(*i.e.*, *22*, *23*, and *24*). The behavior of those complex antacids containing both magnesium and aluminum moieties could be predicted somewhat, based on the knowledge of the mole ratios of aluminum *versus* magnesium present in the parent antacid.

SUMMARY

1. A comparative *in vitro* procedure, based on the the use of the Metrohm Combititrator, has been proposed which provides a simple, rapid, and accurate method for determination of the complete profile of an antacid system. A curve is obtained from which one can determine the initial onset of reaction, rate of reaction, duration of action, and the total acid-consuming capacity.

2. A comparative correlation has been made to show the interchangeability of the method to utilize either 0.1 *N* or 0.3 *N* hydrochloric acid with either slow or fast paper speeds. The use of 0.3 *N* hydrochloric acid with slow paper speeds is recommended as a means of recording all the data for the profile of an antacid on a single sheet of recording paper to facilitate storage of and future reference to the curves.

3. *In vitro* evaluations of 27 antacid materials have been studied by use of Metrohm technique.

4. The effect of pepsin on the titration of the various antacids with 0.3 *N* hydrochloric acid has been studied. Results from titrations of calcium, sodium, and aluminum antacids are consistent with previously reported findings in the literature. Metrohm curves of magnesium antacids, while being consistent in comparison with their own classes, are erratic in their behavior in the presence of pepsin, unlike previously reported work which

claimed magnesium compounds to be unaffected by pepsin.

5. Careful evaluations of the Metrohm curves show variations between various grades of the same antacid. Indeed, significant variations between the same grade of an antacid supplied by different manufacturers become readily apparent. In agreement with Dale and Booth (22), such variations in U.S.P.–N.F. antacid materials suggest the need for more exact test procedures to insure uniformity.

REFERENCES

(1) Mutch, N., *Brit. Med. J.*, **1**, 254(1936).
(2) Desai, S., Gibaldi, M., and Kanig, J. L., *J. Pharm. Sci.*, **52**, 871(1963).
(3) Rossett, N. E., and Flexner, J., *Ann. Intern. Med.*, **18**, 193(1943).
(4) Fuchs, C., *Drug Cosmetic Ind.*, **64**, 692(1949).
(5) Beekman, S. M., *J. Pharm. Sci.*, **49**, 191(1960).
(6) Packman, E. W., *et al.*, *ibid.*, **46**, 545(1957).
(7) Gill, A. M., and Keele, C. A., *Brit. Med. J.*, **2**, 194 (1943).
(8) Holbert, J. M., Noble, N., and Grote, I. W., *J. Pharm. Sci.*, **36**, 149(1947).
(9) *Ibid.*, **37**, 292(1948).
(10) Johnson, E. H., and Duncan, J., *Quart. J. Pharm. Pharmacol.*, **18**, 251(1945).
(11) Murphey, R. S., *J. Pharm. Sci.*, **41**, 361(1952).
(12) Kirsner, J. B., *et al.*, *Ann. Intern. Med.*, **35**, 785(1951).
(13) Naimark, G., *J. Pharm. Sci.*, **46**, 344(1957).
(14) Clark, T., and Hunt, J. N., *Practitioner*, **180**, 334 (1958).
(15) LeVeen, H. H., *Gastroenterology*, **8**, 648(1947).
(16) Bergman, J., Persson, K. O. U., and Westling, H., *Acta Med. Scand.*, **172**, 637(1962).
(17) Persson, K. O. U., and Bunke, B., *Acta Pharmacol. Toxicol.*, **19**, 219(1962).
(18) Best, C. H., and Taylor, N. B., "The Physiological Basis of Medical Practice," 4th ed., The Williams and Wilkins Co., Baltimore, Md., 1950, p. 438.
(19) Corrente, A. M., *J. Pharm. Sci.*, **43**, 242(1954).
(20) Schleif, R. H., *ibid.*, **46**, 179(1957).
(21) Drill, V. A., "Pharmacology in Medicine," 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1958, p. 636.
(22) Dale, J. K., and Booth, R. E., *J. Pharm. Sci.*, **44**, 170(1955).

Notes

Natural Occurrence of 2-Hydroxyxanthone

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2-Hydroxyxanthone has been isolated from the seeds of *Mammea americana* L. and identified by spectroscopic and melting point comparisons of the phenol and its derivations with synthetic samples. This is believed to be the simplest xanthone yet encountered in nature.

