Table V—Partial Mass Spectra of Trifluoroacetyl Derivatives of Noraporphines

Compound	$M^{+\cdot}$	$[M-69]^+$	$[M-97]^+$	$[M-126]^+$
Il	489[a]	420	392	363
	(100)[b]	(21)	(5)	(46)
Im	571	502	474	445
	(100)	(8)	(36)	(85)
In	653	584	556	527
	(0)	(27)	(17)	(100)
Io	571	502	474	445
	(100)	(11)	(12)	(57)
Ip	459	390	362	333
	(53)	(6)	(4)	(100)
Iq	489	420	392	363
	(71)	(10)	(12)	(100)
IIa	503	436	406	377
	(100)	(6)	(30)	(99)
IIc	533	464	436	407
	(43)	(2)	(8)	(100)
IId	391	322	294	265
	(56)	(7)	(8)	(100)
IIe	473	404	376	347
	(76)	(17)	(11)	(100)
IIf	503	434	406	377
	(49)	(2)	(3)	(100)

[a] The *m/e* values. [b] Relative intensity.

1. The *O*-trifluoroacetyl derivatives have increased volatility.
2. The *O*-trifluoroacetyl derivatives of apocodeine and isoapocodeine can be separated by GLC.
3. The mass spectra of the *O*-trifluoroacetyl derivatives of apocodeine and isoapocodeine show characteristically different fragmentation patterns that can be applied to the characterization of 10- or 11-hydroxylated aporphines.
4. A fragmentation leading to the formation of an ion at a mass value corresponding to $[M-126]^+$ can be used diagnostically to determine the degree of substitution on the nitrogen of aporphine alkaloids.

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Decomposition of Aminophylline in Suppository Formulations

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Received January 21, 1980, from the *National Center for Drug Analysis, Food and Drug Administration, St. Louis, MO 63101.* Accepted for publication March 13, 1980.

Abstract □ An aminophylline suppository product, when stored at room temperature, was found to be deficient in ethylenediamine content by the USP XIX assay and by a specific method for primary amines. The product also had a melting point that was considerably higher than body temperature. An accelerated decomposition experiment, conducted on normal suppositories of identical original composition, yielded a product refractory at steam bath temperatures and containing no ethylenediamine measurable by the USP assay. The suppositories from both the original sample and the decomposition experiment contained considerable amounts of a white material, which melted at ~150° and which consisted of the diamide products formed by the reaction of ethylenediamine and the fatty acids present in coconut and palm kernel oils. The results, which confirmed the work of Cieszynski, showed that the ethylenediamine constituent of aminophylline can react with suppository base materials to produce insoluble amide decomposition products.

Keyphrases □ Aminophylline—decomposition in suppository formulations □ Suppositories—aminophylline, decomposition in suppository formulations □ Decomposition—aminophylline in suppository formulations

During a study by the Food and Drug Administration which required the analysis of various dosage forms of xanthine derivative drugs, an aminophylline suppository formulation was encountered that unexpectedly failed to melt when heated in a beaker on a steam bath. In fact, the suppositories barely softened, and a composite was prepared for assay only with great difficulty. Analysis by the USP XIX method (1) showed that the suppository contained approximately the labeled amount of theophylline but considerably less than the compendial requirement for ethylenediamine. The suppository sample had been stored at room temperature for a month before analysis, so the original condition of the product was unknown.

An accelerated decomposition experiment was devised to study the phenomenon of hardening and to elucidate the decomposition that apparently had occurred. Ci-

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eszynski (2) had isolated the decomposition products from aged aminophylline suppositories and identified them as the amide reaction products of ethylenediamine with glyceryl esters of the fatty acids in cocoa butter and a suppository base composed of the triglycerides of C_{12}–C_{18} fatty acids[1]. Identification was based on extensive TLC, GLC, and IR spectral analyses of the isolated amides and of products synthesized from authentic materials.

