Biochemical Pharmacology, Vol. 28, pp. 127–132.
Pergamon Press, Ltd., 1979. Printed in Great Britain.

# METABOLIC REACTIONS *IN VITRO* OF PSORALENS WITH LIVER AND EPIDERMIS*

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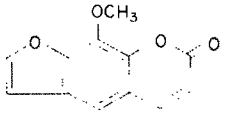
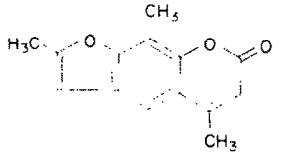
(*Received* 25 *April* 1977; *accepted* 19 *October* 1977)

**Abstract**—In recent years, psoralens have been widely-used clinically, but until now their *in vitro* and *in vivo* metabolic reactions have not been studied. The photochemotherapeutic agent 4,5′,8-trimethylpsoralen (TMeP) is readily metabolized *in vitro* by mouse liver under mixed-function oxidase conditions, with formation of three products. One of the products is 4,8-dimethyl, 5′-carboxypsoralen which has been identified previously as an *in vivo* product of TMeP metabolism in the urine of mice and human subjects receiving oral TMeP. A second product, with a molecular weight of 244, is apparently 4,8-dimethyl, 5′-hydroxymethylpsoralen. A metabolic pathway that integrates *in vivo* and *in vitro* TMeP reactions is proposed. By contrast, 8-methoxypsoralen (8-MOP) apparently is minimally metabolized *in vitro* by mouse liver. Guinea pig epidermis did not show any *in vitro* reactions with either 8-MOP or TMeP. The difference in liver biotransformations of 8-MOP and TMeP may help explain why orally administered TMeP is less photosensitizing and less effective than 8-MOP in phototherapy of skin diseases such as psoriasis.

Certain photochemotherapeutic agents, commonly referred to as furocoumarins or psoralens, are used clinically in treating various skin diseases such as psoriasis [1–3], mycosis fungoides [4], vitiligo [5] and eczema [6]. Furocoumarins like 8-methoxypsoralen (8-MOP) and 4,5′,8-trimethylpsoralen (TMeP) undergo photoconjugation reactions with pyrimidines [7,8]. The psoralens intercalate with double-stranded nucleic acids, and subsequent exposure to



8-Methoxypsoralen (8-MOP)
9-Methoxy-7H-furo [3,2-g] [1]
benzopyran-7-one



4,5′,8-Trimethylpsoralen (TMeP)
2,5,9-Trimethyl-7H-furo [3,2-g] [1]
benzopyran-7-one

long wavelength ultraviolet radiation results in the formation of cyclobutane adducts and cross-links between two pyrimidines belonging to opposite strands of DNA [9,10]. Photoconjugation of psoralens to DNA has been established *in vivo* in several systems, including mammalian skin [11], human fibroblasts [12,13], *Escherichia coli* [9], and other biological systems [14,15]. The light-dependent conjugation of psoralens with epidermal DNA is believed to inhibit DNA synthesis and cell division [1,16], thereby leading to clinical improvement of diseases such as psoriasis.

Although 8-MOP and TMeP have been used clinically, both orally and topically for the past 25 years, little is known of the metabolism of these photoactive compounds either in man or in laboratory animals [17]. Recently, we reported the isolation and identification of a major TMeP metabolite referred to as 4,8-dimethyl, 5′-carboxypsoralen (DMeCP) from the urine of mice and human volunteers receiving oral TMeP [18]. In the present study, we report on the transformation *in vitro* of TMeP and 8-MOP in mammalian liver and skin. TMeP is readily metabolized by the liver, and a metabolic pathway for its biotransformation is proposed.

