SOME NEW DERIVATIVES OF PROTOCATECHUIC ACID FORMED FROM SAFROL AND TWO EXAMPLES OF THE REARRANGEMENT OF THE ACYL GROUP.

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Many investigations have already been made on treating safrol (I) with methanol and caustic alkali for splitting off the methylene-dioxy group and thus obtaining methoxy-isoeugenol (II) and methoxy-isochavibetol (III).(1) On protocatechuic acid derivatives (X) formed from them, some detailed work has been published by Hirao(2) of our laboratory of the Nippon Koryo Yakuhin Kaisha, Ltd., Kobe. The commercial production of vanillin from safrol is practiced by our company by this method on a large scale. The present paper deals with the synthesis of new acids by acetylation, benzoylation, and oxidation of a mixture of phenolic compounds of II and III.

The mixed phenolic compounds II and III are obtained from safrol by treatment with methanol and caustic alkali under pressure. If acetic anhydride alone is used for acetylation, diacetate is formed, while, if anhydrous sodium acetate is also added to a large excess of acetic anhydride, the monoacetates alone are formed. When benzene was used as solvent, there was no reaction observed to take place, while, by taking xylene as the solvent, monoacetate was the principal product. By addition of a drop of concentrated sulphuric acid, diacetate alone is produced.

The authors have succeeded easily in crystallizing out methoxy-isochavibetol benzoate (XIV) by employing the method used by Hirao, namely,

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(1) G. Ciamician and P. Silber, *Ber.*, **23** (1890), 1162; S. Nagai, *J. Soc. Chem. Ind., Japan*, **27** (1924), 631; N. Hirao, *J. Chem. Soc. Japan*, **51** (1930), 441; T. Hiraizumi, *J. Soc. Chem. Ind., Japan*, **34** (1931), 584; T. Kuwata, *ibid.*, **34** (1931), 590.

(2) *J. Chem. Soc. Japan*, **51** (1930), 713; *ibid.*, **54** (1933), 194, 992; etc.

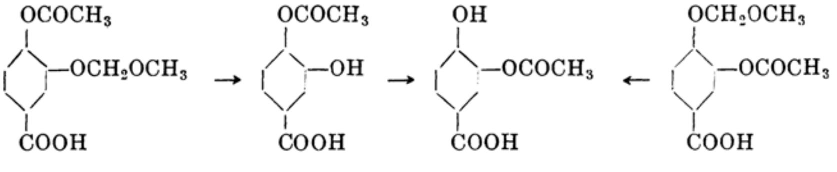
by dissolving the decomposition products of safrol with potassium hydroxide, shaking the solution with benzoyl chloride, treating the soft lump of mixed benzoates with alcohol, and crystallizing out methoxy-isoeugenol benzoate (XIII). The mother liquor contains the compound XIV, which crystallizes out on allowing the mother liquor to stand for about three days. Its m.p. is 55°.

The filtrate from XIII and XIV deposits, when concentrated on the water bath and allowed to stand, propenyl-pyrocatechin benzoate (XV).

When the diacetate of propenyl-pyrocatechin was oxidized with neutral or alkaline potassium permanganate, a resinous product alone was obtained. Both monoacetates (V and VI) could also be oxidized only in acid solution. The monobenzoates XIII and XIV could, however, be oxidized in neutral medium showing that benzoyloxy group is not so easily saponified as acetoxyl group. In this manner, besides the previously known diacetoxy-benzoic acid (VII) the following four new acids were obtained:

VIII 4-Acetoxy-3-(methoxy-methoxy)-benzoic acid, m.p. 112–113°;
IX 3-Acetoxy-4-(methoxy-methoxy)-benzoic acid, m.p. 150–152°;
XVI 4-Benzoyloxy-3-(methoxy-methoxy)-benzoic acid, m.p. 127°;
XVII 3-Benzoyloxy-4-(methoxy-methoxy)-benzoic acid, m.p. 117–118°.