Cieszynski (2) also conducted an accelerated decomposition experiment in which the decomposition reaction described was duplicated. He (2) did not give the melting characteristics of the decomposed suppositories or elemental analyses for the impurities found, but this information may be in one of his earlier papers, which was not available for translation.

The work of Cieszynski allowed this laboratory to concentrate its attention on a small group of possible decomposition compounds. The isolation and identification of the agents responsible for the hardening observed in the aminophylline suppositories are described here.

EXPERIMENTAL

Accelerated Decomposition Study—Fifty 500-mg aminophylline suppositories from another commercial sample of an identical formulation, which originally met all USP XIX requirements, were used. These samples had been stored at room temperature but melted readily on a steam bath and showed only a small loss of ethylenediamine by the USP XIX assay (1). One package of suppositories was stored at 0° during the experiment, and the remaining units were placed in a 40° convection oven. At intervals, four suppository units were removed from the oven. Two were placed in a refrigerator (0°), and the other two were assayed for theophylline (1) and ethylenediamine[2] content.

Isolation of Amide Decomposition Products—The suppository was dispersed in a beaker with 20–30 ml of isooctane[3] to dissolve the fatty base. The undissolved residue was collected on filter paper[4], and the residue was washed with two additional portions of isooctane. The residue on the filter was air dried and washed with two 20-ml portions of hot water to remove the aminophylline and any ethylenediamine or theophylline present. The washed residue was transferred to a beaker, 10 ml of chloroform[3] was added, and the mixture was heated to boiling. Ethanol (95%) was added dropwise until a clear solution was obtained.

The solution was placed in a refrigerator or freezer until crystallization occurred. The precipitate was collected on filter paper and washed with methanol[3]. The material was recrystallized successively from hot methanol and methanol–chloroform (1:1), and the crystals were air dried. Drying was completed in a 105° oven before the melting-point determination or IR scan.

Preparation of Authentic Individual or Mixed Fatty Acid Amides—*Method I (3): Synthesis from Fatty Acids*—Approximately 0.5 g of authentic fatty acid or the fatty acid mixture from saponified base was dissolved in 5 ml of chloroform, 0.2 ml of thionyl chloride was added, and the reaction mixture was cooled. Then 5 ml of chloroform containing 0.5 ml of ethylenediamine[5] (98%) was added slowly, and the mixture was refluxed for an additional 0.5 hr. The mixture was cooled and the precipitated product was collected by filtration. The residue was washed on the filter with methanol and allowed to air dry for ~0.5 hr.

Method II: Preparation from Glyceryl Esters of Fatty Acids—This reaction requires a 2:3 molar ratio of glyceryl ester to ethylenediamine. Approximately 7 g of suppository base was melted in a side-arm test tube and cooled until the onset of crystallization. One milliliter of ethylenediamine was added, and the reactants were mixed thoroughly with a magnetic stirrer. The test tube was fitted with a cold-finger condenser, and the tube was flushed with nitrogen.

The tube was heated in an oil bath, and the reaction mixture was stirred continuously under a nitrogen atmosphere as long as the magnetic bar was operable. The melt gradually became cloudy, and a semisolid appeared as a floating mass. The reaction was allowed to continue until complete solidification occurred. The amide was extracted and the reaction product was recrystallized as described for the isolation of amide decomposition products.

Saponification of Amides—The appropriate amide, 100–500 mg, was placed in a 50-ml round-bottom boiling flask, 10 ml of 20% KOH in propylene glycol was added, and the mixture was refluxed for 3 hr. Then the mixture was cooled, 10 ml of water was added, concentrated hydrochloric acid was added to acidify the solution, and the solution was cooled again. The solution was extracted with methylene chloride in a separator, and the organic phase was evaporated to dryness on a steam bath.

IR Spectra[6]—Sample spectra were prepared neat or as the trifluorovinyl chloride polymer[7] mull of the substance examined.

