## Summary

Vitamin concentrate prepared from brewers' yeast by adsorption on fuller's earth followed by extraction, benzoylation and acetone precipitation as previously described, when dissolved in water and treated with an alcoholic solution of picrolonic acid, yields initial precipitates which are relatively inactive. The filtrate from these when evaporated yields a semi-crystalline deposit rich in the antineuritic vitamin. This picrolonate deposit when purified by recrystallization from methyl alcohol is converted to characteristic rods or prisms which are curative for polyneuritic rats in doses of 0.015 milligram.

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# The Preparation of Certain Cryptophenols

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It has been observed that many phenols when passed through the body become conjugated. This conjugation represents a detoxification, usually accompanied by a corresponding decrease in germicidal activity. A similar loss of germicidal activity may be produced *in vitro*, when the phenol is in contact with organic material. In this case, however, the effect is due to precipitation of the phenol by chemical combination with albumins. It has also been shown in the case of strongly germicidal phenols that the margin between the effective concentration for bacteria and the harmful dose for the host is very small, and that such phenols are in general too toxic and too corrosive to be taken in effective quantities. In view of these facts, it seemed of interest to attack the problem of producing effectively germicidal phenols for internal use from a new standpoint. On the basis of the following considerations, a number of cryptophenols have been prepared and submitted to pharmacological investigation, the results of which will be reported elsewhere.

Cryptophenols are those phenols in which the acidity has been reduced to such an extent that they do not dissolve in aqueous sodium hydroxide, but only in Claisen solution. It might be expected that this change in properties would be accompanied by a simultaneous decrease in corrosive action and susceptibility to conjugation. On the other hand, it seems reasonable to assume, in the light of present knowledge, that such weakly acid phenols would also, in general, be less germicidal than those which are strongly acid, although there is not necessarily a direct proportionality between acidity and germicidal action. If it be found, however, that

cryptophenols are of sufficiently low toxicity to permit ingestion of larger quantities, loss of germicidal power might be compensated for by the administration of greater doses. A further compensation might be effected by the inability of the protective mechanism of the body to conjugate cryptophenols. Thus while the compound might be considerably less germicidal, its lower toxicity would permit administration of larger quantities, which might pass through the body unchanged. The concentration of the antiseptic in the urine, for instance, would in this case be sufficient to produce the required germicidal effect. The following report deals with the chemistry of certain representatives of this type of compound.

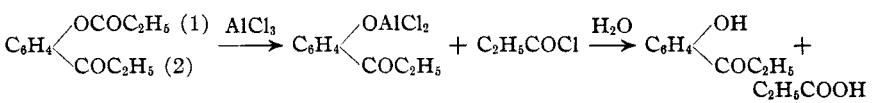
The methods used in this study for the preparation of these derivatives were as follows: (1) the method of Claisen[1] based on the observation that ring substituted alkyl phenols may be prepared by the action of certain alkyl halides on a suspension of the sodium salt of phenols in non-hydrolyzing media such as toluene.

In this manner the following cryptophenols were prepared: 2,4-dibenzylphenol, obtained by Short and Stewart[2] by a different method, *o*-benzyl-*p*-cresol, and 2,6-dibenzyl-*p*-cresol (already prepared by Claisen), and the new derivatives 2-benzyl-4-propylphenol, 2-benzyl-4-*tert*-amylphenol and 2,6-dibenzyl-4-*tert*-amylphenol.

(2) The method of Fries for the rearrangement of phenyl-acyl esters to acyl phenols, with the aid of aluminum chloride, and subsequent reduction according to Clemmensen[3] with amalgamated zinc and hydrochloric acid.

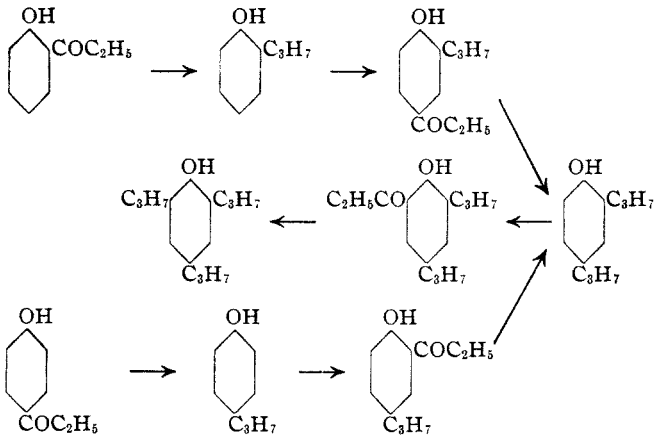
It seemed interesting to study the possibility of introducing more than one propionyl group into phenol, in connection with the preparation of tripropylphenol.

