Tissue Metabolites of Trifluoperazine, Fluphenazine, Prochlorperazine, and Perphenazine in the Rat: Identification and Synthesis

URSULA BREYER ×, AXEL PROX, RUDOLF BERTELE, and HANS JÖRG GAERTNER

Abstract □ Rats were treated chronically with increasing doses of trifluoperazine, prochlorperazine, fluphenazine, or perphenazine *per os*, and drug metabolites were extracted from their livers, kidneys, and lungs. Fluphenazine metabolites were also obtained from tissues of a dog treated with repeated oral doses. Isolation and separation of the compounds were achieved by TLC. Besides the parent drugs and the derivatives formed by removal of the terminal *N*-alkyl group, tissues contained metabolites resulting from degradation of the piperazine ring to form an ethylenediamine structure. This biotransformation occurred with and without concomitant removal of the terminal *N*-alkyl group, so that monosubstituted and symmetrically disubstituted ethylenediamine derivatives were produced from each drug. The structures of the metabolites were elucidated by mass spectrometry and confirmed by chemical synthesis.

Keyphrases □ Phenothiazines (trifluoperazine, fluphenazine, prochlorperazine, perphenazine)—isolation of drugs and metabolites in rat tissue, identification by mass spectrometry, synthesis □ Trifluoperazine and metabolites—isolated from rat tissue, identified by mass spectrometry, synthesis □ Fluphenazine and metabolites—isolated from rat and dog tissues, identified by mass spectrometry, synthesis □ Prochlorperazine and metabolites—isolated from rat tissue, identified by mass spectrometry, synthesis □ Perphenazine and metabolites—isolated from rat tissue, identified by mass spectrometry, synthesis □ Metabolism of phenothiazines—isolation and identification of drug and metabolites from rat tissue □ Piperazine-substituted phenothiazines—isolation and identification of rat tissue metabolites, ethylenediamine derivatives □ Mass spectroscopy—identification, metabolites of trifluoperazine, fluphenazine, prochlorperazine, and perphenazine

Until recently, biotransformation reactions on the piperazine ring contained in drugs were not known. In 1955, Bangham (1) noted: "This is not surprising, since the piperazine ring does not occur in nature and it is unlikely that the body would break down or use such a ring structure."

However, upon chronic administration of the neuroleptic drug perazine to rats, a metabolite was found to accumulate; this metabolite was identified as *N*-[γ-(phenothiazinyl-10)-propyl]ethylenediamine (2). This showed that the piperazine ring can be partially degraded to produce an ethylenediamine structure. The same biotransformation reaction occurred with the antihistamines chlorcyclizine and meclizine (3) and with a thrombocyte aggregation inhibitor (4).

The present paper describes the identification of analogous products resulting from biodegradation of ring-substituted phenothiazine drugs that contain a piperazine ring in the side chain. In contrast to observations on perazine, the ring cleavage occurred to a considerable extent with retention of the methyl or the hydroxyethyl group on the terminal nitrogen atom.

Some results were reported previously (5).

EXPERIMENTAL

Drugs—Trifluoperazine hydrochloride[1], fluphenazine hydrochloride[2], prochlorperazine edisylate[3], and perphenazine (free base)[4] were used.

Animal Treatment—Male Wistar rats, 280–370 g, were daily given aqueous solutions of the drugs as salts by gavage. The doses were slowly increased during 2–10 weeks. Expressed as free base, they were: trifluoperazine, 5–40 mg/kg; fluphenazine, 2–40 mg/kg; prochlorperazine, 5–50 mg/kg; and perphenazine, 2–50 mg/kg. A female beagle dog was given 15–40 mg/kg fluphenazine daily in capsules. Animals were sacrificed 24 hr after the last drug dose.

Isolation of Metabolites from Tissues—Animal tissue (liver, kidney, or lung, 5 g) was extracted as described previously (2, 6). When large quantities were to be obtained for mass spectrometric investigation, mostly liver tissue was used. The purification of the metabolites by TLC on silica gel[5] was performed according to Breyer (6), except that after washing the plates with chloroform–isopropanol (10:1), they were developed in Solvent A (Table I).

For the separation of the ethylenediamine derivatives, Solvent B was used. Prior to mass spectrometry, the metabolites were chromatographed in Solvent B on TLC plates prewashed with hexane and methanol–ammonia (20:1). In this case, elution from the gel was carried out by partitioning between 2 *N* ammonia and benzene.

γ-(2-Trifluoromethylphenothiazinyl-10)-propyl Chloride and γ-(2-Chlorophenothiazinyl-10)-propyl Chloride—These compounds were prepared according to Sherlock and Sperber (7) and freed from colored impurities by chromatography on a column of silica gel[6], with petroleum ether (bp 50–75°)–benzene (10:1).

***N*-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]piperazine (I*a*) and the 2-Chloro Analog (I*b*)**—Compounds I*a* and I*b* were obtained as described previously (8).

***N*-[γ-(2-Chlorophenothiazinyl-10)-propyl]ethylenediamine (III*b*) as Dimalonate**—Compound III*b* was prepared as follows: γ-(2-Chlorophenothiazinyl-10)-propyl chloride (2.5 g) in 10 ml of dry dioxane was added within 1 hr with stirring to 4 ml of ethylenediamine kept at 90°. After 3 hr, the mixture was concentrated *in vacuo* and the residue was distributed between 1 *N* NaOH and chloroform. The reaction product was extracted from the chloroform into 1 *N* acetic acid; after washing with chloroform and alkalinization, it was back-extracted into fresh chloroform.

Following evaporation of the solvent, the product was dissolved in 10 ml of dioxane and added dropwise with stirring to a solution of malonic acid (2.08 g) in 50 ml of absolute ether. The crystalline precipitate was washed with ether and recrystallized twice from absolute ethanol, resulting in nearly colorless needles, mp 158.5–159.5°.