## MATERIALS AND METHODS

### *Materials*

TMeP was tritiated by the New England Nuclear Corp. (Boston, MA). It was purified as described previously [11] and had a specific activity of 40 μCi/μmole. [$^3$H]TMeP was used routinely at about 0.3 μCi/μmole. Tritiated DMeCP was obtained from the urine of mice receiving [$^3$H]TMeP as described recently [18]. Nonradioactive TMeP and 8-MOP were gifts from the Paul B. Elder Co. (Bryan, OH) and were used after repeated crystallization from ethanol. Ether extractions were performed with anhydrous ether from the Mallinckrodt Chemical Co. (St. Louis, MO). All other chemicals were reagent grade.

### *Tissue preparations*

Male mice (strain CD-1 from the Charles River Breeding Laboratories) weighing 25–30 g were sacrificed by cervical dislocation. The liver or kidney was removed, weighed, and homogenized in a glass-Teflon Potter–Elvehjem homogenizer with 3 vol. of

* This work was supported by NCI Grant 2-R01-CA 05003.

either Tris–sucrose buffer (0.25 M sucrose and 0.05 M Tris–chloride, pH 7.4) or phosphate sucrose buffer (0.25 M sucrose, 0.01 M sodium phosphate, pH 7.4, 0.001 M EDTA and 0.05 M nicotinamide).

Guinea pig epidermal homogenates were prepared by the procedure previously described [11]. Briefly, backs of female guinea pigs weighing 400–600 g were epilated 24–48 hr before the animals were sacrificed with ether anaesthesia. The epidermis was scraped off from the stretched skin and homogenized using 10 vol. of sucrose–phosphate buffer. To prepare microsomes, homogenates were centrifuged at 10,000 *g* for 20 min and the resulting supernatant fraction at 105,000 *g* for 60 min. Microsomes were resuspended in homogenizing buffer. Protein was determined by the procedure of Lowry *et al.* [19] after precipitation by 5% trichloroacetic acid.

*Reaction of tissue preparations with psoralens*

The reaction mixture in 2.5 ml contained 50 mM sodium phosphate, pH 7.4; 3 mM glucose 6-phosphate; 4 mM magnesium chloride; 0.16 mM NADP; 0.06 mM NAD; 0.4 mM EDTA; 12 mM nicotinamide; 0.3 units glucose 6-phosphate dehydrogenase; 350–450 nmoles TMeP or 8-MOP; and tissue preparation as indicated in table and figure legends. The reaction was standardly carried out at 37° for 30 min with vigorous shaking in 20 ml glass scintillation counting vials after a 5-min preincubation in the absence of the tissue preparation. The reaction was terminated by adding 10 ml anhydrous diethyl ether. In control reactions, the psoralen or tissue was added after ether. After vigorous shaking by hand, the ether layer was removed and saved. Then 0.3 ml of 1 N HCl was added to the aqueous layer to give a pH of about 2, and the extraction was repeated with 10 ml of additional ether. The ether layers were combined, evaporated to dryness, and the residues dissolved in a small volume (0.2 ml) of ethanol for thin-layer chromatography (t.l.c.) and absorption spectroscopy.

The transformation *in vitro* of [$^3$H]TMeP was quantitated by counting chromatograms. The transformation of nonradioactive 8-MOP or TMeP was measured by eluting the chromatograms with ethanol and obtaining absorption spectra. At 250 nm and a 1 cm light path, 10 $\mu$g TMeP/ml has an optical density of 1.4 or $E^{1}_{2.50} = 3.20 \times 10^{1}$.

*Thin-layer chromatography*

Four solvent systems with the following composition by volume were used for t.l.c.: solvent A: $CHCl_3$/ethyl acetate/acetic acid, 6/3/1; solvent B: $CHCl_3$/ethyl acetate/acetic acid, 5/4/1; solvent C: toluene/acetic acid, 8/2; solvent D: $H_2O$ only. Solvents A, B and C were used with Bakerflex Silica gel 1B or $1B_2$ plates with or without fluorescent indicator; solvent D was used on Bakerflex cellulose plates. Solvent fronts usually ran 12–15 cm. Compounds were detected by their characteristic fluorescence, color and $R_f$ values when viewed in the dark with long-wave (320–400 nm) or short-wave (254 nm) ultraviolet-emitting lamps.

