SYNTHESIS OF 4-HYDROXY-3-ETHOXY-1-ALLYL-BENZENE FROM 4-HYDROXY-3-METHOXY-1-ALLYL-BENZENE (EUGENOL).

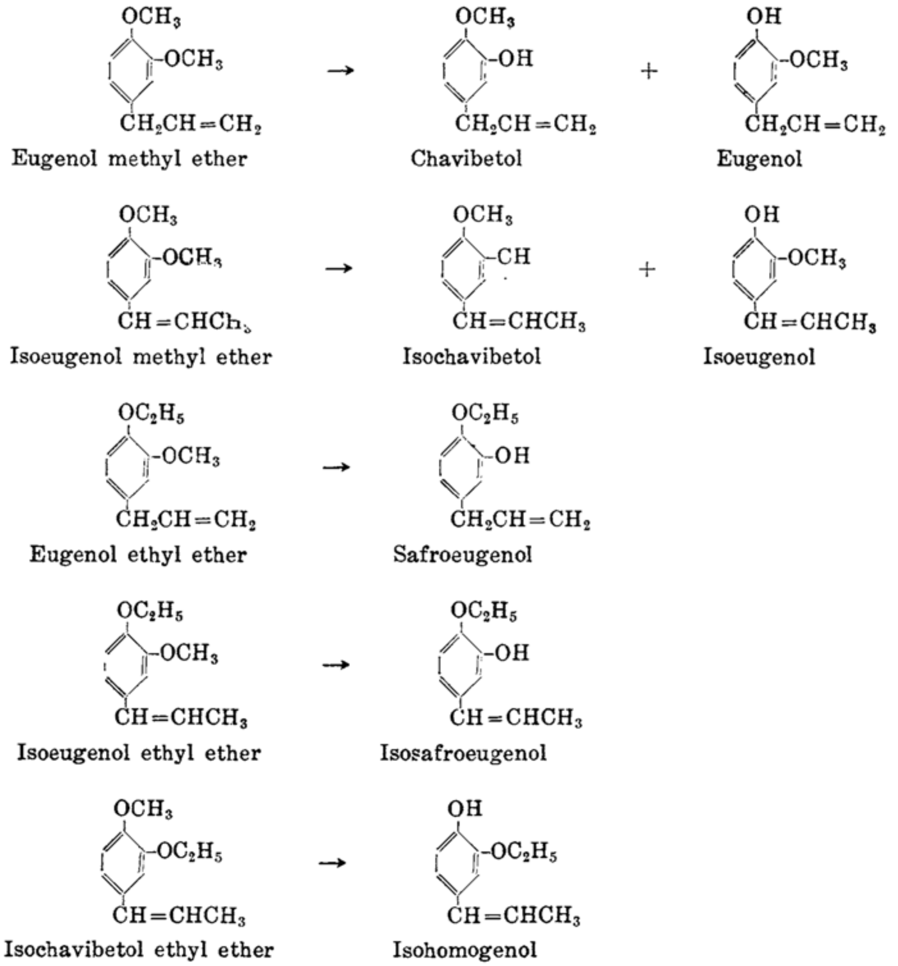
By **Nenokichi HIRAO.**

Received October 31st, 1935. Published March 28th 1936.

On the basis of Grignard's reaction the author prepared eugenol and chavibetol from eugenol methyl ether(1), isoeugenol and isochavibetol from isoeugenol methyl ether(1), safroeugenol from eugenol ethyl ether(1), isosafroeugenol from isoeugenol ethyl ether(1), and 4-hydroxy-3-ethoxy-1-propenylbenzene(2) from isochavibetol ethyl ether(3).

---

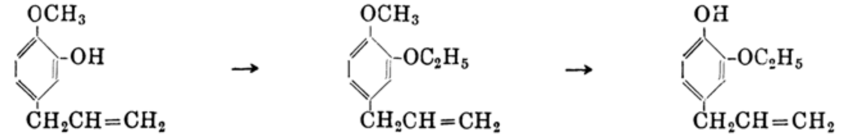
(1) *J. Chem. Soc. Japan*, **52** (1931), 519.
(2) The author proposes to designate Isohomogenol.
(3) *J. Chem. Soc. Japan*, **52** (1931), 263.



