ENZYMATIC DEALKYLATION OF AMINOPYRINE (PYRAMIDON) AND OTHER ALKYLAMINES*

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Many drugs which are alkylamines undergo dealkylation in the body. For example aminopyrine (2), ephedrine (3), codeine (4), meperidine (5, 6), methylamphetamine (7), and mephobarbital (8, 9) are all demethylated in vivo. The removal of ethyl groups has been demonstrated with quinacrine, and an unusual type of dealkylation, the loss of a β-chloroethyl group, occurs in the biotransformation of N-dibenzyl-β-chloroethylamine (Dibenamine) (10).

In spite of the importance of dealkylation in drug metabolism little is known concerning the biochemical mechanism responsible for the removal of the alkyl groups: whether one or a number of enzyme systems are responsible for the dealkylation of various alkylamines; the relationship between structure of alkylamines and their resistance to dealkylation; and finally what function, if any, the dealkylating enzymes serve in normal metabolic processes.

Preliminary studies by Taggart, Poet, and Brodie have shown that aminopyrine (Pyramidon, dimethyl-4-aminoantipyrine) is demethylated to 4-aminoantipyrine on incubation with slices or homogenates of rabbit liver. The present communication presents further studies on the enzymatic dealkylation of aminopyrine and related alkylamines. It will be shown that the dealkylation enzyme system is located in the microsomes of liver cells and requires both oxygen and reduced triphosphopyridine nucleotide. Evidence will be presented that the methyl groups removed from aminopyrine are converted to formaldehyde and that the ethyl group removed from the monoethyl analogue is converted to acetaldehyde.

Materials—Monomethyl-4-aminoantipyrine (henceforth referred to as MMAP) was kindly donated by Dr. Tainter of the Sterling-Winthrop Re-

* A preliminary report of this work was presented at the annual meeting of the Federation of American Societies for Experimental Biology, Chicago, April, 1953 (1).
1 Taggart, J. V., unpublished data.
2 Taggart, J. V., Poet, R., and Brodie, B. B., unpublished data.
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search Institute. Diethyl-4-aminoantipyrine was synthesized by Mr. W. Lott of The Squibb Institute for Medical Research. The monoethyl, monobutyl, and dibutyl derivatives of 4-aminoantipyrine were prepared by Doris Titus. Diphenylpropylacetic acid (SKF acid) and its ester β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF 525-A) were obtained through the courtesy of Dr. Glenn Ulliyot of the Smith, Kline and French Laboratories. TPN (triphosphopyridine nucleotide), DPN (diphosphopyridine nucleotide), and DPNH (reduced DPN) were obtained in about 80 per cent purity from the Sigma Chemical Company. TPNII (reduced TPN) was prepared by the method of Kaplan et al. (11). Glucose-6-phosphate dehydrogenase was purchased from the Sigma Chemical Company. Glucose dehydrogenase was purified from beef liver by the method of Strecker and Korkes (12). Aminopyrine-C¹⁴ labeled in one of the two 4-N-methyl groups was synthesized by Doris Titus and had a specific activity of 1 µc. per µmole. The radioactive aminopyrine was diluted 1:40 with unlabeled compound.

Methods—Male albino rabbits² were stunned, exsanguinated, and the liver or other tissues immediately removed. Tissues were homogenized at 0–3° in 2 volumes of 0.2 M phosphate buffer, pH 7.4, with a Potter-Elvehjem type glass homogenizer. The preparations were usually used immediately, although no loss of activity resulted if they were stored in the cold for several hours.

In most studies of enzymatic dealkylation a 25 ml. Erlenmeyer flask contained 2.0 ml. of enzyme preparation, 100 µmoles of nicotinamide, 75 µmoles of MgCl₂, 0.2 µmole of TPN, 5 µmoles of alkylamine substrate, and water or 0.1 M phosphate buffer, pH 7.4, to give a final volume of 5.0 ml. The reactions were carried out in a metabolic shaking incubator at 37° for 1 hour in an atmosphere of air. At the end of the incubation period the reaction was stopped by the addition of 15 ml. of 6.7 per cent trichloroacetic acid to give a final concentration of 5 per cent trichloroacetic acid, and the precipitated protein was removed by centrifugation. Suitable aliquots, usually 1 to 5 ml. of the supernatant solution, were assayed for remaining substrate or for metabolic product.