Diacetoxy-benzoic acid was saponified by concentrated hydrochloric acid into protocatechuic acid (X) and the latter was changed by benzoylation by the Schotten-Baumann method into a new compound, dibenzoyloxy-benzoic acid benzoylester (XII). The compounds VIII and IX were changed by splitting off the methoxy-methoxy group by treating with acids into a compound melting at 198° corresponding to 3-acetyl-protocatechuic acid (XI) synthesized by Ciamician and Silber,(1) and E. Fischer, M. Bergmann, and W. Lipschilz,(3) and melting at 197–199°. Evidently a rearrangement of the acyl group has taken place:



Such a rearrangement of the acyl group has been observed already by various workers, and the present authors have also obtained, by a similar splitting of the methoxy-methoxy group from XVI and XVII, the same compound with melting points 224° and 225°, corresponding to 3-benzoyl-protocatechuic acid (XVIII) obtained by E. Fischer by the following rearrangement:

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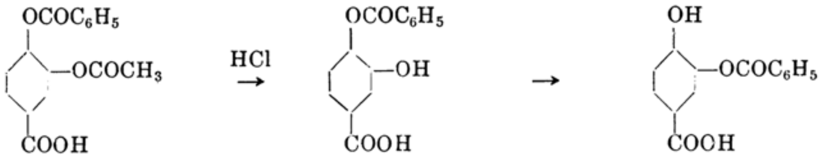
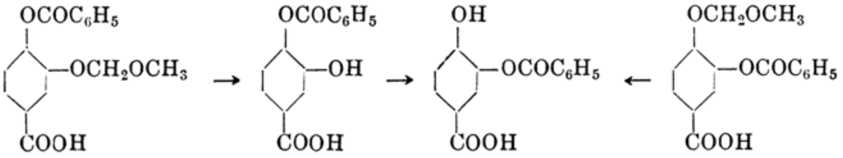
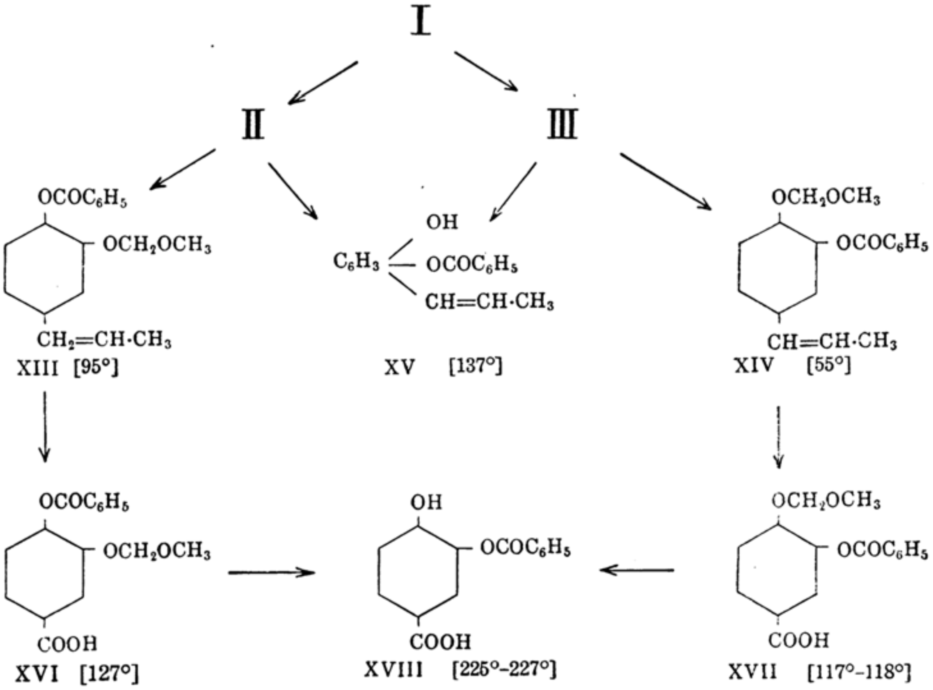
(3) *Ber.*, **51** (1918), 45.