Anal.—Calc. for $C_{17}H_{20}ClN_3S \cdot 2C_3H_4O_4$ (542.0): C, 50.97; H, 5.21; Cl, 6.54; N, 7.75; S, 5.92. Found: C, 50.62; H, 5.23; Cl, 6.53; N, 7.51; S, 5.84.

***N*-[γ-(2-Chlorophenothiazinyl-10)-propyl]-*N'*-methylethylenediamine (II*b*) as Dimalonate**—Compound II*b* was prepared as follows. γ-(2-Chlorophenothiazinyl-10)-propyl chloride (7 g), dissolved in 55 ml of dimethyl sulfoxide, was added within 2 hr with stirring to 19 ml of *N*-methylethylenediamine heated to 90–95°. After 30 min the starting material was no longer detectable

[1] Jatroneural, Röhm & Haas, Darmstadt, Germany.
[2] Lyogen, Byk Gulden Lomberg, Konstanz, Germany.
[3] Témentil, Rhône-Poulenc, Paris, France.
[4] Decentan, Merck, Darmstadt, Germany.
[5] Kieselgel GF_{254}, Merck, Darmstadt, Germany.
[6] Kieselgel 60, Merck, Darmstadt, Germany.

[TLC in petroleum ether–benzene (9:1)]. Following concentration *in vacuo* and distribution between 1 *N* NaOH and chloroform, the product was extracted into 2 *N* acetic acid.

The alkalinized solution was extracted with chloroform which, upon evaporation, left 6.45 g of a colorless oil. As TLC in Solvent A showed, this oil consisted of two isomers, the nondesired unsymmetrically disubstituted ethylenediamine (ninhydrin positive) being in excess. The separation was achieved by column chromatography on 100 g of silica gel with absolute acetone, which eluted the desired II*b* only (2.1 g). The dimalonate was obtained as described for III*b*; the salt was crystallized four times from absolute ethanol, yielding 1.6 g of fine colorless needles, mp 156–157.5°.

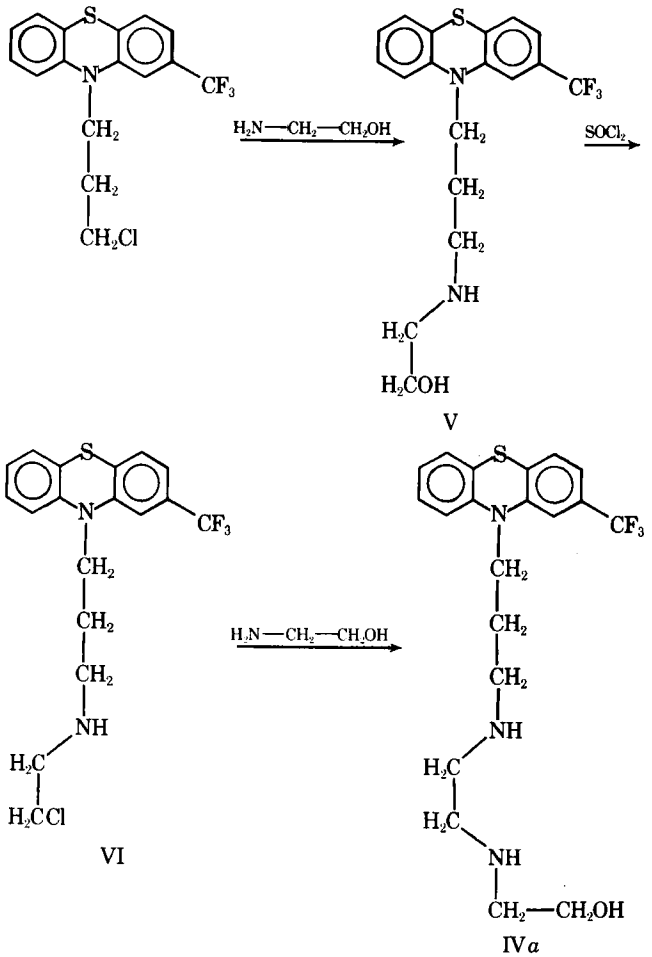
Anal.—Calc. for $C_{18}H_{22}ClN_3S \cdot 2C_3H_4O_4$ (556.0): C, 51.84; H, 5.44; N, 7.56. Found: C, 51.78; H, 5.32; N, 7.41.

***N*-[γ-(2-Chlorophenothiazinyl-10)-propyl]-*N'*-(β-hydroxyethyl)ethylenediamine (IV*b*)**—The reaction between γ-(2-chlorophenothiazinyl-10)-propyl chloride (1 g) and *N*-(β-hydroxyethyl)ethylenediamine (8 g) was carried out in analogy to the preparation of II*b*. Since the two isomers obtained could not be separated by column chromatography with acetone, a small quantity was purified by TLC in Solvents A and B, yielding a colorless oil. In both solvents, the nondesired *N,N*-disubstituted isomer had a higher R_f value than the desired one. It was present in a lower quantity.

***N*-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]ethylenediamine (III*a*) as Dimalonate**—The preparation of III*a* was according to the procedure used for the synthesis of III*b*. The dimalonate was crystallized three times from isopropanol, yielding colorless crystals, mp 141–142°.

Anal.—Calc. for $C_{18}H_{20}F_3N_3S \cdot 2C_3H_4O_4$ (575.6): C, 50.08; H, 4.90; N, 7.30; S, 5.57. Found: C, 50.19; H, 5.20; N, 7.17; S, 5.46.

***N*-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]-*N'*-methylethylenediamine (II*a*)**—A small quantity of Compound II*a* was prepared by reacting γ-(2-trifluoromethylphenothiazinyl-10)-propyl chloride with an excess of *N*-methylethylenediamine. The nondesired isomer was removed by TLC in Solvents A and B.



