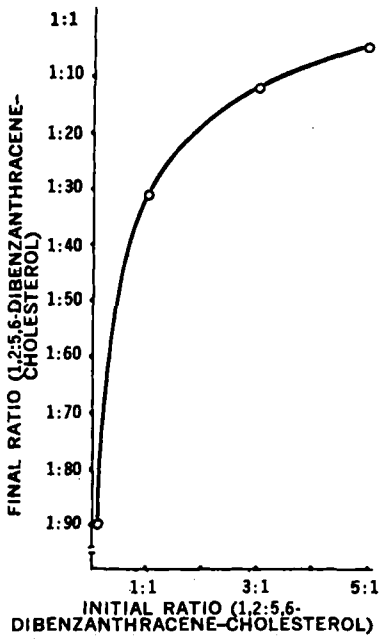

Figure 3—*Degree of association of 1,2:5,6-dibenzanthracene to cholesterol estimated from extrapolated area per molecule.*

present in the film. The molar ratio of carcinogen to cholesterol initially prepared *versus* the association estimated from expansion of the resulting films is plotted in Fig. 3. The data show that after spreading a solution containing a 5:1 carcinogen–cholesterol initial ratio, a 1:4 molecular association results at the interface. Although this association appears to be self-limiting as carcinogen concentration is increased in the film, the limiting value and its significance are still unknown.

Surface potential data reinforced the concept of carcinogen association at the interface. The 3:1 and 5:1 carcinogenic films were statistically different from the noncarcinogenic films regardless of subphase. These results were not unexpected in view of their π–A isotherms, since the 3:1 and 5:1 carcinogen–cholesterol films showed the greatest expanding effect.

These results demonstrate a very useful difference existing between a carcinogenic and a noncarcinogenic or weakly carcinogenic isomer at the air–water interface. This method conceivably may be useful in discriminating between other carcinogenic and noncarcinogenic isomers. Furthermore, cell membrane integrity or disruption at the molecular level may be a cancer-initiating step prior to interaction with other critical targets within the cell.

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Constituents of *Mammea americana* L. XII: Biological Data for Xanthones and Benzophenones

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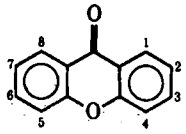
Abstract □ Sarcoma 180 inhibition data are presented for a number of related xanthones and benzophenones; a few showed significant activity. One of these was also tested *in vivo* against Ehrlich ascites tumor. Four hydroxyxanthones isolated from a polar extract of *Mammea americana* L. (Guttiferae) seeds did not account for the activity of the extract. The results of two antibacterial assays for a few of these compounds are also presented.

Keyphrases □ *Mammea americana* L.—xanthone constituents and related benzophenones, antitumor and antibacterial activities □ Xanthones—from *Mammea americana* L., antitumor and antibacterial activities □ Benzophenones—antitumor and antibacterial activities

A previous paper (1) described the isolation and structure determination of a variety of coumarin derivatives from mamey oil (the dewaxed petroleum ether extract of *Mammea americana* L. seeds) and reported the significant antitumor activity (against Sarcoma 180) of the extract as well as that of a number of the constituent coumarins. During these studies the more polar extract, obtained by extraction of the seed residue with

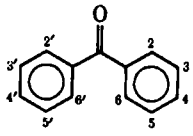
Table I—Growth Inhibitory Activity of Various Simple Xanthones against Sarcoma 180 Tumor Cells

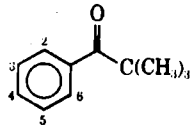


Number	Xanthone	Reference	ID_{50}, mcg./ml.
I	Xanthone[a]	—	11
II	1-Hydroxy	6	21
III	2-Hydroxy	2	25
IV	3-Hydroxy	6	35
V	3-Hydroxy-5,6,7,8-tetrahydro	6	19
VI	4-Hydroxy	3,7	16
VII	1,3-Dihydroxy	7	2.5
VIII	1,3-Dimethoxy	7	120
IX	1,5-Dihydroxy	3,7	6.6
X	1,6-Dihydroxy	3,7	1.8
XI	1,7-Dihydroxy	3,7	8.6
XII	3,4-Dihydroxy	7	23
XIII	3,5-Dihydroxy	3,7	7.0
XIV	3,6-Dihydroxy	6	26
XV	1,3,6-Trihydroxy	6	14
XVI	1,3,8-Trihydroxy	6	10
XVII	1,3,6,8-Tetrahydroxy	6	35
XVIII	1,3,6,7-Tetrahydroxy-2-C-β-D-glucosylxanthone, mangiferin	10	440

[a] Commercially available.