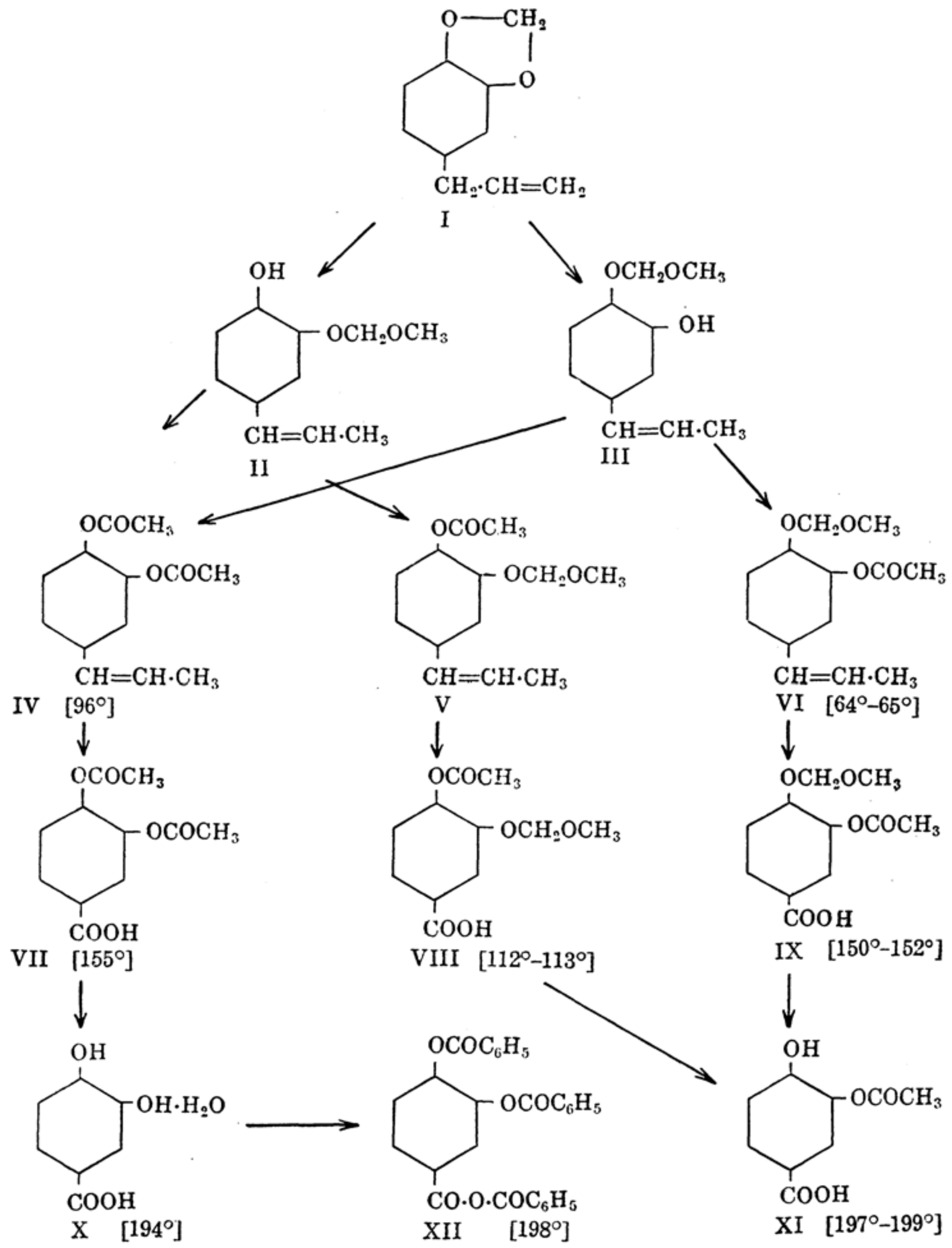


It is evident, therefore, that we have reached the same object of rearrangement by a method different from that of E. Fischer.



The above results are summarized as follows:




O—CH₂
O
CH₂·CH=CH₂
I
OH
OCH₂OCH₃
CH=CH·CH₃
II
OCH₂OCH₃
OH
CH=CH·CH₃
III
OCOCH₃
OCOCH₃
CH=CH·CH₃
IV [96°]
OCOCH₃
OCH₂OCH₃
CH=CH·CH₃
V
OCH₂OCH₃
OCOCH₃
CH=CH·CH₃
VI [64°–65°]
OCOCH₃
OCOCH₃
COOH
VII [155°]
OCOCH₃
OCH₂OCH₃
COOH
VIII [112°–113°]
OCH₂OCH₃
OCOCH₃
COOH
IX [150°–152°]
OH
OH·H₂O
COOH
X [194°]
OCOC₆H₅
OCOC₆H₅
CO·O·COC₆H₅
XII [198°]
OH
OCOCH₃
COOH
XI [197°–199°]

Experimental Part.

