ADVANCES IN
DRUG RESEARCH

Edited by

BERNARD TESTA

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PREFACE: THE PEN AND THE ART OF MONOTONY AVOIDANCE[1]

The present volume of *Advances in Drug Research,* the second edited by the undersigned, contains four chapters featuring interesting differences and analogies.

The first two chapters cover general topics, namely deuterium isotope effects in xenobiotic metabolism and drug design, and drug design in three dimensions. Both are thus closely related to medicinal chemistry, but the stories they tell are quite different. While deuterium isotope effects have proven invaluable in studying enzymatic reaction mechanisms but have found only limited applications in drug design, the combination of structural studies coupled with assessment of structure–activity relationships and computer graphics (three-dimensional drug design) has generated considerable interest and hopes, to say the least.

The third and fourth chapters discuss specific therapeutic classes, namely antiinflammatory agents and benzodiazepines. The former is a short and densely written review providing an incentive for further study. In contrast, the latter offers a truly encyclopedic treatment of recent advances in benzodiazepine research.

The four chapters in this volume differ in their approach, construction and layout, and style, reflecting the personalities and backgrounds of their authors. They also differ considerably in length, but not in their depth of treatment and wealth of information. Writing a review is always a demanding and lengthy task, and we must be grateful to those colleagues who give so much time and effort that might otherwise be applied to other, perhaps better rewarded goals. However, reviews can be highly readable and enriching, as opposed to plain, dull compilations. Accepting to put pen to paper, or having a ready pen, does not imply being a stimulating writer, and a good scientific review requires that its author be both a knowledgeable scientist and a clear and imaginative writer. But since expertise, clarity of mind, and imagination are prerequisites of a good scientist, it is not surprising that so many reviews to be found in journals and books are in fact readable and enriching. The past, present, and future volumes of *Advances in Drug Research* are and shall be aimed at contributing to this common wealth, to this body of reviews, chapters and books which are the fertilizers of scientific research.

BERNARD TESTA

[1]With apologies to Robert M. Pirsig, inspired author of "Zen and the Art of Motorcycle Maintenance," William Morrow & Co., Inc., New York, 1974.

CONTENTS

Recent Advances in the Molecular Pharmacology of Benzodiazepine Receptors and in the Structure–Activity Relationships of Their Agonists and Antagonists

WILLY HAEFELY, EMILIO KYBURZ, MAX GERECKE, AND HANNS MÖHLER

Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design

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1 Introduction

The majority of drugs, when administered to humans and animals, are metabolized, often rapidly and extensively (Testa and Jenner, 1976). Metabolism, which usually occurs mostly in the liver but which can also occur in numerous other organs (Fry and Bridges, 1977), e.g., kidney, lungs, skin, and small intestine, has been regarded as a defense mechanism whereby ingested xenobiotics are converted into more polar derivatives that are excreted more readily either directly or after conjugation. However, in the case of drugs, rapid metabolism may limit plasma levels and half-lives and, consequently, efficacy.

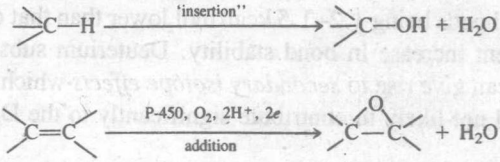
Although some drugs [e.g., cyclophosphamide (Connors *et al.*, 1974)] are activated by metabolism or may be deliberately designed as prodrugs (Bodor, 1981a, 1984), the usual consequence of metabolism is deactivation. Moreover, in addition to being more rapidly excreted, metabolites usually have an affinity for the target (receptor, enzyme, membrane, etc.) lower than that of the parent drug or may have properties which limit access to, and therefore interaction with, the target. Metabolism can also generate products which have a biological activity different from that of the parent drug or which may be toxic and, in some instances, carcinogenic (Jefcoate, 1983).

Thus, the metabolism of drugs is usually an adverse process and its importance is often indicated when candidate drugs which show high activity in *in vitro* assays are inactive *in vivo*. The metabolism-directed approach (Jarman and Foster, 1978; Bodor, 1981b, 1984) to drug design is concerned with the rational modification of molecular structure in order to control adverse metabolism and/or confer desirable characteristics. The ideal starting point for a metabolism-directed design study involves a drug in clinical or experimental use with a known target, metabolism profile, and origin of toxicity. Structure–activity studies can then be undertaken aimed at retarding or blocking adverse metabolism while retaining (preferably, increasing) affinity for the target and ensuring that a plasma level and half-life can be achieved practicably which will optimize interaction with the target.

