[CONTRIBUTION FROM THE RESEARCH LABORATORY OF EX-LAX, INC.]

Carvacrolphthalein

BY MAX H. HUBACHER

According to Curt Ehrlich,[1] carvacrolphthalein has a melting point of 246–247° and produces a prolonged purgative effect as compared with phenolphthalein. The compound obtained in this Laboratory was different in these properties. It melted at 294° and was devoid of laxative activity, showing a potency of under 0.05.[2]

It is believed that Ehrlich's compound of melting point 246–247° was thymolphthalein, the melting point of which is described as being 246–247°[3] and that he probably used impure carvacrol containing a substantial amount of thymol in the preparation of his compound. When a mixture of equal parts of carvacrol and thymol was condensed with phthalic anhydride and the crude product purified by crystallizations, then thymolphthalein was obtained.

Thymolphthalein was also prepared for comparison and likewise found to lack laxative activity,[2] though it is also stated to be a laxative compound.[1] It forms in much higher yields than carvacrolphthalein under the same experimental conditions. Thymolphthalein was found to have a melting point six degrees higher than the one given in the literature.[3]

The diacetate is described here because it has never been mentioned in the literature.

Experimental[4]

Carvacrolphthalein (I).—Zinc chloride as a condensing agent gave only traces of I. The yields on I when using stannic chloride were quite low and various changes such as quantities of condensing agent, temperature, etc., did not improve yields. Technical carvacrol of solidification point −11 to −10° gave the same yields as Eastman Kodak Co. carvacrol of crystallizing point −2°.

15.0 g. (0.1 mole) of carvacrol, 7.4 g. (0.05 mole) of phthalic anhydride and 15.0 g. of anhydrous stannic chloride were stirred for one hour at 100°. Unreacted carvacrol was steamed out and the residual phthalic acid was removed by extraction with hot water. The semi-solid brown crude I was crystallized directly from acetic acid (1 g. in 5 ml.) yielding 1.78 g. of m. p. 264–275° (8%). Further crystallizations from acetic acid (1 g. in 30 ml.) gave colorless crystals of m. p. 293.5–294.7°.

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02; mol. wt., 430. Found: C, 78.30; H, 6.86; mol. wt., 415 ± 44 (Rast, in camphor).

Carvacrolphthalein turns from colorless to blue at a *p*H of 9.5 to 10.5. The solution of I in concd. sulfuric acid is purple-red. The crystals of I are not easily affected by 0.1 *N* sodium hydroxide, but after wetting them first with ethanol, they dissolve quite readily.

Diacetylcarvacrolphthalein (II).—This compound was prepared by refluxing for one hour 2.15 g. of I, 2.0 g. of acetic anhydride, 10 ml. of acetic acid and one drop of concd. sulfuric acid; 2.49 g. (96%) was obtained. The pure compound recrystallized from ethanol (1 g. in 33 ml.) formed cubes and melted at 217.8–219.7°.

Anal. Calcd. for $C_{32}H_{34}O_6$: C, 74.68; H, 6.66; mol. wt., 514. Found: C, 74.97; H, 6.82; mol. wt., 471 ± 13 (Rast, in camphor), 511 ± 40 (Signer method[5]).

Carvacrolphthalein Dimethyl Ether (III).—This compound was prepared by refluxing for ten hours 4.30 g. of I, 2.8 g. of potassium carbonate, 50 ml. of acetone and 3.7 ml. of methyl iodide. The crude was purified by crystallizations from ethanol as well as by sublimation at 180° and 50 microns. The pure III melts partially at 202°, then solidifies and melts again at 211.5–212.2°. III dissolves in concd. sulfuric acid with red color in transmitted light and violet in reflected light.

Anal. Calcd. for $C_{30}H_{34}O_4$: C, 78.57; H, 7.47; $-OCH_3$, 13.52. Found: C, 78.93; H, 7.77; $-OCH_3$, 13.29.

Thymolphthalein (IV).—30.0 grams (0.2 mole) of thymol and 14.8 g. (0.1 mole) of phthalic anhydride were heated to 95°. While stirring, 25 g. of anhydrous stannic chloride was then added over a period of thirty minutes. The reaction was continued for another thirty minutes at 96–103° (oil-bath temperature 99–104°). The reaction mass was taken up in hot 0.1 *N* hydrochloric acid, filtered and washed. The crude IV was finally dissolved in 700 ml. of acetic acid and 450 ml. distilled off from the filtrate: 26.6 to 30.1 g. (62–70% yield) of m. p. 247–252° was obtained. The pure IV obtained by recrystallization from acetic acid (1 g. in 9 ml.) melted at 252.4–253.1° (lit. 246–247°[3]).

When in place of pure thymol a mixture of 15.0 g. of technical carvacrol and 15.0 g. of pure thymol was used and the crude recrystallized twice from acetic acid, it melted at 243–245°. Further crystallization from the same solvent did not increase the melting point, but after two more crystallizations from ethanol, it melted at 251.8–252.4° (no depression when mixed with pure IV).

Thymolphthalein Diacetate (V).—A mixture of 2.15 g. of IV, 2.0 g. of acetic anhydride, 10 ml. of acetic acid and one drop of sulfuric acid was refluxed for one hour: 2.54 g. (99%) of m. p. 150–153° was obtained. Recrystallized twice from ethanol (1 g. in 8.5 ml.) it melted at 153.0–153.6°.

(1) Curt Ehrlich, German Patent 225,983 in *Friedlaender*, **10**, 1298 (1910).

(2) S. Loewe and M. H. Hubacher, *Arch. intern. pharmacodynamie*, **65**, 303 (1941). It was ineffective in the Rhesus monkey even in doses 20 times the Median Laxative Dose of U. S. P. phenolphthalein.