Table II—Growth Inhibitory Activity of Various Benzophenone and Pivalophenone Derivatives against Sarcoma 180 Tumor Cells



Number	Compound	Reference	ID_{50}, mcg./ml.
XIX	Benzophenone[a]	—	33
XX	2-Hydroxy[a]	—	33
XXI	4-Hydroxy[a]	—	29
XXII	2,2',3,4-Tetrahydroxy	7	1.0
XXIII	2,3,3',4'-Tetrahydroxy	3,7	2.6
XXIV	2,2',3,4'-Tetrahydroxy	3,7	18
XXV	2,2',4,4'-Tetrahydroxy[a]	—	17
XXVI	2-Hydroxy-5-*tert*-butyl	11	6.6
XXVII	2-Hydroxy-4,6-di-*tert*-butyl	11	0.066
			
XXVIII	2-Hydroxy-3-*tert*-butyl	12	24
XXIX	4-Hydroxy-3-*tert*-butyl	12	22
XXX	4-Hydroxy-3,5-diisopropyl[b]	—	18

[a] Commercially available. [b] R. A. Finnegan and D. Knutson, unpublished preparation.

benzene (2) and ethanol, also was examined (3, 4). That investigation was prompted by the observation that the ethanol extract provided an ID_{50} value of 5.4 mcg./ml. when assayed against S-180 tumor cells grown in stationary cell culture. Two sets of isomeric xanthones, 2- and 4-hydroxyxanthones (III and VI) and 1,5- and 1,7-dihydroxyxanthones (IX and XI), were subsequently isolated from this polar extract. Their structures were determined by comparison with synthetic materials (2–4). At the same time, a number of other xanthones were prepared (5–7) for comparison purposes and these were also included in the S-180 screen.

EXPERIMENTAL

The Compounds—A few of the test compounds (I, XIX–XXI, and XXV) were commercially available. Some (IX, XXIII, XXIV, XXVI–XXX, and XXXII) were prepared in this laboratory for the first time. The remaining compounds were known and were, in general, prepared by using previously reported procedures. A somewhat improved procedure was used to prepare XXXI. Compound XVIII was used as isolated from *Hiptage madablota* Geartn. Synthetic samples of the compounds isolated from *M. americana* L. (III, VI, IX, and XI) were used.

References to the preparation or isolation of all the compounds are given in the tables. In each case except Compound XXX, experimental details are given as well as relevant literature citations. Compound XXX was prepared by the photo-Fries rearrangement of 2,6-diisopropylphenyl pivalate and details will be provided upon request.

The Tests—A description of the S-180 assay (Tables I and II) was given previously (1). Values for ID_{50} (dose for 50% inhibition of growth) of less than 5 mcg./ml. for a pure compound and less than 20 mcg./ml. for a crude extract are considered significant[1].

The antibacterial results (Table III) were determined[2] using procedures described in the literature (8, 9).

RESULTS AND DISCUSSION

The results shown in Table I indicate that the substances isolated from the extract (III, VI, IX, and XI) are not sufficiently active to account for the activity of the crude extract. However, the synthetic 1,3- and 1,6-dihydroxyxanthones (VII and X) showed noteworthy activity. Further hydroxylation in the equivalent positions of the second ring (Compounds XV–XVII) decreased this activity. Compound XVIII was available in the laboratory (10) and was included for comparison.

A method used for the preparation of certain of the xanthones involves the cyclodehydration of an appropriately substituted benzophenone. Several of these precursors (XXII–XXV and XXXII) were on hand and they were also assayed along with benzophenone (XIX) itself and two of its monohydroxy derivatives (XX and XXI). In addition, a pair of benzophenones (XXVI and XXVII) and a group of pivalophenones (XXVIII–XXX) were available from other studies going on in the laboratory (11, 12) and these were also included. The results are listed in Table II. While two of the tetrahydroxybenzophenones, XXII and XXIII, showed excellent activity, the alkylated hydroxybenzophenone, XXVII, showed activity at least on an order of magnitude greater still. This is reminiscent of the activity exhibited by the alkylated hydroxyketones in the coumarin series (1) and gives a direction to further studies involving alkylated hydroxybenzophenones as well as alkylated hydroxyxanthones.