It is in this context that specific deuterium substitution in drugs and the magnitude and consequences of the resulting deuterium isotope effects are now considered.

A wide variety of pathways of drug metabolism have been identified and categorized as phase I and II reactions (Fry and Bridges, 1977), also designated as functionalization and conjugation reactions (Testa and Jenner, 1978). The former category includes reactions whereby functional groups are introduced (e.g., hydroxylation), modified (e.g., aldehyde oxidation and reduction), or exposed (e.g., O-dealkylation) whereas the latter category includes reactions such as glucuronidation and sulfation. It is within the phase I category that metabolism pathways are found which are susceptible to deuterium isotope ef-

fects, namely, those in which a C—H bond is broken, for example, hydroxylation (C—H → C—OH) and dehydrogenation (CH—OH → C=O). Hydroxylation is a frequently encountered pathway of metabolism which is mediated by the cytochrome P-450 enzymes (mono-oxygenases, mixed function oxidases). Treatises on this category of enzyme are now available (e.g., Schenkman and Kupfer, 1982) so that only the salient relevant points need be noted here. The cytochrome P-450s are heme proteins commonly found as clusters of membrane-bound isoenzymes in the endoplasmic reticulum of many types of cell but they are particularly prevalent in liver cells. Some of these isoenzymes are inducible [e.g., by phenobarbital (PB) and methylcholanthrene], each has a characteristic substrate specificity, and each can generate from molecular oxygen an electrophilic species which will react with, and deliver to, the substrate the formal equivalent of atomic oxygen. The structure of this reactive species remains to be defined precisely but it has been termed oxenoid because its reactions are formally analogous to those of carbenes in adding to double bonds and inserting into single bonds. The overall reactions are as follows:



The so-called "oxygen insertion reaction" is by far the most important metabolism pathway considered in this article (see Section 3.4.2 for comments on mechanism).

2 Deuteration of Drugs and Xenobiotics

Deuterium labeling has found widespread application in studies of drug metabolism in such diverse aspects as identification and quantification (coupled with mass spectrometry) of drugs and metabolites in plasma, urine, and *in vitro* systems, determination of pharmacokinetics in general, and in chronic administration, bioavailability studies, mechanism of enzyme and drug action, elucidation of metabolic and biosynthetic pathways, differential metabolism of enantiomers, and isotope effects. Several reviews have appeared in the past decade dealing with deuterium labeling in the general context of applications of stable isotopes in biomedical research, pharmacology, and medicinal chemistry (Knapp and Gaffney, 1972; Knapp *et al.*, 1973; Gregg, 1974; Gaffney *et al.*, 1974; Nelson and Pohl, 1977; Halliday and Lockhart, 1978; Baillie, 1981; Baillie *et al.*, 1982; Haskins, 1982). Each review has a particular emphasis and viewpoint and all are well worth reading. The review by Blake *et al.* (1975) is devoted to

deuterium and contains an excellent survey of the literature prior to 1975 on, *inter alia,* deuterium isotope effects associated with the metabolism and biological activity of drugs and related compounds. The present article is concerned mainly with deuterium isotope effects and is not intended to be comprehensive but illustrative. Apologies are tendered herewith to those authors whose relevant work is not mentioned.

2.1 DEUTERIUM ISOTOPE EFFECTS

In a reaction (chemical or enzymatic) in which cleavage of a C—H bond is rate determining the same reaction of the C—D analog will be retarded. The ratio (K_H/K_D) of the respective rate constants defines the *primary deuterium isotope effect* (DIE). The maximum theoretical DIE has been calculated (Bigeleisen, 1949) as 18 and although values up to 11–12 have been observed experimentally in metabolism studies (see below) most observed DIEs are relatively small (<5). The origin of DIEs relates to the difference in mass between hydrogen and deuterium which results in the zero-point energy (lowest ground state vibrational level) for C—D bonds being 1.2–1.5 kcal/mol lower than that of the C—H bond with a consequent increase in bond stability. Deuterium substitution near to a reaction center can give rise to *secondary isotope effects* which are usually small (1.05–1.25) and not likely to contribute significantly to the DIEs considered in this article.