In polyhydric phenols the entrance of more than one acyl group in the ring goes with relative ease, but it was found that in the case of phenol a propionyl group in either the ortho or the para position prevents the introduction of a second propionyl group. Thus when *o*-propionyl-phenyl propionate was heated with aluminum chloride and the reaction mass decomposed with dilute hydrochloric acid, *o*-propionylphenol was obtained, the propionyl group being split off as propionyl chloride



The introduction of a second propionyl group was only possible after reduction of the propionyl group already present. Tripropylphenol, therefore, had to be prepared according to the following scheme, in which the intermediate esters have been omitted.

(1) Claisen, *Z. angew. Chem.*, **36**, 478 (1923); *Ann.*, **442**, 238 (1925).
(2) Short and Stewart, *J. Chem. Soc.*, **127**, 553 (1929).
(3) Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 51, 681 (1914).



An attempt was also made to prepare *o*-benzoyl-*p*-*tert*-amylphenol from *p*-*tert*-amylphenyl benzoate through rearrangement of the benzoyl group, and subsequent reduction of the ketone. The benzoate, m. p. 59°, was prepared by the Schotten–Baumann reaction. The benzoyl group could not, however, be made to migrate into the ring. A negative result was also obtained in attempting to rearrange the benzyl ether of *p*-*tert*-amylphenol, in order to prepare its *o*-benzyl derivative.

(3) The method of Paterno and Mazzara[4] for the preparation of *p*-benzylphenol, through the action of benzyl chloride on phenol in the presence of a small piece of zinc: using an excess of benzyl chloride, this method was applied in the preparation of tribenzylphenol.

## Experimental

### Part I

**Preparation of the C-Benzyl Derivatives.**—The sodium salts of the phenols were prepared by adding a toluene solution of the phenol gradually to a suspension of the calculated amount of sodium in toluene, and heating until the salt formation was completed. Benzyl chloride was then added and the mixture refluxed vigorously for five hours. Water was added to dissolve the sodium chloride and the toluene layer was extracted with 10% sodium hydroxide in order to remove any unchanged phenol. The solvent was distilled off and the oily residue dissolved in Claisen solution (equal parts of 50% aqueous potassium hydroxide and methyl alcohol). The Claisen solution was extracted with benzene to remove any benzyl ether that might have been formed, acidified, the precipitating oil dissolved in benzene, dried with anhydrous sodium sulfate and distilled *in vacuo*. The cryptophenols thus obtained gave a green coloration in alcoholic solution with ferric chloride.

The compounds were characterized by preparing their phenyl urethan derivatives. These were made by heating the calculated amounts of phenyl isocyanate and the phenol with about one-fifth of its weight of aluminum chloride, extracting the reaction mass with dilute hydrochloric acid and recrystallizing the residue from alcohol.

The following tables give the experimental and analytical data obtained in the experiments.

(4) Paterno and Mazzara, *Gazz. chim. ital.*, **3**, 254 (1873).

| Reacting phenol | | | Benzyl | Benzyl ether, | | |
|---|---|---|---|---|---|---|
| Name | Quant., g. | Sodium, g. | chloride, g. | g. | m. p., °C. | C-benzyl derivative, g. |
| *p*-Benzylphenol | 18.4 | 2.3 | 13 | .. | | 10 |
| *p*-Cresol | 64.8 | 13.8 | 76 | 10 | 40 | mono-benzyl, 53<br>di-benzyl, 14 |
| *p*-Propylphenol | 27.2 | 4.6 | 25.3 | 8.5 | 56 | 19 |
| *p*-*Tert*-amylphenol | 41 | 5.8 | 31.7 | 4.5 | 65 | 31 |
| *o*-Benzyl-*p*-*tert*-amylphenol | 25.4 | 2.3 | 14 | .. | | 8 |

| Phenols prepared | B. p., °C. | Phenyl urethan N Found, % | N Calcd., % | M. p., °C. |
|---|---|---|---|---|
| 2,4-Dibenzylphenol | 238 (10 mm.) m. p. 84 | 3.49 | 3.56 | 111–112 |
| *o*-Benzyl-*p*-cresol | 147–148 (7 mm.) | 4.37 | 4.42 | 144 |
| 2,6-Dibenzyl-*p*-cresol | 205–207 (5 mm.) | 3.40 | 3.44 | 129–130 |
| 2-Benzyl-4-propylphenol | 186–187 (10 mm.) | 4.12 | 4.08 | 92 |
| 2-Benzyl-4-*tert*-amylphenol | 180–185 (8 mm.) m. p. 46–46.5 | 3.66 | 3.77 | 116 |
| 2,6-Dibenzyl-4-*tert*-amylphenol | 225–230 (7 mm.) | 3.16 | 3.02 | 146 |

In some cases small variations from the above procedure were necessary in the preparation of these phenols. Thus, for example, 2,6-dibenzyl-4-tertiary-amylphenol did not dissolve in Claisen solution but its sodium salt precipitated. Before acidifying, this was filtered off on a fritted glass filter and washed with petroleum ether.