The disappearance of MMAP or aminopyrine could not be used as a measure of dealkylation, since appreciable amounts of these substrates disappeared by an alternative pathway (see below). Dealkylation activity was therefore determined by measuring the amount of 4-aminoantipyrine formed by the dealkylation of aminopyrine or its homologues. Under the

² Rabbit liver homogenates had considerably higher dealkylation activity than liver homogenates of rat and guinea pig with aminopyrine or monomethyl-4-aminoantipyrine as substrates. For this reason the studies described in this paper were made with rabbit liver.
experimental conditions described, 4-aminoantipyrine is metabolized to a small extent, less than 10 per cent, by whole rabbit liver homogenate, but is stable when incubated with microsomal preparations of liver. In most experiments MMAP was used as the substrate, since the demethylation of this compound proceeded about 4 times as rapidly as aminopyrine, its dimethyl analogue.

Analytical Methods—4-Aminoantipyrine was assayed directly in a trichloroacetic acid filtrate of the various enzyme preparations by diazotization and coupling with \( \alpha \)-naphthol, as described by Brodie and Axelrod (2). As applied to liver homogenates incubated with aminopyrine or MMAP, it was presumed that only 4-aminoantipyrine and not any other metabolite was measured, according to the following criteria: The compound determined had a free amino group, since it could be diazotized and coupled with \( \alpha \)-naphthol; the value obtained by direct assay of the filtrate was the same as that obtained by the method involving preliminary extraction of the compound with chloroform (2); and finally the azo derivative formed in the analytical procedure when subjected to ascending chromatography on Whatman No. 1 paper, with butanol saturated with 0.5 N HCl as the solvent system, yielded a single spot having the same \( R_f \) value, 0.78, as the authentic derivative.

Aminopyrine was determined spectrophotometrically after its extraction into ethylene dichloride (2). MMAP was estimated in the same manner as that described for aminopyrine.

Formaldehyde was determined by the chromotropic acid method of MacFadyen (13) as modified by Mueller and Miller (14), except that the formaldehyde was distilled from the deproteinized incubation mixture acidified to a final concentration of 20 per cent trichloroacetic acid instead of with perchloric acid. Formaldehyde was trapped by including 0.01 M semicarbazide in the incubation mixture. This concentration of semicarbazide did not inhibit enzymatic dealkylation. Zero time control flasks containing liver homogenate with added aminopyrine or MMAP contained no measurable formaldehyde, and incubated control flasks without substrate yielded less than 0.1 \( \mu \)mole of formaldehyde.

Acetaldehyde was trapped with 0.01 M semicarbazide and determined after distillation from a tungstic acid filtrate according to the method of Stotz (15).

Estimation of \( ^{14} \)CO\(_2\) and Formaldehyde-\( ^{14} \)C in Enzyme Preparations—The incubation of aminopyrine-\( ^{14} \)C with liver homogenates was carried out in closed vessels, and the carbon dioxide evolved was trapped as carbonate in 20 per cent KOH contained in a center well. At the end of the incubation period trichloroacetic acid was added to the incubation mixture to liberate

\footnote{Axelrod, J., personal communication.}
bound carbon dioxide. The carbonate in the well was precipitated as barium carbonate, and the radioactivity was determined with a low background gas flow counter, corrected for self-absorption.

To determine formaldehyde-C\textsuperscript{14}, 5 mg. of non-radioactive formaldehyde were added to the deproteinated incubation mixture which was made free of radioactive carbon dioxide by flushing with CO\textsubscript{2}. The pH was adjusted to 4.7, and 20 ml. of 0.4 per cent of dimedon (1,1-dimethyl-3,5-diketocyclohexane) were added. After 24 hours, the dimedon formaldehyde derivative was filtered, recrystallized from ethanol, and the derivative plated and counted. Recrystallization from ethanol was repeated until constant specific activity was obtained. Radioactivity was calculated as counts per minute per micromole after correction for self-absorption.