GLC (4)—The gas chromatograph[8] was equipped with a flame-ionization detector and a 3.05-mm i.d. nickel column[9]. The carrier gas was helium at a flow rate of 28 ml/min. The temperature was 250° for the column, injector, and detector.

Derivatization Procedure (Methylation)—(*m*-Trifluoromethylphenyl)trimethylammonium hydroxide[10], 200 μl, was added to 10 mg of the test substance, and the mixture was allowed to stand for 30 min in a covered vial.

Spectrophotometric Determination of Ethylenediamine in Suppositories[2]—The suppository, or a composite mixture equivalent to one unit, was dispersed in 95% ethanol, and the solution was carried through the automated procedure. The standard may be prepared from a previously analyzed aminophylline drug substance or the USP XIX reference standard. The method is specific for primary aliphatic and secondary cyclic amines.

TLC Identification of Amide Reaction Products—A portion of the reacted mixture was washed with three portions of cold isooctane. The residue was dissolved in boiling chloroform–methanol (1:1) and spotted on 75-mm silica gel plates[11]. Solutions of authentic aminophylline and of the diamide reaction product were spotted adjacent to the sample spots. The chromatogram was developed with chloroform–methanol (9:1) and viewed directly under UV light or by daylight after treatment with iodine vapor. Typical R_f values for aminophylline and the diamide are 0.45 and 0.60, respectively.

The isolation of the high-melting substance from the hardened suppositories was based on consideration of the solubility properties of aminophylline, theophylline, ethylenediamine, and the suppository base[12] used in this product.

The fatty base in the formulation was derived from coconut and palm kernel oils (5), which are rich in the glycerides of lauric and myristic acids, along with smaller amounts of the glycerides of oleic, palmitic, capric, and stearic acids (6). Myristic and palmitic acids were selected as representative of the group, and the pure substances were used for the preparation of authentic amide products by reaction with ethylenediamine after their conversion to acid chlorides.

Authentic suppository base also was used to prepare the amide product by direct reaction with ethylenediamine at 40 and 100°. The higher temperature was used to expedite the reaction and to increase the yield of amide. This experiment was repeated using aminophylline. In all experiments, IR spectrophotometry and TLC were used to monitor the final stages of the amide syntheses.

A portion of the purified high-melting substance isolated from the original, decomposed suppositories and a portion of the synthetic amide mixture prepared from the authentic suppository base were saponified to obtain the free acid mixture from each. These mixtures, another portion of suppository base, and individual lauric, myristic, palmitic, stearic, and oleic acid samples were derivatized and chromatographed by GLC for comparison of acid content.

RESULTS AND DISCUSSION

The results accumulated after storage of the samples at 40° for 3 months showed a progressive diminution of the ethylenediamine content, as measured by both colorimetric amine[2] and USP XIX titration (1)

[1] Witespol.
[2] P. A. McCullen, National Center for Drug Analysis, personal communication.
[3] Glass-distilled isooctane, chloroform, and methanol were used throughout the study.
[4] Whatman No. 1.
[5] Mallinckrodt.
[6] Perkin-Elmer model 337 spectrophotometer.
[7] Fluorolube.
[8] Hewlett-Packard model 5830A.
[9] Packed with 10% Silar-10C on Gas Chrom Q, Applied Science Laboratories, State College, Pa.
[10] Applied Science Laboratories, State College, Pa.
[11] No. 60F-254, E. Merck, Darmstadt, West Germany.
[12] Wecobee M.

Table I—Assay Results on Individual Suppository Units after Incubation at 40°

Elapsed Time, months	Ethylenediamine, % of aminophylline	Aminophylline, % of declared
0 (original analysis)	12.6	100.2[a]
1.0 (start of study)	11.8	100.0
1.5	11.9	102.0
2.0	8.9	95.8
3.5	0	99.2
4.0	0	93.2

[a] Average of six individual suppository assays; results ranged from 97.8 to 106.9%.

methods. The theophylline content showed little or no loss until late in the study (Table I).