It has been considered difficult to prepare chavibetol, but the author synthesised it with ease by the above method. The mixture of chavibetol and eugenol was readily separated in their benzoates by fractional recrystallisation from petroleum ether and alcohol in turn.

Chavibetol ethyl ether, a new compound, was prepared by the ethylation of chavibetol with a good yield. It had the following constants: b.p. 114°/6.5 mm., d_4^{25} 1.0073, n_D^{25} 1.5231. On oxidation with potassium permanganate 4-methoxy-3-ethoxy-benzoic acid, m.p. 162–163°, was formed.

4-Hydroxy-3-ethoxy-1-allyl-benzene, a new compound, was prepared in a good yield by the action of Grignard's reagent on chavibetol ethyl ether. The author proposes to designate this new compound "homogenol." It is a clear liquid with an odour resembling eugenol. In alcoholic solution a green colouration was observed upon the addition of ferric chloride.



Chavibetol Chavibetol ethyl ether Homogenol

Homogenol had the following physical constants: b.p. 114.5°/8.5 mm.; d_4^{25} 1.0344, n_D^{25} 1.5292; benzoate, m.p. 45.5°; phenylurethane, m.p. 93.5–94.5°. (Further experiment on the same line is now in progress.)

Experimental.

(1) **Action of Grignard's reagent on eugenol methyl ether.** (a) A solution of 9 g. of eugenol methyl ether in 10 g. of xylene was poured into Grignard's reagent prepared from 1.3 g. of magnesium 8 g. methyl iodide, and 10 g. of dry ethyl ether. The mixture was heated on the oil bath at 160–180° for 2 hours under a reflux condenser. After cooling to room temperature some pieces of ice and dilute acetic acid were added, and the reaction product was distilled in steam. The distillate was extracted with ether and washed with a dilute solution of sodium bicarbonate. Seven grams of a phenolic substance and 0.2 g. of a neutral oil were obtained by shaking with dilute caustic soda in usual manner. The phenolic product had a sweet taste, and the presence of chavibetol was suspected.

(b) *Isomerisation.* One part of the phenolic product and 2 parts of potassium hydroxide were mixed in a test tube, and heated on the oil bath at about 220° for one hour. The mass was dissolved in water and acidified. The crude product was obtained is a yield more than 90 per cent of theory. One part was dissolved in 3 or 4 parts of hot 50% alcohol, and then cooled to room temperature. Isochavibetol crystallised out in glistening thin plates, m.p. 95–96°, and was confirmed by mixed melting point with an authentic specimen.

(c) *Separation of eugenol and chavibetol in their benzoates.* The phenolic product (b.p. 128–129°/6 mm.) (42 g.) was added to a solution of 19 g. of potassium hydroxide and (110 g.) of alcohol, and the solution was cooled with ice. Benzoyl chloride (43 g.) was added in a thin stream with constant stirring. When the reaction was completed, about 500 c.c. of water was added and the separated benzoates collected and washed with water. The benzoates were added to 80 c.c. of hot alcohol, and on cooling 87 g. of crystals were obtained. The crystals were dissolved in 200 c.c. hot petroleum ether (b.p. 30–60°), and, on standing, 10.3 g. of magnificent crystals appeared. The melting point of these crystals was 69°, and they were identified as eugenol benzoate by mixed melting point with an authentic specimen.

About a quarter of the solvent in the mother liquor was distilled off, and then it was allowed to crystallise, when 6.5 g. of crystals, m.p. 49°, separated, which differed from the former. They were chavibetol benzoate. The mother liquor was evaporated to half its volume, when 23 g. of crude product, m.p. 42–62°, crystallised. This is a mixture of the two benzoates. When 1 part of this mixture was treated with 2.5 parts of hot petroleum ether a small quantity of eugenol benzoate remained in crystalline state, and relatively pure chavibetol benzoate crystallised out from the solution. On repetition, it proved possible to separate the two benzoates from the mixture.

(2) **Action of Grignard's reagent on isoeugenol methyl ether.** (a) *Isoeugenol methyl ether*. To the reaction mixture of 32.8 g. of isochavibetol, m.p. 95°, 15 g. of potassium hydroxide and 30 c.c. of water, some pieces of ice and 25.2 g. of dimethyl sulphate were added, and then the mixture was shaken mechanically. The methylated product was treated in the usual manner. Yield 25.5 g.; b.p. 135°/14 mm.; d_4^{25} 1.0504; n_D^{25} 1.5655; M.R. 55.24; $C_{11}H_{14}O_2\vDash_4$ 52.22.