*Scheme I—Synthesis of IV*a. *For chemical names of the compounds, see text.*

Table I—R_f Values of Piperazine-Substituted Phenothiazine Drugs and of Their Tissue Metabolites on Silica Gel

Compound	R_f Value in Solvent[a] A	B
Trifluoperazine	0.86	0.81
N-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]piperazine (CF_3-PPP) (I*a*)	0.44	0.50
N-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]-*N'*-methylethylenediamine (CF_3-PPMED) (II*a*)	0.20	0.49
N-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]ethylenediamine (CF_3-PPED) (III*a*)	0.20	0.70
Fluphenazine	0.76	0.90
N-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]-*N'*-(β-hydroxyethyl)ethylenediamine (CF_3-PPHED) (IV*a*)	0.20	0.54
Prochlorperazine	0.86	0.81
N-[γ-(2-Chlorophenothiazinyl-10)-propyl]piperazine (Cl-PPP) (I*b*)	0.42	0.43
N-[γ-(2-Chlorophenothiazinyl-10)-propyl]-*N'*-methylethylenediamine (Cl-PPMED) (II*b*)	0.15	0.42
N-[γ-(2-Chlorophenothiazinyl-10)-propyl]ethylenediamine (Cl-PPED) (III*b*)	0.15	0.63
Perphenazine	0.76	0.90
N-[γ-(2-Chlorophenothiazinyl-10)-propyl]-*N'*-(β-hydroxyethyl)ethylenediamine (Cl-PPHED) (IV*b*)	0.15	0.47

[a] A = isopropanol–chloroform–25% ammonia–water (32:16:2:1); B = acetone–isopropanol–1 *N* ammonia (27:21:12).

***N*¹-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]-*N*³-methylimidazolidine**—A solution of II*a* (0.2 mg) in 0.5 ml of methanol was mixed with 0.02 ml of 4% aqueous formaldehyde. After 30 min the solution was concentrated and the residue was distributed between 2 *N* ammonia and benzene. TLC of the organic layer showed a single compound with R_f 0.80 in Solvent A and 0.83 in Solvent B.

***N*-[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]-*N'*-(β-hydroxyethyl)ethylenediamine (IV*a*) (Scheme I)**—*N*-[γ-*(2-Trifluoromethylphenothiazinyl-10)-propyl*]-*N*-*(β-hydroxyethyl)amine (V) as Hydrochloride*—Compound V was prepared as follows. γ-(2-Trifluoromethylphenothiazinyl-10)-propyl chloride (0.93 g) in 10 ml of dimethyl sulfoxide was added within 45 min to 3 ml of ethanolamine kept at 90°. After 30 min, the mixture was concentrated *in vacuo* and the residue was taken up in chloroform. The solution was washed several times with 1 *N* NaOH and water and subsequently shaken with 6 ml of 1 *N* HCl. The V-HCl remained in the chloroform layer, which was washed with 1% sodium chloride solution and evaporated, leaving a nearly colorless oil (0.85 g).

N-*[γ-(2-Trifluoromethylphenothiazinyl-10)-propyl]*-*N*-*(β-chloroethyl)amine (VI) as Hydrochloride*—To V-HCl (0.85 g) in 8 ml of dry chloroform was added 0.49 g thionyl chloride. The solution was left overnight at room temperature and then warmed for 3.5 hr to 40° and for 1 hr to 50°. The solvent was removed *in vacuo* and the residue was twice brought to dryness following addition of benzene.

*IV*a *as Dimalonate*—Crude VI-HCl (0.74 g) in 10 ml of dimethyl sulfoxide was added within 15 min to 3 ml of ethanolamine kept at 80° (3 hr) and at 90° (2.5 hr). Following evaporation, the residue was dissolved in ethylene dichloride and washed with 1 *N* NaOH. The product was extracted into 2 *N* acetic acid and back-extracted into ethylene dichloride after alkalinization, and the solvent was removed, leaving 0.55 g of a light-yellow oil.

According to TLC in Solvent A, small quantities only of impuri-

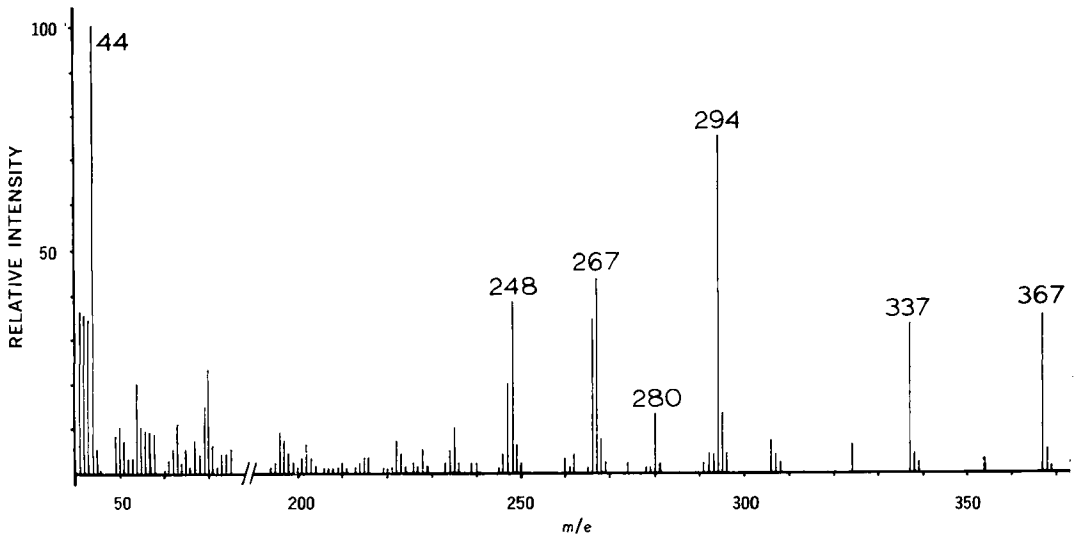


Figure 1—*Mass spectrum (70 ev) of IIIa (M^+, 367) isolated from the livers of rats treated with trifluoperazine.*