## Part II

**Preparation of Phenol Esters.**—The different phenol esters of propionic acid were prepared in the following manner. Thionyl chloride was gradually added at room temperature to propionic acid, in molecular quantities. After the evolution of hydrogen chloride and sulfur dioxide had subsided, the reaction was terminated by heating for a short while on a water-bath. To the crude propionyl chloride thus obtained, the calculated amount of the phenol was added in portions and the mixture heated on an oil-bath for three hours at 130°. The reaction product was washed with water and dilute sodium hydroxide, dried and distilled. The new esters thus prepared were

| Compound | B. p., °C. | Yield, % |
|---|---|---|
| *o*-Propylphenylpropionate | 245 | 80 |
| *p*-Propylphenylpropionate | 254–256 | 74 |
| 2,4-Dipropylphenylpropionate | 277–279 | 68 |

**Rearrangement of the Esters to Ketones.**—Using molecular quantitites, the ester was slowly dropped on finely powdered aluminum chloride, contained in a flask cooled in an ice-bath. The components were mixed by shaking the flask occasionally. After the ester had been added, the mixture was left at room temperature for an hour, heated for two hours at 100° and the reaction terminated at 120°. No more hydrogen chloride was then evolved. After cooling, the dark brittle mass was extracted with dilute hydrochloric acid, the residue taken up in benzene, dried and distilled.

Isomeric ketones, *o*- and *p*-propionylphenol, were only obtained in the rearrangement of phenyl propionate. The para derivative is a solid and was readily separated from the oily *o*-derivative through filtration and washing the remaining crystals with benzene. The *p*-compound may be recrystallized from water.

*p*-Propyl-*o*-propionylphenol and 2,4-dipropyl-6-propionylphenol form fairly insoluble sodium salts, but could be isolated from the acidified reaction mass by steam distillation.

The following ketones were prepared

| Compound | B. p., °C. | $FeCl_3$ | NaOH |
|---|---|---|---|
| *o*-Propionylphenol | 115 (15 mm.) | Bluish-red | Yellow |
| *p*-Propionylphenol | M. p. 148 | No color | No color |
| *o*-Propyl-*p*-propionylphenol | M. p. 77 | No color | No color |
| *p*-Propyl-*o*-propionylphenol | 270 | Bluish-red | Yellow |
| 2,4-Dipropyl-6-propionylphenol | 295–298 | Bluish-green | Yellow |

The following table gives the quantitative data concerning the preparation of these ketones

| Compound | Quant., g. | $AlCl_3$, g. | Ketone, g. | Yield, % |
|---|---|---|---|---|
| Phenyl propionate | 150 | 135 | 64.5 (para) | 43 |
| | | | 45 (ortho) | 30 |
| *o*-Propylphenyl propionate | 26 | 25 | 18 | 70 |
| *p*-Propylphenyl propionate | 52 | 50 | 43 | 83 |
| 2,4-Dipropylphenyl propionate | 50 | 40 | 31 | 62 |

**Reduction of the Ketones.**—The ketones were reduced according to Clemmensen by boiling vigorously in a flask provided with stirrer and reflux condenser, for four hours, with about five times their weight of amalgamated zinc and crude hydrochloric acid, diluted with two parts of water.

2,4-Dipropylphenol may be obtained from *o*-propyl-*p*-propionylphenol, as well as from the isomeric *o*-propionyl-*p*-propylphenol. It stands on the border-line of the crypto-phenols, since it will not dissolve in dilute alkali but does dissolve in concentrated alkali. Tripropylphenol is distinctly crypto-phenolic in character.

| | | | Phenyl urethan | | |
|---|---|---|---|---|---|
| Compound | Yield, % | B. p., °C. | N found, % | N calcd., % | M. p., ° C. |
| *o*-Propylphenol | 71 | 223–225 | 5.43 | 5.49 | 106 |
| *p*-Propylphenol | 73 | 230–232 | 5.53 | 5.49 | 128.5–129 |
| *o,p*-Dipropylphenol | 70 | 263 | 4.85 | 4.71 | 124 |
| Tripropylphenol | 71 | 288–289 | .. | .. | ..... |

## Part III

**Tribenzylphenol.**—This compound was prepared by heating a mixture of 24 g. of phenol and 128 g. of benzyl chloride in the presence of a small quantity of mossy zinc. The temperature was kept below 70°, however, in order to avoid a too violent reaction. When the evolution of gas had practically stopped, the reaction product was dissolved in benzene, and washed with water to remove the hydrochloric acid. On distillation in vacuum, only a small amount of benzylphenol was obtained, the distillate consisting of a mixture of di- and tri-benzylphenol. By this method 18 g. of tribenzylphenol, b. p. 272° (10 mm.), was obtained. Its phenylurethan derivative was prepared, m. p. 120°. Calcd. for $C_{34}H_{29}O_2N$: N, 2.89. Found: N, 2.90.

## Summary

With a view to their possible use as germicidal agents, certain crypto-phenols and their derivatives have been prepared. The bacteriological and pharmacological properties of some of these compounds are being investigated and will be reported elsewhere.

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