(b) A solution of 9 g. of isoeugenol methyl ether and 10 c.c. of xylene was added to Grignard's reagent prepared from 1.44 g. of magnesium, 8.5 g. of methyl iodide, and 10 c.c. of ether. After the usual procedure 6 g. of a phenolic product was separated. On recrystallisation from 50% alcohol 1.3 g. of isochavibetol, m.p. 94°, was yielded. Most of the residue of the mother liquor consisted of isoeugenol, which was confirmed by the formation of its benzoate melting at 103.5°.

(3) **Action of Grignard's reagent on eugenol ethyl ether. Synthesis of safroeugenol.** (a) *Eugenol ethyl ether*. Ethyl iodide (20.8 g.) and methanol (10 g.) were added to the reaction mixture containing 21.6 g. of eugenol, 10 g. of potassium hydroxide, and 7 c.c. of water. The mixture was boiled under a reflux condenser for an hour. Yield 22 g.; b.p. 122–125°/12 mm.; d_4^{25} 1.0099; n_D^{25} 1.5254.

(b) *Safroeugenol*. Eugenol ethyl ether and xylene (10 g.) were added to Grignard's reagent prepared from 1.3 g. of magnesium, 8 g. of methyl iodide, and 10 g. of ether. The usual treatment yielded 3.2 g. of a phenolic product. B.p. 129.5°/20 mm.; m.p. 34.5°; d_4^{25} 1.0335; n_D^{25} 1.5304 (in supercooled state); M.R. 53.23; $C_{11}H_{14}O_2\vDash_4$ 52.10. (Found: C, 73.88; H, 8.19. Calc. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.87%.) Phenylurethane, m.p. ca. 58°.

Isomerisation. The phenolic product (0.5 g.) and potassium hydroxide (1 g.) were heated in a small test tube in the oil bath at 200° for one and a half hours. The reaction product was dissolved in water and acidified with acetic acid. Lustrous thin plates crystallised out, and after recrystallisation from 50% alcohol, they melted at 85°. They were isosafroeugenol, and identification was established by mixed melting point with an authentic specimen.

The above data show that the phenolic product is safroeugenol.

(4) **Action of Grignard's reagent on isoeugenol ethyl ether. Synthesis of isosafroeugenol.** (a) *Isomerisation of eugenol ethyl ether*. In a test tube 5 g. of eugenol ethyl ether and 5 g. of potassium hydroxide were heated in the oil bath at 200° for 2 hours. The reaction mixture was dissolved in water and the separated crystals were collected and washed with water. The yield of the crystals was 4.8 g. These white crystals melted at about 61°, and after recrystallisation from 90% alcohol the melting point was raised to 63°, identical with that of isoeugenol ethyl ether.

(b) *Isosafroeugenol*. Isoeugenol ethyl ether (4.7 g.) and xylene (15 g.) were added to Grignard's reagent prepared from 0.65 g. of magnesium, 3.8 g. of methyl iodide and 10 c.c. of ether. The mixture was treated as above, and 4.1 g. of a phenolic product was produced in white crystals (theoretical yield 4.37 g.). Its melting point was 83°, but, after one recrystallisation from 50% alcohol, rose to 85°, identical with that of isosafroeugenol.

(5) **Action of Grignard's reagent on isochavibetol ethyl ether. Synthesis of isohomogenol.** (a) *Isochavibetol ethyl ether*. To the reaction mixture of 32 g. of isochavibetol, 12 g. of potassium hydroxide, and 20 c.c. of water, 37 g. of potassium ethyl sulphate was added, and the mixture was heated in the oil bath at 150–160° for 2 hours, and after cooling, a dilute solution of sodium hydroxide was added. Twenty three grams of white crystals were separated and readily purified by recrystallisation from 90% alcohol, m.p. 49.5° (Found: C, 74.84; H, 8.39. Calc. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33%). On oxidation with 3% potassium permanganate solution 4-methoxy-3-ethoxy-benzoic acid, m.p. 162–163°, was formed, which was identified by mixed melting point with an authentic specimen. These data show that the white crystalline substance is isochavibetol ethyl ether.