DIEs in chemical reactions were reviewed by Wiberg (1955), and Wolfsberg (1982) has given a general theoretical analysis. Northrop (1982) has presented a detailed consideration of enzyme-catalyzed reactions in terms of a family of DIEs and emphasized the fact that the observed DIE (^Dv), which relates to the rates of disappearance of substrate and/or appearance of products, can be very much smaller than the intrinsic DIE (^Dk), which is associated with the conversion of the substrate into product(s) within the activated enzyme–substrate(product) complex. The mechanisms of action of various enzymes which can be involved in drug metabolism studies have been clarified on the basis of DIEs, e.g., aldehyde dehydrogenase (Feldman and Weiner, 1972), xanthine oxidase (Edmondson *et al.*, 1973), urocanase (Egan *et al.*, 1981), liver alcohol dehydrogenase (Cook and Cleland, 1981), and dopamine β-monooxygenase (Miller and Klinman, 1982). Deuterium labeling has also been used elegantly to probe the steric requirements of drug–receptor interaction of neuromuscular blocking agents in the norcoralydine series (Stenlake and Dhar, 1978). However, this article is concerned primarily with "observed" DIEs, frequently expressed as K_H/K_D or V^H_{max}/V^D_{max} [^Dv in Northrop's (1982) terminology], which reflect the gross effect of deuterium substitution on the rate and pathways of metabolism of drugs and xenobiotics and on their biological activity. Unless stated otherwise in the sections below, the term DIE connotes the observed deuterium isotope effect.

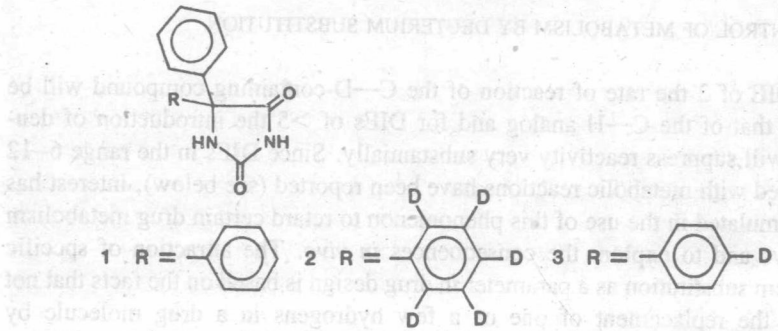
2.2 CONTROL OF METABOLISM BY DEUTERIUM SUBSTITUTION

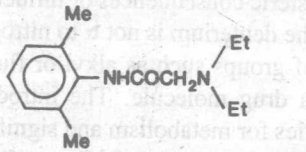
For a DIE of 2 the rate of reaction of the C—D-containing compound will be 50% of that of the C—H analog and for DIEs of >5 the introduction of deuterium will suppress reactivity very substantially. Since DIEs in the range 6–12 associated with metabolic reactions have been reported (see below), interest has been stimulated in the use of this phenomenon to retard certain drug metabolism pathways and to explore the consequences *in vivo*. The attraction of specific deuterium substitution as a parameter in drug design is based on the facts that not only is the replacement of one or a few hydrogens in a drug molecule by deuterium the smallest structural change that can be made but also such a change will have negligible steric consequences or influence on physicochemical properties (providing that the deuterium is not α to nitrogen, see Section 5.1). This is in contrast to the use of groups such as alkyl or fluorine to block metabolism at a particular point in a drug molecule. The introduction of an alkyl group may create new possibilities for metabolism and significantly change lipophilicity and the introduction of fluorine may markedly modify the character of neighboring functional groups or remote ones if there is an intervening conjugated or aromatic system.

Cytochrome P-450-mediated aromatic hydroxylation usually involves initial oxene addition to give an epoxide (arene oxide) which, *inter alia*, can rearrange into a phenol. Although for deuterated aromatic compounds deuterium migration occurs (NIH shift; Daly *et al.*, 1968, 1969), the DIE is negligible for the overall hydroxylation process (e.g., Farmer *et al.*, 1975) when hydroxyl groups are introduced into the o- and p-positions in substituted aromatics. It was inferred that a different mechanism operates for m-hydroxylation *in vitro* and *in vivo* and for which DIEs of 1.3–1.75 have been observed (Tomaszewski *et al.*, 1975).