*Preparation of TMeP metabolites*

Products $M_1$, $M_2$ and $M_3$ were prepared from standard TMeP incubations, using mouse liver homogenate and t.l.c. $1B_2$ plates for chromatography in solvent A. Fluorescent substances $M_1$ and $M_2$ with $R_f$ values of 0.12 and 0.35, respectively, were eluted with ethanol along with corresponding bands from control t.l.c. plates. After ethanol evaporation, $M_1$ and $M_2$ were sometimes further purified by ether extraction from acidified aqueous solution.

*Radioactivity determination*

Tritium was counted in a Packard model 3300 Tri-Carb liquid scintillation counter using 10 ml Aquasol (New England Nuclear Corp.). Chromatograms were cut into thin strips which were placed in counting vials with 1 ml ethanol. Aquasol was added after shaking for 15 min. Counting efficiency was about 35 per cent. All data are corrected for background.

*Spectroscopy*

The mass spectra were taken on an AEI MS-9 double focusing mass spectrometer with an electron impact source at 70 eV. The source temperature was the minimum required to obtain adequate ion intensity. Ultraviolet absorption of ethanolic solutions of the metabolites were obtained between 220 and 400 nm on a Bausch and Lomb Spectronic 505 recording spectrophotometer. The activation and emission spectra of ethanolic solutions of the metabolites were obtained on an Aminco-Keirs spectrophotophosphorimeter, model J-48201.

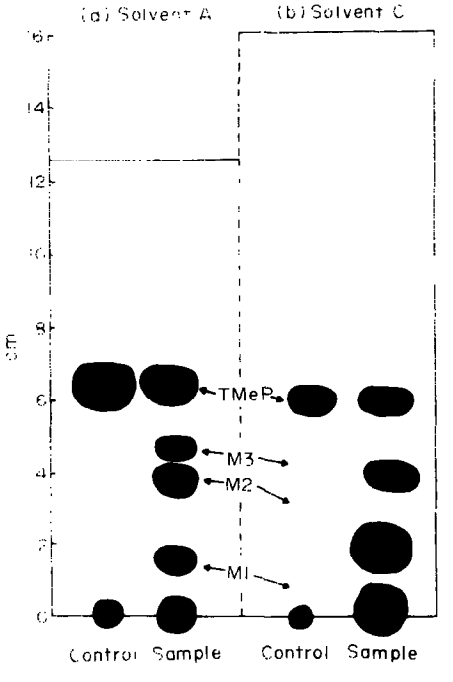



Fig. 1. Fluorescent spots on t.l.c. plates after reacting mouse liver homogenate with TMeP. Reaction samples were incubated for 30 min with homogenate equivalent to 75 mg fresh wt liver. For controls, liver was added after ether. Ether-extractable material was dissolved in 200 $\mu$l of ethanol, and 20 $\mu$l of ethanol solution was run on t.l.c. plates in solvent A (a) and solvent C (b).

Table 1. Demonstration that mouse liver reaction with TMeP proceeds via mixed-function oxidase*

| Reaction mixture | Relative reaction (%) | |
|---|---|---|
| | Microsomes | Homogenate |
| Complete | 100 | 100 |
| Omit NAD | 82 | 82 |
| Omit NADPH | 6 | 21 |
| Omit NAD and NADPH | 3 | 3 |
| Omit $O_2$† | 11 | 3 |
| Omit liver | 0 | 0 |

* Incubations were conducted for 10 min with microsomes equivalent to 100 mg fresh wt liver, or for 30 min with homogenate equivalent to 50 mg liver.

† Nitrogen was bubbled through these samples, and activities were compared to samples through which air was bubbled.

