. 53.44 (theoretical 52.71). On standing, it solidified and it melted at 57–58° after recrystallisation from alcohol. (Found: C, 63.38, 63.02; H, 6.10, 6.09. Calc. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.78%.)

(E) *Oxidation of the homopyrocatechin-diacetate.* The diacetate (0.2 g.), mixed with 0.5 N-sulphuric acid (20 c.c.), was oxidized with 2% potassium permanganate on the water-bath. The obtained diacetate of protocatechuic acid melted at 143°. After double recrystallisation from water, it was identified with the diacetate of protocatechuic acid(8) by the mixed melting point.

4. **Methylation and Oxidation of Homopyrocatechin.** A mixture of homopyrocatechin (4.5 g.), caustic potash (6 g.), water (30 c.c.), and impure sodium methylsulphate (9 g.) was refluxed for 2.5 hours. Then the contents were dissolved in water, and the dimethylated ether (homoveratrol) was extracted with ether. The residue was acidified with dil. hydrochloric acid and the monomethylated ether (creosol) was extracted with ether.

(A) Homoveratrol, weighing 1.0 g., was obtained as yellowish oil from the ethereal solution. B.p. 216–218°, n_D^{28} 1,5250, d_4^{29} 1.051 (Found: M.R. 44.29; C, 70.66; H, 7.99. Calc. for $C_7H_{12}O_2{\ulcorner}_3$: M.R. 43.65; C, 71.05; H, 7.90%). For the identification, the homoveratrol was oxidized with 2.5% potassium permanganate. It gave veratric acid, melting at 179°.

(B) Creosol was obtained as yellowish oil. It weighed 1.2 g. and smelled somewhat of guaiacol. B.p. 218-225°, n_D^{27} 1.5347, d_4^{27} 1.100.

(C) *Oxidation of Creosol.* Ethyl nitrite, prepared from sodium nitrite (2.5 g,), alcohol, and sulphuric acid by Wallach's method,(9) was passed into the solution of creosol (0.3 g.) in alcohol (0.5 g.) cooled with ice and salt. NO_2-gas evolved. The contents became reddish-dark and some white precipitates were produced. After filtration and extraction of the filtrate with ether, the ether was evaporated off and the resulting tarry residue was extracted with hot water. To the water extract were added semicarbazide hydrochloride (0.1 g.), potassium acetate (0.1 g.), and alcohol (1 c.c.). On the next day, crystals of the resulting semicarbazone separated, were collected. M.p. 220–225°. After recrystallisation it melted at 227–229°, and proved to be vanillin-semicarbazone by the mixed melting point.

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(7) Cousin gives b.p. 264°.

(8) M. Imoto, *J. Chem. Soc. Japan,* **55** (1934), 523.

(9) O. Wallach, *Ann.,* **245** (1889), 251. M. Imoto, *J. Chem. Soc. Japan,* **55** (1934), 120.