VARIOUS PARTS of the mamey tree (*Mammea americana* L.) have attracted scientific attention for many years, and the results of previous chemical examinations have been recently summarized (1). The structures of three rather closely related

phenolic polysubstituted coumarins, mammein (2), mammeisin (3), and mammeigin (4), have been elucidated previously, as has the nature of the wax (mamey wax) which was isolated from the seed oil (1). The continuing chemical investigation of mamey seed extracts has led to the discovery and identification of yet another phenolic constituent. The present article is an account of this work.

The benzene extract of ground mamey seeds, which had been extracted previously with isohexane, was partitioned in the usual manner into acidic,

neutral, and phenolic fractions. The phenolic mixture was chromatographed on alumina and from the benzene–ethanol eluates was obtained a yellow crystalline solid (I), which melted at 241–241.5° after being recrystallized several times from boiling ethanol. Microanalytical data coupled with a molecular weight determination led to the formulation, $C_{13}H_8O_3$. The phenolic nature of at least one of the oxygen atoms was indicated by the solubility properties of the compound, by hydroxyl absorption in the infrared spectrum (Nujol) at 3322 cm.$^{-1}$, and by the bathochromic shift of the ultraviolet maxima in the presence of alkali. (See *Experimental.*) A second oxygen was evidently present as a highly conjugated ketone carbonyl group which gave rise to strong absorption at 1656 cm.$^{-1}$, while the third oxygen was assigned to an ether function inferred from the presence of a strong band at 1238 cm.$^{-1}$. Additional evidence for the presence of a single hydroxyl group was obtained by the formation of a mono-acetate, $C_{15}H_{10}O_4$, m.p. 164.8–165.2°. Subsequently, a mono-methyl ether, $C_{14}H_{10}O_3$, m.p. 133.8–134.4°, was also obtained. The nuclear magnetic resonance spectrum of I showed the complete absence of aliphatic or vinyl protons; the only absorption consisted of a complex aromatic pattern between 8 and 9 p.p.m. and the phenolic hydroxyl proton at 10.96 p.p.m. in the relative amounts of approximately 7 to 1.

The data so far accumulated were strongly suggestive of an hydroxyxanthone structure for I, and it remained only to decide between the four isomeric possibilities. The 1-hydroxy isomer was eliminated readily on the basis of its reported melting point, 147° (5), 148–149° (6). The 4-hydroxy isomer, m.p. 242° (7), could be distinguished from the 2-isomer—m.p. 231° (8), 235–236° (9), 240° (10)—and the 3-isomer, m.p. 242° (11, 12), 246° (13), 249–250° (14)—by virtue of the melting points of its acetate, m.p. 145° (15), and methyl ether, m.p. 173° (7), derivatives. The reported melting points of the 2-acetoxy, m.p. 161° (8), and the 3-acetoxy, m.p. 156° (11), 160° (12), as well as those of the 2-methoxy—m.p. 130–131° (10), 131–132° (16), 131° (7)—and 3-methoxy, m.p. 129–130° (14), 135° (17), derivatives, were not sufficiently divergent to allow a clear choice to be made. The infrared and ultraviolet maxima observed for I were in better agreement with those data reported (16, 18, 19) for the 2-isomer than those for the 3-isomer. Accordingly, we assigned to I the structure of 2-hydroxyxanthone and proceeded to verify this

conclusion by comparison with an authentic specimen.

The preparation of I followed, with minor variations, the methods outlined by Davies *et al.* (9), as indicated in Scheme I. Ullmann condensation of *o*-chlorobenzoic acid with *p*-methoxyphenol provided the diphenyl ether II, which was cyclized without purification to yield 2-methoxyxanthone (III). The sample of III thus obtained was indistinguishable from that derived from naturally occurring I. Although the acid II has been encountered previously (7, 9) as a crude intermediate in this scheme, it appears not to have been characterized adequately. Therefore, its purification was undertaken; these details are recorded also under *Experimental.* Finally, the ether link of III was cleaved by heating in toluene in the presence of aluminum chloride which produced I, identical with the natural phenol.

Although more than 20 naturally occurring xanthones are known (20, 21), 2-hydroxyxanthone (I) is the simplest and first mono-hydroxyxanthone to be encountered in nature, and the only one which does not bear a hydroxyl group at the 1 or 8 positions.