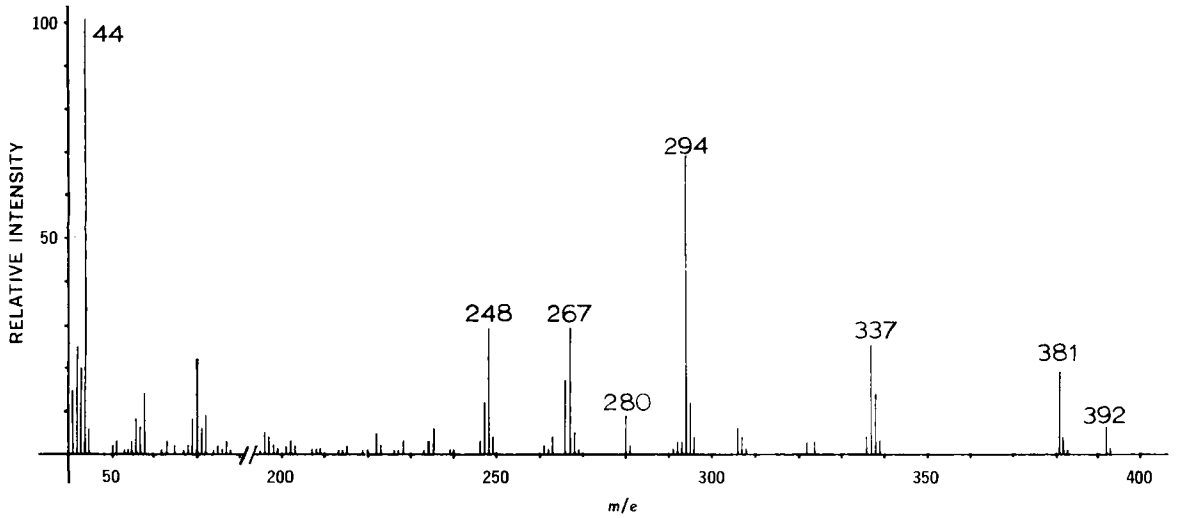


Figure 2—*Mass spectrum (70 ev) of IIa (M^+, 381) isolated from the livers of rats treated with trifluoperazine.*

ties were admixed with IV*a*, but a crystalline malonate could not be obtained. Therefore, part of the product was subjected to preparative TLC in Solvent A, followed by isolation of the compound by partitioning between 2 *N* ammonia and chloroform. From the residue of the organic layer, a colorless dimalonate was prepared and recrystallized from isopropanol, mp 144.5–146°.

Anal.—Calc. for $C_{20}H_{24}F_3N_3OS \cdot 2C_3H_4O_4$ (619.6): C, 50.40; H, 5.21; N, 6.78. Found: C, 50.97; H, 5.24; N, 6.97.

For mass spectrometric investigation, synthetic compounds obtained as salts were converted to the free bases by addition of ammonia to their solutions in water. They were extracted into benzene and the extracts were evaporated.

Mass Spectrometry—High- and low-resolution mass spectra were recorded[7]. All samples were directly introduced into the ion source, the temperature of which varied between 120 and 150°. A trap current of 500 and 100 μamp was used for recording the high- and low-resolution mass spectra, respectively. High-resolution mass spectrometry was performed on-line with a 16-sec scan and a resolving power better than 10,000. All mass measurements were within 10 ppm.

RESULTS

In tissues of animals that had received trifluoperazine, fluphenazine, prochlorperazine, or perphenazine, the parent drugs were consistently present, as were the metabolites produced by removal of the terminal *N*-alkyl group, I*a* and I*b*. The identification of these compounds was achieved by TLC comparisons in Solvents A and B (Table I).

A further band on chromatograms of tissue extracts in Solvent A could be resolved into two main components in Solvent B. The one with the higher R_f value was similar to *N*-[γ-(phenothiazinyl-10)-propyl]ethylenediamine, a perazine metabolite (2), in its chromatographic properties. In addition, it was ninhydrin positive, and the product formed from trifluoperazine proved to be identical to that resulting from fluphenazine; the same applied to the metabolites of prochlorperazine and perphenazine with similar TLC behavior. Therefore, these compounds were assumed to be the monosubstituted ethylenediamines III*a* and III*b*, respectively.

The metabolites exhibiting lower R_f values in Solvent B differed from one another; therefore, the terminal *N*-alkyl group was assumed to be still present. On the other hand, their low mobility in Solvent A pointed to the presence of two secondary (or primary) amino groups, so that symmetrically disubstituted ethylenediamines (II*a*, II*b*, IV*a*, and IV*b*) were taken into consideration. The mass spectra of the isolated metabolites proved that the proposed structures were correct. Further confirmation came from chromatographic and mass spectrometric comparison with synthetic compounds, mostly prepared by reacting a 2-substituted phenothiazinylpropyl chloride with ethylenediamine, *N*-methylethylenediamine, or *N*-(β-hydroxyethyl)ethylenediamine.

The mass spectra of the metabolites deriving from trifluoperazine and fluphenazine are shown in Figs. 1–3. The presence of sev-

[7] MS 902 S-DS 30 instrument, A.E.I., Manchester, England.