## RESULTS

### *Reaction* in vitro *of TMeP with mouse liver*

TMeP metabolism *in vitro* was detected after incubating the drug with mouse liver homogenate, and separating ether-extractable substances by t.l.c. Three new fluorescent products clearly appeared in sample incubations, whereas control incubations showed unchanged substrate and a spot at the origin attributable to substances present in the liver extract (Fig. 1). With [$^3$H]TMeP as substrate, new products were also confirmed as radioactive spots.

The transformation *in vitro* of TMeP by liver homogenate and microsomes appears to involve a mixed-function oxidase system (Table 1) [20]. Kinetics of the homogenate reaction with TMeP showed that the reaction rate was roughly linear with time and protein concentration until about 10 per cent of the initial TMeP had been metabolized (Fig. 2). Mouse liver homogenate reacted with TMeP at a rate of about 2.0 nmoles/mg of protein/min, or 320 nmoles/g fresh weight/min. Since TMeP is virtually insoluble in aqueous solution, we did not study the kinetic effects of changing its concentration.

Table 2. $R_f$ values of metabolites of TMeP*

| Compound | $R_f$ values | | |
|---|---|---|---|
| | *A* | *C* | *D* |
| $M_1$ | 0.12 | 0.026 | 0.16 |
| $M_2$ | 0.35 | 0.12 | 0.13 |
| $M_3$ | 0.43 | 0.23 | 0.53 |
| DMeCP | 0.43 | 0.24 | 0.54 |
| TMeP | 0.57 | 0.37 | 0.0 |

* Solvent systems: (A) $CHCl_3$/ethyl acetate/acetic acid, 6/3/1 by volume; (C) toluene/acetic acid, 8/2 by volume; and (D) water. Solvents A and C are run on Silica gel plates; D is run on cellulose plates.

### *Characterization of TMeP metabolites*

The three fluorescent products, designated $M_1$, $M_2$ and $M_3$, formed when liver homogenate reacts with TMeP, were investigated further. Experiments were carried out to determine whether $M_3$ was DMeCP, since both substances had the same $R_f$ in solvent A (Table 2), and both DMeCP and $M_3$ exhibited blue fluorescence under short-wave ultraviolet light. By contrast, $M_1$ and $M_2$ exhibited white fluorescence.

$M_3$ was isolated from an incubation mixture *in vitro* and rechromatographed in solvents A, C and D along with authentic DMeCP. Both $M_3$ and DMeCP have the same $R_f$ values in the three solvents tested (Table 2). Furthermore, DMeCP and $M_3$ had the same ultraviolet absorption spectra with a characteristic double peak at 260 and 267 nm [18]. These results show that DMeCP is formed from TMeP after incubation *in vitro* with liver homogenate.

To characterize products $M_1$ and $M_2$, the compounds were prepared from reaction mixtures *in vitro* and chromatographed in solvents C and D. Ultraviolet absorption spectra of $M_1$ and $M_2$ were very similar to that of TMeP, with peaks at 250, 295 and 337 nm. The fluorescence spectrum of $M_2$ showed maximum excitation and emission wavelengths of 350 and 450 nm, respectively. Corresponding values for TMeP were 350 and 430 nm.

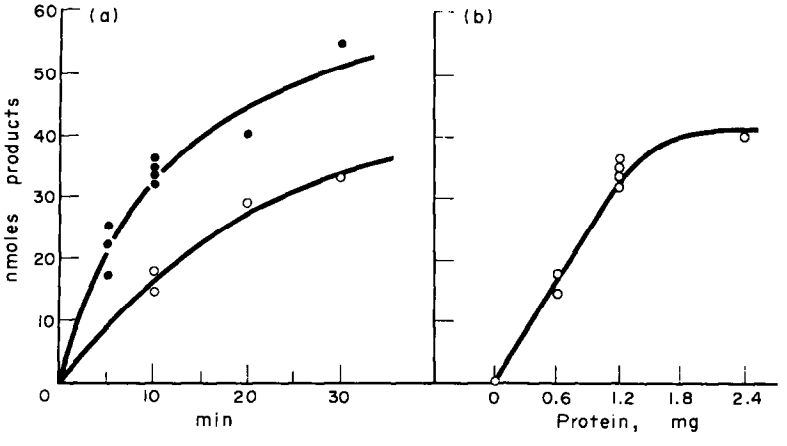



Fig. 2. Kinetics of TMeP reaction with mouse liver homogenate. Panel a: Reactions were carried out using 0.6 mg (○) or 1.2 mg protein (●). b: Reactions were incubated for 10 min with the indicated amount of protein.