The biological activity of xenobiotics can sometimes be modified by polydeuteration (see review by Blake *et al.*, 1975) but a remarkable effect of monodeuteration has been reported by Dumont *et al.* (1981). The anticonvulsant potency of diphenylhydantoin (**1**) was enhanced by pentadeuteration of one phenyl group (→ **2**) and even more so by p-deuteration (→**3**). The mechanistic significance of these findings is not clear. p-Hydroxylation of one phenyl group is the main initial metabolism pathway for (**1**) and Hoskins and Farmer (1982) found no significant DIE for p- and m-hydroxylation of d_5-diphenylhydantoin (**2**) by liver microsomes (PB-induced rats) or in humans. Moreover, Moustafa *et al.* (1983) concluded that m- and p-hydroxylation of diphenylhydantoin (**1**) proceeded via the 3,4-epoxide. These findings contrast with those of Tomaszewski *et al.* (1975) noted above and suggest that m-hydroxylation could involve a duality of mechanisms.

Progressive replacement of hydrogen in a drug or another xenobiotic molecule with deuterium will progressively change the lipophilicity and the magnitude of





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this effect can be conveniently assessed by normal (Farmer *et al.*, 1978) and reversed-phase high-pressure liquid chromatography (HPLC) (Tanaka and Thornton, 1976). The shake-flask and HPLC methods were recently compared (El Tayar *et al.*, 1984). The results indicated deuterated compounds to be less lipophilic than the corresponding protium forms by ~0.006/D on the log P_{oct} scale. The effect of deuteration on binding, for example, to microsomal cytochrome P-450, is usually given by the ratio of the Michaelis constants K_m^D/K_m^H. When this ratio is <1 (see Section 5.1), stronger binding of the deuterated compound to the enzyme is indicated. Amines are an exception in that deuteration at the α-carbon will give a K_m^D/K_m^H ratio of >1. For example, deuteration of the NEt_2 moiety of lidocaine (**4**) results (Nelson *et al.*, 1975) in a K_m^D/K_m^H ratio of 1.23 (for rat liver microsomes) for the $N(CD_2CH_3)_2$ analog in contrast to a ratio of 0.92 for the $N(CH_2CD_3)_2$ analog.

2.2.1 Metabolic Switching

When a drug is metabolized by two or more alternative pathways a possible consequence of deuteration is "metabolic switching." This term was introduced by Horning *et al.* (1976), who found that the metabolism of antipyrine (**5**), after intraperitoneal (ip) injection into rats and as reflected by the urinary metabolites, was switched from oxidation of the C-3-methyl group (normal major pathway) to N-demethylation (normal minor pathway) on trideuteration of the former group.

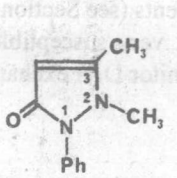
The effect was even more marked *in vitro*. Using the 10,000 *g* supernatant of homogenized rat liver, the ratio of 3-hydroxymethylantipyrine to 4-hydroxyan-

tipyrine from antipyrine was 1.3 and 1.6 when the N-methyl group was trideuterated. However, the ratio changed dramatically to <0.1 when the C-3-methyl group was trideuterated. This low ratio corresponded to a DIE of ~15.

A similar situation was encountered by Gorumaru *et al.* (1981) for the metabolism of aminopyrine (**6**) administered orally to rats. Analysis of the urinary metabolites revealed that trideuteration of the C-3-methyl group switched metabolism to N-demethylation of the C-4-dimethylamino group. No metabolic switching occurred when the N-2-methyl group or the C-4-dimethylamino group was fully deuterated.

Horning *et al.* (1978) showed that for methsuximide (**7**), N-demethylation was suppressed and hydroxylation of the phenyl group was increased when the N-methyl group was trideuterated.

In studies with caffeine (**8**), Horning *et al.* (1976) found that trideuteration of the N-1-methyl group depressed N-demethylation at N-1 and, for the rat and ip administration, 1,3-dimethylxanthine (theophylline) became the major urinary metabolite. Likewise, trideuteration of the N-7-methyl group resulted in 1,7-dimethylxanthine being the major urinary metabolite. The same group (Horning *et al.*, 1979) also found that after ip injection into rats the plasma half-lives of caffeine (**8**) and its derivatives with the N-1-, N-7-, or N-9-methyl groups trideuterated were similar. However, the plasma half-life of the derivative with all these N-methyl groups trideuterated was twice that of caffeine (**8**). These results were taken to indicate that N-demethylation at positions 1, 7, and 9 occurred at the same rate *in vivo* and that replacement of CH_3 by CD_3 switches metabolism to de-N-methylation of an unlabeled methyl group.