The suppositories hardened during the accelerated decomposition experiment, but the increase in their melting point was not readily discernible until the melting point exceeded the steam bath temperature. The accelerated decomposition study had been in progress for 10 weeks by this time, and the ethylenediamine assay results were zero.

A large amount of a white, waxy substance, mp 145–147°, was isolated from the original sample of hardened suppositories. The high melting point of this substance could easily account for the refractory behavior of the suppositories at steam bath temperatures.

The IR spectrum of the trifluorovinyl chloride polymer mull of the dried, extracted material exhibited the following absorption bands: 3290 (NH stretch, amide), 3120 (NH stretch, purine from theophylline), 2930, 2850 (CH_2 symmetrical and unsymmetrical stretch), 1740 (C=O stretch, ester from fatty base), and 1640 (C=O stretch, amide) cm^{-1}. The interpretation was made with the aid of additional IR spectra of the neat suppository base[12], neat ethylenediamine, and the trifluorovinyl chloride polymer mulls of a refrigerated suppository fragment, trimyristin, and the reaction product of myristic acid and ethylenediamine *via* myristoil chloride.

The IR spectrum of the isolated high-melting product is consistent with that of a mixture of an alkyl amide and an alkyl ester (7) and includes all of the principal bands found by Cieszynski (2) in his spectra of amide decomposition products. An alkyl ester band found at 1750 cm^{-1} in the spectrum is believed to be due to unreacted suppository base since the band was absent in the spectrum obtained from the substance recrystallized from hot methanol. A minor NH amide band at 3290 cm^{-1} was found in the spectrum of the refrigerated suppository, which indicates that a small amount of decomposition may have occurred during storage after the original analysis; this observation accounts for the small reduction in the ethylenediamine content of the suppositories between the time of the original analysis and the start of the study.

The recrystallized *N,N'*-(1,2-ethanediyl)bisamides, synthesized from myristic and palmitic acids, had melting points of 150–152° and 147.5–148.0°, respectively, and gave IR spectra that showed the same prominent bands at 3290 and 1640 cm^{-1} that had been obtained from the high-melting substance previously isolated from the suppository.

The purified substance, obtained by direct reaction of myristin and ethylenediamine, melted at 148.5–150° and showed the same prominent IR bands at 3290 and 1640 cm^{-1}.

The spectra of the amide products that had been synthesized directly from aminophylline exhibited strong bands at 3290 and 1640 cm^{-1}, confirming the generation of an amide product by a reaction between aminophylline and the suppository base.

The distribution of fatty acid peaks found by GLC of the substance isolated from the suppositories was the same in kind and rank order as that of the authentic suppository base, confirming the source of the acyl components of the amides (Table II). It was not expected that the ratio percentage of each acid would be the same in both, because the suppository base material is derivatized directly whereas the amide must be saponified and the acids must be extracted before derivatization and GLC.

Table II—Fatty Acid Composition (Percent) of Products Analyzed by GLC

Product	Lauric	Myristic	Palmitic	Stearic	Oleic
Synthetic diamide mixture	45.0	18.2	10.6	26.0	0.2
Suppository base	43.8	17.9	11.1	24.7	2.3
High-melting substance	37.0	18.2	13.4	31.2	0.2

Table III—Elemental Composition of Analyzed Products[a]

Product	C	H	N	Melting Point
Isolated diamide mixture	74.49	12.67	5.84	148.5–149.5°
Synthetic diamide mixture	74.05	12.33	5.73	148.5–150.0°
Calculated for diamide mixture	74.93	12.55	5.79	
Synthetic bispalmitamide	76.21	13.41	5.04	147.5–148.0°
Calculated for *N,N'*-(1,2-ethanediyl)bis-palmitamide	76.06	12.77	5.21	

[a] Based on ratio percent distribution of fatty acids found in suppository base by GLC, expressed as bisamides.