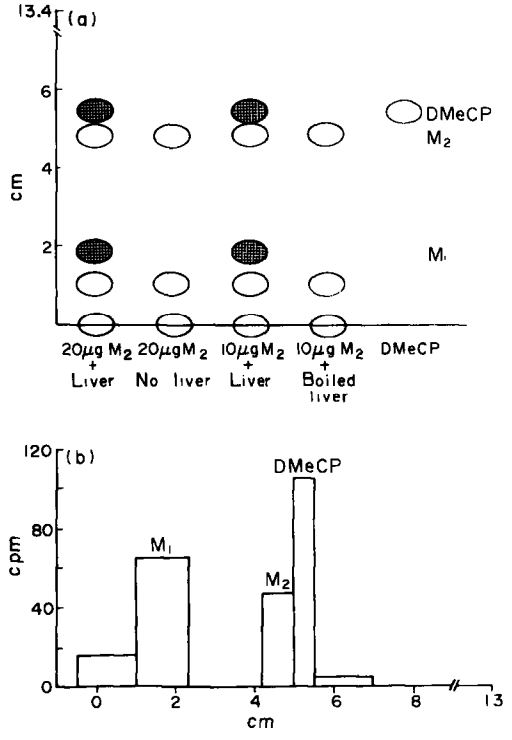



Fig. 3. Reaction of radioactive $M_2$ with mouse liver homogenate. Panel a: Indicated amounts of [$^3$H]$M_2$ (120 cpm/$\mu$g) were incubated for 30 min. with liver homogenate equivalent to 75 mg fresh wt. Aliquots of ether-extractable material were subjected to t.l.c. in solvent A. The observed fluorescent materials are schematically shown. The hatched areas show products formed. Panel b: Radioactivity distribution on the t.l.c. plate of liver reaction with 10 $\mu$g [$^3$H]$M_2$.

Mass spectroscopy of the isolated $M_1$ and $M_2$ revealed that $M_1$ has a molecular weight of 260, which is 32 higher than TMeP. Besides the $M_1$ parent ion at 260, other major ions were detected with mass numbers 243, 232, 231, 215 and 187. $M_2$ showed a molecular weight of 244, and additional major ions appeared with mass numbers 227, 215 and 199. Mass spectra of the t.l.c. eluates obtained from corresponding control bands lacked the ions listed above.

*Interrelationship of TMeP metabolites*

The metabolites $M_1$, $M_2$ and DMeCP were each tested as substrates in a standard reaction mixture *in vitro* containing mouse liver homogenate and about 50 nmoles substrate. $M_2$ was transformed both to DMeCP and to $M_1$, based on t.l.c. results in solvent A (Fig. 3) and solvent C (not shown). The experiments in Fig. 3 were repeated at least twice with cold $M_2$ as well as [$^3$H]$M_2$ as substrate, and the data shown are reproducible and significant. The DMeCP formed from $M_2$ also was eluted with ethanol and showed a characteristic DMeCP ultraviolet absorption spectrum. DMeCP was not detectably metabolized further. With [$^3$H]DMeCP as substrate, control and sample t.l.c. plates showed identical radioactive profiles in solvents A and C, with 95 per cent recovery of starting radioactivity. $M_1$ also did not show any *in vitro* conversion.