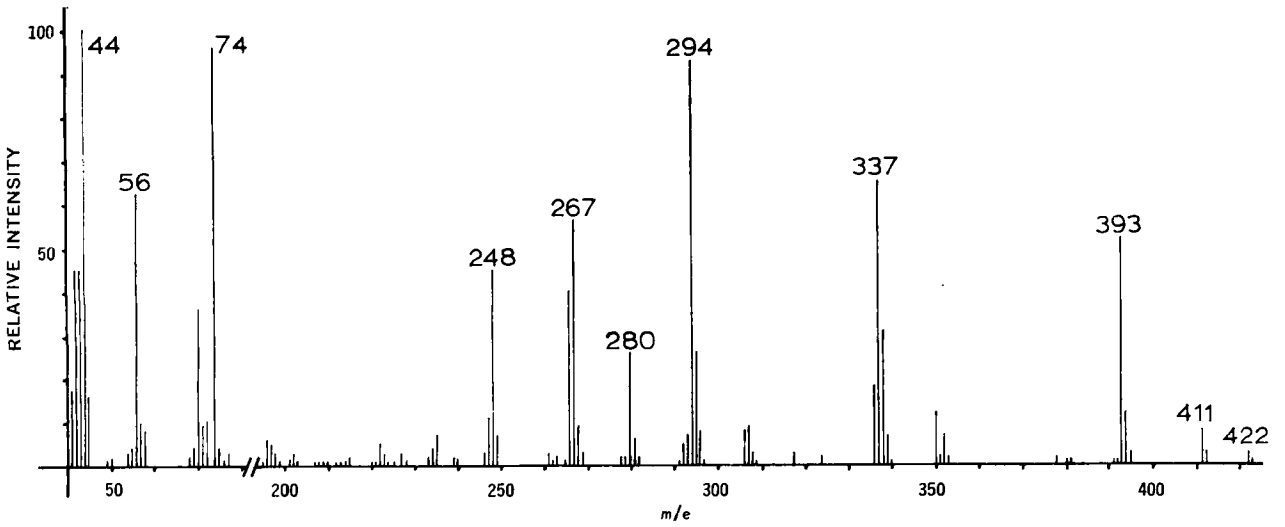


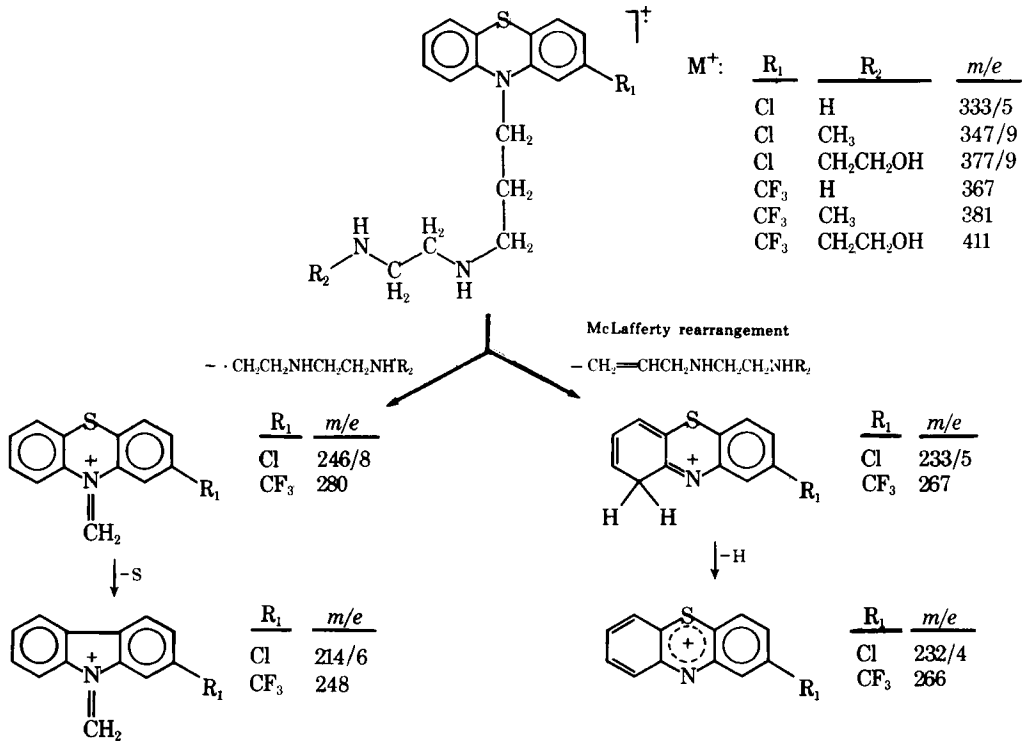
Figure 3—*Mass spectrum (70 ev) of IV*a (*M*$^+$, *411*) *isolated from the liver of a dog treated with fluphenazine.*

eral functional groups in the side chain at the phenothiazine nitrogen atom complicates the breakdown of the metabolites in the mass spectrometer. In particular, the substituent R_2 at the ethylenediamine group affects the mode of their fragmentation. Thus, the unambiguous elucidation of the metabolite structures using their mass spectra only is somewhat complicated. However, all metabolites can be immediately recognized as phenothiazine derivatives by the occurrence of abundant ions of the 2-substituted phenothiazine moiety in their mass spectra (9, 10).