**EXPERIMENTAL**

**Distribution of Dealkylation Enzyme System in Various Tissues**—1.0 \mu mole of aminopyrine was incubated with about 500 mg. of slices of rabbit liver, skeletal muscle, kidney, intestinal mucosa, and spleen in 3.0 ml. of Krebs-Ringer-phosphate buffer at pH 7.4. Only liver was found to demethylate aminopyrine; about 0.1 \mu mole of 4-aminoantipyrine was formed by this tissue in 1 hour.

**Requirements of Enzyme System in Liver Homogenates**—Preliminary experiments showed that unless nicotinamide was added very little demethylation of MMAP to 4-aminoantipyrine occurred in homogenates of rabbit liver. This suggested that DPN or TPN might be required, though the addition of these coenzymes did not increase the extent of demethylation in the presence of nicotinamide. A definite requirement for TPN was demonstrated after decreasing the endogenous supply of pyridine nucleotides by preincubation of the homogenate without added nicotinamide at 37° for 8 minutes. The activity of the homogenate was reduced by about half by this procedure, but could be restored by the addition of TPN but not by DPN.

Further evidence that TPN was essential for dealkylation activity was obtained after dialysis of the homogenate overnight at 6° against 0.02 M phosphate buffer, pH 7.4. The resulting loss of activity could be partially restored by the addition of TPN but not by DPN. Other requirements were also evident after dialysis of the homogenate (Table I). Mg\textsuperscript{++} increased the activity of the dealkylation system, though the concentration required for maximal activity was rather large, about 0.015 M. The addition of glucose-6-phosphate also stimulated the activity, nearly doubling the extent of dealkylation. Mg\textsuperscript{++} and glucose-6-phosphate also increased the activity of the undialyzed homogenate, but to a much smaller extent.

Oxygen was found to be required for dealkylation activity. For example
when 5 μmoles of MMAP and the supplemented liver homogenate were incubated with air or oxygen as the gas phase, 1.76 and 1.75 μmoles, respectively, of 4-aminoantipyrine were formed. In contrast, 0.06 μmole was produced in the reaction carried out in an atmosphere of nitrogen.

Variation of the pH of the incubation medium showed that optimal activity occurred in the range of 6.8 to 7.5 and was considerably reduced above or below these values.

The amount of 4-aminoantipyrine determined after various periods of incubation showed that no further demethylation took place after 1 hour with amounts of substrate ranging from 1 to 5 μmoles. At this time about one-third of the substrate had been dealkylated. On the addition of more

### Table I

**Requirements for Enzymatic Demethylation of Monomethyl-4-aminoantipyrine by Dialyzed Liver Homogenate**

2 ml. of liver homogenate were dialyzed overnight against 0.02 M phosphate buffer and then incubated for 1 hour at 37° with 5 μmoles of MMAP and additions, as indicated, in a final volume of 5 ml.

<table>
<thead>
<tr>
<th>Nicotinamide, 100 μmoles</th>
<th>TPN, 0.2 μmole</th>
<th>Mg²⁺, 75 μmoles</th>
<th>Glucose-6-phosphate, 15 μmoles</th>
<th>DPN, 0.2 μmole</th>
<th>4-Aminoantipyrine formed</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.06 μmole</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.64 μmole</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0.87 μmole</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>1.54 μmole</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.26 μmole</td>
</tr>
</tbody>
</table>

substrate no further activity was observed, indicating that the enzyme system had been inactivated during the incubation period.

**Location of Dealkylation Enzyme System within Liver Cell**—Rabbit liver homogenates were centrifuged at 9000 × g for 10 minutes to sediment nuclei and mitochondria. Dealkylation activity was found to remain entirely in the supernatant fraction which contained the microsomes and the soluble enzymes (Table II).