It was of interest to examine whether $M_1$ or $M_2$, as well as DMeCP, was present in the urine of mice and human volunteers receiving oral TMeP (2 mg/mouse; 40 mg/70 kg for humans). Urine was extracted with ether, DMeCP was precipitated, and the remaining ether solutions were subjected to t.l.c. in solvents A, C and D. We could not detect any fluorescent substances resembling $M_1$ or $M_2$ that were present in sample urines but absent from control urines.

Table 3. Recovery of 8-MOP and TMeP after incubation with mouse liver microsomes*

| | TMeP (nmoles) | 8-MOP (nmoles) |
|---|---|---|
| Initial substrate | 700 | 920 |
| Ether-extracted material | 420 | 700 |
| Amount run on t.l.c. | 84 | 140 |
| Amount recovered from t.l.c. | 52 | 105 |
| Amount recovered from t.l.c. as products | 32 | $<4$ |
| Amount recovered from t.l.c. as substrate | 20 | 105 |
| Per cent of recovered materials as products | 60% | $<5$% |

* Microsomes from 1 g weight of liver were incubated for 2 hr in 5 ml of reaction mix. Ether-extractable material was dissolved in ethanol. A portion was run on t.l.c. in solvent A, and fluorescent material was eluted with 1.5 ml ethanol and roughly quantitated by ultraviolet absorption spectroscopy: 0.012 $O.D._{300}$ = 1 nmole 8-MOP/ml; 0.011 $O.D._{295}$ = 1 nmole TMeP/ml.

*Reaction of mouse liver fractions with 8-MOP*

Incubation experiments were undertaken to see whether 8-MOP, like TMeP, was metabolized by mouse liver *in vitro*. Homogenate equal to 75 mg fresh weight was incubated in a standard reaction with or without 8-MOP. Thin-layer chromatography in solvent B showed that the amount of 8-MOP in the incubated sample appeared undiminished when compared visually with the unincubated control. When 40 nmoles 8-MOP instead of the usual 400 nmoles was incubated, again no products appeared.

We also investigated the ability of liver microsomes to react with 8-MOP (see Table 3 for experimental details). After t.l.c. on $IB_2$ F plates, sample incubations showed small amounts of two new fluorescent spots with $R_f$ values of 0.20 and 0.32 in solvent A, and $R_f$ values of less than 0.1 in solvent C. Non-fluorescent products were not detected.

The extent of liver microsomal reaction with 8-MOP and TMeP was compared. Data in Table 3 show that 8-MOP is apparently minimally transformed to ether-extractable metabolites, whereas TMeP is readily transformed. Essentially all material recovered from the 8-MOP incubation has the same $R_f$ and ultraviolet absorption spectrum as 8-MOP, and is presumed to be 8-MOP. Fluorescent 8-MOP metabolites were not formed in quantities sufficient to obtain absorption spectra.

*Reaction of psoralens with guinea pig epidermis and mouse kidney*

Since psoralens are used topically in treating certain human skin diseases, we investigated whether

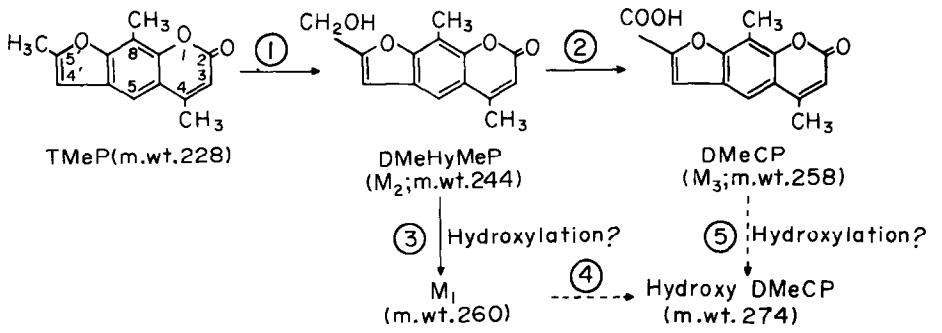



Fig. 4. Proposed scheme for *in vitro* and *in vivo* metabolism of TMeP. Reactions 1, 2 and 3 were detected *in vitro*; reactions 4 and 5 are speculative. Products DMeCP and proposed hydroxy-DMeCP were isolated from mouse urine [18]. Abbreviations: TMeP = 4,5′,8-trimethylpsoralen; DMeHyMeP = 4,8-dimethyl, 5′-hydroxymethylpsoralen; DMeCP = 4,8-dimethyl,5′-carboxypsoralen.