(b) *Isohomogenol*. A solution of 6.4 g. of isochavibetol ethyl ether in 30 g. of xylene was added to Grignard's reagent prepared from 0.9 g. of magnesium, 5.5 g. of methyl iodide, and 10 c.c. of dry ether, and the mixture boiled for 2 hours under a reflux condenser. Two grams of a crystalline phenolic substance was produced, and recrystallised from 50% alcohol. It melted at 53–54°. (Found: C, 74.06; H, 7.97. Calc. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.89%.) The melting point of its benzoate was 87°, identical with that of isohomogenol benzoate.

(6) **Action of Grignard's reagent on chavibetol ethyl ether. Synthesis of homogenol.** (a) *Chavibetol*. In alcoholic solution, 49 g. of the pure chavibetol benzoate, m.p. 49°, described above, was saponified with 18 g. of potassium hydroxide. Yield 23 g.; b.p. 113°/8 mm. (oil bath 130°); $d^{25}_{.5}$ 1.0646, d^{25}_{4} 1.0613; n^{25}_{D} 1.5379; M.R. 48.33; $C_{10}H_{12}O_2\vDash_4$ 47.48.

(b) *Chavibetol ethyl ether*. In a pressure bottle, a solution of 23 g. of chavibetol, 9.3 g. of potassium hydroxide, 100 c.c. of alcohol, and 17 g. of ethyl bromide was heated at 80–90° on the water bath for 3 hours. Chavibetol (1.5 g.) was recovered. Yield 23.8 g.; b.p. 114°/6.5 mm. (oil bath 140°); d^{25}_{25} 1.0104, d^{25}_{4} 1.0073; n^{25}_{D} 1.5231; M.R. 58.23; $C_{12}H_{16}O_2\vDash_4$ 56.83. (Found: C, 74.82· H, 8.45. Calc. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33%.) It had a faint odour. This ethyl ether (1.7 g.) was oxidised with 2.5% potassium hydroxide solution (200 c c.), the reaction mixture was filtered, and the filtrate acidified with acetic acid. 4-Methoxy-3-ethoxy-benzoic acid (m.p. 161–162°, 0.5 g.) was obtained as white crystals. It was identified by mixed melting point with an authentic specimen.

(c) *Homogenol*. The solution of the foregoing ethyl ether (23.8 g.) in xylene (30 c.c.) was added to Grignard's reagent prepared from magnesium (3 g.), methyl iodide (18 g.) and ether (50 g.), and the product treated in the usual manner. A phenolic product (homogenol 18.5 g.) was obtained. B.p. 112°/6.5 mm.; d^{25}_{25} 1.0375, d^{25}_{4} 1.0344; n^{25}_{D} 1.5292; M.R. 52.81; $C_{11}H_{14}O_2\vDash_4$ 52.10. (Found: C, 73.89; H, 8.07. Calc. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.89%.) It is a colourless oil with eugenol-like odour. In alcoholic solution a greenish tinge was given with ferric chloride.

Phenylurethane. After standing for 2 months, the mixture of homogenol (1 g.) and carbanil (0.9 g.) crystallised completely, and the product was recrystallised from 80% methanol, m.p. 93.5–94.5° (sharp). (Found: C, 72.55; H, 6.50. Calc. for $C_{18}H_{19}O_3N$: C, 72.73; H, 6.40%.)

Benzoate. In ice cooling, benzoyl chloride (1.4 g.) was added to a solution of homogenol (1.65 g.) and potassium hydroxide (0.7 g.) in alcohol (10 g.). Yield of crude benzoate, 3 g. On standing, the solution of the benzoate in petroleum ether gave beautiful plates, m.p. 45.5° (sharp). (Found: C, 76.25; H, 6.52. Calc. for $C_{18}H_{18}O_3$: C, 76.60; H, 6.38%).

Isomerisation. In a small test tube, homogenol (1.3 g.) and potassium hydroxide (1.5 g.) were heated on the oil bath at 180–200° for 2 hours. The reaction mixture was dissolved in water and the solution acidified with acetic acid, when white crystals separated out. Yield 1.1 g. Benzoate was prepared and recrystallised from alcohol, m.p. 85.5–86.2°. It is identical with the isohomogenol benzoate.

In conclusion, the author wishes to express his gratitude to Dr. Kashichi Ono for his kind guidance during this investigation.

Research Laboratory of
Saisei Shōnō Kabushiki Kaisha, Kobe.