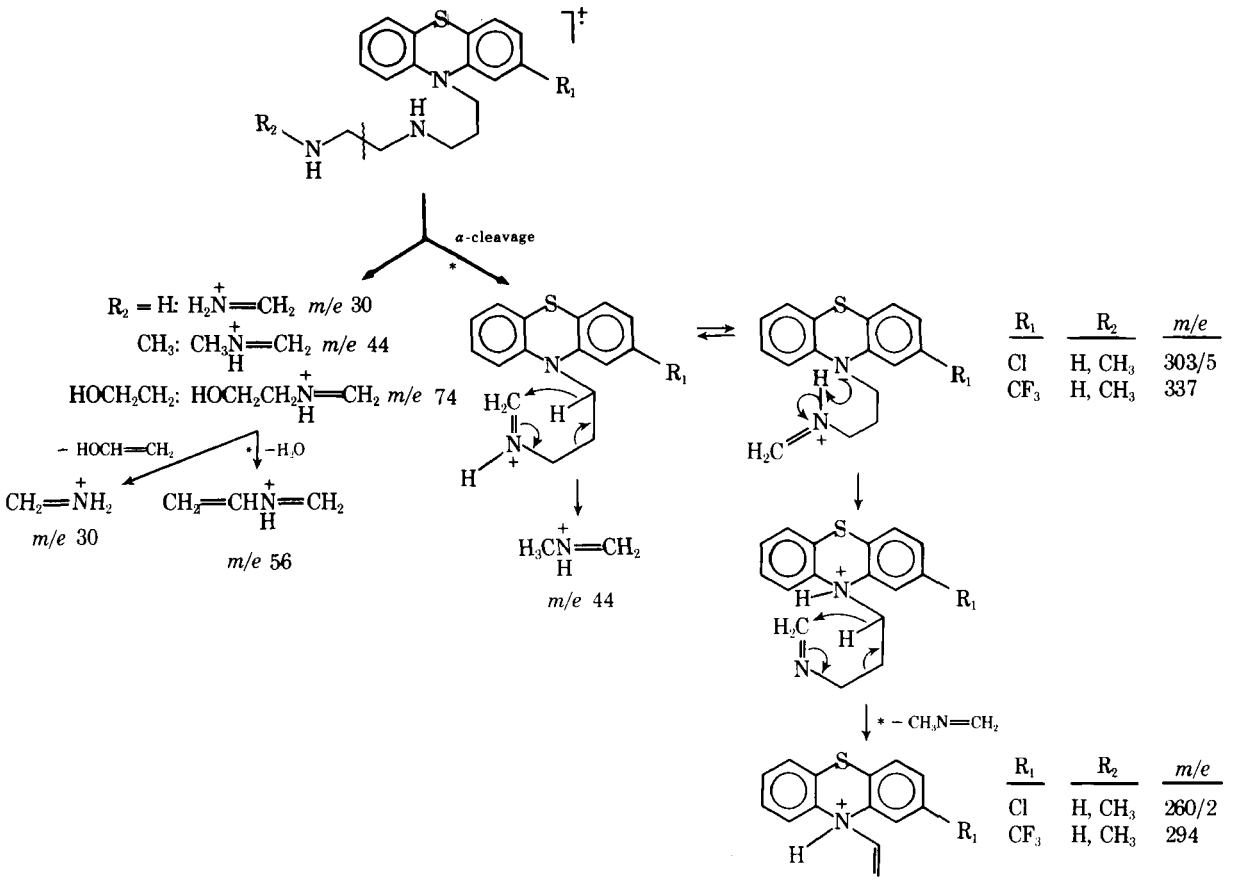
As depicted in Scheme II, the elimination of the *N*-side chain by a McLafferty rearrangement leads to the formation of the 2-substituted phenothiazine radical ion (R_1 = Cl, *m/e* 233/5; R_1 = CF_3, *m/e* 267), which further loses a hydrogen atom. Besides this ion doublet, the less abundant fragment ion formed by a simple α-cleavage is observed (R_1 = Cl, *m/e* 246/8; R_1 = CF_3, *m/e* 280). It is characterized by the elimination of the sulfur atom from the phenothiazine ring system (R_1 = Cl, *m/e* 214/6; R_1 = CF_3, *m/e* 248). The size of the side chain in the phenothiazine metabolites can thus be calculated using these ions and the corresponding molecular ions. The intensity of the molecular ions varies according to the ethylenediamine substituent R_2. In all cases where R_2 represents a hydrogen atom or a methyl group, quite abundant molecular ions are observed (Figs. 1 and 2).

As can be expected, the ethylenediamine moiety induces a strong α-cleavage of the ethylene C—C bond, with the possibility of charge retention at either of the nitrogen atoms. Some ions in the low mass range derive from this primary cleavage, *i.e.*, *m/e* 74 (C_3H_8NO) and in part *m/e* 44 (C_2H_6N) and *m/e* 30 (CH_4N). As illustrated in Scheme III, the ion *m/e* 74 not only eliminates a water molecule but also acetaldehyde as a neutral fragment, giving rise to the occurrence of the ions *m/e* 56 (C_3H_6N) and *m/e* 30 (CH_4N), respectively.

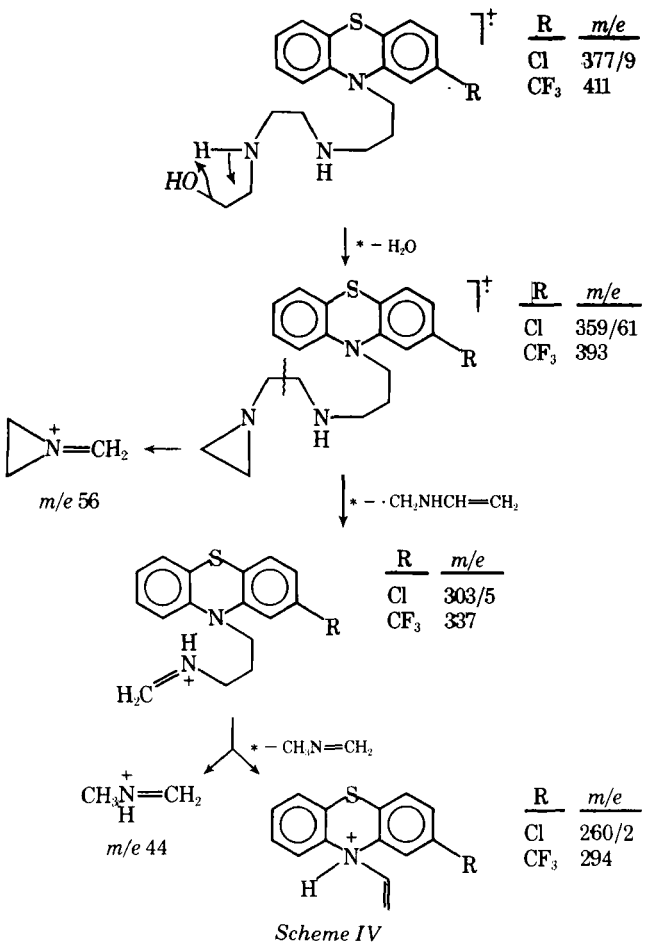
Thus, the ion *m/e* 30 may also derive from other processes than a primary α-cleavage. Therefore, an abundant ion *m/e* 30 in the mass spectra of the metabolites does not necessarily imply the presence of a primary amino group. The same is true for the very