epidermis could readily metabolize 8-MOP or TMeP. No reaction products were detected by t.l.c. when guinea pig epidermal tissue fractions (whole homogenate, 10,000 *g* supernatant fraction or microsomes) were incubated with 8-MOP or TMeP under mixed-function oxidase conditions. The assay with [$^3$H]TMeP would have detected a reaction rate greater than 0.2 nmole/g fresh wt/min; for 8-MOP, the estimated sensitivity is about 2 nmoles/g fresh wt/min. Recovery studies indicated that non-ether-extractable metabolites were apparently not being formed by epidermal homogenate, since recovery of starting material was greater than 95 per cent.

The guinea pig liver 10,000 *g* supernatant fraction appeared similar to mouse liver fractions both in forming $M_1$ and $M_2$ from TMeP and in not reacting readily with 8-MOP, based on fluorescent spots seen on t.l.c. plates.

Mouse kidney homogenate and the 10,000 *g* supernatant fraction failed to form detectable products from [$^3$H]TMeP or [$^3$H]DMeCP *in vitro*.

## DISCUSSION

Although 8-MOP and TMeP have been widely used clinically since 1952, very little is known of their *in vivo* metabolic reactions. We have studied the metabolism of these two important photochemotherapeutic agents, and our observations enable us to propose a possible pathway for TMeP biotransformation. The fate of 8-MOP, however, remains to be established. It seems likely that furocoumarins such as TMeP are metabolized primarily in the liver and that liver mixed-function oxidases that require oxygen and NADPH are involved in this metabolism.

Three fluorescent products ($M_1$, $M_2$ and $M_3$) have been isolated after *in vitro* reaction of liver fractions with TMeP. Based on recovery experiments with [$^3$H]TMeP as a substrate, these three products appear to account for all the ether-extractable compounds that are formed from TMeP. Figure 4 shows a possible interrelationship of the various products obtained from *in vivo* and *in vitro* metabolism of TMeP. Product $M_3$ is DMeCP, an end product of TMeP metabolism which has been identified in urine of mice and humans receiving TMeP orally [18].

Based on the following facts, we propose that $M_2$ is 4,8-dimethyl, 5′-hydroxymethylpsoralen (DMeHyMeP): (a) $M_2$ is enzymatically transformed to DMeCP by liver homogenate; (b) the molecular weight of $M_2$ is 244, which is 16 more than the molecular weight of TMeP; and (c) the tricyclic psoralen ring structure in $M_2$ is apparently intact, since the absorption spectra of $M_2$ and TMeP are essentially the same. $M_2$ could be metabolized to DMeCP either by a mixed-function oxidase reaction or by a dehydrogenase using NAD or NADP as a co-factor. Additional experiments are necessary to distinguish these possibilities.

We propose that $M_1$ could be a hydroxy derivative of $M_2$. Further reaction of $M_1$ could involve oxidation of the 5′-hydroxymethyl group, giving a 5′-carboxy compound related to DMeCP with a molecular weight of 274. In fact, we have recently isolated such a compound from mouse urine [18]. Mass fragmentation did not allow us to determine the location of the proposed hydroxy group on $M_1$ or on the material of molecular weight 274, but n.m.r. studies, which have not yet been performed, should give the structures of the compounds. Since $M_1$ and TMeP have similar ultraviolet absorption spectra, the hydroxylation may be on the 4 or 8 methyl group rather than directly on one of the rings. Hydroxylation of a ring position would be expected to show large spectral shifts when compared with TMeP.