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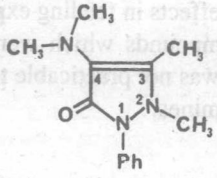

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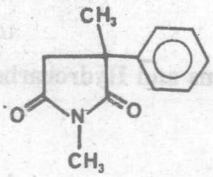

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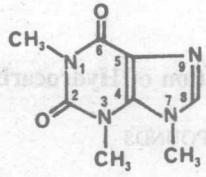

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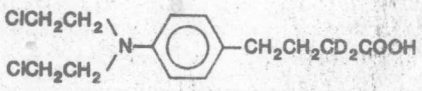
The foregoing results variously illustrate metabolic switching of three types, namely C→N, N→C, and N→N. An example of C→C switching associated with 7-ethylcoumarin is noted in Section 4.1.

The possibility exists, although apparently not yet realized, of using metabolic switching in drug design to deflect metabolism away from a pathway yielding a toxic metabolite to one (or more) leading to innocuous products or away from a pathway leading to inactive metabolites toward one yielding an active metabolite.

2.2.2 D/H Exchange

In *in vitro* and *in vivo* studies of the metabolism of deuterated drugs and other xenobiotics it is essential that the deuterium content of unchanged drug and its metabolites be monitored by mass spectrometry if other techniques are used for quantification. This precaution is essential in order to ensure that D/H exchange does not occur. Where enzymes, receptors, or other macromolecules are involved there is always the possibility of microenvironments in which D/H exchange can be promoted. Thus, following ip administration of α-d_2-chlorambucil (**9**) to rats, monitoring of the drug in the plasma by mass spectrometry revealed that D/H exchange was complete within 30 min even though chemically the deuterium was not intrinsically labile (Farmer *et al.*, 1979). Perel *et al.* (1967) found that, after administration of-*p*-deuterophenobarbital (**10**) to dogs, the drug excreted in the urine had undergone 13–26% D/H exchange. Singer and Lijinsky (1979) have noted that, for nitrosamines deuterated α to nitrogen, pronounced biological isotope effects in feeding experiments (see Section 5.4) were observed only for those compounds which were not very susceptible to base-catalyzed D/H exchange. It was not practicable to monitor D/H exchange *in vivo* for these deuterated nitrosamines.



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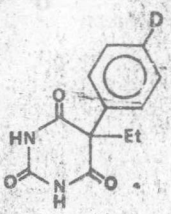

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3 Hydroxylation of Hydrocarbons and Hydrocarbon Moieties

3.1 ALIPHATIC COMPOUNDS

3.1.1 Hydrocarbons

The outcome of microsomal hydroxylation of linear, saturated aliphatic hydrocarbons depends on the chain length and the inducer used. For the homologous

series $CH_3(CH_2)_nCH_3$ when $n = 1$ or 2, two monohydroxy derivatives are possible, three when $n = 3$ or 4, four when $n = 5$ or 6, etc. Also, for hydroxylation at some secondary positions, the possibility of stereoselectivity exists and D- and/or L-alcohols can be formed. The regioselectivity associated with microsomal hydroxylation is illustrated by the results for *n*-hexane ($n = 4$) and *n*-heptane ($n = 5$).

Using liver microsomes (PB-treated rats) the ratio of 1- (ω), 2- (ω−1), and 3-hexanols (ω−2) from *n*-hexane was ~1:11:2 and diols were also formed (1,2, 1,3, and 2,3; ratio ~1.6:0.3:0.7) (Kramer *et al.*, 1974). The ratio of the three hexanols was not changed dramatically when noninduced microsomes were used. Under essentially similar conditions the ratio of 1- (ω), 2- (ω−1), 3- (ω−2), and 4-heptanols (ω−3) from *n*-heptane was ~1:19.5:3.7:1.5 (Frommer *et al.*, 1972). The relative proportions of the four heptanols was not greatly changed when noninduced microsomes were used but with benzpyrene-induced microsomes the ratio became ~1:16.5:13.8:21.4. Thus, for non- and PB-induced microsomes (ω−1)-hydroxylation of linear, saturated aliphatic hydrocarbons preponderates.