Scheme II



Scheme III



Scheme IV

intense fragment ion *m/e* 44, which is found in the mass spectra of all metabolites regardless of the nature of the substituent R_2 at the ethylenediamine group.

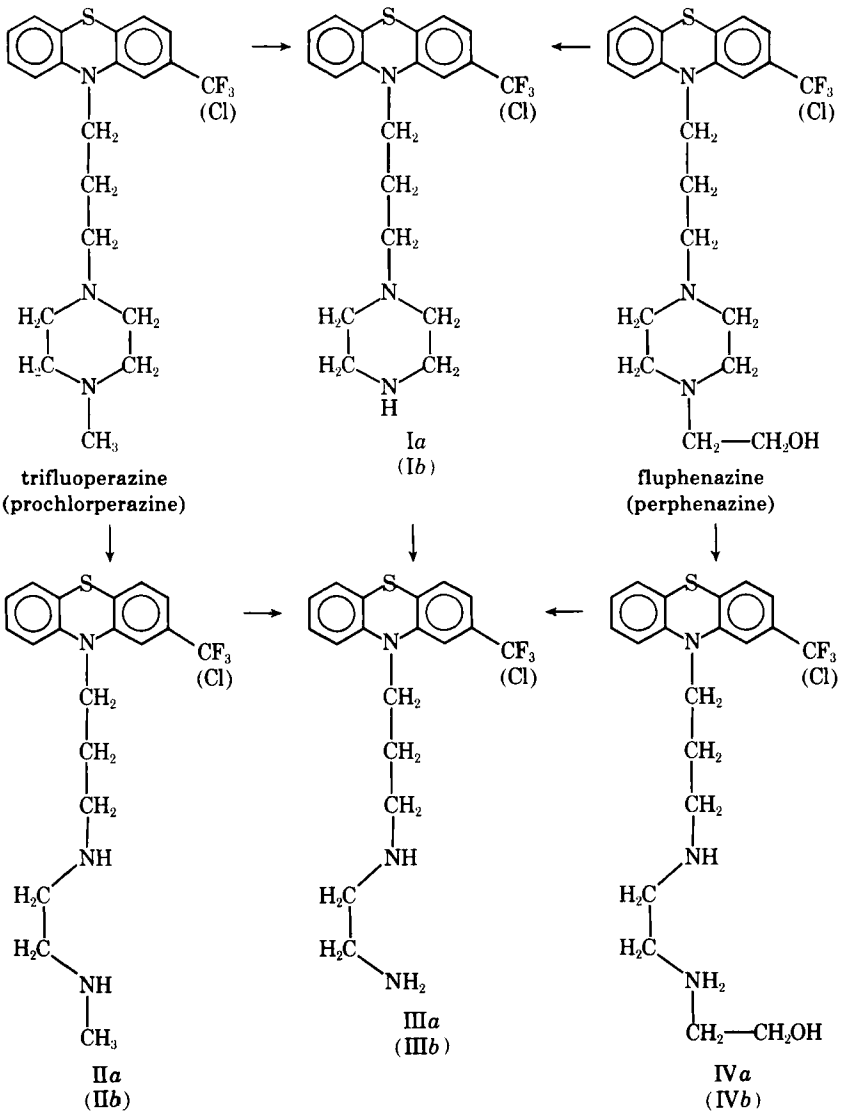
The counterions of the initial α-cleavage are only observed when the substituent R_2 is a hydrogen atom or a methyl group. As visualized in Scheme III, these ions decompose in two ways. Hydrogen rearrangement caused by the immonium ion generates the very abundant fragment ion *m/e* 44 (C_2H_6N). Thus, a methyl substituent (R_2) at the ethylenediamine group cannot be deduced from the observation of this fragment ion.

Charge exchange between the two nitrogen atoms by a proton transfer triggers the elimination of a $CH_3—N=CH_2$ molecule (43 amu). This gives rise to the formation of one of the most abundant ions in the mass spectra of the phenothiazine metabolites (R_1 = Cl, *m/e* 260/2; $R_1 = CF_3$, *m/e* 294). As indicated in Scheme III by an asterisk (*), a strong metastable ion can be observed for this process. Following the outlined degradation process, the structure of the *N*-side chain can be deduced without any ambiguity.

In contrast, the loss of a water molecule is the primary process in the mass spectra of the metabolites having a hydroxyethyl group at the ethylenediamine moiety. This elimination is the reason for the low intensity of the corresponding molecular ions (Fig. 3). Several possibilities can be envisaged to explain this elimination process, but only one has been depicted in Scheme IV. α-Cleavage of the resulting ions (R_1 = Cl, *m/e* 359/61; $R_1 = CF_3$, *m/e* 393) leads to the formation of the fragment ion *m/e* 56 (C_3H_6N) and the elimination of a C_3H_6N radical as well. The further breakdown of the ions (R_1 = Cl, *m/e* 303/5; $R_1 = CF_3$, *m/e* 337) generated by the loss of a C_3H_6N radical has already been outlined (Scheme III).