DMeCP was not further metabolized *in vitro* by mouse liver homogenate or the 10,000 *g* supernatant fraction, or by kidney tissue fractions. This lack of reaction is expected for a metabolic end product. It is not yet clear whether $M_2$ is excreted in urine after oral administration of TMeP, or whether $M_2$ is completely transformed to DMeCP under *in vivo* conditions. Results obtained after feeding mice [$^3$H]TMeP indicate that $M_1$ is not excreted in mouse urine (B. Mandula and M. Pathak, unpublished observations).

In the reaction of TMeP with liver fractions *in vitro*, only ether-extractable substances were studied further, although up to 10 per cent of total radioactivity remained in the aqueous phase. This non-volatile, nonextractable material could be either: (a) TMeP metabolites; or (b) reduced pyridine nucleotides, possibly formed in a dehydrogenase reaction.

In our studies of TMeP metabolism, we have not found significant differences among species. Both mice and humans receiving oral TMeP excrete

DMeCP. In addition, *in vitro* studies with guinea pig and mouse liver strongly suggest that livers from both animals form $M_1$ and $M_2$ from TMeP.

Urine specimens from mice and humans given 8-MOP orally show at least two ether-extractable fluorescent metabolites and little undegraded 8-MOP (B. Mandula and M. Pathak, unpublished observations). Therefore, the compound is clearly metabolized *in vivo*. However, when 8-MOP was incubated *in vitro* with liver fractions under mixed-function oxidase conditions, we were unable to detect substantial formation of products. Several possible explanations may account for these negative results with 8-MOP: (a) the liver may not be the main site of metabolism of 8-MOP; (b) the incubation conditions may not fulfill the requirements for the reactions including the activation or solubilization of the substrate; (c) product or substrate inhibition may prevent the reaction of 8-MOP proceeding to any great extent; (d) products may be unstable or non-ether-extractable; or (e) products may lack both fluorescence and a typical furocoumarin absorption spectrum. The first two possibilities seem less likely than the remaining three possibilities, which could be investigated with radioactive 8-MOP.

Failure to detect products from 8-MOP or TMeP after incubation with guinea pig epidermis could indicate that the appropriate enzyme system is either absent or present in amounts too low to be detected by our assay. Although benzpyrene hydroxylase activity (cytochrome P-448) at low levels has been observed in skin from humans [21], rats [22,23] and mice [24,25], we are unaware of any evidence demonstrating cyctochrome P-450 mixed-function oxidases in skin.

The observation that TMeP is rapidly transformed *in vitro* by the liver but not by the epidermis may be related to therapeutic differences seen in topical and systemic photochemotherapy. Recent unpublished studies in our laboratory have indicated that in man topically applied TMeP at low concentrations (1–5 $\mu g/2.5\ cm^2$) is very photoreactive and induces marked skin photosensitization reactions (e.g. erythema, edema and cell death). On the other hand, orally administered TMeP (40–120 mg/70 kg) is significantly less active than topical TMeP, orally administered 8-MOP (40 mg/70 kg) or topical 8-MOP (1–5 $\mu g/2.5\ cm^2$). The decreased TMeP reactivity *in vivo* could be related to its rapid biotransformation and excretion. DMeCP, one of the major metabolites of TMeP, is apparently inactive and nonphotosensitizing when tested on guinea pig skin [18]. Recent unpublished clinical experiments showed that topical TMeP cleared psoriasis, whereas orally administered TMeP was ineffective in the same patients. Additional studies are needed, however, to understand the differences in the photoreactivity of 8-MOP and TMeP after oral administration.

*Acknowledgements*—We acknowledge Dr. Gerald Dudek and Ms. Linda Sher for their invaluable technical help. This investigation was partially supported by a research grant from the GTE Sylvania Lighting Products Group.

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