The acute LD_{50} of Compound XXVII in mice was found to be greater than 500 mg./kg., and the 5-day dose LD_{50} was greater than 100 mg./kg.[3]. Against Ehrlich ascites tumor in mice, the ID_{50} (5-day dosing) of XXVII was 100 mg./kg.[3].

Finally, several of the compounds were examined for antibacterial activity against *Escherichia coli* and *Streptococcus faecalis* with the results shown in Table III. A few of the compounds (I, XXI, and

[1] The authors thank Professor N. Back, Department of Biochemical Pharmacology, State University of New York at Buffalo, for obtaining these data.

[2] Under the direction of Professor A. Bloch, Roswell Park Memorial Institute, Buffalo, N. Y.

[3] These data were obtained through the courtesy of Prof. Peter Hebborn of the Department of Biochemical Pharmacology, State University of New York at Buffalo.

Table III—Antibacterial Activity of Some Xanthones and Benzophenones against *Escherichia coli* (K12) and *Streptococcus faecalis* (8043)

Number	Compound	—ID_{50}, moles/l.— *E. coli*	*S. faecalis*
I[a]		$>10^{-3}$	1×10^{-5} [b]
XV[c]		$>10^{-3}$	9×10^{-4}
XVII[c]		$>10^{-3}$	8×10^{-5}
XIX		$>10^{-3}$	1×10^{-3}
XX[c]		—[d]	—[d]
XXI[e]		3×10^{-4}	3×10^{-5} [f]
XXV		$>10^{-3}$	$>10^{-3}$
XXVII[e]		1×10^{-3}	9×10^{-5}
XXXI[c]	1,8-Dihydroxyxanthone (6)	$\gg 10^{-3}$	$\gg 10^{-3}$
XXXII	2,2′,3,3′-Tetrahydroxybenzophenone (5, 6)	6×10^{-5} [b]	1×10^{-5} [b]

[a] Suspension. [b] One hundred percent inhibition at 10^{-3} *M*. [c] Compound precipitated when test solution was added to medium. [d] No effect at 10^{-5} *M*; at 10^{-3} *M*, a 36% growth enhancement was observed. [e] No effect at 10^{-5} *M*; at 10^{-3} *M*, an 81% growth enhancement was observed. [f] One hundred percent inhibition at 10^{-4} *M*.

XXXII) showed borderline activity (ID_{50} values of about 10^{-5} *M*) against one or the other of these organisms.

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Synthesis and Antifungal Activity of Polyhalophenyl Esters of *p*-Sulfamoylcarbanilic Acid

G. MOHTAT, N. REZVANI, M. EMAMI, and I. LALEZARI▲

Abstract □ Several polyhalophenyl esters of *p*-sulfamoylcarbanilic acid were prepared and tested for antifungal activity against *Candida albicans*, *Penicillium notatum*, and *Aspergillus niger*. Pentachloro-, tribromo-, and triiodophenyl esters were found to be the most active.

Keyphrases □ *p*-Sulfamoylcarbanilic acid, polyhalophenyl esters—synthesized and screened as potential antifungal agents □ Antifungal agents, potential—synthesis and screening of polyhalophenyl esters of *p*-sulfamoylcarbanilic acid

Recently, it was reported that polyhalophenyl esters of *p*-substituted carbamic acids as well as polyhalophenyl esters of pyridyl- and quinolyl-4-carbamic acids (1, 2) showed significant antifungal activities.

In the present work, a series of polyhalophenyl esters of *p*-sulfamoylcarbanilic acid was prepared by interaction of *p*-sulfamoylbenzoyl azide and the appropriate phenol in boiling toluene or xylene (Scheme I).

$$p\text{-}NH_2SO_2C_6H_4CON_3 + ArOH \xrightarrow[\text{or xylene}]{\text{boiling toluene}} p\text{-}NH_2SO_2C_6H_4NHCOOAr + N_2$$

Scheme I

The physical data of all new compounds are reported in Table I. The antifungal activity of all compounds was determined[1] *in vitro* against *Candida albicans* 1959-2, *Penicillium notatum* 154-3, and *Aspergillus niger* A-23. Concentrations of 5, 10, and 25 mcg./ml. of each compound were used.

Compounds II–IV were dissolved in acetone, Compounds I and V were dissolved in 60% ethanol, and Compounds VI–XI were dissolved in 96% ethanol, all at concentrations of 5 mg./10 ml. These solutions were diluted with hot culture medium to the desired concen-

[1] Using BBL Sabouraud dextrose agar medium. The microorganisms were obtained from the Department of Parasitology, Public Health Institute, Iran.