The intracellular location of the dealkylation enzyme system was determined more precisely by fractionating rabbit liver homogenates by differential centrifugation with isotonic sucrose, as described by Schneider and Hogeboom (16). The microsomal fraction was washed once with isotonic sucrose and suspended in 0.1 m phosphate buffer, pH 7.4, and the soluble fraction was dialyzed overnight at 6° against 0.01 m phosphate buffer, pH 7.4. Assay of the cellular fractions for dealkylation activity indicated that components of both the microsomal and soluble fractions were necessary for dealkylation activity (Table II).
Role of Soluble Fraction—The requirement for TPN and oxygen in the dealkylation system at first suggested that removal of the methyl group involved dehydrogenation, TPN acting as a hydrogen acceptor. But, as shown in Table I, dialyzed liver homogenate produced much lower dealkylation activity if glucose-6-phosphate was omitted. In addition, the soluble fraction of the cell contained considerable glucose-6-phosphate dehydrogenase activity as measured spectrophotometrically (17). This suggested that TPN was converted in the complete system to the reduced form. Experiments were therefore undertaken to see whether the actual cofactor was TPNH. Washed microsomes were incubated with MMAP,

**Table II**

**Cellular Localization of Enzyme Activity**

Cell fractions were incubated with 5 μmoles of monomethyl-4-aminoantipyrine as described under "Methods," except that 30 μmoles of glucose-6-phosphate were also added.

<table>
<thead>
<tr>
<th></th>
<th>4-Aminoantipyrine formed</th>
<th>μmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole homogenate*</td>
<td></td>
<td>1.40</td>
</tr>
<tr>
<td>Supernatant fraction†</td>
<td></td>
<td>1.45</td>
</tr>
<tr>
<td>Microsomes‡</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Soluble fraction of supernatant§</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Microsomes + soluble fraction</td>
<td></td>
<td>1.45</td>
</tr>
</tbody>
</table>

* Homogenate (equivalent to 0.66 gm. of liver) prepared in phosphate buffer, pH 7.4, as described in "Methods."
† Supernatant fraction (equivalent to 0.66 gm. of liver) prepared by centrifugation of homogenate for 10 minutes at 9000 × g to remove nuclei and mitochondria.
‡ Microsomes (equivalent to 0.66 gm. of liver) prepared in isotonic sucrose (16).
§ 2 ml. of dialyzed soluble fraction equivalent to 200 mg. of liver.

glucose-6-phosphate dehydrogenase, glucose-6-phosphate, and TPN in the absence of the soluble fraction of the cell. Under these conditions high dealkylation activity was observed (Table III). The soluble fraction could also be replaced by glucose dehydrogenase, glucose, and TPN. Direct evidence that TPNH was involved in dealkylation was obtained when the addition of chemically prepared TPNH to MMAP and washed microsomes effected the formation of 4-aminoantipyrine (Table III). As would be expected, DPNH could not replace TPNH in these experiments. It may be concluded, therefore, that the dealkylation enzyme system is located in the microsomal fraction of the liver cell and that the soluble fraction participates in the over-all reaction by maintaining TPN in its reduced form.

The effect of Mg++ ion was measured in a system consisting of microsomes, MMAP, and TPNH. Equivalent dealkylation activity was ob-
served with or without the addition of 75 μmoles of Mg++. It may be presumed, therefore, that the stimulation previously noted in liver homogenates by Mg++ is due to an effect of the ion on the enzyme system which produces TPNH in the soluble portion of the cell.

Other Cofactors Tested—The following cofactors failed to increase activity when added to the liver homogenate system containing monomethyl-4-aminoantipyrine: 30 μg of flavin adenine dinucleotide, 200 μg of flavin monophosphate, 15 μg of folic acid, 5 μmoles of ascorbic acid, 4 μg of vitamin B12, 15 units of coenzyme A, 50 μmoles of cysteine, and 5 μmoles of glutathione.

Table III

| Requirement for TPNH in Dealkylation of Monomethyl-4-aminoantipyrine by Liver Microsomes |
|---------------------------------|---------------------------------|
| Microsomal preparations equivalent to 1 gm. of liver were incubated with 5 μmoles of MMAP as described under "Methods," except that 30 μmoles of glucose-6-phosphate were also added. |

<table>
<thead>
<tr>
<th>Components</th>
<th>μmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsomes + 2 ml. dialyzed soluble fraction + 0.2 μmole TPN</td>
<td>2.21</td>
</tr>
<tr>
<td>&quot; + 0.2 μmole TPN</td>
<td>0.12</td>
</tr>
<tr>
<td>&quot; + 0.2 μmole &quot; + glucose-6-phosphate dehydrogenase</td>
<td>1.46</td>
</tr>
<tr>
<td>Microsomes + TPNH*</td>
<td>0.90</td>
</tr>
<tr>
<td>&quot; + DPNH*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* A total of 7 μmoles of the reduced pyridine nucleotides was added to the incubation system, 2 μmoles at zero time and 1 μmole at 10 minute intervals thereafter, since both reduced coenzymes disappeared rapidly even in the absence of substrate. Mg++ and glucose-6-phosphate were omitted.