(3) R. Willstätter and E. Waldschmidt, *Ber.*, **56**, 488 (1923), footnote.

(4) All melting points are corrected.

(5) E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941). Acetone was used as a solvent and azobenzene as a standard.

Anal. Calcd. for $C_{32}H_{34}O_6$: C, 74.68; H, 6.66; -CO-CH_3, 16.71; mol. wt., 514. Found: C, 74.88; H, 6.71; -$COCH_3$, 16.43; mol. wt., 488 ± 7 (Rast, in camphor).

Thymolphthalein Dimethyl Ether (VI).—4.3 g. (0.01 mole) of IV, 3.73 ml. (0.06 mole) of methyl iodide, 50 ml. of acetone and 2.76 g. (0.02 mole) of potassium carbonate were refluxed for ten hours. The crude was recrystallized from ethanol (1 g. in 24 ml.) yielding 4.03 g. (88%) of m. p. 175–176°. After two more crystallizations, it melted at 175.9–176.7°.[6]

(6) Lin Che Kin, *Ann. chim.*, **13**, 344 (1940), reports m. p. 177°. He prepared VI by condensing the methyl ether of thymol with the methyl ether of the 2-thymoylbenzoic acid in the presence of aluminum chloride.

Summary

Carvacrolphthalein was shown to melt at 294° and to be devoid of laxative effect. The melting point of 247° given in the literature for this compound is wrong. Thymolphthalein was prepared with a melting point 6° higher than reported heretofore. The diacetyl derivative and the dimethyl ether of both compounds were prepared.

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Isolation of Lupeol from the Osage Orange (*Maclura pomifera* Raf.)[1]

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In the isolation of osajin by Walter, Wolfrom and Hess[2] the dried osage oranges were first extracted with petroleum ether to remove latex and other interfering substances. In this paper the isolation of lupeol from this extract is described, and its crystallographic optical properties recorded. A wax-like material, to be described later, was also obtained.

Lupeol was discovered by Schulze[3] and described by Likiernik[4] and has since been isolated from several latex bearing plants. Ruzicka[5] recently proposed a structure for lupeol.

A characteristic reaction of lupeol is the red color it gives with concentrated sulfuric acid and acetic anhydride when in chloroform solution. This test also is given by the dried latex of the osage orange.

Acknowledgment.—We are indebted to Dr. M. L. Wolfrom, Department of Chemistry, Ohio State University for some of the extract used in this work.

Experimental

Isolation of Lupeol. The dried, ground osage oranges were completely extracted with low boiling petroleum ether. The extract was concentrated and passed through an aluminum silicate adsorbent described by Kraybill, *et al.*,[6] which removed the wax-like material. The concentrated petroleum ether extract was saponified with twice its volume of 95% ethanol saturated with potassium hydroxide. The mixture was diluted with water and extracted with ether. The ether was evaporated and the residue was mixed with about an equal weight of Nuchar W. The mixture was extracted in a Soxhlet apparatus with ether which was subsequently evaporated. Repeated crystallizations from acetone and then from 85% ethanol gave a product melting at 208–211°. Final purification was effected through formation of the acetate and saponification of this to get lupeol melting at 214–215°; yield, 5.1 g. of crude lupeol or 2.3 g. of pure lupeol from 1 kg. of dried osage oranges.

Anal. of lupeol. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81; mol. wt., 426.7. Found: C, 84.45; H, 11.88; mol. wt. (freezing point depression using stearic acid), 448, 458; $[\alpha]^{22}D$ +27.63° ($CHCl_3$, c = 3.926). Ruzicka (7) obtained +27.2°.

Lupeol acetate was prepared by the method of Ruzicka[7]; yield, 1.88 g. (from 2.16 g. of lupeol) m. p. 216–216.5°. Ruzicka[7] reported a m. p. of 215–217°.

Anal. of lupeol acetate. Calcd. for $C_{30}H_{49}(OCOCH_3)$: C, 81.99; H, 11.18; mol. wt., 46.78. Found: C, 81.79; H, 11.29; mol. wt. (saponification equivalent), 469.5; $[\alpha]^{25}D$ +41.95° ($CHCl_3$, c = 1.652). Ruzicka obtained +40.7°.

Lupeol benzoate was prepared by the method of Ruzicka.[7] Lupeol (1.8 g.) yielded 1.57 g. of the benzoate m. p. 263–265°.

Anal. of lupeol benzoate. Calcd. for $C_{30}H_{49}(OCOC_6H_5)$: C, 83.72; H, 10.25; mol. wt., 530.8. Found: C, 83.59; H, 9.80; mol. wt. (saponification equivalent), 543; $[\alpha]^{25}D$ +61.36° ($CHCl_3$, c = 0.9908). Ruzicka obtained +60.9°.

(1) A portion of a thesis to be submitted by Lyle J. Swift to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Journal Paper No. 37, Purdue University Agricultural Experiment Station.

(2) E. D. Walter, M. L. Wolfrom and W. W. Hess, THIS JOURNAL, **60**, 574 (1938).

(3) E. Schulze and E. Steiger, *Landw. Vers.-Sta.*, **36**, 391 (1889).

(4) A. Likiernik, *Z. physiol. Chem.*, **15**, 415 (1891).

(5) L. Ruzicka and M. Brenner, *Helv. chim. acta.*, **23**, 1325 (1940).

(6) H. R. Kraybill, P. H. Brewer and M. H. Thornton, U. S. Patent No. 2,174,177, Sept. 26, 1939.

(7) L. Ruzicka and M. Brenner, *Helv. chim. acta*, **22**, 1523 (1939).