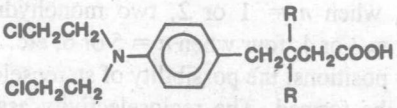
Although the microsomal hydroxylation of cyclohexane and cyclohexane-d_{12} has been studied (see Section 3.4.1) apparently there has been no comparable investigation of linear aliphatic hydrocarbons.

3.1.2 Fatty Acids

The regioselectivity of microsomal hydroxylation of saturated linear fatty acids is dependent on chain length. Thus, for decanoic acid, $CH_3(CH_2)_8COOH$ (Hamberg and Björkhem, 1971), the ratio of 10- (ω) and 9-hydroxylation (ω−1) was >9:<1. Metabolism of the 10-d_3 and 9-d_2 derivatives of decanoic acid revealed a DIE (1.5–2 based on yields of products) only for 9-hydroxylation. The ratio of the D- and L-forms of 9-hydroxydecanoic acid was ~1:3 and this was changed to ~2:1 when 9-d_2-decanoic acid was hydroxylated.

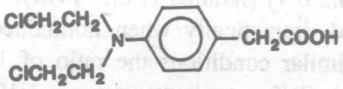
A somewhat different situation was encountered with lauric acid, $CH_3(CH_2)_{10}COOH$ (Björkhem and Hamberg, 1972). The ratio of microsomal 12- (ω) and 11-hydroxylation (ω−1) was ~3:2 but for 11-d_2-lauric acid this ratio changed to >9:<1, reflecting a significant DIE (~2.5 based on yields of products). The ratio of D- and L-forms of the 11-hydroxy derivative was ~3:2, which, apparently, was not affected by deuteration at position 11.

The antitumor alkylating agent chlorambucil (**11**) is metabolized *in vivo* to give, *inter alia*, phenylacetic mustard (**12**) presumably via β-oxidation. This metabolism pathway is probably adverse since the therapeutic index of the metabolite (**12**) is inferior to that of the parent drug (**11**) against, for example, the Walker 256 carcinoma in rats. Moreover, the neurotoxicity associated with high doses of chlorambucil (**11**) could be due to the formation of (**12**). Following ip administration of β-d_2-chlorambucil (**13**) to rats the plasma levels of phe-



11 R = H

13 R = D



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nylacetic mustard (**12**) were lower than those from the parent drug but the therapeutic index was not altered significantly (Farmer *et al.*, 1979).

Reinsch *et al.* (1980) have reported a remarkably high DIE for the reaction of perdeuterobutyryl-CoA with fatty acyl-CoA dehydrogenase:

$$RCH_2CH_2COSCoA \rightleftharpoons RCH_2\bar{C}HCOSCoA \rightleftharpoons RCH{=}CHCOSCoA$$

A DIE of 2 was found for the first step (H^+ abstraction) and a value of 30–50 was found for the second step.

3.1.3 Barbiturates

The effect of specific deuteration of the *n*-butyl group in 5-*n*-butyl-5-ethylbarbituric acid (**14,** butethal) has been explored. Soboren *et al.* (1965) observed that dideuteration at position 3 (→**15**) doubled the sleep time of mice whereas trideuteration at position 4 (→**16**) had no effect. That the modified behavior of **15** reflected a DIE was suggested by the identification of the 3-hydroxy derivative **17** as a microsomal metabolite of butethal. The same group (Tanabe *et al.*, 1969) showed later that dideuteration at position 3 in butethal (→**15**) increased the half-life from 100 to 270 min on incubation with the postmitochondrial supernatant of homogenized liver. They confirmed the 3-hydroxy derivative **17** to be the major metabolite and noted a DIE of ~1.6. Similar results were reported by Mark *et al.* (1971) for 5-ethyl-5-(1-methylbutyl)barbituric acid (**18,** pentobarbital). Thus, dideuteration at position 3 (→**19**) virtually doubled the plasma half-life on administration iv to dogs or ip to mice and delayed the time to peak sedation but prolonged the total sleep time.

The major metabolic route for 5-ethyl-5-phenylbarbituric acid (**20,** phenobarbital) is p-hydroxylation of the phenyl moiety. As would now be expected (Tomaszewski *et al.*, 1975), no DIE was found (Perel *et al.*, 1967) when the p-deutero derivative **21** was administered iv to dogs and rats.