EXPERIMENTAL[1]

Isolation of I.—Thirty-five kilograms of dried and ground seeds of *M. americana* L., previously extracted with isohexane, were extracted in portions with a total of 20 L. of benzene in a Soxhlet extractor. Removal of the solvent under reduced pressure afforded 142 Gm. of residue, which was redissolved in 2 L. of benzene, and extracted successively with four 150-ml. portions of 10% sodium bicarbonate solution and four 250-ml. portions of cold 5% aqueous sodium hydroxide. This latter extract was acidified with concentrated hydrochloric acid and extracted with 2 L. of ether. After being dried over Drierite, the ether was removed by distillation under reduced pressure to yield 82 Gm. of black viscous oil. This oil was chromatographed on Merck acid washed alumina (two columns; total alumina, 2570 Gm.). During elution with benzene containing 0.5% ethanol, several hundred milligrams of yellow semisolid material was obtained from each column. These materials were combined and recrystallized from boiling ethanol to yield 310 mg. of crystals, m.p. 244.0–244.5° (uncorrected). (9 × 10^{-4}% yield, based on dry seed.) Recrystallization afforded the analytical sample, m.p. 241.0–241.5°, λ_{max}^{EtOH} 238, 250 (sh), 302, 370 mμ (log ϵ: 4.64, 4.52, 3.62, 3.86); $\lambda_{max}^{EtOH-NaOH}$ 252, 270 (sh), 422 mμ (log ϵ: 4.60, 4.46, 3.71).

Anal.—Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80; O, 22.62; mol. wt., 212.2. Found: C, 73.63; H, 3.80; O, 22.70; mol. wt., 207 (Rast).

Acetate of I.—A solution containing 102 mg. of I, 5 ml. of pyridine, and 2 ml. of acetic anhydride was allowed to stand for 24 hr. before it was poured into 30 ml. of water. The precipitate was collected
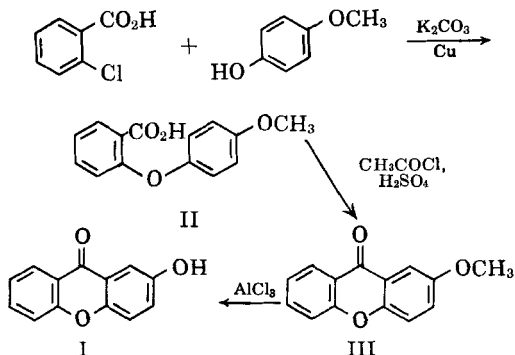
Scheme I

on a filter, washed with 40 ml. of water, and air-dried to give 116 mg. of colorless needles, m.p. 164.5–165.5° (uncorrected). A single recrystallization from a chloroform–isohexane mixture afforded an analytical sample, m.p. 164.8–165.2°, $\nu_{max.}^{KBr}$ 1773, 1667, 1661, 1212, 1198 cm. $^{-1}$.

Anal.—Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.23; H, 4.01.

Methyl Ether of I.—A mixture consisting of 34 mg. of I, 112 mg. of anhydrous potassium carbonate, 4 drops of dimethyl sulfate, and 2 ml. of acetone was heated on a steam bath for 4 hr. After filtration and evaporation of the filtrate nearly to dryness, dilute aqueous alkali was added to the residue. The precipitate, after being washed with 2 N sodium hydroxide and water, weighed 28 mg., m.p. 125–129°. Two recrystallizations from a chloroform–isohexane mixture gave the product, m.p. 133.8–134.4°.

2-Carboxyphenyl 4-Methoxyphenyl Ether (II).—A mixture of 5.11 Gm. (32.6 mmoles) of *o*-chlorobenzoic acid, 4.9 Gm. (39.5 mmoles) of *p*-methoxyphenol, 10.1 Gm. (73 mmoles) of anhydrous potassium carbonate, 0.14 Gm. of moist copper, and 30 ml. of *n*-butanol was refluxed with stirring for 11 hr. The mixture was cooled to room temperature, acidified with concentrated hydrochloric acid, diluted with water, and filtered to remove the copper. The aqueous portion of the filtrate was extracted with ether, which was combined with the organic phase. This solution then was washed with water followed by saturated bicarbonate solution. The bicarbonate extract was acidified and cooled. The resulting precipitate was collected on a filter, dissolved in chloroform, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 6.2 Gm. of orange oil, which solidified on cooling to room temperature. An additional 1.2 Gm. of material was obtained by extraction of the acidified filtrate mentioned above. The infrared spectra of these products showed them both to be mixtures of II with *o*-chlorobenzoic acid. Chromatography on silica gel allowed the recovery of 700 mg. of the starting benzoic acid along with 3.85 Gm. of colorless solid, m.p. 112–119°. This product, still a mixture although enriched in II, was used in the cyclization step described below.