(1) **Decomposition of Safrol.** Potassium hydroxide (17 g.) was dissolved in 30 g. of methanol and transferred to the autoclave with 30 g. of safrol, and the mixture was kept at 200°–208° for three hours in an oil bath and then allowed to cool. The contents were poured out into water and the isomerized product, isosafrol, was extracted with ether. On distilling off the ether, 3 g. of isosafrol was obtained. The aqueous layer was cooled with ice and acidified with 110% of the theoretical amount of dilute sulphuric acid. The phenolic substance which floated out was extracted with ether. By distilling off the ether, 31 g. of the raw product was obtained which gave by redistillation 27 g. of the mixture of II and III.

(2) **Acetylation.** (A) *Preparation of the di-acetate.* (a) The decomposition product (100 g.) of safrol and acetic anhydride (105 g.) were kept at 140–145° on an oil bath for 3 hours. Water (150 c.c.) was added and the whole was warmed for 30 minutes on the water bath. On cooling, di-acetate separated out in crystals.

(b) The decomposed phenolic substance (40 g.) was dissolved in 40 g. of xylene, 24 g. of acetic anhydride and one drop of concentrated sulphuric acid were added, and the whole was heated under reflux condenser for two hours. The contents were poured into water, warmed on the water bath for 30 minutes, and cooled. The crystals thus separated were recrystallized from alcohol and showed the m.p. 95°. Yield was 24 g.

(B) *Preparation of the mono-acetates.* (a) The decomposed phenolic substance (100 g.), anhydrous sodium acetate (100 g.), and acetic anhydride (400 g.) were heated under a reflux condenser for 3.5 hours. The contents were poured into a double volume of water, warmed for one hour on the water bath, and then extracted with benzene. On distilling off the benzene, an oily substance was obtained which was subjected to fractional distillation under a reduced pressure of 14 mm.

Fraction	Temperature	Quantity distilled	d_{18}	n_{15}
1	–170°	5 g.		
2	170–172°	105 g.	1.1114	1.5383
3	172–176°	12 g.		

Molecular refraction of fraction 2 was found 66.0, the calculated value for $C_{13}H_{16}O_4\overline{|4}$ being 63.05, and hence $\varDelta = 3.05$. As the similar derivatives of propenyl-benzene always show $\varDelta = 2-3$, the figures thus obtained seem to correspond to those of monoacetyl compound. Fraction 2 (90 g.) was changed to a soft lump by treating with the freezing mixture according to Kuwata.

On filtration by suction, it was separated into 25 g. (27.8%) of crystals (VI) and 65 g. (71.2%) of an oily matter (V). The crystals melted, after washed with cooled alcohol, at 64°.

(b) The decomposed phenolic substance (50 g.), xylene (50 g.), and acetic anhydride (28 g.) were heated under a reflux condenser for 1.5 hours. The product was warmed with water for 30 minutes. The floating oily matter was fractionated under 13 mm. pressure. The fraction 2 gave a beautiful green coloration with $FeCl_3$ and proved to be the unchanged phenolic substance. The fraction 5 was the product aimed at and gave by freezing crystals melting at 64°.

Fraction	Temperature	Quantity
1	xylene	
2	-165°	2 g.
3	165-167°	23.5 g.
4	167-170°	0.5 g.
5	170-171°	13.2 g.

(3) **Benzoylation.** The decomposition product of safrol (50 g.) was dissolved in KOH solution (15 g. in 250 c.c. of water); after adding benzoyl chloride (35 g.), the mixture was well stoppered and shaken for 3 hours. The soft lump formed was separated and treated with 150 c.c. of alcohol, from which 20 g. of crystals melting at 95° separated out. From the mother liquor allowed to stand for 3 days, there separated out 12 g. of crystals melting at 52°. The last filtrate was concentrated on the water bath to about 40 c.c. and allowed to stand when a third crop of crystals came out, which on recrystallization from alcohol melted at 137°.

(4) **Oxidation.** (a) *Protocatechuic acid di-acetate* (VII). Six grams of IV was mixed with 500 c.c. of water and 30 c.c. of 10% sulphuric acid and the mixture was subjected to oxidation by treating it on the water bath with a 2 per cent. solution of 20 g. of $KMnO_4$. The filtrate was salted out and then extracted with ether. After evaporation of ether 1.1 g. of white crystals were left behind, m.p. 142-150°. By repeating this process, 1.5 g. of crystals melting at 149° were obtained.