In conclusion, the structures of the phenothiazine metabolites can be elucidated by their mass spectra, taking into account the degradation processes and the resulting different fragment ions. The mass spectra of the corresponding synthetic compounds were identical with those obtained using the isolated metabolites (Figs. 1-3).

However, the mass spectrometric analysis was complicated by the presence of impurities showing higher masses than the molecular ions, namely, M + 11 and M + 12. The impurities were present in the synthetic products as well as in the metabolites isolated



Scheme V—Biodegradation of piperazine-substituted phenothiazine drugs to tissue metabolites. For names of the compounds, see Table I.

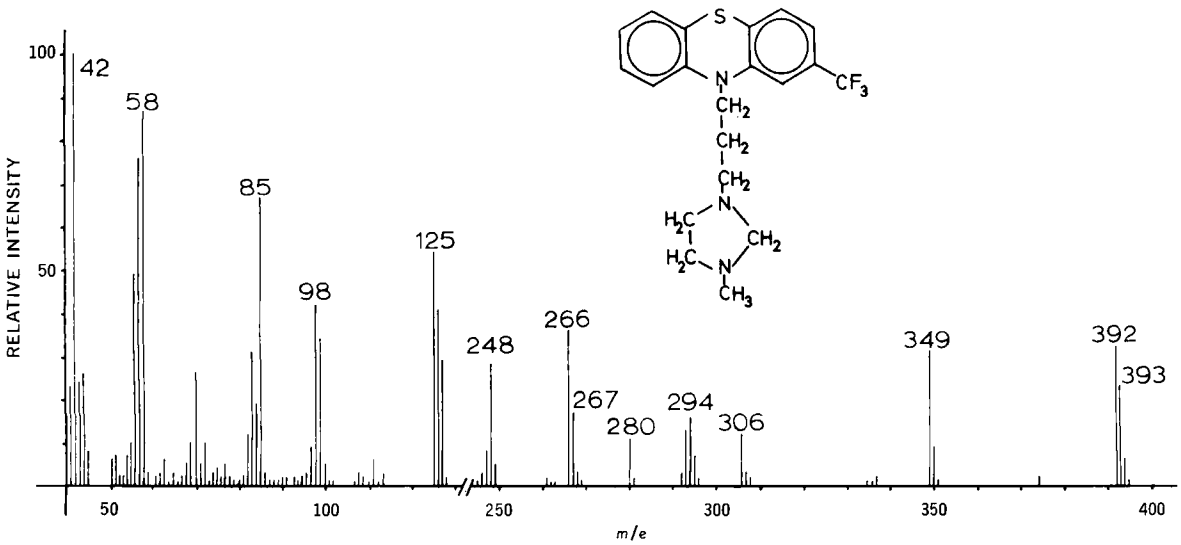


Figure 4—*Mass spectrum (70 ev) of* N¹-[γ-(*2-trifluoromethylphenothiazinyl-10*)-*propyl*]-N³-*methylimidazolidine* (M^+, *393*).

from tissues, although they occurred in greater quantities in the metabolites. In the case of II*a*, the contaminant could be shown to be N^1-[γ-(2-trifluoromethylphenothiazinyl-10)-propyl]-N^3-methylimidazolidine. Therefore, it was prepared from II*a* and formaldehyde and found to form very readily. Its mass spectrum is shown in Fig. 4.

The impurities increased with time upon storage of the samples at room temperature. Therefore, it can be concluded that the contaminants had formed *in vitro* in some stage of the preparation of the samples for mass spectrometry and were not due to additional metabolites in the tissues.

Based on the results of these investigations, the reaction sequences shown in Scheme V are suggested to be operative *in vivo*, leading to tissue metabolites of the four drugs. According to Scheme V, the monosubstituted ethylenediamines III*a* and III*b* originate by two different routes. Ring degradation starting from the terminally dealkylated metabolite has been demonstrated using desmethyl-perazine as a precursor of *N*-[γ-(phenothiazinyl-10)-propyl]ethylenediamine (6). On the other hand, terminal *N*-dealkylation of a *N,N'*-disubstituted ethylenediamine could be shown to occur by administering II*b* to rats. After 12 hr, their livers contained small quantities of III*b* in addition to II*b*.

Piperazine ring degradation to ethylenediamines is not confined to rats, since the tissues of the dog treated with fluphenazine contained the same metabolites as rat tissues. The identity was proven by TLC and mass spectrometric comparison of III*a* and IV*a* isolated from dog and rat liver.

DISCUSSION

The piperazine ring cleavage demonstrated here can be assumed to proceed *via* two consecutive *N*-dealkylation reactions, but intermediates confirming this concept have, until now, not been detected. Due to rapid aromatic hydroxylation of the drugs, the ring degradation pathway is probably a minor one in the total biotransformation in the rat. *In vitro*, it could not be demonstrated (8).

In vivo experiments on fluphenazine revealed the sulfoxide and the 7-hydroxy derivative as major excretion products in acutely and chronically treated dogs (11, 12), but elimination studies following repeated doses did not give an indication of an accumulation of these metabolites[8]. Rats given a single dose of one of the four drugs investigated here excreted in urine nearly exclusively the sulfoxide and the terminally dealkylated sulfoxide (8).

In long-term treatment with high doses, however, the ethylenediamine derivatives represent an important fraction of total tissue metabolites due to their tendency to accumulate[8] (6). Under the conditions used in the present study, their concentrations are comparable to or higher than those of the parent drugs and the dealkylation products I*a* and I*b*. Details on their kinetics in chronically treated animals will be published subsequently[8].

Pharmacological tests have not yet been carried out on the ethylenediamine metabolites. Even if they prove to be inactive by themselves, a possible significance lies in their ability to serve as precursors for biodegradation to phenothiazinylpropylamines that are metabolites common to dimethylamino-substituted and piperazine-substituted phenothiazine drugs (9).

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