The amide decomposition products isolated from the suppositories are believed to be the 1,2-ethanediamides based on the following experimental evidence. A single stretching band was found at 3290 cm^{-1}. If any primary amide were present, a doublet would have been seen in the region of 3300–3500 cm^{-1} in the IR spectrum. No color reaction was seen with the 2,3-dichloro-1,4-naphthoquinone reagent (8). No monoamide precipitated upon neutralization of the hydrochloric acid extract of the solid material. There was no blue color change when the spot separated by TLC was sprayed with bromcresol green.

Additional confirmation of the presence of diamides was obtained by quantitative elemental microanalyses[13] (Table III).

The results obtained in this study confirm the finding of Cieszynski (2) that the ethylenediamine moiety of aminophylline is capable of reacting with the glyceryl esters of some suppository bases to form insoluble, high-melting amide decomposition products. In a concurrent study conducted in this laboratory, a chemically similar decomposition occurred in rectal theophylline ethanolamine solutions preserved with parabens[14].

The reactions were carried out with authentic materials under conditions likely to exist during the commercial manufacture of suppositories. The reaction between the suppository base and free ethylenediamine at 40° began within 1 hr under an atmosphere of nitrogen, which also showed that prior rancidity was not a necessary condition for the formation of amide products. The reaction of the suppository base with aminophylline at 40° was much slower. Conditions that initiate the reaction, other than heat, have not been determined.

The significance of these results becomes apparent when the manufacturing process for suppositories (3) is examined. Aminophylline is stirred into molten suppository base; the melt is poured into heated molds and slowly cooled to minimize the formation of an unwanted α-state of the base. The maximum batch temperature exceeds 50° for a short time before the addition of drug substance and is kept just above the melting point of the base during pouring. The total elapsed heating time may last up to 1 day, depending on the size of the batch.

The manufacturing process could result in the formation of amide reaction products if temperature and process times are not controlled carefully, especially for the units poured at the end of a large batch run. The same reaction takes place slowly if the finished suppositories are not kept refrigerated, especially under summer temperatures.

A limited number of current commercial products was examined by IR spectrophotometry, which showed the presence of small quantities of amide reaction products. These products were indicated by a weak amide band at 3290 cm^{-1} and a shoulder at 1640 cm^{-1} in most of these spectra. The formulations containing hydrogenated coconut and palm kernel oil mixtures appear to be the most susceptible to decomposition. This observation may be due to the manufacturing process or it may be inherent in the product.

An IR limit test for 1,2-ethanediamides or a melting-point test is recommended for inclusion in the USP monograph for aminophylline suppositories.

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Oxidative Degradation of Hydrocortisone in Presence of Attapulgite

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Abstract □ Degradation of hydrocortisone in attapulgite suspensions was monitored by high-pressure liquid chromatography and UV spectrophotometry. The rate of oxidative degradation of hydrocortisone was accelerated significantly in the presence of attapulgite. In addition, degradation appeared to be composed of two apparent first-order reactions rather than the single apparent first-order degradation reaction observed for hydrocortisone solutions. However, the same degradation products were obtained in both hydrocortisone solutions and attapulgite suspensions, indicating that interaction with attapulgite did not alter the degradation pathway. Kinetic and adsorption studies suggested that hydrocortisone is adsorbed weakly by attapulgite and undergoes oxidative degradation, which is catalyzed by adsorbed iron oxides or hydroxides as well as by structural ferric iron at the clay surface. Since clay minerals generally contain surface ferric iron, the potential for accelerating the oxidative degradation of drugs should be considered whenever clays and drugs are combined.