(b) *Methoxy-vanillic acid acetate* (VIII). Three grams of the oily part of the monoacetate described above was mixed with 300 c.c. of water and 20 c.c. of 10% sulphuric acid and the mixture was subjected to oxidation by adding 500 c.c. of water containing 10 g. of $KMnO_4$ on the water bath. After filtering and cooling, the product was treated exactly the same as in the case of the di-acetate mentioned above. The crystals obtained by recrystallizing twice from water melted at 112-113°. (Found: C, 54.7; H, 4.9; molecular weight (in camphor), 249.3. Calc. for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0%; mol. wt., 240.)

(c) *Methoxy-isovanillic acid acetate* (IX). With the compound VI melting at 64°, the same treatment was repeated as in the case (b). The pure white crystalline product, after recrystallized three times from water, melted at 150-152°. (Found: C, 54.8; H, 5.1. Calc. for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0%.)

(d) *Methoxy-isovanillic acid benzoate* (XVII). Two grams of the substance XIV melting at 55° was treated with 5 g.of $KMnO_4$ in 500 c.c. of water on the water bath as usual. Sulphuric acid was not added in this case, and the oxidation was found to be very slow. After warming for three hours on the water bath, a small quantity of methanol was added to reduce the remaining $KMnO_4$. The product was then filtered, acidified with acetic acid, and extracted with ether. The pure white needle crystals obtained by recrystallizing twice melted at 117-118°. (Found: C, 62.9; H, 5.1. Calc. for $C_{16}H_{14}O_6$: C, 63.6; H, 4.6%.)

(e) *Methoxy-vanillic acid benzoate* (XVI). With the compound XIII melting at 95°, exactly the same treatment as in the case (d) was carried out. The pure white crystals obtained by recrystallizing twice melted at 127°. (Found; C, 63.3; H, 4.8. Calc. for $C_{16}H_{14}O_6$: C, 63.6; H, 4.6%.)

(5) **Saponification and the Rearrangement of Acyl Group.** (a) *Protocatechuic acid* (X). The substance VII (1 g.) was heated with 10 c.c. of methanol and 1 c.c. of concentrated hydrochloric acid under the reflux condenser for 1.5 hours. Water (30 c.c.) was then added, methanol was distilled off, and the residue was extracted with ether. The solid matter left on evaporating off ether was recrystallized from water. It melted now at 195° and weighed 0.5 g. When mixed with a pure sample of protocatechuic acid there was no change of m.p., showing the completeness of saponification.

(b) *Rearrangement of the acyl group from VIII to XI.* The substance VIII (0.2 g.) melting at 112-113° was warmed with 3 c.c. of glacial acetic acid and one drop of concentrated hydrochloric acid on the water bath for an hour. Water is then added and the product was extracted with ether. The ethereal extract was washed with water; on evaporation of ether, the residue was twice recrystallized from water, yield 0.05 g. The substance melted at 198° and when mixed with protocatechuic acid, depression of the melting point resulted.

(c) *Partial saponification from IX to XI.* The substance IX (0.1 g.) was warmed with 3 c.c. of 30% alcohol and 2 drops of 10% sulphuric acid on the water bath for 3 hours. The reaction product was extracted with ether as usual. A small quantity of a substance melting at 198°

was obtained which did not lower the m.p. when mixed with the substance obtained in (b).

(d) *Rearrangement from XVI to XVIII and from XVII to XVIII.* The substance XVI (0.5 g.) was warmed with 5 c.c. of glacial acetic acid and 1 c.c. of concentrated hydrochloric acid on the water bath for 1.5 hours, when a rather strong resinification took place. The product was extracted as usual with ether and a small amount of a substance melting at 224° after recrystallized from water was obtained. Another substance with m.p. 225° was obtained from XVII on treating it exactly in the same manner. The two substances did not show any lowering of melting point when mixed together, showing that they are the same compound.

Addendum. *Dibenzoyloxy-benzoic acid benzoylester* (XII). Protocatechuic acid (1 g.) and NaOH (4 g.) were dissolved in 36 g. of water. Under ice cooling, 9.1 g. of benzoyl chloride was added and the whole was shaken, when a white substance separated copiously. It was collected with suction, and recrystallized four times with use of activated charcoal, m.p. 198°. (Found: C, 71.7; H, 3.4, molecular weight (in camphor), 449. Calc. for $C_{28}H_{18}O_7$: C, 72.1; H, 3.8%, mol. wt., 466.)

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