B12, 15 units of coenzyme A, 50 μmoles of cysteine, and 5 μmoles of glutathione.

Inhibitors of Dealkylation—The dealkylation system was not inhibited by cyanide, azide, fluoride, or iodoacetate at 1 × 10^{-8} M concentration. Cytochrome c, 4 × 10^{-6} M, and vitamin K, 1 × 10^{-3} M, produced about 30 per cent inhibition. 10 μmoles of pyruvate, α-ketoglutarate, or citrate had no inhibitory effect. However, diphenylpropylacetic acid and its ester diethylaminoethyl diphenylpropylacetate (SKF 525-A), which have been shown to inhibit the biotransformation of a large variety of drugs (18, 19), exerted a marked inhibition. At 2 × 10^{-4} M concentration these compounds inhibited the demethylation of aminopyrine and MMAP by about 50 per cent.

Substrate Specificity—The metabolic removal of alkyl groups by rabbit liver homogenate was compared in a series of aminopyrine homologues.
The data in Table IV show that the monosubstituted compounds are more easily dealkylated than the disubstituted homologues and that the extent of dealkylation decreases with increasing size of the alkyl group.

**Products of Reaction**—The fate of the methyl groups removed from aminopyrine was determined by radioactive and chemical procedures. In preliminary experiments 5 μmoles of C14-methyl-labeled aminopyrine containing 57,000 c.p.m. were incubated with the supplemented rabbit liver homogenate preparation to determine whether the methyl groups were oxidized to carbon dioxide. C14O2 equivalent to about 75 per cent of the methyl groups removed from aminopyrine (as calculated from the amount of 4-aminoantipyrine formed) was recovered. The deproteinized incubation mixture was analyzed for labeled formaldehyde and was found to contain about 5 per cent of the methyl group activity as this compound. The presence of traces of formaldehyde raised the possibility that the methyl groups in aminopyrine were converted to formaldehyde, the major portion of which then underwent oxidation to carbon dioxide.

Conclusive evidence that formaldehyde was a primary product in the demethylation of MMAP in the rabbit liver homogenate was obtained by trapping formaldehyde with 0.01 m semicarbazide. At the end of the incubation period the trapped formaldehyde was found to be equivalent to the 4-aminoantipyrine formed (Table V). 2 moles of formaldehyde were found for each mole of 4-aminoantipyrine produced with aminopyrine as substrate, indicating that both methyl groups of this compound are converted to formaldehyde.

The results in Table V show that about twice as much MMAP or aminopyrine disappeared as could be accounted for by the appearance of 4-aminoantipyrine or formaldehyde, indicating that another metabolic pathway...
for these substrates is present in liver. Preliminary work reveals that the system which catalyzes this unknown pathway is also present in microsomes.

By analogy from the fate of the methyl groups, it might be expected that an ethyl group attached to nitrogen would be converted to acetaldehyde. The fate of the ethyl group in monoethyl-4-aminoantipyrine was studied after incubation of 5 μmoles of substrate in liver homogenate in the presence of 0.01 M semicarbazide. The aldehyde arising from dealkylation of monoethyl-4-aminoantipyrine was identified as acetaldehyde by determination of the absorption spectrum of its derivative with p-hydroxydiphenyl (15). Authentic samples of formaldehyde, acetaldehyde, and glycolaldehyde after reaction with this reagent gave characteristic absorption peaks at 605, 560, and 585 μm, respectively. Glyoxylic acid did not form a colored derivative. The p-hydroxydiphenyl derivative formed with the aldehyde from monoethyl-4-aminoantipyrine had an absorption spectrum identical with that formed with acetaldehyde. Balance studies showed that acetaldehyde and 4-aminoantipyrine were formed in equivalent amounts (0.35 μmole).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>4-Aminoantipyrine formed</th>
<th>Formaldehyde formed</th>
<th>Substrate disappeared</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>μmoles</td>
<td>μmoles</td>
<td>μmoles</td>
</tr>
<tr>
<td>MMAP</td>
<td>1.1</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Aminopyrine</td>
<td>0.35</td>
<td>0.70</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Experiments described in this paper indicate that there is an enzyme system in liver which catalyzes the oxidative demethylation of aminopyrine as outlined by the accompanying equations. This pathway postulates that the methyl groups are removed from aminopyrine in a stepwise fashion. It has not been possible to show this directly, since MMAP, the monomethyl derivative, is demethylated considerably more rapidly than is aminopyrine.