Attempts to obtain a pure sample of II by recrystallization of the crude product, m.p. 112–119°, from ethyl acetate or from chloroform–isohexane mixtures proved fruitless. Purification was achieved finally by repeated washing of an ether solution of the mixture with cold water. After being dried, the ether was removed, leaving material with m.p. 141–148°. Four recrystallizations from chloroform–isohexane afforded pure II, m.p. 148.0–149.2°. $\nu_{max.}^{Nujol}$ 1686, 1597, 1577, 1225, 1196, 1087, 877, 840 cm. $^{-1}$; $\lambda_{max.}^{EtOH}$ 226, 290 mμ (log ϵ: 4.54, 4.26).

Anal.—Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.26; H, 4.87.

2-Methoxyxanthone (III).—To a solution of 1.0 Gm. of crude II (m.p. 112–119°) in 11 ml. of acetyl chloride was added cautiously 0.2 ml. of concentrated sulfuric acid. After the initial reaction subsided, the reaction flask was stoppered and allowed to stand for 10 min. Excess acetyl chloride was removed then by distillation on a steam bath, and the residue was poured into 100 ml. of cold water. The solid obtained was dissolved in ether and washed with saturated bicarbonate solution. After being dried over magnesium sulfate, the ether was removed; the residue was recrystallized from a chloroform–isohexane mixture, giving 184 mg. of white crystals, m.p. 133.2–134.0°. $\lambda_{max.}^{EtOH}$ 236, 250 (sh), 303, 362 mμ (log ϵ: 4.55, 4.49, 3.60, 3.78). The infrared spectrum was identical to that of the ether obtained by methylation of natural I above, and the mixed melting point was 133.2–134.8°.

2-Hydroxyxanthone (I).—A mixture of 65 mg. of III, 689 mg. of freshly ground anhydrous aluminum chloride, and 5 ml. of toluene in a 25-ml. conical flask fitted with a drying tube was heated on a steam bath for 2 hr. The reaction mixture then was cooled to room temperature and concentrated hydrochloric acid was added dropwise until the reaction had subsided. Fifty milliliters of water then was added, and the mixture was extracted with ether. This ether solution then was extracted with 5% aqueous sodium hydroxide. The solid obtained when the alkaline extract was acidified was recrystallized twice from boiling ethanol, yielding 21 mg. of yellow needles, m.p. 240.2–240.9°. The infrared spectrum of this material was identical to that of the naturally derived I; the mixed melting point was 240.0–241.0°.

REFERENCES

(1) Finnegan, R. A., and Eisenbraun, E. J., THIS JOURNAL, 53, 1506(1964).
(2) Djerassi, C., *et al.*, *J. Org. Chem.*, 25, 2164(1960).
(3) Finnegan, R. A., Morris, M. P., and Djerassi, C., *ibid.*, 26, 1180(1961).
(4) Finnegan, R. A., and Mueller, W. H., *Chem. Ind.*, 1964, 1065.
(5) Ullmann, F., and Panchaud, L., *Ann.*, 350, 115(1906).
(6) Pankajamani, K. S., and Seshadri, T. R., *J. Sci. Ind. Res. India*, 13B, 396(1954).
(7) Ullmann, F., and Zlokasoff, M., *Ber.*, 38, 2111(1905).
(8) von Kostanecki, S., and Rutishauser, R., *ibid.*, 25, 1648(1892).
(9) Davies, J. S. H., Lamb, F., and Suschitzky, H., *J. Chem. Soc.*, 1958, 1790.
(10) Ullmann, F., and Kipper, H., *Ber.*, 38, 2120(1905).
(11) Davies, J. S. H., Scheinmann, F., and Suschitzky, H., *J. Org. Chem.*, 23, 307(1958).
(12) Van Allen, J. A., *ibid.*, 23, 1679(1958).
(13) Atkinson, H., and Heilbron, I. M., *J. Chem. Soc.*, 1926, 2688.
(14) Mittal, O. P., and Seshadri, T. R., *J. Sci. Ind. Res. India*, 14B, 76(1955).
(15) Dimroth, O., *Ann.*, 446, 114(1925).
(16) Bonvicino, G. E., *et al.*, *J. Org. Chem.*, 26, 2383(1961).
(17) Baeyer, A., *Ann.*, 372, 102(1910).
(18) Scheinmann, F., *Tetrahedron*, 18, 853(1962).
(19) Mull, R. P., and Nord, F. F., *Arch. Biochem. Biophys.*, 4, 419(1944).
(20) Dean, F. M., "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, p. 266.
(21) Roberts, J. C., *Chem. Rev.*, 61, 591(1961).