Keyphrases □ Attapulgite—effect on hydrocortisone degradation, kinetic and adsorption studies □ Hydrocortisone—oxidative degradation in attapulgite suspensions □ High-pressure liquid chromatography—monitoring of degradation of hydrocortisone in attapulgite suspensions □ Adsorption—hydrocortisone onto attapulgite, oxidative degradation of hydrocortisone

A recent study of the interaction of montmorillonite with digoxin revealed that the clay surface, through its ability to concentrate both digoxin and protons, accelerated the acid-catalyzed hydrolysis of digoxin and suggested that other neutral drugs which are degraded by acid-catalyzed hydrolysis may be affected similarly by interaction with a clay (1). Since oxidation also is a major mechanism of drug degradation, a study was undertaken to determine if interaction with a clay surface could result in accelerated oxidative degradation.

BACKGROUND

Montmorillonite, a member of the smectite group of clays, promotes the oxidation of a number of organic compounds, including the conversion of pyrogallol to quinones of poorly defined structure (2), of dihydroxyquinones to *p*-benzoquinone (3), and of benzidine to a blue monovalent semiquinone (4). In addition, hectorite, a clay belonging to the same structural group as montmorillonite, catalyzes the oxidation of benzidine (5, 6). Surface-adsorbed contaminants or structural ferric iron at the clay surface have been suggested as being responsible for the oxidation of organic materials by these clays.

Attapulgite was chosen for this study because: (*a*) it belongs to the fibrous group of minerals whose effect on oxidative degradation has not been studied extensively, (*b*) the oxidizing action of Fe^{3+} in attapulgite has been demonstrated (7), and (*c*) it is used in pharmaceuticals as a GI adsorbent (8) or excipient. Hydrocortisone was chosen as the model drug because it is known to degrade by oxidation, it may be coadministered orally with a clay-containing pharmaceutical, and it is used in topical dosage forms that also may contain a clay.

Degradation of the C-17 dihydroxyacetone side chain of corticosteroids has been studied extensively (9–13). Transformations and elimination of the side chain occur in both the presence and the absence of oxygen (12). However, autoxidation appears to be the major mechanism of degradation of corticosteroids in pharmaceutical dosage forms (12).

Factors influencing the degradation of prednisolone in aqueous solution were investigated, and trace metals present as contaminants in the buffer reagents were indicated as the cause of accelerated degradation (11).

EXPERIMENTAL

Materials—All chemicals were official or reagent grade. Attapulgite was obtained commercially[1]. X-ray diffraction of the clay sample confirmed that attapulgite was the major mineral but that a small amount of quartz also was present.

The effect of surface ferric iron was studied by treating the attapulgite by the citrate–dithionite procedure (14), which extracts nonstructural iron from the clay surface. The iron extracted was quantified by the *o*-phenanthroline method (15), and the total iron content was determined by the hydrofluoric acid dissolution procedure (16).

Hydrocortisone Assay—A high-pressure liquid chromatographic (HPLC) method, which was recommended for the analysis of hydrocortisone tablets (17), was modified slightly for this study. The liquid chromatograph[2] was equipped with a UV detector operating at 254 nm and a 20-μl injector loop[3]. A commercially packed octadecylsilane[4] column was used with acetonitrile–water (35:65) as the mobile phase. The operating parameters were: flow rate, 1 ml/min; pressure, 1000–1200 psi; temperature, ambient; and UV attenuator, 0.02 aufs. Linear calibration curves were used to quantify hydrocortisone, while the relative concentration of the observed degradation products was characterized by peak heights.

Changes in the A-ring of hydrocortisone were monitored by UV spectrometry at 254 nm.

Self-supporting films were prepared for IR analysis[5] by pipetting appropriate volumes of either the attapulgite or the hydrocortisone–atta-

[1] Pharmabsorb, colloidal, Engelhard Minerals and Chemicals Corp., Menlo Park, N.J.
[2] Model ALC 202, Waters Associates, Framingham, Mass.
[3] Rheodyne, Berkeley, Calif.
[4] Partisil-10 ODS, Whatman Inc., Clifton, N.J.
[5] Model 180, Perkin-Elmer Corp., Norwalk, Conn.

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