The dealkylation enzyme preparation has several unusual features: it requires both TPNH and oxygen; it is unusually non-specific; and it is localized in liver microsomes.
A requirement for both TPNH and oxygen was previously reported for the enzyme system which deaminates amphetamine (20). The requirement for both of these factors is difficult to explain. The possibility is being explored that one enzyme component in the system is a flavoprotein and that hydrogen peroxide formed in the process of oxidation of TPNH may be utilized in the dealkylation reaction.

The wide range of foreign compounds dealkylated by the microsomal enzyme preparation is indicated by work now in progress. Other compounds dealkylated by liver microsomes include quinacrine (Atabrine), meperidine (Demerol), N-dibenzyl-β-chloroethylamine (Dibenamine), methylandantipyrine, methylaniline, and ethylaniline. However, epinephrine is not demethylated by the microsomal preparation. It is not yet known whether one or several systems are involved in the demethylation of various methylated alkylamines, nor even whether the same enzymatic mechanism is capable of removing methyl, ethyl, and butyl groups. The enzyme system in rat liver described by Mueller and Miller (14), which demethylates 4-dimethylaminoazobenzene and related dyes, is similar in some respects to the system which demethylates aminopyrine. Under Mueller and Miller's experimental conditions, however, both DPN and TPN are required for the demethylation of the dyes, and it has not been shown that the active cofactor is TPNH.
The nature of the normal substrate for the dealkylation enzyme system remains an open question. If there is a function other than the metabolism of foreign compounds, it is most unusual that such a wide range of alkylamines is attacked. In an attempt to find a normally occurring substrate, the influence of the preparation on a number of methyl compounds normally found in the body is now under investigation. In this respect, it is of interest that enzyme systems which demethylate sarcosine and dimethylglycine have been reported by Mackenzie et al. (21) to be located in liver mitochondria.

Recent work has shown that diethylaminoethyl diphenylpropylacetate (SKF 525-A) markedly prolongs the action of a variety of drugs in vivo by blocking their rate of biotransformation (18). Among the metabolic pathways inhibited by SKF 525-A both in vivo and in liver homogenates are side chain oxidation (e.g., barbiturates), ether cleavage (e.g., codeine), deamination (e.g., amphetamine), and dealkylation (e.g., aminopyrine and ephedrine) (19). These findings suggested that a diversity of drug metabolic pathways possessed a number of factors in common. Studies in this laboratory have shown that the systems which oxidize barbiturates (22), deaminate amphetamine (20), and cleave ethers also require TPNH and oxygen and are localized in microsomes. Recent studies from this laboratory (23) indicate that the enzyme system which hydroxylates aniline, acetanilide, and quinoline is also located in liver microsomes and requires oxygen and TPNH.

SUMMARY

Aminopyrine (dimethyl-4-aminoantipyrine) and its ethyl and butyl homologues are dealkylated in rabbit, rat, and guinea pig liver homogenates to yield 4-aminoantipyrine. The methyl groups of aminopyrine and monoethyl-4-aminoantipyrine are converted to formaldehyde, and the ethyl group of the monoethyl homologue yields acetaldehyde. Both TPNH and oxygen are required, and the dealkylation system is located in the microsomes.

Diethylaminoethyl diphenylpropylacetate (SKF 525-A) inhibits the dealkylation of aminopyrine and monomethyl-4-aminoantipyrine. This inhibitor also affects the metabolism of a diversity of other types of drug enzyme systems which are located in microsomes and require TPNH and oxygen.

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